Bladder Relaxant Preparations
Therapeutic Class Review (TCR)

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Magellan Rx MANAGEMENT℠

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
darifenacin (Enablex®)[1]	generic, Allergan	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
fesoterodine ER (Toviaz®)[2]	Pfizer	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
mirabegron ER (Myrbetriq®)[3]	Astellas	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency Treatment of overactive bladder with symptoms or urge urinary incontinence, urgency, and urinary frequency in combination solifenacin
oxybutynin[4]	generic	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (e.g., urgency, frequency, urinary leakage, urge incontinence, dysuria)
oxybutynin ER (Ditropan® XL)[5]	generic, Janssen	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency; Treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida)
oxybutynin hydrochloride gel (Gelnique®)[6]	Allergan	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
oxybutynin transdermal (Oxytrol® [Rx], Oxytrol® for Women [OTC])*[7]	Allergan (Rx) Allergan, Bayer, MSD (OTC)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency Oxytrol for Women is only approved for use in women (≥ 18 years of age)
solifenacin (Vesicare®)[8]	generic, Astellas	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency
tolterodine (Detrol®)[9]	generic, Pfizer	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
tolterodine ER (Detrol® LA)[10]	generic, Pfizer	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
trospium[11]	generic	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency
trospium ER[12]	generic	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency

ER = extended-release

*In September 2013, oxybutynin transdermal patch (Oxytrol for Women) became available over-the-counter (OTC) for treatment of OAB in women ages 18 years and older.[13] It is the first treatment for OAB to become available OTC. Oxytrol patches remain available only by prescription for men.

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 (8 or more voiding episodes per 24 hours) and nocturia (awakening 1 or more times per night to void).[14] 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).[15] The overall prevalence of OAB occurs equally in men (16%) and women (16.9%); however, more women suffer from OAB with incontinence.[16] The prevalence of OAB is almost 20% in those older than 60 years of age.

Many conditions are associated with 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). In addition, OAB and urinary incontinence (UI) are associated with skin infections and irritations, and, in the elderly, an increased risk of falls and fractures.[17,18,19]

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 thereby sending signals from the spinal cord to brain centers, resulting in the sensation of urge due to increased bladder filling.[20]

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.[21]

The management of OAB includes both pharmacological and non-pharmacological (e.g., bladder training, pelvic floor muscle exercises) interventions.[22,23] Antimuscarinic agents that relax the detrusor muscle or prevent a bladder contraction are effective for OAB.

In their amended 2019 guidelines, the American Urological Association (AUA) recommends behavioral therapy (e.g., bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) as first-line therapy.[24] Pharmacological therapy may be combined with behavioral therapy as first-line treatment as well. Oral antimuscarinics or beta-3 adrenergic receptor agonists should be offered as second-line therapy. There may be consideration of combination anti-muscarinic and beta-3 adrenergic receptor agonist in patients refractory to monotherapy with either mechanism alone. Surgery is reserved for patients with severe refractory OAB symptoms or who are not candidates for oral therapy.

In September 2013, oxybutynin transdermal patch (Oxytrol for Women) became available for over-the-counter (OTC) use to treat OAB in women. The transdermal patch (Oxytrol) is available with a prescription to treat OAB in men and women. The OTC product was not approved for use in men due to the concern of prostate related complications.

PHARMACOLOGY[25,26,27,28,29,30,31,32,33,34,35,36]

Contractility of the human detrusor muscle is predominantly controlled by the parasympathetic nervous system. 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 located on the detrusor muscle.[37] There are 5 known muscarinic receptor subtypes labeled M_1 through M_5. Although the detrusor muscle contains a greater number of M_2 than M_3 receptors (3:1 ratio), 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 (GI) smooth muscle, saliva production, central nervous system (CNS) function, cardiac function, 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.

Darifenacin (Enablex) is a competitive muscarinic receptor antagonist. It is a selective antagonist at M_3 receptors.[38] 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 other available agents.

Fesoterodine extended-release (ER) (Toviaz) is rapidly and extensively hydrolyzed to its active metabolite, 5-hydroxymethyl tolterodine. Both are non-selective competitive antagonists of muscarinic M_1 through M_5 receptors. The active metabolite has greater potency than the parent compound.[39,40] In contrast to tolterodine, the conversion of fesoterodine to its metabolite bypasses the CYP system, although CYP3A4 and CYP2D6 are involved in subsequent inactivation of the active metabolite.

Mirabegron ER (Myrbetriq), a beta-3 adrenergic receptor agonist, relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle, thereby increasing bladder capacity.

Oxybutynin (Ditropan, Ditropan XL, Gelnique, Oxytrol, Oxytrol for Women) is a tertiary amine ester that is a potent, nonselective, competitive muscarinic 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 adverse effects consistent with anticholinergic actions in the CNS, parotid gland, and GI tract. Oxybutynin also possesses minor local anesthetic properties.

Solifenacin (Vesicare) is a competitive M_3-selective muscarinic receptor antagonist but has some effect on all muscarinic receptors.[41] 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 adverse effects are minimal.

