OPTUMRx

Therapeutic Class Overview
Urinary antispasmodics

INTRODUCTION

- Overactive bladder (OAB) is defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of a causative infection or pathological conditions. 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 (*Gormley 2019, Coyne et al 2008, Haab 2014, International Continence Society 2015).*
  - OAB affects approximately 1 in 7 (14%) adults, both men and women, in the United States (U.S.). OAB symptom prevalence and severity tend to increase with age, and affects ~33% of people ≥ 75 years of age. Urge urinary incontinence (UUI) is consistently more common in women than in men (*FDA Gemtesa clinical review 2020, Gormley et al 2019*).
- Neurogenic detrusor overactivity (NDO) is a subtype of OAB, defined by the International Children's Continence Society (ICCS) as detrusor overactivity (ie, occurrence of involuntary detrusor contractions that are spontaneous or provoked during the filling phase) due to a relevant neurological cause (*Austin et al 2016, Food and Drug Administration [FDA] Vesicare LS clinical review 2020, Franco et al 2020*).
  - In NDO, involuntary detrusor contractions simultaneously coincide with sphincter dyssynergia and result in high bladder pressure and eventual renal damage (*FDA Vesicare LS clinical review 2020, Franco et al 2020, Wu et al 2019*).
  - NDO can develop as a result of a lesion at any level in the nervous system; the most prevalent cause of NDO in children is due to various subtypes of spina bifida resulting from neural tube closure defects during fetal development (*FDA Vesicare LS clinical review 2020, Franco et al 2020, Nepple and Cooper 2019*).
  - NDO prevalence is not easily quantifiable and epidemiology data in the pediatric population are limited. In 2009, prevalence of patients who were diagnosed with NDO in the European Union was estimated at 1.8 per 10,000 children (*FDA Vesicare LS clinical review 2020, Franco et al 2020*).
- In OAB, 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. Urinary antispasmodics, including anticholinergics and the beta-3 adrenergic agonist, mirabegron, are recommended as first-line pharmacological therapy in OAB (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).
- In children with NDO, first-line therapy for the majority of patients is medical treatment with an oral anticholinergic coupled with clean intermittent catheterization (CIC) 4 to 5 times a day (*Blok et al 2020, FDA Vesicare LS clinical review 2020, Franco et al 2020, Rawashdeh et al 2012, Stein et al 2020*).
- Urinary antispasmodics belong to 2 classes of drugs, which include anticholinergic compounds known as muscarinic receptor antagonists, and beta-3 adrenergic agonists. All urinary antispasmodics, with the exception of flavoxate, are Food and Drug Administration (FDA)-approved for the treatment of OAB.
  - The anticholinergic agents act as antagonists of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle in the bladder and decreasing bladder contractions.
    - Oral immediate-release (IR) and extended-release (ER) formulations (LA, XL, and XR) are available for oxybutynin (Ditropan), tolterodine (Detrol), and trospium, while darifenacin (Enablex), fesoterodine (Toviaz), and solifenacin (Vesicare, Vesicare LS) are available as oral ER formulations.
    - Oxybutynin is also formulated as a topical gel (Gelnique) and transdermal patch (Oxytrol, Oxytrol for Women). Oxytrol for Women is an over-the-counter (OTC) product previously available as a prescription; it is specifically indicated for women ≥ 18 years of age, while Oxytrol is FDA-approved for use in men *(Oxytrol for Women Drug Facts 2016).*
    - Ditropan XL (oxybutynin) has an additional indication for pediatric patients with NDO, while IR oxybutynin tablets and syrup and solifenacin suspension are specifically FDA-approved for pediatric patients with NDO.
    - Flavoxate tablets are FDA-approved for the relief of symptoms of cystitis, prostatitis, urethritis, or urethrocystitis/ urethrotrigonitis.
  - Mirabegron (Myrbetriq, Myrbetriq Granules) and vibegron (Gemtesa) are adrenergic agonists of the human beta-3 adrenergic receptor. They relax the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 adrenergic receptor, which increases bladder capacity.

