Therapeutic Class Overview
Urinary antispasmodics

INTRODUCTION

- Overactive bladder (OAB) is defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia. Urinary incontinence has been shown to greatly reduce quality of life in areas such as mental and general health in addition to physical and social functioning (*American Urological Association 2019, Coyne et al 2008, International Continence Society 2015).*
- Behavioral therapies (eg, bladder training, bladder control strategies, pelvic floor muscle training and fluid management) are considered first-line treatment in all patients with OAB *(American Urological Association 2019).*
- Urinary antispasmodics are used as first-line pharmacological therapy in OAB (*American Urological Association 2019, American College of Obstetricians and Gynecologists 2015, Blok et al 2019, Burkhard et al 2018*).
- The urinary antispasmodics used for the treatment of OAB belong to 2 classes of drugs, which include anticholinergic compounds known as muscarinic receptor antagonists, and the beta-3 adrenergic agonist, mirabegron. The anticholinergic agents act as antagonists of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle in the bladder and decreasing bladder contractions. Both immediate-release (IR) and extended-release (ER) formulations (LA, XL, and XR) are available for oxybutynin (Ditropan), tolterodine (Detrol), and trospium. Darifenacin (Enablex) and fesoterodine (Toviaz) are also supplied as ER tablets.
  - Oxybutynin is also formulated as a topical gel (Gelnique) and transdermal patch (Oxytrol).
  - Oxytrol for Women is an over-the-counter (OTC) product that was previously available as a prescription. Oxytrol for Women is an oxybutynin transdermal system applied every 4 days. It is specifically indicated for women ≥ 18 years of age with 2 or more of the following symptoms for at least 3 months: urinary frequency (the need to urinate more often than usual; typically more than 8 times in 24 hours), urinary urgency (a strong need to urinate right away), and urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate) *(Oxytrol for Women Drug Facts 2016).*
- Myrbetriq (mirabegron) is an agonist of the human beta-3 adrenergic receptor (AR). Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR, which increases bladder capacity.
- All urinary antispasmodics, with the exception of flavoxate, are Food and Drug Administration (FDA)-approved for the treatment of OAB. Flavoxate is FDA-approved for the relief of symptoms of cystitis, prostatitis, urethritis, or urethrocystitis/urethrotrigonitis. The IR oxybutynin formulation is also indicated for the relief of symptoms of neurogenic or reflex neurogenic bladder, and the ER tablet is approved for the treatment of detrusor overactivity.
- The anticholinergic urinary antispasmodics have demonstrated a similar safety and efficacy profile compared to one another; however, they primarily differ in their receptor selectivity and tolerability profiles. The M2 and M3 muscarinic receptor subtypes are highly concentrated in the bladder and are responsible for detrusor contraction, while M1, M4, and M5 are located throughout the body.
  - Preclinical studies suggested that solifenacin and darifenacin may be “uroselective” for the M3 receptor in the bladder; however, the clinical implications of this suggestion have not been established *(Brown et al 2018).*
- The development of ER formulations with more predictable pharmacokinetics has led to a lower incidence of anticholinergic adverse events (AEs). Oxybutynin undergoes first-pass metabolism to an active metabolite with a high incidence of dry mouth; however, transdermal oxybutynin formulations bypass this metabolism, maintaining the efficacy of oxybutynin with a lower incidence of AEs *(Dmochowski et al 2005).*
- Trospium, a water-soluble compound, has low penetration through the blood brain barrier and the gut; however, clinical studies have not demonstrated a lower incidence of AEs with trospium compared to other agents within the class.
- Fesoterodine, a prodrug, is rapidly metabolized by plasma esterases to 5-hydroxymethyl tolterodine, the same active metabolite as tolterodine.
- Botox injection (onabotulinumtoxinA) also has 2 FDA-approved indications for OAB. The OAB indications for BOTOX include the treatment of OAB with symptoms of urge urinary incontinence, urgency, and frequency in adults who have an inadequate response to or are intolerant of an anticholinergic medication; and the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, spinal cord injury [SCI], multiple sclerosis [MS]) in adults who have an inadequate response to or are intolerant of an anticholinergic medication *(Botox prescribing information 2019).* Botox is not included in this review.

- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review focuses on the use of the urinary antispasmodics for OAB.
- Medispan class: Urinary Antispasmodics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Anti-muscarinic (Anticholinergic)	
Detrol (tolterodine)	✔
Detrol LA (tolterodine ER)	✔
Ditropan XL (oxybutynin ER)	✔
Enablex (darifenacin ER)	✔
Gelnique (oxybutynin) topical gel 10%	-†
oxybutynin	✔
Oxytrol (oxybutynin transdermal patch)	-
Oxytrol for Women (oxybutynin transdermal patch)*	-
trospium‡	✔
trospium ER‡	✔
Toviaz (fesoterodine)	-†
Vesicare (solifenacin)	✔
Beta-3 Adrenergic Agonists	
Myrbetriq (mirabegron)	-
Direct Muscle Relaxants	
flavoxate	✔

Abbreviations: ER = extended-release
*OTC product
†An oxybutynin topical gel that is AB rated to Gelnique has been approved by the FDA, but is not currently commercially available. Additionally, the FDA has approved a fesoterodine tablet that is AB rated to Toviaz, but it is currently commercially unavailable.
‡Branded product (Sanctura) is no longer available.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Darifenacin (Enablex)	Fesoterodine (Toviaz)	Flavoxate	Mirabegron (Myrbetriq)	Oxybutynin (Ditropan XL, Gelnique, Oxytrol‡)	Solifenacin (Vesicare)	Tolterodine (Detrol and Detrol LA)	trospium
Treatment of OAB	✔ *	✔ *		✔ *	✔ * (patch, gel, XL)	✔ *	✔ *	✔ *
Treatment of OAB in combination with solifenacin				✔ *				
Treatment of detrusor overactivity					✔ † (XL)			
Treatment of bladder instability in patients with uninhibited neurogenic or reflex neurogenic bladder					✔ (IR)			
Symptomatic relief of cystitis, prostatitis, urethritis, or urethrocystitis/urethrotrigonitis			✔					

Abbreviations: IR = immediate-release; OAB = overactive bladder; XL = extended-release
***** In patients with symptoms of urge urinary incontinence, urgency, and urinary frequency.

† In pediatric patients ≥ 6 years of age with symptoms of detrusor overactivity associated with a neurological condition.
‡ Oxytrol for Women is available OTC and is approved for women ≥ 18 years of age with ≥ 2 of the following symptoms for at least 3 months: urinary frequency, urinary urgency, and urge incontinence; Oxytrol is approved for overactive bladder in men.