The tertiary amine tolterodine (Detrol, Detrol LA) and its active metabolite, 5-hydroxymethyl tolterodine, 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.[42,43] Trospium is an antispasmodic, competitive antimuscarinic agent that has high affinity for the M_1, M_2, and M_3 receptor subtypes with lower affinity for the M_4 and M_5 receptors.[44] 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 adverse effects such as sedation and dizziness.[45,46]

PHARMACOKINETICS[47,48,49,50,51,52,53,54,55,56,57,58,59]

Drug	Time to Peak (hour)	Route of Metabolism	Half-life (hour)
darifenacin (Enablex)	6.49-7.61	CYP2D6*, CYP3A4	13-19
fesoterodine ER (Toviaz)	5	CYP2D6, CYP3A4	7.31-8.59
mirabegron ER (Myrbetriq)	3.5	CYP2D6, CYP3A4	50
oxybutynin (Ditropan)	< 1	CYP3A4	2-3
oxybutynin ER (Ditropan XL)	11.8-12.7	CYP3A4	12.4-13.2
oxybutynin gel (Gelnique)	n/a	CYP3A4†	64
oxybutynin transdermal (Oxytrol, Oxytrol for Women)	10-48	CYP3A4†	7-8
solifenacin (Vesicare)	3-8	CYP3A4	45-68
tolterodine (Detrol)	1-2	CYP2D6, CYP3A4	2-2.2‡
tolterodine ER (Detrol LA)	2-6	CYP2D6, CYP3A4	6.9-8.4§
trospium	5-6	Ester hydrolysis	18.3
trospium ER	5	Ester hydrolysis	36

* Bioavailability of darifenacin is increased by 77% to 131% in poor metabolizers of CYP2D6.

† 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 ER capsules can be up to 18 hours in slow metabolizers.

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.

Like tolterodine, fesoterodine (Toviaz) is rapidly and extensively hydrolyzed to the 5-hydroxymethyl tolterodine, the active metabolite that is responsible for its antimuscarinic activity. With virtually the entire moiety converted to the active metabolite, fesoterodine functionally acts as a prodrug. In addition, its conversion to 5-hydroxymethyl tolterodine bypasses the CYP system, unlike tolterodine.

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

Although administration of mirabegron ER (Myrbetriq) with a high fat meal resulted in increased peak serum concentration and exposure, in phase 3 clinical studies mirabegron ER was given irrespective of food intake. Mirabegron ER can be taken with or without food at the recommended dosage. Mirabegron ER is metabolized by multiple pathways, including dealkylation, oxidation, glucuronidation,

and hydrolysis is the major circulating component. Mirabegron is the major circulating component; the 2 major metabolites are inactive.

CONTRAINDICATIONS/WARNINGS[60,61,62,63,64,65,66,67,68,69,70,71]

All bladder relaxants in this review, except mirabegron ER (Myrbetriq), are contraindicated in patients with uncontrolled narrow-angle glaucoma or gastric and/or urinary retention. All bladder relaxants are also contraindicated in patients with hypersensitivity to the primary drug or any of its ingredients. In addition, tolterodine (Detrol, Detrol LA) is contraindicated in patients with hypersensitivity to fesoterodine fumarate ER tablets which are metabolized to 5-hydroxymethyl tolterodine.

All bladder relaxants, should be used with caution in patients with obstruction of the GI tract, decreased GI motility (e.g., intestinal atony, megacolon, paralytic ileus), myasthenia gravis (except solifenacin), severe colitis, and obstructive uropathy. Oxybutynin should also be used with caution in patients with gastric reflux or on concurrent drugs that exacerbate esophagitis. Heat prostration due to decreased sweating may occur in patients taking anticholinergic medications while in environments experiencing excessive heat.

Most orally administered bladder relaxants can be associated with CNS effects, such as confusion and somnolence. Patients should be monitored for CNS side effects, especially after beginning treatment or increasing the dose. If CNS side adverse effects are observed, dose reduction or medication discontinuation should be considered. Patients should be advised not to drive or operate heavy machinery until they know how the medication will affect them. This has not been reported with mirabegron use. There have been reports of increased risk of hallucinations with tolterodine.

Angioedema, particularly of the face, lips, tongue and/or larynx, have been reported with darifenacin (Enablex), fesoterodine (Toviaz), mirabegron ER (Myrbetriq), oxybutynin-containing products, solifenacin (Vesicare), and tolterodine and trospium immediate- and extended-release. In certain instances, this has occurred after the first dose and cases may be life-threatening. If this reaction occurs, the medication should be discontinued immediately, and appropriate therapy provided.

Increases in systolic and diastolic blood pressure (SBP, DBP) of approximately 3.5 and 1.5 mmHg, respectively, have been reported in clinical trials with mirabegron ER. It is not recommended for use in patients with severe uncontrolled hypertension (SBP ≥ 180 mm Hg and/or DBP ≥ 110 mm Hg).

Transfer of oxybutynin to another person may occur when vigorous skin-to-skin contact is made with the application site of the transdermal gel (Gelnique). To minimize this potential, patients should cover the application site with clothing after the gel has dried if direct skin-to-skin contact at the application site is anticipated. Patients should wash their hands immediately after application of the gel.

Additionally, oxybutynin transdermal gel is an alcohol-based gel and is therefore flammable. Open fire or smoking until the gel has dried should be avoided.

Alcohol should not be consumed within 2 hours of trospium ER.

Oxybutynin extended-release (Ditropan XL) should be used with caution in patients with autonomic neuropathy due to the risk of aggravation of symptoms of decrease GI motility, and in patients with Parkinson's disease due to the risk of aggravation of symptoms.

There have been rare cases of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations. Use caution when

prescribing oxybutynin extended-release (Ditropan XL) in patients with preexisting severe GI narrowing.

Solifenacin (Vesicare) should be used with caution in patients with a known history of QT prolongation or patients taking medications known to prolong the QT interval.