  - Mirabegron tablets and vibegron are indicated for treatment of OAB. Mirabegron tablets have an additional indication for pediatric patients with NDO, while mirabegron granules are specifically FDA-approved for pediatric patients with NDO.
- 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 (*Brown et al 2018, Rawashdeh et al 2012*).
  - Preclinical studies have 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).*
- Botox injection (onabotulinumtoxinA) is also indicated in OAB and NDO in patients who have an inadequate response to or are intolerant of an anticholinergic medication. In adults, Botox is indicated for the treatment of OAB with symptoms of UUI, urgency, and frequency, and also for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, spinal cord injury [SCI], multiple sclerosis [MS]). In children, Botox is indicated for the treatment of NDO in pediatrics ≥ 5 years of age and older (*Botox prescribing information 2021).* 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 10% topical gel)	-
oxybutynin	✔
Oxytrol (oxybutynin transdermal patch)	-
Oxytrol for Women (oxybutynin transdermal patch)*	-
trospium	✔
trospium ER	✔
Toviaz (fesoterodine)	-†
Vesicare (solifenacin)	✔
Vesicare LS (solifenacin)	-
Beta-3 Adrenergic Agonists	
Gemtesa (vibegron)	-
Myrbetriq (mirabegron)	-
Myrbetriq Granules (mirabegron)	-
Direct Muscle Relaxants	
flavoxate	✔

*OTC product
†The FDA has approved a generic fesoterodine tablet AB rated to Toviaz, but it is not currently commercially available.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	darifenacin (Enablex)	fesoterodine (Toviaz)	flavoxate	mirabegron (Myrbetriq)	mirabegron (Myrbetriq Granules)	oxybutynin (Ditropan XL)	oxybutynin (Gelnique, Oxytrol)	oxybutynin tablets, syrup	solifenacin (Vesicare)	solifenacin (Vesicare LS)	tolterodine (Detrol, Detrol LA)	trospium, trospium ER	vibegron (Gemtesa)
Treatment of OAB with symptoms of UUI, urgency, and urinary frequency	✔	✔		✔ *		✔	✔ †		✔		✔	✔	✔
Treatment of pediatric patients with symptoms of detrusor overactivity associated with a neurological condition (eg, spina bifida)						✔ ‡							
Treatment of NDO in pediatric patients		✔ ‡		✔ ‡	✔ ‡					✔ ‡			
Treatment of bladder instability in patients with uninhibited neurogenic or reflex neurogenic bladder								✔ ‡					
Symptomatic relief of cystitis, prostatitis, urethritis, or urethrocystitis/ urethrotrigonitis			✔										

* Either alone or in combination with the muscarinic antagonist solifenacin succinate.
† 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 OAB in men.
‡ Toviaz is indicated in patients ≥ 6 years of age with a body weight > 25 kg; Ditropan XL is indicated in patients ≥ 6 years of age; Myrbetriq Granules is indicated in patients ≥ 3 years of age, Myrbetriq tablets are indicated in patients ≥ 3 years of age with a body weight ≥ 35 kg; Vesicare LS is indicated in patients ≥ 2 years of age; the safety and efficacy of oxybutynin tablets and syrup have been demonstrated for pediatric patients ≥ 5 years of age.

(Oxytrol for Women Drug Facts 2016; Prescribing information: Detrol 2016, Detrol LA 2018, Ditropan XL 2021, Enablex 2016, flavoxate 2018, Gelnique 2019, Gemtesa 2020, Myrbetriq/Myrbetriq Granules 2021, oxybutynin tablets 2020, oxybutynin syrup 2020, Oxytrol 2017, Toviaz 2021, trospium tablets 2020, trospium extended-release capsules 2021, Vesicare 2020, Vesicare LS 2020)

