Therapeutic Class Overview
Urinary Antispasmodics

Therapeutic Class

- **Overview/Summary:** Overactive bladder (OAB) is characterized as urinary urgency, with or without urge incontinence, usually with frequency and nocturia.[1] 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.[2] The urinary antispasmodics that are Food and Drug Administration-approved for the treatment of OAB are listed in Table 1.[3-16] Many of the urinary antispasmodics are anticholinergic compounds that act as antagonists of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle in the bladder and reducing bladder contractions.[3-9,11-16] Mirabegron (Myrbetriq®) is the first β-3 adrenergic receptor agonist to be approved for the treatment of OAB. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle, thereby increasing bladder capacity.[17] The muscarinic receptor antagonists have demonstrated similar safety and efficacy; 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 suggest 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.[18] The muscarinic receptor antagonists are associated with various adverse events including blurred vision, dry mouth, constipation and urinary retention. Central nervous system adverse events such as dizziness, somnolence and headaches may also occur.[3] The development of extended-release (ER) formulations with more predictable pharmacokinetics has led to a lower incidence of anticholinergic adverse events compared to immediate-release (IR) products. Several urinary antispasmodics are currently available generically in both IR and ER formulations.[19] Because it acts via the beta-3 adrenergic receptor rather than through muscarinic cholinergic receptors, mirabegron may have a better tolerability profile compared to other urinary antispasmodics.[17]

Table 1. Current Medications Available in the Class[3-16]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Darifenacin (Enablex®)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	Extended-release tablet: 7.5 mg 15 mg	-
Fesoterodine (Toviaz®)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	Extended-release tablet: 4 mg 8 mg	-
Flavoxate (Urispas®*)	Symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis and urethrocystitis/urethrotrigonitis	Tablet: 100 mg	✔
Mirabegron (Myrbetriq®)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	Extended-release tablet: 25 mg 50 mg	-
Oxybutynin (Ditropan®*, Ditropan XL®*, Gelnique®, Oxytrol®)	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder, treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, treatment of pediatric patients aged six years and older with symptoms of	Extended-release tablet (Ditropan XL®): 5 mg 10 mg 15 mg Gel (Gelnique®): 3% (pump)	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	detrusor overactivity associated with a neurological condition	10% (sachet) Syrup (Ditropan®): 5 mg/5 mL Tablet (Ditropan®): 5 mg Transdermal patch (Oxytrol®): 3.9 mg/24 hours	
Solifenacin (VESIcare®)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency	Tablet: 5 mg 10 mg	-
Tolterodine (Detrol®*, Detrol LA®)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	Extended-release capsule (Detrol LA®): 2 mg 4 mg Tablet (Detrol®): 1 mg 2 mg	✔
Trospium (Sanctura®*, Sanctura XR®*)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	Extended-release capsule (Sanctura XR®*): 60 mg Tablet (Sanctura®): 20 mg	✔

ER, LA, XL and XR=extended-release.
*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- The results of a Cochrane systematic review demonstrate that the improvement in quality of life is similar between tolterodine immediate-release (IR) and oxybutynin IR (standardized mean difference [SMD], -0.00; 95% confidence interval [CI], -0.18 to 0.18); however, there is a lower risk of discontinuation (risk ratio [RR], 0.52; 95% CI, 0.40 to 0.66) and dry mouth with tolterodine (RR, 0.65; 95% CI, 0.60 to 0.71). No differences in efficacy were reported. The efficacy between oxybutynin and trospium IR formulations is similar; however, there is a lower risk of withdrawing due to adverse events (RR, 0.66; 95% CI, 0.48 to 0.91) and dry mouth with trospium (RR, 0.64; 95% CI, 0. 52 to 0.77).[20]
- Solifenacin significantly improves quality of life compared to tolterodine (SMD, -0.12; 95% CI, -0.23 to -0.01), and fesoterodine improves quality of life parameters compared to tolterodine extended-release (LA, XL) (SMD, -0.20; 95% CI, -0.27 to -0.14). There was a higher report of cure or improvement in symptoms (RR, 1.25; 95% CI, 1.13 to 1.39) leakage episodes/24 hours (weighted mean difference [WMD], -0.30; 95% CI -0.53 to -0.08) and urgency episodes/24 hours (WMD, -0.43; 95%CI, -0.74 to -0.13) with solifenacin compared to tolterodine. The rates of withdrawal due to adverse events were similar between solifenacin and tolterodine.[20]
- Fesoterodine significantly increases the chance of patient reported cure or improvement in symptoms (RR, 1.11; 95% CI, 1.06 to 1.16), leakage episodes (WMD, -0.19; 95% CI, -0.30 to -0.09), urinary frequency (WMD, -0.27; 95% CI, -0.47 to -0.06) and urgency episodes/24 hours (WMD, -0.44; 95%CI, -0.72 to -0.16) compared to tolterodine LA. Fesoterodine has a higher risk of withdrawal due

to adverse events compared to tolterodine LA (RR, 1.45; 95% CI, 1.07 to 1.98) and higher risk of dry mouth (RR, 1.80; 95% CI, 1.58 to 2.05).[20]

- A meta-analysis comparing oxybutynin and tolterodine IR formulations reported that oxybutynin improved the number of incontinence episodes/24 hours (WMD, 0.41; 95% CI, 0.04 to 0.77) and increased the volume voided per micturition (WMD, 8.24; 95% CI, 2.38 to 14.11) compared to tolterodine. No statistically significant difference was reported between the treatments with regard reduced micturition frequency (WMD, 0.0; 95% CI, -0.38 to 0.38); however, tolterodine was associated with a 46% reduction in the risk of dry mouth compared to oxybutynin (RR, 0.54; 95% CI, 0.48 to 0.61).[21]
- Studies have not consistently demonstrated a lower incidence of adverse events with oxybutynin XL compared to the IR formulation.[22-24]
- Mirabegron was evaluated in three 12-week, placebo-controlled trials of patients with overactive bladder and symptoms of urge urinary incontinence, urgency and urinary frequency. Results from all three studies demonstrated statistically significant improvements in incontinence episodes and micturitions/24 hours across all doses of mirabegron (25, 50 and 100 mg) compared to placebo. In one study using tolterodine as a reference arm, tolterodine ER was not significantly more effective compared to placebo for the primary endpoints. In two studies, both the 100 and 50 mg doses of mirabegron were associated with statistically significant improvements in secondary endpoints compared to placebo. In a third study, the change from baseline in the mean volume voided per micturition was only significant in the mirabegron 50 mg group, but not for the other doses.[25-27]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) are considered first-line treatment in all patients with overactive bladder (OAB).[28.29]
  - Behavioral therapies may be combined with antimuscarinic therapies.[28.29]
  - Oral antimuscarinics are recommended as first-line pharmacologic therapy; no one agent is recommended over another. If adverse events occur, a dose reduction or a switch to a different antimuscarinic medication should be considered.[28.29]
  - If both an immediate-release (IR) and an extended-release (ER) formulation are available, the ER formulations are preferred over IR formulations due to lower rates of dry mouth.[28.29]
  - Transdermal oxybutynin (patch or gel) may be considered if oral agents cannot be tolerated.[28.29]
  - The role of mirabegron in the management if OAB is not clearly defined within current guidelines.[28.29]
- Other Key Facts:
  - Trospium has low penetration through the blood brain barrier and gut; however, clinical studies have not demonstrated a lower incidence of adverse events with trospium compared to others within the class.[18]
  - Fesoterodine, a prodrug, is metabolized by plasma esterases to 5-hydroxymethyl tolterodine, the same active metabolite as tolterodine.[4,5,16]
  - The oral ER and transdermal formulations may be associated with a lower incidence of dry mouth compared to the IR products.[3-16]
  - Mirabegron is the first beta-3 adrenergic receptor agonist to be approved for the treatment of overactive bladder.[17]