DRUG INTERACTIONS[72,73,74,75,76,77,78,79,80,81,82,83]

darifenacin (Enablex)

Darifenacin metabolism is primarily mediated by CYP2D6 and CYP3A4. Inducers of CYP3A4 or inhibitors of either enzyme may alter the pharmacokinetics of darifenacin. No dosing adjustments are recommended in the presence of CYP2D6 inhibitors.

The daily dose of darifenacin should not exceed 7.5 mg when coadministered with potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, and nefazodone).

Caution is recommended when darifenacin is used concomitantly with medications that have a narrow therapeutic index and that are primarily metabolized by CYP2D6 (e.g., tricyclic antidepressants). Administration of imipramine with darifenacin results in a 70% increase in bioavailability of the antidepressant.

fesoterodine ER (Toviaz)

Doses of fesoterodine ER greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors such as such as ketoconazole, itraconazole, and clarithromycin. Induction of CYP3A4 may lead to reduced plasma levels. No dosage adjustments are necessary in the presence of CYP3A4 inducers.

Interactions with CYP2D6 inhibitors have not been studied; however, no dosage adjustments are recommended in the presence of CYP2D6 inhibitors.

mirabegron ER (Myrbetriq)

Mirabegron is a moderate CYP2D6 inhibitor. Systemic exposure of drugs metabolized by CYP2D6 enzyme (e.g., metoprolol, desipramine) may be increased when coadministered with mirabegron ER. Appropriate monitoring and dose adjustment may be necessary with concomitant use. Concurrent use of mirabegron ER and digoxin may increase digoxin exposure by about 25%; serum digoxin concentrations should be monitored.

oxybutynin (Ditropan, Ditropan XL, Gelnique, Oxytrol, Oxytrol for Women)

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 GI motility.

solifenacin (Vesicare)

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%. It is recommended not to exceed a 5 mg daily dose of solifenacin when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors.

tolterodine (Detrol, Detrol LA)

Fluoxetine, a potent inhibitor of CYP2D6 activity, significantly inhibits the metabolism of tolterodine. The result is a 4.8-fold increase in tolterodine area-under the curve (AUC), a 52% decrease in maximum serum concentration (C_{max}), and a 20% decrease in AUC of the 5-hydroxymethyl metabolite. The amounts of unbound serum concentrations of tolterodine and its metabolite are only 25% 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

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, and tenofovir). Monitoring is recommended in patients receiving trospium and a drug eliminated in this manner.

ADVERSE EFFECTS[84,85,86,87,88,89,90,91,92,93,94,95,96]

Drug	Constipation	Diarrhea	Dry mouth	Dyspepsia	Dizziness
darifenacin 7.5-15 mg (Enablex)	14.8 – 21.3	0.9 – 2.1	20.2 – 35.3	2.7 – 8.4	0.9 – 2.1
fesoterodine ER (Toviaz)	4.2 – 6	nr	18.8 – 34.6	1.6 – 2.3	nr
mirabegron ER (Myrbetriq)	1.6	1.2 – 1.5	2.8	< 1	2.7
oxybutynin 5-20 mg (Ditropan)	15.1	1 – < 5	71.4	6	16.6
oxybutynin ER 5-30 mg (Ditropan XL)	13	9	61	7	6
oxybutynin gel 1 sachet/day (Gelnique)	1.3	nr	1.9 – 7.5	nr	1.5 – 2.8
oxybutynin transdermal 3.9 mg/day (Oxytrol; Oxytrol for Women)	3.3	3.2	4.1 – 9.6	nr	nr
solifenacin 5-10 mg (Vesicare)	5.4 – 13.4	nr	10.9 – 27.6	1.4 – 3.9	1.8 – 1.9
tolterodine 4 mg (Detrol)	7 (4)	4 (3)	35 (10)	4 (1)	5 (3)
tolterodine ER 4 mg (Detrol LA)	6 (4)	reported	23 (8)	3 (1)	2 (1)
trospium 40 mg	9.6	nr	20.1	1.2	nr
trospium ER 60 mg	8.5 – 9	nr	10.7 – 11.1	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 or all-inclusive or all inclusive. Incidences for placebo group are indicated in parentheses. nr = not reported.

Most agents in this class are anticholinergics (except mirabegron ER) and, accordingly, have the expected adverse effects of dry mouth and constipation. The incidences of the adverse effects are higher with immediate-release products but still demonstrated to a lesser degree with extended-

release products. The withdrawal rates in trials due to the adverse effects for drugs were similar among all available agents although there is a lack of direct comparative data.

Pruritus at the application site occurs in 14% to 17% of patients treated with the oxybutynin transdermal patch (Oxytrol; Oxytrol for Women).[97] Pruritus at the application site for the topical oxybutynin gel (Gelnique) was reported in 1% to 2% of patients while overall application site reactions occurred in 2% to 6% of patients. Application site reaction for oxybutynin gel was the most common reason for patient discontinuation of the medication.

The most commonly reported adverse reactions reported with mirabegron ER use were hypertension (7.5% to 11.3%), nasopharyngitis (3.5% to 3.9%), urinary tract infection (2.9% to 4.2%) and headache (2.1% to 3.2%).