- 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 2021).* 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 it 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 number 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).*
- Vibegron was studied in a Phase 3, 12-week, placebo-controlled, multi-center, randomized controlled EMPOWUR trial in 1518 adult patients with OAB (*Staskin et al 2020*). Patients were randomized to vibegron 75 mg daily, tolterodine ER 4 mg, or placebo. Micturitions decreased an average of 1.8 episodes per day with vibegron vs 1.3 with placebo ($p < 0.001$) and 1.6 for tolterodine. UUI episodes also decreased by 2 per day with vibegron vs 1.4 for placebo ($p < 0.0001$) and 1.8 with tolterodine). Efficacy was maintained up to 40 weeks without additional safety concerns (*Staskin et al 2021*).
- The efficacy of mirabegron for the treatment of NDO was evaluated in a Phase 3, 52-week, open-label, baseline-controlled, multicenter, dose titration study in 86 pediatric patients 3 to 17 years of ages with NDO on CIC (*Myrbetriq/Myrbetriq Granules prescribing information 2021*). All patients initially received a weight-based starting dose equivalent to a 25 mg daily dose followed by dose titration to a 50 mg equivalent; 94% of patients were treated at the maximum dose. A total of 68 patients had valid urodynamic measurements for evaluation of efficacy. The mean change from baseline in MCC in patients 3 to < 12 years (n = 43) was 72 mL (95% C, 45 to 99), and 113 mL (95% CI, 79 to 147) in patients 12 years to 17 years of age (n = 25).
- The efficacy and safety of solifenacin suspension for the treatment of pediatric patients (6 months to < 18 years of age of age) with NDO were evaluated in 2 open-label, baseline-controlled, Phase 3 studies. Patients were treated with sequential doses of solifenacin 2.5 to 10 mg for 12 weeks to determine an optimal dose, followed by a fixed dose for ≥ 40 weeks. The primary outcome was the change in maximum cystometric capacity from baseline to 24 weeks. Results revealed that maximum cystometric capacity significantly improved after 24 weeks of treatment (37 mL for children 6 months to < 5 years of age; $p < 0.001$ and 57.2 mL for children 5 to < 18 years of age; $p < 0.001$). Improvement continued through 52 weeks of treatment. Results for all secondary endpoints were also significant at week 24. Treatment-emergent AEs were mostly mild or moderate in nature (*Franco et al 2020*).
- In an unpublished manufacturer-sponsored, randomized, open-label trial, 124 pediatric patients between 6 and 17 years of age with NDO were randomized to receive either fesoterodine 4 mg, 8 mg or oxybutynin. The primary outcome of maximum bladder capacity improved from baseline to week 12 in all 3 treatment groups. Between group comparisons did not demonstrate significant differences in the primary outcome (*Toviaz prescribing information 2021, Clinicaltrials.gov 2021)*

CLINICAL GUIDELINES

OAB

- The 2019 American Urological Association (AUA) guideline on non-neurogenic overactive bladder, the 2021 European Association of Urology (EAU) guideline on non-neurogenic female LUTS, and the 2021 EAU guideline on the management of non-neurogenic male LUTS recommend behavioral therapies (eg, bladder training, bladder control strategies, pelvic floor muscle training, fluid management) as first-line management for OAB (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).
- Pharmacologic therapy with an oral anticholinergic or beta-3 adrenergic agonist (ie, mirabegron) is recommended as second-line therapy, with agents from both therapeutic classes at the same grade of recommendation (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).
  - If a patient experiences inadequate symptom control and/or unacceptable AEs with 1 anticholinergic, then a dose modification, a different anticholinergic, an alternative anticholinergic formulation, or a beta-3 adrenoceptor agonist may be tried (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).

- ER formulations of anticholinergics should be considered whenever possible and preferentially be prescribed over IR formulations, due to lower rates of dry mouth and AEs (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).
- Combination therapy with an antimuscarinic and beta-3 adrenoceptor agonist may be appropriate for patients who are refractory to monotherapy (*Gormley et al 2019*).
- Anticholinergics cause relatively high rates of dry mouth and constitutional effects (fatigue, constipation, gastrointestinal AEs) and should be avoided in older adults due to increased risks of cognitive impairment (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018, Staskin et al 2020*).
- Vibegron is the most recent beta-3 adrenergic agonist approved by the FDA for the treatment of OAB and is not included in any current OAB guidelines (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).

- The 2019 American Geriatrics Society (AGS) Beers criteria strongly recommend that anticholinergic agents (including antimuscarinic agents for urinary incontinence: darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, and trospium) be avoided in older adults with or at high risk for delirium or dementia, and concomitant use of anticholinergics be avoided in older adults due to increased risk of cognitive decline (*AGS 2019*).