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Therapeutic Class Review
Urinary Antispasmodics

Overview/Summary

The International Continence Society defines overactive bladder (OAB) as urinary urgency, with or without urge incontinence, usually with frequency and nocturia.[1] 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.[2] The urinary antispasmodics that are Food and Drug Administration (FDA)-approved for the treatment of OAB include darifenacin (Enablex®), fesoterodine (Toviaz®), mirabegron (Myrbetriq®), oxybutynin (Ditropan®) solifenacin (VESIcare®), tolterodine (Detrol®) and trospium (Sanctura®). Extended-release (ER, LA, XL and XR) formulations are available for oxybutynin (Ditropan XL®), tolterodine (Detrol LA®) and trospium (Sanctura XL®). Oxybutynin is also available as a topical gel (Gelnique®) and transdermal patch (Oxytrol®). Flavoxate is FDA-approved for the relief of symptoms of cystitis, prostatitis, urethritis, or urethrocystitis/urethrotrigonitis.[3-16] The immediate-release (IR) oxybutynin is also indicated for the relief of symptoms of neurogenic or reflex neurogenic bladder, and the XL tablet is approved for the treatment of detrusor overactivity.[6,7] Several urinary antispasmodics are currently available generically in both IR and XL formulations.[17]

Many of the urinary antispasmodics used for the treatment of urinary incontinence belong to a class of anticholinergic compounds known as muscarinic receptor antagonists. These agents act as antagonists of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle in the bladder and reducing bladder contractions. [3-9,11-16] The muscarinic receptor antagonists have a similar safety and efficacy profile; 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 suggest 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.[18] Mirabegron is the first beta-3 adrenergic receptor agonist to be approved for the treatment of OAB. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle which increases bladder capacity. Because it acts via the beta-3 adrenergic receptor rather than through muscarinic cholinergic receptors, mirabegron may have a better tolerability profile compared to other urinary antispasmodics.[19]

As a result of the many muscarinic receptor subtypes and locations in organs throughout the body, muscarinic receptor antagonists are associated with various adverse events including blurred vision, dry mouth, constipation and urinary retention. Central nervous system adverse events such as dizziness, somnolence, and headaches may also occur.[3] The development of ER formulations with more predictable pharmacokinetics has led to a lower incidence of anticholinergic adverse events. While oxybutynin IR undergoes first-pass metabolism to an active metabolite with a high incidence of dry mouth, transdermal oxybutynin formulations bypass this metabolism, resulting in a lower incidence of dry mouth while maintaining the efficacy of oxybutynin IR.[20] Trospium, a water soluble compound, has low penetration through the blood brain barrier and gut; however, clinical studies have not demonstrated a lower incidence of adverse events with trospium compared to others within the class.[13,14,18] Fesoterodine, a prodrug, is metabolized by plasma esterases to 5-hydroxymethyl tolterodine, the same active metabolite as tolterodine.[4,5,16]

According to current guidelines for the management of OAB, oral antimuscarinics are considered first-line pharmacologic therapy following behavioral modification attempts (e.g., bladder training and bladder control strategies), without one agent recommended over another. The American Urological Association recommends giving preference to ER formulations over IR formulations as a result of improved tolerability and lower rates of dry mouth associated with their use. To date, the role of mirabegron in the management of OAB has not been established. According to the National Institute for Health and Clinical Excellence, flavoxate is not recommended for the treatment of urinary incontinence or OAB in women.[21-23]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Darifenacin (Enablex®)	Urinary antispasmodic	-
Fesoterodine (Toviaz®)	Urinary antispasmodic	-
Flavoxate (Urispas®*)	Urinary antispasmodic	✔
Mirabegron (Myrbetriq®)	Urinary antispasmodic	-
Oxybutynin (Ditropan®*, Ditropan XL®*, Gelnique®, Oxytrol®)	Urinary antispasmodic	✔
Solifenacin (VESIcare®)	Urinary antispasmodic	-
Tolterodine (Detrol®*, Detrol LA®)	Urinary antispasmodic	✔
Trospium (Sanctura®*, Sanctura XR®*)	Urinary antispasmodic	✔

ER, LA, XL and XR=extended-release.
*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration (FDA)-Approved Indications[3-16]

Generic Name	Treatment of Overactive Bladder	Treatment of Detrusor Overactivity	Treatment of Bladder Instability in Patients with Uninhibited Neurogenic or Reflex Neurogenic Bladder	Symptomatic Relief of Symptoms of Cystitis, Prostatitis, Urethritis, or Urethrocystitis/ Urethrotrigonitis
Darifenacin	✔ *			
Fesoterodine	✔ *			
Flavoxate				✔
Mirabegron	✔ *			
Oxybutynin	✔ * (XL)	✔ †(XL)	✔ (IR)	
Solifenacin	✔ *			
Tolterodine	✔ *			
Trospium	✔ *			

ER, LA, XL, XR=extended-release, IR=immediate 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.

In addition to the Food and Drug Administration approved indications listed above, oxybutynin (various formulations) has been used off-label for primary nocturnal enuresis in children and for its antispasmodic effects in a number of gastrointestinal disorders.[17]

Pharmacokinetics

Table 3. Pharmacokinetics[3-16]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Darifenacin	15 to 19	60	Not reported	13 to 19
Fesoterodine	52	70	5-hydroxymethyl tolterodine	7
Flavoxate	Not reported	57	Methyl flavones carboxylic acid	Not reported
Mirabegron	29 to 35	6.0 to 12.2	None	50
Oxybutynin	6 (IR)	<0.1	Desethyloxybutynin	2 to 3 (IR)

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
	~9.36 (XL)			13.2 (XL)
Solifenacin	90	69	4R-hydroxy solifenacin	45 to 68
Tolterodine	>77	77	5-hydroxymethyl tolterodine	2 to 10 (IR) 7 to 18 (ER)
Trospium	<10	5.8	Not reported	20 (IR) 35 (XR)

ER, LA, XL, XR=extended-release, IR=immediate release.

Clinical Trials

Although used for urinary incontinence, flavoxate has not consistently demonstrated efficacy in randomized, controlled trials for this condition.[24] The clinical studies demonstrating the safety and efficacy of the urinary antispasmodics in their respective Food and Drug Administration (FDA)-approved indications are included in Table 4.[25-68]

In a pooled analysis of three double-blind, randomized controlled trials, statistically significant improvements in all overactive bladder (OAB) symptoms (except nocturnal awakenings) occurred with darifenacin 7.5 mg and 15 mg compared to placebo at two, six and 12 weeks. At 12 weeks, symptoms of incontinent episodes improved from baseline by 69 and 78% with darifenacin 7.5 mg and 15 mg, respectively, compared to placebo (P<0.001). Urinary urgency improved by 29 and 31%, urgency urinary incontinence (UUI) episodes by 71 and 80%, severity of urgency by 15 and 17% and significant leaks by 74 and 75%, with darifenacin 7.5 mg and 15 mg respectively, compared to placebo (P<0.001 for all).[25] In a small cross over study by Zinner et al comparing darifenacin 15 mg and 30 mg to oxybutynin immediate-release (IR) and placebo (n=76), all active treatments significantly improved the weekly number of incontinence episodes, mean daily number of urgency episodes and severity of urgency episodes compared to placebo (P<0.05). A significant reduction in the incidence of dry mouth occurred in patients receiving darifenacin 15 mg compared to darifenacin 30 mg and oxybutynin IR (P<0.05).[26] Kay and colleagues evaluated the cognitive effect of darifenacin and oxybutynin extended-release (ER, LA, XL, XR) in healthy patients ≥60 years of age. Patients randomized to oxybutynin XL experienced a significantly greater memory deterioration with regard to name-face recall compared to those in the both placebo and darifenacin treatment groups, while darifenacin was comparable to placebo with regard to object-recall (P<0.05).[27]