A 12-month randomized, double-blind study assessed the safety (primary endpoint) and efficacy (secondary endpoint) of mirabegron ER (50 mg or 100 mg) or tolterodine ER (4 mg) once daily in adults with OAB symptoms (n=2,444).[98] In total, 81.3% of patients had participated in previous mirabegron phase 3 trials. Similar proportions (21% to 24%) of patient previously received placebo, mirabegron 50 mg, or mirabegron 100 mg. The primary endpoint was incidence and severity of treatment-emergent adverse events (TEAEs). The secondary endpoint was change from baseline at months 1, 3, 6, 9, and 12 in key OAB symptoms. Patient-reported outcomes were assessed using the OAB questionnaire, Patient Perception of Bladder Condition (PPBC) scale (baseline and month 12), and the Treatment Satisfaction Visual Analog Scale (TS-VAS; baseline and month 12). Overall a similar percentage of patients reported TEAEs between the groups; most were mild or moderate. Serious TEAEs were reported in 5.2%, 6.2%, and 5.4% of patients, for mirabegron 50 mg and 100 mg, and tolterodine ER, respectively. The most common TEAEs were similar across groups. Dry mouth was reported by 2.8%, 2.3%, and 8.6% of patients, respectively. Adjusted mean changes from baseline to final visit in morning systolic blood pressure were 0.2 mm Hg, 0.4 mm Hg, and -0.5 mm Hg for mirabegron 50 mg, 100 mg, and tolterodine ER 4 mg, respectively. Mirabegron and the active-control, tolterodine ER, resulted in similar improvements in key OAB symptoms, such as mean number of micturitions per 24 hours, mean number of incontinence episodes per 24 hours, and mean volume voided/micturition from month-1 and throughout the 12 month treatment period.

In one reported case, concurrent use of oxybutynin with carbamazepine and dantrolene was associated with vomiting, drowsiness, confusion, unsteadiness, slurred speech and nystagmus, suggestive of carbamazepine toxicity.

SPECIAL POPULATIONS[99,100,101,102,103,104,105,106,107,108,109,110]

Pediatrics

Oxybutynin (immediate-release tablets and syrup) are approved for use in pediatric patients ages 5 years and older, and oxybutynin ER tablets are approved for use in pediatric patients 6 years and older with symptoms of detrusor activity associated with neurological conditions. The safety and efficacy of darifenacin (Enablex), fesoterodine (Toviaz), mirabegron ER (Myrbetriq), oxybutynin gel (Gelnique), oxybutynin transdermal (Oxytrol, Oxytrol for Women), solifenacin (Vesicare), trospium, and trospium ER in pediatric patients have not been established. Efficacy data are not available for tolterodine (Detrol). The effectiveness of tolterodine ER (Detrol LA) has not been established in pediatric patients,

and 2 randomized, placebo-controlled, double-blind, 12-week studies demonstrated higher adverse effects with tolterodine ER compared to placebo in pediatric patients ages 5 to 10 years old.

Pregnancy

Oxybutynin extended-release (Ditropan XL) is Pregnancy Category B. Previously Pregnancy Category B, product labeling for oxybutynin (Gelnique, Oxytrol) have been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and now advise that there are no studies of the product conducted in pregnant women to inform of potential risk to the mother or fetus.

The other drugs in this class are or were Pregnancy Category C. Darifenacin (Enablex), solifenacin (Vesicare), and trospium labeling continue to note Pregnancy Category C. Labeling for fesoterodine ER (Toviaz), mirabegron ER (Myrbetriq), and tolterodine (Detrol, Detrol LA) have been updated to comply with the PLLR and instruct that their use during pregnancy should occur only if the benefits outweigh the potential risks.

Geriatric Use

No overall differences in safety or efficacy have been observed between patients over 65 year of age and younger patients with darifenacin, mirabegron ER, solifenacin, tolterodine, trospium, and fesoterodine. However, in clinical studies, the incidence of adverse effects with trospium and fesoterodine among elderly patients aged 75 years and older was higher compared to younger patients.

Although no overall differences in safety and efficacy have been observed between younger and elderly patients using solifenacin, certain pharmacokinetic parameters, including time to peak plasma concentration and half-life have been shown to be 20% to 25% higher in elderly populations. Caution may be prudent in administration of solifenacin to geriatric patients.

In general, caution should be used when selecting an oral oxybutynin dose in elderly patients due to, at least in part, on the greater frequency of concomitant diseases or other drug therapy. . Therapy should be initiated at the low end of the dosing range. While no overall differences in safety and efficacy with oxybutynin gel or transdermal dosage forms were noted between younger and elderly patients, greater sensitivity of older individuals cannot be ruled out.

Hepatic Insufficiency

All oral agents in this class require a degree of caution or dosage adjustment in patients with hepatic impairment. See the dosage table in this therapeutic class review. There is no experience with the use of oxybutynin in patients with hepatic insufficiency.

Mirabegron ER use has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), and therefore is not recommended in this patient population.

Renal Insufficiency

Darifenacin is the only oral agent in this class that does not require caution or dosage adjustment in patients with renal impairment. There is no experience with the use of oxybutynin in patients with renal insufficiency.

Mirabegron ER use has not been studied in patients with end stage renal disease, and therefore is not recommended in this patient population.

Trospium ER is not recommended for patients with severe renal impairment (creatinine clearance < 30 mL/minute).