NDO

- The 2012 International Children's Continence Society's (ICCS) recommendations for congenital neuropathic bladder in children state that first-line therapy for the majority of children with NDO is clean intermittent catheterization (CIC) 4 to 5 times a day, coupled with or without medical treatment with an oral antimuscarinic (*Rawashdeh et al 2012*).
  - The antimuscarinic agent oxybutynin has been the standard of care medical therapy for NDO; it was the only FDA- There is excellent evidence (Level 1) to support the efficacy of anticholinergics to reduce bladder storage pressure and detrusor overactivity and intravesical storage.
    - The antimuscarinic agent oxybutynin has been the standard of care for NDO; at the time the ICCS recommendations were published, oxybutynin was the only FDA-approved medication for treatment of NDO in patients ≥ 5 years of age.
  - Non-surgical interventions should be promoted before undertaking major surgery, and include pharmacologic agents (ie, antimuscarinics, botulinum-A toxin, and antibiotics), medical devices (ie, CIC), and neuromodulation.
  - Indications for non-surgical treatments depend on issues related to intravesical pressures, upper urinary status, UTI prevalence, and degree of incontinence.
- The 2020 EAU guideline on the management of neurogenic bladder in children and adolescents recommends the use of oxybutynin in patients with detrusor overactivity with the caveat of dose-limiting side effects. The guideline cites studies that report the safe use of tolterodine, solifenacin, and trospium; however, it highlights that their use in neonates and young children is considered off-label. Due to evidence limited to case reports, the guideline makes no recommendation on use of mirabegron in this patient population (*Stein et al 2020*).

SAFETY SUMMARY

Anti-muscarinic (anticholinergic) agents

- The anticholinergic urinary antispasmodics are contraindicated with uncontrolled narrow angle glaucoma, gastric retention, and urinary retention.
- 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 or in patients with pre-existing dementia treated with cholinesterase inhibitors. Solifenacin is not recommended for use in patients at high risk for QT prolongation and cautious use of tolterodine is suggested in these patients.
- Anticholinergic-related AEs are commonly associated with these agents due to their anticholinergic mechanism of action. The most common AEs include dry mouth and constipation.

Beta-3 adrenergic agonists

- A key warning and precaution with vibegron is the risk of urinary retention, especially in patients with bladder outlet obstruction and in those taking muscarinic antagonist medications for OAB. Key warnings and precautions with mirabegron include increases in blood pressure, urinary retention in patients with bladder outlet obstruction and in those taking anticholinergics for OAB, and angioedema.

- Common AEs for the beta-3 adrenergic agonists include nasopharyngitis, urinary tract infection, and headache. Additional commonly reported AEs of hypertension and tachycardia have been reported for mirabegron.
- Concomitant use of either vibegron or mirabegron with digoxin increases digoxin maximal concentrations. Mirabegron is a cytochrome P450 (CYP)2D6 inhibitor and may interact with drugs metabolized by CYP2D6.

Direct muscle relaxant

- Flavoxate is contraindicated in patients with achalasia, pyloric or duodenal obstruction, obstructive intestinal lesions or ileus, gastrointestinal hemorrhage, and obstructive uropathy.
- Flavoxate has a warning for patients with suspected glaucoma and a precaution that drowsiness and blurred vision may occur.
- AEs include nausea, vomiting, dry mouth, vertigo, headache, mental confusion (especially in the elderly), drowsiness, tachycardia, palpitation, blurred vision, and dysuria.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Darifenacin	Tablet (ER)	Oral	Once daily	• Dose should 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). • Dose should not exceed 4 mg/day in: ○ Adults with severe renal impairment (eGFR < 30 mL/min/1.73m^2). ○ Pediatric patients weighing > 35 kg with eGFR between 15 and 29 mL/min/1.73 m^2. ○ When co-administered with potent CYP3A4 inhibitors for adults and pediatric patients weighing > 35 kg. • Initial dose, titration, and adjustments for pediatric patients is based on weight. The use of fesoterodine is not recommended for: ○ Pediatric patients weighing between 26 and 35 kg with eGFR < 30 mL/min/1.73 m^2. ○ Pediatric patients weighing > 35 kg with eGFR < 15 mL/min/1.73 m^2 or requiring dialysis. ○ Pediatric patients weighing between 26 and 35 kg taking strong CYP3A4 inhibitors.
Flavoxate	Tablet	Oral	3 to 4 times daily	• With improvement of symptoms, the dose may be reduced.
Mirabegron	Tablet (ER), granules	Oral	Once daily	• Not recommended for use in ESRD (eGFR < 15 mL/min/1.73 m^2 or requiring dialysis) or severe hepatic impairment (Child-Pugh C). • Dose limitations are recommended in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or moderate hepatic impairment (Child-Pugh Class B)