In an open-label study of patients unsatisfied with prior oxybutynin XL or tolterodine LA treatment (n=500), darifenacin significantly improved micturition frequency, urgency episodes and UUI episodes compared to baseline, in both the overall study population and after stratification by prior treatments (P<0.0001 for all).[44]

The efficacy of fesoterodine in the treatment of OAB has been established in various placebo-controlled and head-to-head studies. In a large 12-week study against placebo, fesoterodine treatment significantly reduced the number of micturitions/24 hours compared to placebo (-2.9 vs -2.1; P=0.0002). A significant reduction in urgency episodes (P<0.05) and UUI episodes was also reported in the fesoterodine group compared to placebo.[28] Results from another placebo-controlled study demonstrated that both the 4 mg and 8 mg doses of fesoterodine significantly reduced daily micturition frequency compared to placebo (-1.61 and -2.09 vs -1.08 for both doses compared to placebo, respectively; P<0.001). Fesoterodine was associated with a significantly higher treatment response rate compared to placebo (74 vs 45%; P<0.001).[29] In a flexible-dose study by Wyndaele et al, both fesoterodine 4 mg and 8 mg were safe and effective in treating symptoms of OAB; however, approximately half of the patients in the 4 mg group needed an increase to the 8 mg dose to achieve satisfactory control of symptoms.[45] In another study, patients were randomized to receive fesoterodine, tolterodine LA or placebo for 12 weeks. Patients in the fesoterodine and tolterodine groups showed statistically significant improvements in all primary endpoints including micturitions/ 24 hours (P<0.001), the number of UUI episodes (P=0.001) and proportion of positive treatment responses (72 to 79 vs 53% with placebo; P<0.001).[30] The effects of fesoterodine and tolterodine LA were directly compared in a study by Herschorn et al in which patients randomized to

fesoterodine experienced significant improvements in UUI episodes/24 hours compared to patients receiving tolterodine LA (-1.72 vs -1.61; *P*<0.05). Fesoterodine significantly increased the mean voided volume compared to both tolterodine LA and placebo (*P*<0.05 for both). There was no statistically significant difference between fesoterodine, tolterodine LA and placebo with regard to micturitions/24 hours (*P*>0.05).[46] In a study by Kaplan et al, patients receiving fesoterodine achieved significant improvements in micturition frequency, nocturnal micturitions, urgency episodes and severe urgency episodes compared to tolterodine LA (*P*<0.05 for all).[47]

The results of several studies have generally demonstrated no significant differences in the efficacy between oxybutynin IR and XL.[48-50] Moreover, studies have not consistently demonstrated a lower incidence of adverse events with oxybutynin XL. One small study reported a significantly lower incidence of dry mouth with the XL formulation compared to the IR (68 vs 87%; *P*<0.04), while results from another study showed a numerical, but not statistically significant difference in dry mouth between the XL and IR formulations (47.7 vs 59.1%, respectively; *P*=0.09). A third study suggests a similar incidence between formulations (68 vs 72%, respectively; *P* value not reported). Compared to placebo, oxybutynin topical gel significantly improved the number of urinary incontinence episodes per day (*P*<0.0001), the average daily urinary frequency (*P*=0.0017) and the average urine volume per void (*P*=0.0018). Application-site reactions were more common with the gel.[36] The oxybutynin transdermal patch demonstrated comparable efficacy to oxybutynin IR and tolterodine IR, in separate studies. The results of these trials also suggest that the transdermal formulation is associated with a lower incidence of adverse events compared to either oral agent.[37,51]

A meta-analysis of four studies comparing oxybutynin IR to tolterodine IR reported that oxybutynin improved the number of incontinence episodes/24 hours (weighted mean difference [WMD], 0.41; 95% CI, 0.04 to 0.77) and increased the volume voided per micturition (WMD, 8.24; 95% CI, 2.38 to 14.11) compared to tolterodine IR. No statistically significant difference was reported between the treatments with regard to a reduction in micturition frequency (WMD, 0.0; 95% CI, -0.38 to 0.38); however, tolterodine IR was associated with a 46% reduction in the risk of dry mouth compared to oxybutynin (risk reduction [RR], 0.54; 95% CI, 0.48 to 0.61).[54] In two studies comparing oxybutynin XL and tolterodine IR, oxybutynin significantly improved UUI episodes and total incontinence episodes compared to tolterodine; however, the incidence of adverse events was similar between the treatments (*P*>0.05 for both).[56,57] Oxybutynin XL and tolterodine LA were directly compared in the OPERA study and demonstrated similar improvements in OAB symptoms while dry mouth was more common in patients receiving oxybutynin (*P*=0.02).[58] The results of a subanalysis of OPERA did not show a difference between treatments when patients were stratified by prior anticholinergic treatments.[59]

In a trial by Halaska et al, trospium IR was comparable to oxybutynin IR in terms of OAB symptom improvement although adverse events were more common with oxybutynin (*P*<0.01). Results of a second demonstrated that trospium IR was non inferior to oxybutynin IR with regard to the reduction in UUI episodes per week after four and 12 weeks. The median change after 12 weeks was -11.0 in both groups (*P*<0.001 for non inferiority). The change in micturitions/24 hours, and scores for urgency did not differ significantly between treatments (*P*>0.05).[60,61] In two, 12-week, randomized, double-blind, placebo-controlled trials, trospium XR treatment significantly reduced urinary frequency, incontinence episodes and increased voided volume compared to placebo. A significant reduction in incontinence episodes occurred within the first week of treatment (*P*<0.001). Central nervous system adverse events such as headache were more frequent in patients receiving placebo compared to trospium XR.[39,40] Two subanalysis in men and patients ≥75, concluded that trospium XR significantly improves OAB symptoms relative to placebo in these patient populations.[41,42]

Mattiasson and colleagues compared solifenacin (5 to 10 mg) monotherapy to solifenacin (5 mg to 10 mg) in addition to bladder training in a 16-week open-label trial. Combination therapy significantly improved micturition frequency/24 hours compared to solifenacin monotherapy (-3.11 vs -2.42; *P*<0.001); however, changes in urgency episodes/24 hours and UUI episodes/24 hours were not significantly different (*P*=NS).[62] In a 12-week randomized controlled trial, patients receiving solifenacin 5 mg or 10 mg experienced statistically significant reductions in the mean number of urgency episodes/24 hours (52 and

55 vs 33%; *P*<0.001), UUI episodes/24 hours (65 vs 63 vs 40%; *P*<0.01) and incontinence episodes/24 hours compared to placebo (59 and 47 vs 29%; *P*<0.01).[38] In a small study evaluating the tolerability of solifenacin compared to oxybutynin IR, patients treated with solifenacin had a lower incidence of dry mouth (35 vs 83%; *P*<0.0001) and fewer patients experienced one or more adverse events compared to oxybutynin IR (*P*=0.009).[52] In the 12-week STAR study (n=1,177), solifenacin treatment significantly improved micturition frequency (*P*=0.004), urgency episodes (*P*=0.035), UUI episodes (*P*=0.001) and overall incontinence episodes (*P*=0.006) compared to tolterodine LA.[63] In a subanalysis of women in the STAR study, no difference was reported between treatments with regard to ratings for patient perception of bladder control (*P*=0.87), total voided volume (*P*=0.82) or volume voided per micturition (*P*=0.88)