DOSAGES[111,112,113,114,115,116,117,118,119,120,121,122]

Drug	Usual Dose	Patients with Hepatic and/or Renal Dysfunction	Availability
darifenacin (Enablex)	7.5 to 15 mg daily	7.5 mg daily (for moderate hepatic dysfunction only)	7.5 mg, 15 mg ER tablets
fesoterodine ER (Toviaz)	4 to 8 mg daily	4 mg daily (for severe renal insufficiency), not recommended for severe hepatic impairment	4 mg, 8 mg ER tablets
mirabegron ER (Myrbetriq)	25 to 50 mg daily (may be used with or without solifenacin 5 mg once daily)	25 mg daily (for moderate hepatic impairment and severe renal impairment)	25 mg, 50 mg tablets
oxybutynin	5 mg 2 or 3 times daily	--	5 mg tablet 5 mg/mL oral solution
oxybutynin ER (Ditropan XL)	5 to 10 mg daily	--	5 mg, 10 mg, 15 mg ER tablets
oxybutynin gel (Gelnique)	Sachet: contents of 1 sachet applied per day Pump: 1 pump of the 10% gel once per day	--	10%: 1 gm (1.14 mL) of 100 mg/g oxybutynin gel per sachet, 10%: metered pump dispenser delivering 30 metered 1 g doses
oxybutynin transdermal (Oxytrol [Rx], Oxytrol for Women [OTC])	1 patch applied twice weekly	--	3.9 mg/24 hours transdermal patch
solifenacin (Vesicare)	5 to 10 mg daily	5 mg daily (for severe renal impairment and for moderate hepatic impairment) Not recommended for severe hepatic impairment	5 mg, 10 mg tablets
tolterodine (Detrol)	2 mg twice daily	1 mg twice daily	1 mg, 2 mg tablets
tolterodine ER (Detrol LA)	4 mg daily	2 mg daily	2 mg, 4 mg ER capsules
trospium	20 mg twice daily	20 mg daily (for severe renal impairment only)	20 mg tablet
trospium ER	60 mg daily in the morning	Not recommended for severe renal impairment	60 mg ER capsule

Mirabegron ER tablets should be taken with water, and should not be chewed, divided, or crushed.

For pediatric patients over 5 years of age, oxybutynin immediate-release tablets or syrup are given at a dosage of 5 mg twice a day. The maximum recommended dose is oxybutynin 5 mg three times a day. For pediatric patients 6 years of age and older, the recommended starting dose of oxybutynin ER

tablets is 5 mg once daily. The dosage may be adjusted in 5 mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg per day).

Oxybutynin gel should be applied to dry, intact skin on the abdomen, upper arms/shoulders, or thighs. Rotate application sites, avoiding use of the same site on consecutive days.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved 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% 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.

The approval of the OTC oxybutynin transdermal patch (Oxytrol for Women) was based on controlled clinical trials, safety data, and postmarketing experience of the prescription oxybutynin transdermal patch (Oxytrol).[123] An actual use study (AUS), labeling comprehension studies (LCSs), and self-selection studies (SSSs) were also conducted.

darifenacin (Enablex) versus placebo

A multicenter, double-blind, parallel-group study enrolled 561 patients (ages 19 to 88 years; 85% female) with OAB symptoms for at least 6 months into a 12-week study.[124] After washout and a 2-week placebo run-in, patients were randomized (1:4:2:3) 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 2. At the conclusion of the study, 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 ($p=0.01$ 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 ($p<0.04$, $p<0.001$), 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 (less than 1%). There were no reports of blurred vision, and the safety profile was comparable to placebo.

fesoterodine (Toviaz) versus tolterodine ER (Detrol LA)

A multicenter, double-blind, placebo- and active-controlled trial with tolterodine ER was performed to assess the efficacy and safety of fesoterodine.[125] Subjects, at least 18 years of age, with a history of OAB greater than 6 months and increased micturition frequency and urgency and/or urgency urinary incontinence (UUI), were randomized to placebo (n=279), fesoterodine 4 mg (n=265), fesoterodine 8 mg (n=276), or tolterodine ER 4 mg (n=283) for 12 weeks. The primary efficacy endpoint was a change from baseline to week 12 in micturitions per 24 hours. At the end of treatment, the mean number of micturitions per 24 hours significantly reduced from baseline in all active drug groups compared to placebo (-1.73 tolterodine ER, -1.76 fesoterodine 4 mg, and -1.88 fesoterodine 8 mg; p≤0.001). Dry mouth was the most experienced adverse effect and was reported significantly more often in the treatment groups (7.1% placebo, 16.9% tolterodine ER, 21.7% fesoterodine 4 mg, and 33.8% fesoterodine 8 mg). Overall, 3.2% of subjects discontinued the study prematurely owing to an adverse effect (2% placebo, 3% tolterodine ER, 3% fesoterodine 4 mg, and 5% fesoterodine 8 mg).

fesoterodine (Toviaz) versus tolterodine ER (Detrol LA) versus placebo

A 12-week, randomized, double-blind, double-dummy placebo-controlled, parallel-group multicenter trial with a 2-week single-blind placebo run-in period was conducted to assess the efficacy of fesoterodine in comparison to tolterodine ER and placebo.[126] Subjects, at least 18 years of age, with a history of OAB symptoms for at least 3 months prior to screening and a mean of 1 or more urgency urinary incontinence (UUI) episodes per 24 hours and 8 or more micturitions reported in a 3-day baseline period, were randomized to fesoterodine 8 mg, tolterodine ER 4 mg, or placebo in a 2:2:1 ratio. A total of 1,712 patients were randomized with 1,697 patients receiving at least 1 dose of study medication (fesoterodine, n=679; tolterodine ER, n=684; placebo, n=334). The primary efficacy endpoint was a change from baseline to week 12 in UUI per 24 hours. Both the fesoterodine group and the tolterodine group produced a significantly greater improvement in UUI episodes than the placebo group, ($p<0.001$ and $p=0.011$, respectively). The fesoterodine improvement in UUI compared to the tolterodine ER group was also statistically significant ($p=0.017$). Dry mouth was the most experienced adverse effect and was reported significantly more often in the treatment groups (16% for tolterodine ER 4 mg and 28% for fesoterodine 8 mg) than placebo (6%).