(Oxytrol for Women Drug Facts 2016; Prescribing information: Detrol 2016, Detrol LA 2018, Ditropan XL 2019, Enablex 2016, flavoxate 2018, Gelnique 10% 2019, Myrbetriq 2018, oxybutynin tablets 2019, oxybutynin syrup 2018, Oxytrol 2017, Toviaz 2017, trospium tablets 2018, trospium extended-release capsules 2014, Vesicare 2019)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- A 2018 Agency for Healthcare Research and Quality (AHRQ) systematic review update of nonsurgical treatments for urinary incontinence in women concluded that behavioral therapy, alone or in combination with other interventions, is generally more effective than other first- or second-line interventions (including pharmacologic interventions) alone for both stress and urgency urinary incontinence (*Balk et al 2018*). For women with urgency urinary incontinence, anticholinergics were significantly more likely to result in "cure" (odds ratio [OR], 1.80; 95% confidence interval [CI], 1.29 to 2.52) or improvement (OR, 1.79; 95% CI, 1.18 to 2.7) as compared to placebo. Additionally, anticholinergics overall were found to improve quality of life compared with no treatment, but there was inconsistency both within and across studies regarding the comparative effect of these medications on various aspects of quality of life.
- Although used for urinary incontinence, flavoxate is no more effective than other drugs used for urge incontinence or related disorders *(Micromedex 2020).* No recent clinical trials have been published with flavoxate.
- The results from clinical studies have demonstrated each of the urinary antispasmodics to be more effective vs placebo with regard to improvements in micturition frequency, urgency and urge incontinence episodes *(Chapple et al 2004, Chapple et al 2007, Dmochowski et al 2003, Dmochowski et al 2008, Dmochowski et al 2010, Herschorn et al 2010(b), Kaplan et al 2011, Kay et al 2006, Khullar et al 2011, MacDiarmid et al 2011, Mattiasson et al 2010, Nitti et al 2007, Nitti et al 2013, Salinas-Casado et al 2015, Sand et al 2011, Staskin et al 2007, Staskin et al 2009, Wagg et al 2013, Zinner et al 2005).*
- Head-to-head studies with the urinary antispasmodics have not consistently found one agent to be superior to other agents within the class *(Anderson et al 1999, Anderson et al 2006, Appell et al 2001, Barkin et al 2004, Batista et al 2015, Chapple et al 2005, Chapple et al 2007, Davila et al 2001, Diokno et al 2003, Dmochowski et al 2003, Dmochowski et al 2010, Ercan et al 2015, Halaska et al 2003, Harvey et al 2001, Herschorn et al 2010(a), Herschorn et al 2010(b), Hsiao et al 2011, Kaplan et al 2011, Kay et al 2006, Kilic et al 2006, Kinjo et al 2018, Kobayashi et al 2018, Sand et al 2004, Versi et al 2000, Zellner et al 2009).*
- The evidence to support the efficacy and safety of the oxybutynin transdermal patch (Oxytrol for Women) as an OTC product was based on the completed studies with the prescription product *(Dmochowski et al 2002, Dmochowski et al 2003, FDA Oxytrol for Women Medical Review 2013*). The Oxytrol for Women transdermal patch is the same formulation and dose as the prescription Oxytrol transdermal patch.
- A 2012 Cochrane review reported that IR formulations of oxybutynin, tolterodine, and trospium have similar efficacy, but oxybutynin was associated with more AEs. In addition, solifenacin improved symptoms of OAB more than tolterodine IR, while fesoterodine was more effective than tolterodine ER *(Madhuvrata et al 2012).*
- Another review demonstrated that all anticholinergics for OAB showed similar small benefits. For urgency urinary incontinence, the drugs showed 20% or less difference from placebo in the rate of achieving urinary continence or improvement in urinary continence. The numbers needed to treat (NNT) to achieve continence in 1 woman were similar across drugs (range for NNT, 6 to 12). Dose-related efficacy effects were evident for fesoterodine, solifenacin, and oxybutynin. Small differences were apparent in the AEs among the anticholinergics. Dry mouth and constipation were the most common AEs. Treatment discontinuation due to AEs was greater than with placebo for all drugs except darifenacin and tolterodine (*Shamliyan et al 2012*).
- A network meta-analysis of 5 randomized controlled trials ranked the antispasmodics for treatment of OAB in women in the following order from highest to lowest efficacy: solifenacin 10 mg once daily, oxybutynin 3 mg 3 times daily, solifenacin 5 mg once daily, darifenacin 15 mg once daily, fesoterodine 8 mg once daily, darifenacin 7.5 mg once daily, and tolterodine 4 mg once daily. However, solifenacin 10 mg had the most AEs while darifenacin 7.5 mg once daily caused the least AEs. The authors concluded that solifenacin 5 mg once daily was preferred for OAB followed by oxybutynin 3 mg 3 times daily based on efficacy, AEs, and cost (*Nalliah et al 2017*).