The results of a Cochrane systematic review demonstrate no significant differences in quality of life between tolterodine and oxybutynin IR formulations (standardized mean difference [SMD], -0.00; 95% CI, -0.18 to 0.18); however, tolterodine is associated with a lower risk of treatment discontinuation from adverse events (risk ratio [RR], 0.52; 95% CI, 0.40 to 0.66) and a lower incidence of dry mouth compared to oxybutynin (RR, 0.65; 95% CI, 0.60 to 0.71). A similar proportion of patients receiving tolterodine or oxybutynin reported a cure or improvement in symptoms (RR, 1.01; 95% CI, 0.93 to 1.11) or leakage episodes/voids over 24 hours (WMD, 0.33; 95% CI, -0.08 to 0.73). There was no difference in patient reported cure or symptom improvement between oxybutynin and trospium (RR, 1.00; 95% CI, 0.90 to 1.11); however, trospium may be associated with fewer treatment withdrawals (RR, 0.66; 95% CI, 0.48 to 0.91) and a lower incidence of dry mouth (RR, 0.64; 95% CI, 0. 52 to 0.77). Solifenacin significantly improves quality of life compared to tolterodine (SMD, -0.12; 95% CI, -0.23 to -0.01), and fesoterodine demonstrated improvements in quality of life parameters compared to tolterodine LA (SMD, -0.20; 95% CI, -0.27 to -0.14). Solifenacin is associated with a higher patient report of cure or improvement in symptoms compared to tolterodine (RR, 1.25; 95% CI, 1.13 to 1.39). Solifenacin significantly reduced the number of leakage episodes/24 hours (WMD, -0.30; 95% CI -0.53 to -0.08) and urgency episodes/24 hours relative to treatment with tolterodine (WMD, -0.43; 95%CI, -0.74 to -0.13). The rates of withdrawal due to adverse events and dry mouth were similar between solifenacin and tolterodine; however, after excluding one study using tolterodine LA, dry mouth rates were significantly lower with solifenacin (RR, 0.69; 95% CI, 0.51 to 0.94). Fesoterodine significantly increases the risk of patient reported cure or improvement in symptoms (RR, 1.11; 95% CI, 1.06 to 1.16), leakage episodes (WMD, -0.19; 95% CI, -0.30 to -0.09), frequency (WMD, -0.27; 95% CI, -0.47 to -0.06) and urgency episodes/24 hours (WMD, -0.44; 95%CI, -0.72 to -0.16) compared to tolterodine LA, although fesoterodine has a higher risk of withdrawal due to adverse event compared to tolterodine LA (RR, 1.45; 95% CI, 1.07 to 1.98) and higher risk of dry mouth (RR, 1.80; 95% CI, 1.58 to 2.05).[67]