Another 12-week, randomized, double-blind, double-dummy placebo-controlled trial evaluated the efficacy of fesoterodine (4 mg for 1 week followed by 8 mg for 11 weeks) versus tolterodine ER (4 mg) or placebo, in 2,417 patients with OAB.[127] There were no differences between fesoterodine 4 mg and tolterodine ER 4 mg at the end of week 1. At week 12, fesoterodine 8 mg showed superiority over tolterodine ER 4 mg and placebo for mean improvement in urge urinary incontinence (UUI) episodes (primary endpoint), micturitions, urgency, severe urgency episodes and frequency-urgency sum. UUI episodes per 24 hours decreased by 100% in all 3 groups and median micturitions per 24 hours decreased by 18.2%, 20.8% and 23.5% in the placebo, tolterodine ER 4 mg and fesoterodine 8 mg groups, respectively. Differences in nocturnal micturitions and mean voided volume between the 2 active treatment arms were not significant. On the Patient Perception of Bladder Condition (PPBC) and the Urgency Perception Scale (UPS) both fesoterodine and tolterodine groups were superior to placebo and fesoterodine was superior to tolterodine. Fesoterodine 8 mg was superior to tolterodine ER 4 mg on all OAB Questionnaire scales and domains (all $p<0.05$). The superiority of fesoterodine 8 mg over tolterodine ER 4 mg was seen in all diary endpoints except nocturnal micturitions as early as week 4. Dry mouth and constipation rates were 28% and 4% with fesoterodine, 13% and 3% with tolterodine

ER, and for placebo 5% and 2%. Discontinuation rates due to adverse events for fesoterodine, tolterodine ER, and placebo, were 5%, 3%, and 2%, respectively.

mirabegron ER (Myrbetriq) versus placebo

Mirabegron ER was evaluated in 3, 12-week, randomized, double-blind, placebo-controlled, clinical trials in patients with OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.[128] In Studies 1 and 2, patients were randomized to placebo, mirabegron ER 50 mg or 100 mg, once daily. In Study 3, patients were randomized to placebo, mirabegron ER 25 mg or 50 mg once daily. The co-primary efficacy endpoints in all the trials were change in mean number of incontinence episodes per 24 hours at week 12 and change in mean number of micturitions per 24 hours (based on a 3-day micturition diary) at week 12. Mean number of incontinence episodes per 24 hours for mirabegron 50 mg decreased by 1.57 (p=0.003), 1.47 (p=0.026), and 1.38 (p=0.001) in Studies 1, 2, and 3, respectively, and by 1.36 for mirabegron 25 mg in Study 3 (p=0.005). Mean number of micturitions per 24 hours for mirabegron ER 50 mg decreased by 1.93 (p=0.001), 1.66 (p=0.001), and 1.6 (p=0.015) in Studies 1, 2, and 3, respectively, and by 1.65 for mirabegron 25 mg in Study 3 (p=0.007). Mirabegron ER 25 mg was effective in treating OAB symptoms within 8 weeks and mirabegron 50 mg was effective in treating OAB symptoms within 4 weeks. Efficacy of both strengths was maintained through the 12 week treatment period.

mirabegron ER (Myrbetriq) versus tolterodine ER (Detrol LA)

The PREFER study was a 2-period, 8-week crossover, double-blind trial in treatment-naive adults with overactive bladder for at least 3 months.[129] Included patients were randomized to 1 of 4 treatment sequences in a 5:5:1:1 ratio (mirabegron/tolterodine, tolterodine/mirabegron, mirabegron/ mirabegron, or tolterodine/tolterodine), with each treatment separated by a washout period of 2 weeks (n=358). Drug tolerability was the primary endpoint, measured using the Medication Tolerability scale of the OAB Treatment Satisfaction (OAB-S) questionnaire at end of treatment (EoT). The effect of drug order was assessed using period-by-treatment interactions. Patient preference, change from baseline in OAB symptoms, and treatment-emergent adverse events were all evaluated. The mean OAB-S Medication Tolerability score was significantly higher, indicating better tolerability, for mirabegron (mean, 86.29; 95% CI, 83.5 to 89.08) than for tolterodine (mean, 83.4; 95% CI, 80.59 to 86.2; p=0.004). In addition, improvements in OAB-S Medication Tolerability scores at EoT were more evident in women, patients aged ≥ 65 years, patients without baseline incontinence, and those using mirabegron. There were no significant differences in improvements in OAB symptoms. Mirabegron had fewer anticholinergic treatment-emergent adverse effects (20.4% versus 27.4%; p=0.042) and was noted to be generally better tolerated than tolterodine.

oxybutynin gel (Gelnique) versus placebo

The efficacy and safety of oxybutynin gel were evaluated in single, randomized, double-blind, placebo-controlled, parallel-group, 12-week study for the treatment of overactive bladder (OAB) with symptoms of urge incontinence, urgency, and frequency.[130] Adult patients were included if they had 4 or more incontinence episodes in a 3-day period and at least 8 micturitions daily. A total of 789 were randomized to receive either oxybutynin gel 1 gm (10% w/w) (n=389) or placebo gel (n=400). Each patient had an average duration of urinary incontinence of 8.5 years, and 75% of patients had no prior pharmacologic treatment for the condition. Patients treated with oxybutynin gel had a statistically

significant decrease in the mean number of urinary incontinence episodes per day from baseline to endpoint compared with placebo (-3 versus -2.5 per day, p<0.0001). Dry mouth was reported by 6.9% of the oxybutynin gel group compared to 2.8% of the placebo group. Application site reactions were observed in 5.4% and 1% of the oxybutynin gel and placebo-treated groups, respectively.