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments

				• The choice of mirabegron tablets or granules should be based on the indication and patient's weight.
				  ○ In pediatric patients weighing < 35 kg, mirabegron granules are recommended with a weight-based starting dose. After 4 to 8 weeks of treatment, the dose may be increased to the lowest effective dose without exceeding the maximum recommended dose.
				  ○ In pediatric patients weighing ≥ 35 kg, mirabegron tablets or granules may be administered.
				  ○ A recommended dosage for mirabegron granules for adults has not been determined.
				• Mirabegron tablets and granules are 2 different products and are not substitutable on a mg-per-mg basis.
				• Mirabegron tablets should be swallowed whole with water and not chewed, divided, or crushed, and may be administered with or without food.
				• Mirabegron granules should be reconstituted with 100 mL of water and prepared as an ER oral suspension. The suspension should be administered with food to reduce potential exposure-related risks.

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 of age (IR) and ≥ 6 years of age (ER) • Dose adjustment of tablets (IR) is recommended in the frail elderly due to prolonged elimination half-life.
Solifenacin	Tablet, suspension	Oral	Once daily	Tablet: • Dose should 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). Suspension: • Recommended daily dose is based on patient weight. • Administration of dose should be followed with liquid (eg, water or milk). • The recommended starting dose should not be exceeded in patients with severe renal impairment (CrCl < 30 mL/min), when coadministered with

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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-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.
Vibegron	Tablet	Oral	Once daily	• Tablet should be swallowed whole with water (with or without food); may be crushed and mixed with applesauce in adults. • Not recommended in ESRD or severe hepatic impairment.

Abbreviations: CrCl = creatinine clearance, eGFR = glomerular filtration rate, ER = extended-release, ESRD = end-stage renal disease, IR = immediate-release

See the current prescribing information for full details.

CONCLUSION

- The urinary antispasmodics (with the exception of flavoxate) 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.
  - Ditropan XL (oxybutynin), Toviaz (fesoterodine), and mirabegron tablets have an additional indication for pediatric patients with NDO, while IR oxybutynin tablets and syrup, solifenacin suspension, and mirabegron granules are specifically FDA-approved in pediatric patients with NDO.
- The urinary antispasmodics include 2 classes of medications: muscarinic receptor antagonists including darifenacin (Enablex), fesoterodine (Toviaz), flavoxate, oxybutynin, solifenacin (Vesicare, Vesicare LS), tolterodine (Detrol), and trospium; and the beta-3 adrenergic agonists, mirabegron (Myrbetriq, Myrbetriq Granules) and vibegron (Gemtesa). 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.

- To reduce dosing frequency and anticholinergic 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 indicated in women ≥ 18 years of age.
- Mirabegron and vibegron have a different mechanism of action and AE profile compared with the anticholinergic agents.

- 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, urge incontinence episodes, and cystometric capacity (solifenacin suspension). 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.
  - 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.
- Behavioral therapy is recommended first-line for OAB. Second-line pharmacologic therapies include the urinary antispasmodics: anticholinergic agents for urinary incontinence (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) and the beta-3 adrenergic receptor agonist, mirabegron.
- For NDO, first-line therapy for the majority of children with NDO is CIC 4 to 5 times a day, coupled with or without medical treatment with an oral antimuscarinic; oral oxybutynin has been the standard of care medical therapy for NDO.
- 2019 AGS Beers criteria strongly recommend that anticholinergic agents be avoided in older adults with or at high risk for delirium or dementia, and concomitant use of anticholinergics be avoided in older adults due to increased risk of cognitive decline.

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