Mirabegron was approved based on the results from three 12-week, placebo-controlled trials of patients with OAB and symptoms of UUI, urgency and urinary frequency. The change from baseline to the end of treatment in mean number of incontinence episodes and micturitions/24 hours were the co-primary endpoints in all studies. The results of all three studies demonstrate statistically significant improvements in incontinence episodes and micturitions/24 hours across all doses of mirabegron (25, 50 and 100 mg) compared to placebo. In one study that used tolterodine ER as a reference arm, tolterodine was not significantly more effective compared to placebo for the primary endpoints. In two of the studies, both the 100 and 50 mg doses of mirabegron were associated with statistically significant improvements in secondary endpoints compared to placebo. In the third study, the change from baseline in the mean volume voided per micturition was only significant in the mirabegron 50 mg group, but not for the other doses.[32-34]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Overactive Bladder/Urinary Incontinence				
Khuller et al[25] Darifenacin 7.5 mg QD vs darifenacin 15 mg QD vs placebo	Pooled analysis of 3 DB, MC, PC, PG, RCT Patients ≥18 years of age with symptoms of OAB for ≥6 months, with 5 to 50 incontinence episodes weekly, ≥8 voids/24 hours, and ≥1 urgency episode/24 hours	N=1,053 12 weeks	Primary: Change from baseline in incontinence episodes/24 hours, episodes of urgency/24 hours, severity of urgency, micturitions/24 hours, bladder capacity, significant leaks and number of awakenings at night due to OAB symptoms Secondary: Not reported	Primary: Treatment with either dose of darifenacin was associated with significant improvements in all primary endpoints at weeks two, six and 12 compared to placebo. The difference in nocturnal awakenings at 12 weeks was only significant for darifenacin 15 mg. The number of incontinent episodes improved by 69 and 78% with darifenacin 7.5 and 15 mg at 12 weeks, respectively, compared to placebo (*P*<0.001). At week 12, significant reductions in urinary urgency occurred in both the 7.5 mg (29%) and 15 mg (31%) treatment groups compared to the placebo group (*P*<0.001). Similarly, UUI episodes decreased by 71 and 80% with both darifenacin doses, respectively compared to placebo (*P*<0.001). The severity of urinary urgency improved by 15 and 17%, and significant leaks were reduced by 74 and 75%, with darifenacin 7.5 and 15 mg compared to placebo (*P*<0.001 for both). At both week two and week 12, the median change from baseline was statistically significant with darifenacin compared to placebo for all symptoms, except nocturnal awakenings (*P*<0.001 for all). At the earliest time point evaluated (days six through eight), incontinence episodes were reduced by six and 13.2% with darifenacin 7.5 and 15 mg, respectively, compared to placebo (*P*≤0.001). At days nine to 11 and days 12 to 14, darifenacin 7.5 mg reduced incontinence episodes by 4.5 and 7.7%, respectively, while the 15 mg dose reduced episodes by 11.5 and 12.2%, respectively, compared to placebo (*P*≤0.001 for all). Micturition frequency was reduced by up to 5.8 and 7.3% over the first two weeks with darifenacin 7.5 mg and 15 mg, respectively, compared to placebo (*P*≤0.001 for all). Over the first two weeks, darifenacin 7.5 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment reduced daily urgency episodes by up to 9.9% compared to placebo, while the 15 mg dose reduced these daily episodes by up to 13.5% (*P*≤0.001). Secondary: Not reported
Zinner et al[26] Darifenacin 15 mg QD vs darifenacin 30 mg QD vs oxybutynin IR 5 mg TID vs placebo	DB, PC, RCT, XO Patients 18 to 85 years of age, with urge incontinence and urinary frequency	N=76 8 weeks	Primary: Change in the number of daily incontinence episodes, severity of urgency episodes, frequency of urgency episodes, micturitions and adverse events Secondary: Not reported	Primary: All treatment groups exhibited statistically significant improvements in the mean weekly number of incontinence episodes, mean daily number of urgency episodes, and severity of urgency episodes, compared to placebo (*P*<0.05 for all). Only darifenacin 30 mg was associated with a statistically significant reduction in the frequency of micturition compared to placebo (*P*<0.05). Treatment-related adverse events were mild to moderate in severity. Darifenacin 15 mg was associated with a statistically significant reduction in the incidence of dry mouth compared to both darifenacin 30 mg and oxybutynin IR regimens (*P*<0.05 for both). Darifenacin 30 mg was associated with a statistically significant increase in the incidence of constipation compared to oxybutynin IR (*P*<0.05). The only patients to experience blurred vision or dizziness were those randomized to the oxybutynin IR group; however, the difference compared to placebo was not statistically significant (*P*>0.05). Secondary: Not reported
Kay et al[27] Darifenacin 7.5 to 15 mg QD vs	DB, DD, MC, PC, PG, RCT Healthy patients 60 years of age and older	N=150 3 weeks	Primary: Recall on the name-face association test, first-last name association test, misplaced objects	Primary: In terms of name-face delayed recall, oxybutynin XL therapy was associated with significantly greater memory deterioration compared to both placebo and darifenacin therapy (*P*<0.05). In terms of first-last name recall, darifenacin was comparable with placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oxybutynin XL 10 to 20 mg QD vs placebo			test at week three and adverse events Secondary: Not reported	while oxybutynin XL therapy was associated with significantly greater memory deterioration compared to placebo (*P*<0.05). Darifenacin was comparable to placebo with regard to object recall while oxybutynin XL therapy was associated with significantly greater memory deterioration than placebo (*P*<0.05). Dry mouth and constipation were the most frequently reported adverse events. Dry mouth occurred in 13 patients treated with darifenacin, 20 patients taking oxybutynin XL and six patients receiving placebo. Constipation was reported by 10 patients treated with darifenacin, two patients taking oxybutynin XL and one patient receiving placebo. Secondary: Not reported
Dmochowski et al[28] Fesoterodine 4 to 8 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with OAB for ≥3 months with a mean of ≥8 micturitions/24 hours, ≥3 urgency episodes/24 hours	N=896 12 weeks	Primary: Change from baseline in the number of micturitions/24 hours Secondary: Change from baseline in UUI episodes/24 hours, urgency episodes/24 hours, frequency-urgency sum, nocturnal micturitions, nocturnal urgency episodes, OAB-q, PPBC and UPS scores	Primary: The LS mean change from baseline in micturitions/24 hours was significantly greater with fesoterodine compared to placebo (-2.9 vs -2.1; *P*=0.0002). Secondary: Patients randomized to receive fesoterodine experienced a significantly greater reduction in urgency episodes compared to patients treated with placebo (-4.0 vs -3.0; *P*<0.05). Similarly, UUI episodes were significantly lower at 12 weeks following treatment with fesoterodine compared to placebo (-1.5 vs 1.2; *P*<0.05). Improvements in frequency-urgency sum were significantly greater in the fesoterodine treatment group compared to the placebo group (-13.6 vs -10.3; *P*<0.05). There were no significant between-group differences with regard to nocturnal micturitions (*P*=0.32) and nocturnal urgency episodes (*P*=0.08).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The changes in PPBC and UPS scores significantly favored fesoterodine over placebo throughout the evaluation period at weeks two, six and 12 (*P*<0.05 for all). Mean OAB-q symptoms scores significantly improved with fesoterodine over placebo for symptom bother scale (*P*<0.001), total HRQL score (*P*<0.001), concern (*P*<0.001), coping (*P*<0.001), sleep (*P*=0.0044) and social Interactions (*P*<0.0007).
Nitti et al[29] Fesoterodine 4 mg QD vs fesoterodine 8 mg QD vs placebo	DB, MC, PC, PG, PRO, RCT Patients ≥18 years old with OAB and ≥6 urinary urgency episodes or ≥3 UUI episodes recorded in the three day bladder diary	N=836 12 weeks	Primary: Mean change in the number of micturitions, UUI episodes/24 hours and treatment response ("yes" or "no" on treatment benefit scale) Secondary: Bladder diary changes such as nocturnal micturitions, MVV/void, number of continent days, number of urgency episodes/ 24 hours and adverse events	Primary: Compared to the placebo group, patients in the fesoterodine group showed statistically significant improvements in the number of micturitions/24 hours (fesoterodine 4 mg, -1.61; *P*<0.001, fesoterodine 8 mg, -2.09; *P*<0.001, placebo, -1.08), decrease in the number of UUI episodes/24 hours (fesoterodine 4 mg, -1.65; *P*<0.001, fesoterodine 8 mg, -2.28; *P*<0.001, placebo, -0.96) and treatment response (fesoterodine 4 mg, 74%; *P*<0.001, fesoterodine 8 mg, 74%; *P*<0.001, placebo, 45%). Secondary: Patients in the fesoterodine 4 mg group showed statistically significant reductions in the mean number of nocturnal micturitions (*P*<0.05), urgency episodes (*P*<0.001) and continent days weekly (*P*<0.001). Patients in the fesoterodine 8 mg group showed statistically significant improvements in MVV/void (*P*<0.001), number of urgency episodes (*P*<0.001), number of daytime micturitions (*P*<0.001) and continent days/week (*P*< 0.001). Adverse events occurred in 55% of the total study population with dry mouth being the most commonly reported event in both the 4 and 8 mg groups at 61 and 69% respectively.
Chapple et al[30] Fesoterodine 4 mg QD vs fesoterodine 8 mg QD vs	AC, DB, MC, PC, PRO, RCT Patients >18 years old with ≥6 months of urinary urgency (≥8 micturitions/24 hours and either ≥6 urgency episodes or ≥3 UUI	N=1,135 12 weeks	Primary: Change in micturitions/24 hours, number of UUI episodes and treatment response ("yes" or "no" on treatment benefit scale"	Primary: Patients in both the fesoterodine and tolterodine LA groups showed statistically significant improvements in micturitions/24 hours (fesoterodine 4 mg, -1.76; *P*<0.001, fesoterodine 8 mg, -1.88; *P*<0.001, tolterodine LA, -1.73; *P*=0.001, and placebo, -0.095.), mean decrease in the number of UUI episodes (fesoterodine 4 mg, -1.95; *P*=0.001, fesoterodine 8 mg, -2.22; *P*<0.001, tolterodine LA 4 mg, -1.74; *P*=0.008, and placebo, -1.14) and number of positive treatment responses (fesoterodine 4 mg, 75%; *P*<0.001, fesoterodine 8 mg, 79%; *P*<0.001, tolterodine LA 4 mg, 72%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tolterodine LA 4 mg QD vs placebo	episodes/24 hours)		Secondary: Change in MVV/void, daytime micturitions/24 hours, nocturnal micturitions/24 hours, urgency episodes/24 hours, continent days/week and adverse events	*P*<0.001 and placebo, 53%). Secondary: Patients in both the fesoterodine and tolterodine LA groups showed significant improvements in most secondary endpoints (*P*<0.001). Only the number of nocturnal micturitions was not significant between the treatments. The most frequently reported adverse event was dry mouth, which occurred in 50 and 58% of patients in the 4 mg and 8 mg fesoterodine groups respectively.
Van Kerrebroeck et al[31] Fesoterodine 4 to 8 mg QD	ES, MC, OL ES of Chapple et al[30] for patients completing the12-week DB study without meeting the discontinuation criteria and who did not experience an adverse event	N=417 Up to 32 months	Primary: Long-term safety and tolerability Secondary: Change in bladder diary variables, subject-reported KHQ, bladder-related problems and treatment satisfaction	Primary: Of the patients enrolled in the ES, 161 (39%) discontinued treatment prior to 24 months of follow-up, primarily due to adverse events (n=47), withdrawal of consent (n=36) or insufficient clinical response (n=36). A total of 315 patients (76%) experienced at least one treatment-emergent adverse event during OL treatment, of which 219 (53%) were considered treatment-related. The most common treatment-related adverse events included dry mouth (33.8%), constipation (5%) and urinary tract infection (2.9%). Dry mouth was rated as “mild” or “moderate” in intensity for 86% of patients. Forty-eight patients (12%) experienced treatment-emergent adverse events during the OL period that led to discontinuation. This included eight patients due to dry mouth and five due to of constipation. Four subjects discontinued because of symptomatically assessed urinary retention. No clinically significant changes in residual urine volume, vital signs, electrocardiogram measurements, physical, urological or urogynecological outcomes were reported during the open label-period. Secondary: Compared to baseline of the OL period, significant improvements were observed at 24 months with fesoterodine for urgency episodes/24 hours,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				micturitions/24 hours and MVV/void (*P*<0.0001 for all). Significant improvements in KHQ domains were reported at 12 and 24 months compared to OL baseline for all components with the exception of "general health perception (*P*≤0.02 for all). Similarly, OL treatment with fesoterodine was associated with significant improvements in ICIQ-SF scores at months four, 12 and 24 of the OL period (*P*<0.0001 for all). Subject's assessment of bladder-related problems were significantly improved at months for, 12 and 24 compared to scores during the OL baseline period (*P*<0.0001 for all).
Khullar et al[32] Mirabegron 100 mg QD vs mirabegron 50 mg QD vs tolterodine ER 4 mg QD vs placebo	AC, DB, MC, PC, PG, RCT Patients ≥18 years of age, with OAB symptoms for ≥3 months and an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period	N=1,978 12 weeks	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes/24 hours, change from baseline to end of treatment in the mean number of micturitions/24 hours Secondary: Change from baseline to end of treatment in the MVV, change from baseline to week four in the mean number of	Primary: The change from baseline to end of treatment in the mean number of incontinence episodes/24 hours was -1.46 in the mirabegron 100 mg group, -1.57 in the mirabegron 50 mg group, -1.27 in the tolterodine ER group and -1.17 in the placebo group. Compared to placebo, the change from baseline was statistically significant with mirabegron 100 mg and 50 mg (*P*<0.05 for both) but not for tolterodine ER (*P* value not reported). The change from baseline to end of treatment in the mean number of micturitions/24 hours was -1.77 in the mirabegron 100 mg group, -1.93 in the mirabegron 50 mg group, -1.59 in the tolterodine ER group and -1.34 in the placebo group. Compared to placebo, the change was statistically significant in the mirabegron 100 mg (*P*<0.05) and 50 group (*P*<0.05) but not in the tolterodine ER group (*P* value not reported). Secondary: The change from baseline to end of treatment in the MVV was 25.6 mL in the mirabegron 100 mg group, 24.2 mL in the mirabegron 50 mg group, 25.0 mL in the tolterodine ER group and 12.3 mL in the placebo group. All changes were statistically significant compared to placebo (*P*<0.05 for all). The change from baseline to four weeks in the mean number of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			incontinence episodes/24 hours, change from baseline to week four in the mean number of micturitions/24 hours, change from baseline to final visit in mean level of urgency, change from baseline to final visit in mean number of urgency incontinence episodes/24 hours, change from baseline to final visit in grade three or four urgency episodes/24 hours, change from baseline to final visit in mean number of nocturia episodes and safety	incontinence episodes/24 hours was -1.03 in the mirabegron 100 mg group, -1.04 in the mirabegron 50 mg group, -1.00 in the tolterodine ER group and -0.65 in the placebo group. All changes were statistically significant compared to placebo (*P*<0.05 for all). The change from baseline to four weeks in the mean number of micturitions/24 hours was -1.29 in the mirabegron 100 mg group, -1.16 in the mirabegron 50 mg group, -1.10 in the tolterodine ER group and -0.77 in the placebo group. All changes were statistically significant compared to placebo (*P*<0.05 for all). The change from baseline to final visit in mean level of urgency was -0.30 in the mirabegron 100 mg group, -0.31 in the mirabegron 50 mg group, -0.29 in the tolterodine ER group and -0.22 in the placebo group (*P* values not reported). The change from baseline to final visit in mean number of urgency incontinence episodes/24 hours was -1.33 in the mirabegron 100 mg group, -1.46 in the mirabegron 50 mg group, -1.18 in the tolterodine ER group and -1.11 in the placebo group (*P* values not reported). The change from baseline to final visit in grade three or four urgency episodes/24 hours was -1.96 in the mirabegron 100 mg group, -2.25 in the mirabegron 50 mg group, -2.07 in the tolterodine ER group and -1.65 in the placebo group (*P* values not reported). The change from baseline to final visit in mean number of nocturia episodes was -0.56 in the mirabegron 100 mg group, -0.41 in the mirabegron 50 mg group, -0.50 in the tolterodine ER group and -0.45 in the placebo group (*P* values not reported). Mirabegron and tolterodine ER were well tolerated and the incidence of adverse events was similar across all groups. Adverse events reported in ≥2% of the placebo, mirabegron 50 mg group, mirabegron 100 mg and tolterodine ER group respectively included hypertension (7.7 vs 5.9 vs 5.4