- A network meta-analysis that compared solifenacin 5 mg/day to other antimuscarinic agents found that solifenacin was more effective than tolterodine 4 mg/day for incontinence and urgency. In addition, solifenacin had a lower risk of dry mouth compared to other antimuscarinics (*Nazir et al 2018*).
- A 2019 network meta-analysis of 128 studies of anticholinergics concluded that all the anticholinergic medications were better than placebo for patients with OAB; however, there was no clear best treatment for cure or improvement. In this analysis, transdermal oxybutynin was shown to cause less dry mouth than the other treatments (*Herbison et al 2019*).
- Three 12-week, randomized, placebo-controlled clinical trials evaluated the efficacy and safety of mirabegron 25 mg, 50 mg, or 100 mg once daily vs placebo. Mirabegron significantly reduced the mean number of incontinence episodes and the mean number of micturitions per 24 hours compared to placebo *(Nitti et al 2013).*
- Mirabegron compared with either tolterodine IR or tolterodine LA demonstrated comparable efficacy in 2 trials. However, tolterodine IR patients had more AEs *(Kuo et al 2015, Yamaguchi et al 2014).* A 2-period, 8-week crossover trial comparing mirabegron and tolterodine ER found greater tolerability with mirabegron; however, patient treatment preference and symptoms were similar between treatments (*Staskin et al* 2018). An indirect treatment comparison meta-analysis concluded that mirabegron had similar efficacy to most other antispasmodics; however, solifenacin demonstrated improved symptom control compared to mirabegron *(Obloza 2017).* Another systematic review and meta-analysis concluded that mirabegron demonstrated similar efficacy to tolterodine and solifenacin with regard to improvement in micturitions, incontinence, and nocturia with a lower incidence of dry mouth and no higher risk of hypertension (*Chen et al 2018*).
- A systematic review compared treatment with mirabegron 50 mg to several different active treatments (including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) in regard to micturitions, incontinence, and dry rate (*Kelleher et al 2018*). Mirabegron had similar efficacy to other active treatments with a few exceptions: solifenacin 10 mg monotherapy and solifenacin 5 mg plus mirabegron 50 mg were found to be more efficacious at reducing micturition frequency than mirabegron 50 mg; solifenacin 5 mg plus mirabegron 25/50 mg and fesoterodine 8 mg were found to be more efficacious at reducing urgency urinary incontinence than mirabegron 50 mg; and solifenacin 5 mg plus mirabegron 25/50 mg, trospium 60 mg, solifenacin 10 mg, and fesoterodine 8 mg were associated with an improved dry rate when compared to mirabegron 50 mg. In general, mirabegron was associated with a significantly lower frequency of AEs compared to other active treatments.
- Studies examining combination therapy of mirabegron and solifenacin have demonstrated decreased frequency of incontinence, urgency episodes, and/or micturition frequency with a similar AE profile to monotherapy *(Drake et al 2016, Herschorn et al 2017, Kosilov et al 2015, Yamaguchi et al 2015).* A 12-month long-term trial of mirabegron and solifenacin also found the combination to be well tolerated with greater improvement in OAB symptoms as compared to monotherapy with either agent (*Gratzke et al 2018*). Similarly, the combination of low-dose trospium and solifenacin has also resulted in decreased frequency of incontinence in elderly patients with moderate symptoms *(Kosilov et al 2014).*