oxybutynin (Ditropan) versus oxybutynin transdermal (Oxytrol, Oxytrol for Women)

A total of 76 patients with detrusor instability who were currently responding to oxybutynin immediate-release were enrolled in a double-blind, dose-titration study.[131] Those patients presenting with recurrence of incontinent symptoms after a 2-week washout period underwent confirmatory cystometrogram with subsequent randomization to transdermal or oral oxybutynin treatment. Patients applied 2 to 4 transdermal oxybutynin 1.3 mg/day transdermal patches twice weekly or oxybutynin 5 mg orally 2 or 3 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% of patients reaching the maximum dose compared with 32% of patients in the oral group. Daily incontinent episodes decreased in the transdermal group from 7.3 to 2.4 (66% reduction) and in the oral group from 7.4 to 2.6 (72% reduction; p=0.39). The visual analog scale reduction in urinary leakage improved from washout in both groups (p<0.0001) 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%) compared with those in the oral group (94%; p<0.001). Of the patients in the transdermal group, 67% 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 2 weeks of treatment with an initial dose of either tolterodine 2 mg or oxybutynin 2.5 or 5 mg twice daily for 8 weeks.[132] 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 10 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%, respectively, p=0.01), notably less dry mouth (37% versus 61%, p<0.0001), as well as a lower incidence of dose reduction (6% versus 25%, p<0.0001) than those in the oxybutynin group.

oxybutynin (Ditropan) versus trospium

In a randomized, double-blind, multicenter trial, 95 patients with spinal cord injuries and detrusor hyperreflexia were evaluated.[133] Treatment consisted of a 2-week administration period of either oxybutynin 5 mg 3 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 significantly different 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 group (4%) than in the oxybutynin group (23%). Withdrawal from treatment was less frequent in those receiving trospium (6%) than in those receiving oxybutynin (16%).

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.[134,135] 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% with trospium and 34% with oxybutynin (p=not significant [NS]). Adverse events occurred in 65% of the patients treated with trospium and 77% of those treated with oxybutynin (p<0.01). Gastrointestinal adverse effects were reported by 39% and 51% (p=0.02), while dry mouth was reported by 33% and 50% (p<0.01) of trospium-treated and oxybutynin-treated patients, respectively. Very good tolerability was reported for 63% of patients in the trospium group compared with 42% of patients in the oxybutynin group (p=0.004). The evaluation of vital parameters, laboratory results, and electrocardiograms (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, daily doses of oxybutynin ER 10 mg or tolterodine ER 4 mg 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.[136] 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% of women taking oxybutynin ER compared with 16.8% 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, Oxytrol for Women) versus tolterodine ER (Detrol LA)

A double-blind, double-dummy trial compared the effects of transdermal oxybutynin with those of tolterodine ER in patients with urge or mixed urinary incontinence who had responded well to prior pharmacologic treatment.[137] After withdrawal of their previous therapy, 361 adult patients were randomized to receive 12 weeks of 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 pruritus occurring in 14% of patients and resulting in discontinuation in nearly 10% 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%, respectively) and constipation (5.7% and 3.3%, 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% discontinued therapy because of fatigue or dizziness. The manufacturer of oxybutynin transdermal patches, which also employed one of the study authors, funded the study.

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.[138] Adult patients with symptomatic OAB for at least 3 months were eligible. After a single-blind, 2-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; $p=0.0038$). Compared with placebo, the mean number of voids per 24 hours was significantly lower in patients receiving tolterodine (-1.88; $p=0.0145$), 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 3 active treatments ($p<0.001$). The most common adverse effect, dry mouth which was mostly mild, was reported in 18.6% of patients receiving tolterodine, 14% receiving solifenacin 5 mg, and 21.3% 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, 2-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.[139] After the first 4 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 adverse effects were mild with a low discontinuation rate for both groups.

solifenacin (Vesicare) plus mirabegron ER (Myrbetriq) versus solifenacin monotherapy

BESIDE, a 12-week, double-blind, randomized, active-controlled, multicenter clinical trial, assessed the addition of mirabegron to incontinent OAB patients using solifenacin for 4 weeks requiring additional relief (n=2,174).[140] Patients were randomized 1:1:1 to solifenacin 5 mg, solifenacin 10 mg, or solifenacin 5 mg plus mirabegron ER 25 mg once daily (mirabegron ER 50 mg after 4 weeks). The primary end point was a change from baseline to EoT in the mean number of incontinence episodes per 24 hours, and the combination was found to be superior to solifenacin 5 mg, with significant improvements in daily incontinence (mean difference, -0.26; 95% CI, -0.47 to -0.05; p=0.001).

solifenacin (Vesicare) plus mirabegron ER (Myrbetriq) versus solifenacin monotherapy versus mirabegron ER monotherapy versus placebo