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				vs 8.1%), nasopharyngitis (1.6 vs 2.8 vs 2.8 vs 2.8%), dry mouth (2.6 vs 2.8 vs 2.8 vs 10.1%), headache (2.8 vs 3.7 vs 1.8 vs 3.6%), influenza (1.6 vs 2.2 vs 2.0 vs 1.4%), UTI (1.4 vs 1.4 vs 1.8 vs 2.0%) and constipation (1.4 vs 1.6 vs 1.6 vs 2.0%).
Nitti et al[33] Mirabegron 100 mg QD vs mirabegron 50 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age, with OAB symptoms for ≥3 months and with an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period	N=1,328 12 weeks	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes/24 hours, change from baseline to end of treatment in the mean number of micturitions/24 hours Secondary: Change from baseline to end of treatment in the MVV, change from baseline to four weeks in the mean number of incontinence episodes/24 hours, change from baseline to week four in the mean number of micturitions/24 hours, change from baseline to final visit	Primary: The change from baseline to end of treatment in the mean number of incontinence episodes/24 hours was -1.63 in the mirabegron 100 mg group, -1.47 in the mirabegron 50 mg group and -1.13 in the placebo group (*P*<0.05 for both compared to placebo). The change from baseline to end of treatment in the mean number of micturitions/24 hours was -1.75 in the mirabegron 100 mg group, -1.66 in the mirabegron 50 mg group, and -1.05 in the placebo group (*P*<0.05 for both compared to placebo). Secondary: The change from baseline to end of treatment in the MVV was 18.0 mL in the mirabegron 100 mg group, 18.2 mL in the mirabegron 50 mg group and 7 mL in the placebo group (*P*<0.05 for both compared to placebo). The change from baseline to four weeks in the mean number of incontinence episodes/24 hours was -1.18 in the mirabegron 100 mg group, -1.20 in the mirabegron 50 mg group, and -0.72 in the placebo group (*P*<0.05 for both compared to placebo). The change from baseline to four weeks in the mean number of micturitions/24 hours was -1.37 in the mirabegron 100 mg group, -1.19 in the mirabegron 50 mg group and -0.77 in the placebo group (*P*<0.05 for both compared to placebo). The change from baseline to final visit in mean level of urgency was -0.21 in the mirabegron 100 mg group, -0.19 in the mirabegron 50 mg group, and -0.08 in the placebo group (*P*<0.05 for both compared to placebo). The change from baseline to final visit in mean number of urgency