CLINICAL GUIDELINES

- Current consensus guidelines recommend the use of urinary antispasmodics in patients with OAB symptoms caused by detrusor overactivity with or without urgency incontinence. Behavioral therapies should generally be used as initial treatment (eg, bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) with urinary antispasmodics recommended as second-line therapy or in combination with behavioral therapy *(American Urological Association 2019, Burkhard et al 2018, Lightner et al 2019, Qaseem et al 2014).*
- The American Geriatrics Society recommends avoiding anticholinergics, including oral antimuscarinics and flavoxate, in elderly patients with delirium, dementia or cognitive impairment due to worsening central nervous system AEs *(American Geriatric Society 2019).*
- No one urinary antispasmodic is recommended over another; however, ER formulations are associated with lower incidences of AEs and similar efficacy as compared to IR products. Due to different tolerability profiles, patients experiencing an AE or inadequate efficacy (despite dose optimization) with one antispasmodic agent may be switched to another agent within the class *(American Urological Association 2019, Burkhard et al 2018).* The American College of Physicians recommends the choice of pharmacologic treatment be based on AEs, tolerability, convenience, and cost *(Qaseem et al 2014)*.

SAFETY SUMMARY

- The anticholinergic urinary antispasmodics are contraindicated with uncontrolled narrow angle glaucoma and urinary retention. Flavoxate is contraindicated in patients with achalasia, pyloric or duodenal obstruction, obstructive intestinal lesions or ileus, gastrointestinal hemorrhage, and obstructive uropathy.

- Warnings and precautions for most of the anticholinergic agents include the risk of angioedema, decreased gastrointestinal motility, urinary retention, and central nervous system effects such as dizziness, somnolence, confusion, and hallucinations. Anticholinergic agents should be used with caution in patients with myasthenia gravis or ulcerative colitis. Ditropan XL should be used with caution in patients with Parkinson's disease.
- In general, due to the anticholinergic mechanism of action of the urinary antispasmodics, these agents are commonly associated with anticholinergic-related AEs. The most common AEs include dry mouth and constipation. AEs for mirabegron include hypertension, nasopharyngitis, urinary tract infection, and headache.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Darifenacin	Tablet (ER)	Oral	Once daily	• Do not exceed 7.5 mg/day with moderate hepatic impairment (Child-Pugh B) or when co-administered with potent CYP3A4 inhibitors; not recommended for use in severe hepatic impairment (Child-Pugh C).
Fesoterodine	Tablet (ER)	Oral	Once daily	• Not recommended for use in severe hepatic impairment (Child-Pugh C). • Do not exceed 4 mg/day in severe renal impairment (CrCL < 30 mL/min) or when co-administered with potent CYP3A4 inhibitors.
Flavoxate	Tablet	Oral	3 to 4 times daily	• With improvement of symptoms, the dose may be reduced.
Mirabegron	Tablet (ER)	Oral	Once daily	• Not recommended for use in ESRD or severe hepatic impairment (Child-Pugh C). • Do not exceed 25 mg/day in patients with severe renal impairment (CrCL 15 to 29 mL/min) or moderate hepatic impairment (Child-Pugh B).
Oxybutynin	Tablet (IR), tablet (ER), syrup, gel, transdermal patch	Oral, transdermal	Tablet (IR), Syrup: twice to 3 times daily Tablet (ER): once daily Gel: once daily Patch: once every 3 to 4 days (Oxytrol); once every 4 days (Oxytrol for Women)	• FDA-approved for use in children ≥ 5 years (IR) and ≥ 6 years (ER) • Dose adjustment of tablets (IR) is recommended in the frail elderly due to prolonged elimination half-life.
Solifenacin	Tablet	Oral	Once daily	• Do not exceed 5 mg/day in patients with severe renal impairment (CrCL < 30 mL/min), when co-administered with potent CYP3A4 inhibitors, and in moderate hepatic impairment (Child-Pugh B). • Not recommended for use in severe hepatic impairment (Child-Pugh C).
Tolterodine	Capsule (ER), tablet	Oral	Capsule (ER): once daily Tablet: twice daily	• Dose adjustment is required for the capsule (ER) in patients with severe renal impairment, mild to moderate hepatic impairment, and those co-