The SYNERGY double-blind trial evaluated combination therapy with solifenacin + mirabegron ER to each agent alone and to placebo.[141] After a 4-week placebo run-in, 3,527 patients aged ≥ 18 years with wet OAB (urgency, urinary frequency, and urinary incontinence [UI]) were randomized to solifenacin 5 mg + mirabegron 25 mg (S5/M25); solifenacin 5 mg + mirabegron 50 mg (S5/M50); solifenacin 5 mg; mirabegron 25 mg; mirabegron 50 mg; or placebo for 12 weeks. Co-primary efficacy endpoints were change from baseline in the mean number of UI episodes/24 hour and micturitions/24 hour. The combination was superior to solifenacin 5 mg for UI (mean adjusted difference, 0.2 UI episodes/24 hour; 95% CI, -0.44 to 0.04; p=0.033), but was not superior to mirabegron 50 mg (mean adjusted difference, -0.23 UI episodes/24 hour; p=0.052). Since the primary objective for the superiority to monotherapy for S5/M50 was not met, the hypotheses for mean number of micturitions/24 hour and the S5/M25 combination were not tested. In secondary analyses, all active treatment groups had greater improvements in UI episodes/24 hour compared to placebo. In addition, the effect sizes regarding UI episodes/24 hour for both combined therapies were substantially higher than with either monotherapy (S5/M50: 0.65; S5/M25: 0.7; mirabegron 25 mg: 0.37; and solifenacin 5 mg: 0.45). Adjusted change from baseline in micturitions/24 hour was greater with combined therapy compared to monotherapy and placebo (p≤0.04 for all). Slightly more treatment-associated adverse events were reported with combination therapy compared to monotherapy; all reports were mild or moderate events. The discontinuation rate due to adverse events were similar between groups.

The SYNERGY II trial, a 52-week, double-blind, randomized, active-controlled, parallel group, multicenter clinical trial in 1,794 patients with OAB, assessed the long-term effects of combination therapy.[142] Included patients were randomized to solifenacin 5 mg, mirabegron 50 mg, or solifenacin 5 mg plus mirabegron 50 mg once daily. Higher improvements from baseline in the mean number of incontinence episodes were demonstrated with the combination group and were maintained through the year-long study (combination versus mirabegron: adjusted mean difference, -0.5 [95% CI, -0.7 to -0.2; p<0.001]; combination versus solifenacin: adjusted mean difference, -0.1 [95% CI, -0.4 to 0.1; p=0.002]).

tolterodine (Detrol) versus tolterodine ER (Detrol LA)

In a placebo-controlled safety and efficacy evaluation, 1,529 patients with urinary frequency (8 or more micturitions every 24 hours) and urge incontinence (5 or more episodes per week) were randomized in a double-blind fashion to tolterodine ER 4 mg once daily, tolterodine 2 mg twice daily, or placebo.[143] Efficacy was assessed at the end of the treatment period on the basis of the micturition diary variables. Tolerability and safety were assessed by evaluating the adverse events, electrocardiogram parameters, laboratory values, and treatment withdrawals. Both active dosage forms significantly decreased the number of urge incontinence episodes per week (by 71% and 60%, respectively) compared to placebo (33%). Micturition frequency decreased and volume increased in both tolterodine groups. The incidence of dry mouth was 23% in the tolterodine ER group, 30% in the tolterodine group, and 8% 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.[144] 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

Trospium was compared with tolterodine in a double-blind, placebo-controlled study enrolling 234 patients with urgency or urge incontinence.[145] Patients were randomly assigned therapy with either 20 mg trospium, 2 mg tolterodine, or placebo, each given twice daily for 3 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 versus placebo

A multicenter, double-blind, placebo-controlled study enrolled 601 patients with OAB symptoms into a 12-week study.[146] 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 1 through week 12. The most common adverse events were dry mouth (trospium 8.7 versus placebo 3%) and constipation (trospium 9.4% versus placebo 1.3%). Central nervous system adverse events were rare (headache with trospium 1% versus placebo 2.6%). No clinically meaningful changes in laboratory, physical examination, or electrocardiogram parameters were noted.

META-ANALYSES

A Cochrane database systematic review of 86 randomized trials and meta-analysis of 70 trials in 31,249 patients with OAB symptoms compared different doses and formulations of 4 anticholinergic agents.[147] Although most trials were double-blind, other aspects of quality were variable. Tolterodine was better tolerated than oxybutynin, although efficacy was similar, and extended-release formulations of these agents were better tolerated than immediate-release. Fesoterodine had better efficacy than tolterodine ER but had a higher rate of dry mouth leading to drug discontinuation. Solifenacin was more effective and better tolerated than immediate-release tolterodine. Data were not available for other comparisons. There were incomplete data to make conclusions about quality of life or long-term outcomes.

SUMMARY

In comparative trials, oral oxybutynin formulations (Ditropan, Ditropan XL) have been associated with greater incidences of anticholinergic adverse effects but were otherwise as effective as the comparators. The transdermal oxybutynin medications (Gelnique, Oxytrol, Oxytrol for Women) appear to cause fewer anticholinergic adverse effects, likely by avoiding first-pass metabolism to N-desethyloxybutynin, an active metabolite partly responsible for such effects. However, both the gel and transdermal patches are associated with a relatively high rate of cutaneous reactions, which can result in discontinuation of the agent.

Head-to-head studies reveal little to no difference in efficacy among these agents, and there are little to no variations among subpopulations within studies. Furthermore, those studies where immediate-

acting agents were compared to their extended-release counterparts found no important differences in efficacy and only statistical variations in adverse effects. The agents in this class may be considered therapeutically interchangeable and product selection may depend on individual patient requirements, response, and tolerance.

Mirabegron ER (Myrbetriq) is the first beta-3 adrenergic agonist approved for the treatment of OAB. Rather than binding to muscarinic receptors in the bladder and inhibiting involuntary bladder contractions as demonstrated with anti-muscarinic agents, mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder which increases bladder capacity. There are no published trials comparing mirabegron with the antimuscarinic agents. Results from a comparison trial of combination therapy with solifenacin and mirabegron ER suggested an additive effect of the products; mirabegron ER is approved for use as monotherapy or in combination with solifenacin.

Oxybutynin (Oxytrol for Women) patch is available over-the-counter for treatment of OAB for women only. Oxybutynin (Oxytrol) patch for use in men and women with OAB is still available with a prescription.

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