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			in mean level of urgency, change from baseline to final visit in mean number of urgency incontinence episodes/24 hours, change from baseline to final visit in grade three or four urgency episodes/24 hours, change from baseline to final visit in mean number of nocturia episodes and safety	incontinence episodes/24 hours was -1.45 in the mirabegron 100 mg group, -1.32 in the mirabegron 50 mg group and -0.89 in the placebo group (*P*<0.05 for both compared to placebo). The change from baseline to final visit in grade three or four urgency episodes/24 hours was -1.76 in the mirabegron 100 mg group, -1.57 in the mirabegron 50 mg group, and -0.82 in the placebo group (*P*<0.05 for both compared to placebo). The change from baseline to final visit in mean number of nocturia episodes was -0.57 in the mirabegron 100 mg and mirabegron 50 mg groups compared to -0.38 in the placebo group (*P*<0.05 for both compared to placebo). Mirabegron was well tolerated and the incidence of adverse events was similar across all groups. Adverse events reported in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively were hypertension (6.6 vs 6.1 vs 4.9%), UTI (1.8 vs 2.7 vs 3.7), headache (2.0 vs 3.2 vs 3.0%), nasopharyngitis (2.9 vs 3.4 vs 2.5%), URI (2.6 vs 2.7 vs 2.1%), diarrhea (1.3 vs 2.3 vs 2.3%), sinusitis (2.2 vs 2.0 vs 2.1%), dry mouth (1.5 vs 0.5 vs 2.1%), constipation (1.8 vs 1.4 vs 1.6%). Serious adverse events were reported in 2.0, 2.5 and 3.2% of patients in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively. Treatment discontinuation due to adverse events was reported in 3.8, 4.1 and 4.4% of patients in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively.
Chapple et al[34] Mirabegron 100 mg QD vs mirabegron 50 mg QD vs	DB, MC, RCT Patients ≥18 years of age with OAB symptoms for ≥3 months and with an average baseline micturition frequency of ≥8 micturitions/24	N=2,444 12 months	Primary: Incidence and severity of treatment-emergent adverse events, vital signs and laboratory tests Secondary:	Primary: The incidence of treatment-emergent adverse events was similar among patients treated with mirabegron 50 mg (59.7%), 100 mg (61.3%) or tolterodine ER (62.6%). Most events were categorized as mild or moderate in severity. The most frequent treatment-related adverse events included hypertension, dry mouth, constipation, and headache, occurring at a similar incidence across all treatment groups, except for dry mouth, which was highest in the tolterodine group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tolterodine ER 4 mg QD	hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period		Change from baseline in micturition frequency and urgency frequency at one, three, six, nine and 12 months; OAB-q, PPBC and VAS scores, proportion of treatment responders (≥50% decrease from baseline in the incontinence episodes/24 hours or those with zero incontinence episodes at final visit)	Discontinuations resulting from adverse events were similar between treatment groups, with 6.4, 5.9 and 6.0% of patients treated with mirabegron 50 mg, 100 mg and tolterodine ER 4 mg, discontinuing treatment, respectively. Urinary retention occurred in one patient each in the mirabegron 50 mg and 100 mg group compared to three patients treated with tolterodine ER. Urinary retention requiring catheterization was reported in one patient receiving mirabegron 100 mg and tolterodine ER. There was a higher incidence of cardiac arrhythmias with tolterodine ER 4 mg (6.0%) compared to mirabegron 50 mg (3.9%) and 100 mg (4.1%). Mean changes from baseline in systolic blood pressure with mirabegron 50 mg, 100 mg and tolterodine were 0.2, 0.4 and -0.5 mm Hg for morning measurements and -0.3, 0.1 and 0.0 mm Hg for evening measurements, respectively. The mean changes in diastolic blood pressure were -0.3, 0.4, and 0.1 mm Hg, respectively for morning measurements and 0.0, 0.1 and 0.6 mm Hg, respectively for evening measurements. There was a higher incidence of neoplasm (benign, malignant and unspecified including cysts and polyps) in the mirabegron 100 mg group (1.3%) compared to the 50 mg group (0.1%) and tolterodine ER 4 mg (0.5%). Secondary: There were similar improvements between treatments with regard to the mean number of micturitions/24 hours (-1.27 for mirabegron 50 mg, -1.41 for mirabegron 100 mg and -1.39 for tolterodine ER 4 mg; *P* values not reported). Improvements in the mean number of incontinence episodes/24 hours (-1.01 for mirabegron 50 mg, -1.24 for mirabegron 100 mg and -1.26 for tolterodine ER 4 mg) and MVV (17.5 mL for mirabegron 50mg, 21.5 mL for mirabegron 100 mg and 18.1 mL for tolterodine ER 4 mg) were similar among treatment groups (*P* values not reported). At the final visit, the proportion of treatment responders (≥50% reduction