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				administered potent CYP3A4 inhibitors (2 mg once daily); not recommended for use in severe hepatic impairment (Child-Pugh C). • Capsule (ER) is not recommended in patients with CrCL < 10 mL/min. • Dose adjustment is required for the tablet in patients with significantly reduced hepatic or renal function or those currently taking potent CYP3A4 inhibitors (1 mg twice daily).
Trospium	Capsule (ER), tablet	Oral	Capsule (ER): once daily Tablet: twice daily	• Should be administered at least 1 hour before meals or on an empty stomach. • Dose adjustment is recommended in severe renal impairment for the tablet (20 mg once daily); capsule (ER) not recommended for use in severe renal impairment (CrCL < 30 mL/min). • Should be used with caution in patients with moderate to severe hepatic dysfunction.

Abbreviations: CrCL = creatinine clearance, CYP = cytochrome P450, ER = extended-release, ESRD = end-stage renal disease, IR = immediate-release

See the current prescribing information for full details.

CONCLUSION

- The urinary antispasmodics are FDA-approved for the management of OAB, defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia.
  - In the absence of treatment, urinary incontinence has been shown to greatly reduce quality of life in areas such as physical and social functioning, as well as mental and general health *(Coyne et al 2008).*
- The urinary antispasmodics include 2 classes of medications: muscarinic receptor antagonists include darifenacin (Enablex), fesoterodine (Toviaz), flavoxate, oxybutynin, solifenacin (Vesicare), tolterodine (Detrol), and trospium (Sanctura); and the beta-3 adrenergic agonist, mirabegron (Myrbetriq). The anticholinergic agents antagonize the effects of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle tissue in the bladder and consequently decreasing bladder contractions. In an effort to reduce dosing frequency and AEs, ER (LA, XL, and XR) formulations are available for oxybutynin (Ditropan XL), tolterodine (Detrol LA), and trospium.
  - Oxybutynin is the only agent that is also available in a topical gel (Gelnique) and transdermal patch (Oxytrol). Oxytrol for Women is an OTC transdermal patch for women ≥ 18 years for OAB treatment.
  - Mirabegron has a different mechanism of action and AE profile.
- The results from clinical studies have demonstrated each of the urinary antispasmodics to be more effective compared to placebo in regard to improvements in micturition frequency, urgency, and urge incontinence episodes. Head-to-head studies with the urinary antispasmodics have not consistently found one agent to be superior to other agents within the class.
- A 2012 Cochrane review reported that IR formulations of oxybutynin, tolterodine, and trospium have similar efficacy, but oxybutynin was associated with more AEs. In addition, solifenacin improved symptoms of OAB more so than tolterodine IR, while fesoterodine was more effective than tolterodine ER *(Madhuvrata et al 2012).*
- A 2018 AHRQ systematic review update of nonsurgical treatments for urinary incontinence in women concluded that behavioral therapy, alone or in combination with other interventions, is generally more effective than other first- or second-line interventions (including pharmacologic interventions) alone for both stress and urgency urinary incontinence (*Balk et al* 2018). For women with urgency urinary incontinence, anticholinergics were significantly more likely to result in "cure" (OR, 1.80; 95% CI, 1.29 to 2.52) or improvement (OR, 1.79; 95% CI, 1.18 to 2.7) as compared to placebo.

- Current consensus guidelines recommend the use of urinary antispasmodics in patients with OAB symptoms caused by detrusor overactivity with or without urgency incontinence. Behavioral therapies should generally be used as initial treatment (eg, bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) with urinary antispasmodics recommended as second-line therapy or in combination with behavioral therapy. Anticholinergics should be avoided in elderly patients with delirium, dementia, or cognitive impairment. In general, ER formulations of urinary antispasmodics are associated with lower incidences of AEs with similar efficacy as compared to IR products. Pharmacologic treatment should be based on AEs, tolerability, convenience, and cost *(American Geriatric Society 2019, American Urological Association 2019, Burkhard et al 2018, Lightner et al 2019, Qaseem et al 2014*).

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