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				from baseline in the mean number of incontinence episodes/24 hours was 63.7, 66.3 and 66.8% for patients treated with mirabegron 50 mg, 100 mg and tolterodine ER, respectively; *P* values not reported). The proportion of patients who reported zero incontinence episodes at the final visit was 43.4, 45.8 and 45.1%, respectively; *P* values not reported). Both doses of mirabegron showed numerical improvements on the other secondary efficacy variables including OAB-q symptom bother and QOL, treatment satisfaction, number of nocturia episodes and PPBC.
Burgio et al[35] Oxybutynin XL 5 mg to 30 mg QD vs behavioral treatment consisting of pelvic floor muscle training, delayed voiding, monitoring with bladder diaries and urge suppression techniques	DB, MC, RCT Male veterans with OAB, manifested by urgency and frequent urination with or without urge incontinence as well as ≥8 urinary voids daily	N=143 8 weeks	Primary: 24-hour posttreatment voiding frequency (nocturia, urgency and incontinence) Secondary: GPI, PSQ, ratings of activity restriction, adverse events and satisfaction with treatment	Primary: Patients randomized to receive behavioral therapy experienced a mean reduction of 2.2 daily voids (-18.8%), while patients receiving oxybutynin XL had 2.09 (-16.9%) fewer daily voids compared to baseline values (*P*<0.001 for both). An equivalence analysis indicated that the posttreatment voiding frequencies between the treatment groups were equivalent (*P*=0.006). Following treatment, a greater reduction in nocturia frequency was achieved in the behavioral group compared to the oxybutynin XL group (-0.70 vs -0.32; *P*=0.05). Oxybutynin XL was associated with significantly lower mean urgency scores compared to behavioral therapy (*P*=0.007). Greater reductions in urgency scores and lower maximum scores for urgency were reported in the oxybutynin XL group compared to the behavior therapy group (*P*=0.04 and *P*=0.02, respectively). Incontinence episodes were reduced by 88.2% with behavioral therapy compared to 75.2% in patients randomized to oxybutynin treatment; however, the difference was not statistically significant (*P*=0.33). Secondary: There was no significant difference between oxybutynin XL treatment and behavioral therapy with regard to the percentage of patients reporting symptomatic improvement as “much better” or “better” (86.4 vs 84.1%,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				respectively; *P*=0.69). Similarly, there was no difference between oxybutynin XL and behavioral therapy with regard to patients who were "completely" satisfied with treatment (42.4 vs 56.5%, respectively; *P*=0.16). No differences were reported between the treatment groups with regard to GPI (*P*=0.56). At week eight, significantly fewer men who completed behavioral treatment reported bothersome adverse events compared to oxybutynin XL (12.6 vs 28.8%, *P*=0.01) and fewer wished to receive another form of therapy (29 vs 50%; *P*=0.02).
Staskin et al[36] Oxybutynin topical gel 1 g applied QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with OAB, urge or mixed urinary incontinence with predominance of UUI episodes as well as ≥8 daily urinary voids and ≥4 daily UUI episodes	N=789 12 weeks	Primary: Change in mean number of daily incontinence episodes Secondary: Mean change in urinary frequency, urinary volume per void, number of nocturia episodes, proportion of patients achieving complete urinary continence and safety	Primary: Patients receiving oxybutynin topical gel reported a significantly greater decrease in the mean number of daily incontinence episodes compared to patients receiving placebo (-3.0 vs -2.5; *P*<0.0001). Secondary: Oxybutynin topical gel was associated with a significant improvement in the mean number of episodes of urinary frequency (-2.7 vs -2.0; *P*=0.0017) and voided urinary volume compared to placebo (21.0 vs 3.8 mL; *P*=0.0018). The difference between groups in the number of nocturia episodes did not reach statistical significance (-0.75 daily for oxybutynin topical gel compared to -0.65 daily for placebo; *P*=0.1372). Complete urinary continence was demonstrated in 27.8% patients receiving oxybutynin topical gel patients compared to 17.3% of patients randomized to placebo (*P* value not reported). Compared to placebo, oxybutynin topical gel was associated with a higher incidence of dry mouth (6.9 vs 2.8%; *P*=0.0060) and application site dermatitis (1.8 vs 0.3%; *P*=0.0358).
Dmochowski et al[37] Oxybutynin transdermal patch applied twice weekly	DB, RCT Patients ≥18 years of age with OAB and ≥4 UUI episodes, with	N=361 12 weeks	Primary: Change in the number of daily urinary incontinence episodes,	Primary: The oxybutynin transdermal patch was associated with a statistically significant reduction in the number of daily urinary incontinence episodes compared to placebo (75 vs 50%; *P*=0.0137).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs tolterodine LA 4 mg QD vs placebo	either pure urge or a predominance of urge episodes, ≥24 voids, and an average urinary void volume ≤350 mL		proportion of patients achieving complete continence, frequency of daily micturitions, MVV/void, QOL and adverse events Secondary: Not reported	Tolterodine LA was associated with a statistically significant reduction in the number of daily urinary incontinence episodes from baseline compared to placebo (75 vs 50%; *P*=0.0011). Patients randomized to receive the oxybutynin transdermal patch experienced comparable reductions from baseline in the number of daily urinary incontinence episodes compared to tolterodine LA (*P*=0.216). A greater proportion of patients randomized to the oxybutynin transdermal patch or tolterodine LA experienced complete continence compared to placebo (39 and 38 vs 22%; *P*=0.014). Both treatment groups experienced comparable reductions from baseline in the daily frequency of micturitions (*P*=0.276). Both treatment groups experienced comparable improvements from baseline in MVV/void (*P*=0.769) and when compared to placebo (*P*<0.01). More treatment-related adverse events occurred with tolterodine LA compared to the oxybutynin transdermal patch (*P* value not reported). The most common treatment-related adverse events with the oxybutynin transdermal patch were application site reactions, including erythema and pruritus. Anticholinergic adverse events were the most common treatment-related adverse events reported in association with tolterodine LA therapy. Secondary: Not reported
Chapple et al[38] Solifenacin 5 mg QD vs	DB, MC, RCT Patients ≥18 years of age with symptoms of OAB for ≥3 months, ≥8 daily voids and ≥3	N=1,033 12 weeks	Primary: Change in the number of urgency episodes and all incontinence and UUI episodes	Primary: Patients in the solifenacin 5 mg and 10 mg groups experienced statistically significant reductions in the mean number of urgency episodes/24 hours compared to placebo (52 and 55 vs 33%, respectively; *P*<0.001). While tolterodine IR was also associated with a reduction in the mean number of urgency episodes/24 hours, the change was not statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
solifenacin 10 mg QD vs tolterodine IR 2 mg BID vs placebo	daily urgency or incontinence episodes during three-day voiding diary period		Secondary: Change in the mean number of voids/24 hours, MVV/void and adverse events	compared to placebo (38 vs 33%; *P*=0.0511). Patients randomized to receive solifenacin 5 mg or 10 mg experienced statistically significant reductions in the number of UUI episodes/24 hours compared to placebo (65 and 63 vs 40%, respectively; *P*<0.01). While tolterodine IR therapy was also associated with reduction in the number of UUI episodes/24 hours, the change was not statistically significant compared to placebo (58 vs 40%; *P*=0.239). Treatment with solifenacin 5 and 10 mg was associated with a statistically significant reduction in the number of incontinence episodes/24 hours compared to placebo (59 and 47 vs 29%, respectively; *P*<0.01). While tolterodine IR therapy also reduced the number of incontinence episodes/24 hours, the change was not significant compared to placebo (59 vs 29%; *P*=0.112). Secondary: Patients receiving solifenacin 5 mg, 10 mg and tolterodine IR experienced statistically significant reductions in the mean number of voids/24 hours compared to placebo (17, 20 and 15 vs 8%, respectively; *P*<0.05 for all). Statistically significant reductions in the MVV/void occurred with solifenacin 5 mg, 10 mg and tolterodine IR compared to placebo (25, 29 and 20 vs 9%, respectively; *P*<0.001). Discontinuation rates due to adverse events were comparable with solifenacin 5 mg, 10 mg tolterodine IR and placebo groups (3.2, 2.6 and 1.9 vs 3.7%; *P* values not reported). The incidence of dry mouth was lowest in the solifenacin 5 mg group and highest with solifenacin 10 mg (14.0 vs 21.3%; *P* value not reported). The incidence of constipation was lowest in the tolterodine IR group and highest with solifenacin 10 mg (2.6 vs 7.8%; *P* value not reported). The incidence of blurred vision was lowest in the tolterodine IR group and highest with solifenacin 10 mg (1.5 vs 5.6%; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dmochowski et al[39] Trospium XR 60 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with OAB for ≥6 months with symptoms of urinary frequency, urgency and UUI	N=564 12 weeks	Primary: Change in the number of daily toilet voids and the number of UUI episodes Secondary: Urgency severity, MVV/void, dry rate (no UUI episodes during the diary collection period), responder rate (≤8 toilet voids/day and no UUI episodes) and adverse events	Primary: Treatment with trospium XR resulted in a significant reduction from baseline in the mean number of daily toilet voids compared to placebo (19.3 vs 13.1%; *P*<0.05). Patients treated with trospium XR experienced a statistically significant reduction from baseline in daily UUI episodes compared to patients treated with placebo (58.9 vs 37.1%; *P*<0.001). Secondary: Treatment with trospium XR resulted in a significant reduction from baseline in the mean urgency severity associated with toilet voids compared to placebo (*P*<0.001). Treatment with trospium XR resulted in a significant increase in the MVV/void from baseline compared to placebo (*P*<0.01). A significantly greater proportion of patients treated to trospium XR were "dry" during the diary collection period compared to patients treated with placebo (*P*<0.05). A significantly greater proportion of patients treated with trospium XR responded to therapy compared to patients treated with placebo (*P*<0.05). Treatment-related adverse events occurred in 55% of trospium XR-treated patients and 45.8% of patients receiving placebo. Dry mouth occurred in 12.9% of subjects treated with trospium XR compared to 4.6% of those receiving placebo. Constipation occurred in 7.5% of those given trospium XR compared to 1.8% in the placebo group.
Staskin et al[40] Trospium XR 60 mg QD vs	DB, OL, RCT Patients ≥18 years of age with symptoms of OAB for ≥6 months	N=601 12 weeks; 9 months OL phase	Primary: Calculated changes in daily urinary frequency and daily UUI episodes	Primary: Treatment with trospium XR resulted in a significant improvement in daily urinary frequency compared to placebo (*P*<0.01). Treatment with trospium XR resulted in a significant reduction in daily UUI episodes compared to placebo at week 12 (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			Secondary: Normalization rate (defined as no UUI episodes and a daily void frequency ≤8), urgency severity, volume voided/void, the number of daily urgency voids and adverse events	Subjects treated with trospium XR experienced an average decrease in daily voids from 12.8 at baseline to fewer than 10.0 at week 12 (*P*<0.001). Participants treated with trospium XR experienced an average decrease in daily UUI episodes from 4.1 at baseline to 1.6 at week 12 (*P*<0.01). Secondary: Twice as many subjects treated with trospium XR achieved normalization at week 12 compared to those given placebo (20.5 vs 11.3%; *P*<0.01) Treatment with trospium XR resulted in a significant improvement in daily urgency severity, volume voided/void and the number of daily urgency voids compared to placebo at week 12 (*P*<0.01). Dry mouth occurred in 8.7% of subjects treated with trospium XR compared to 3.0% of patients treated with placebo. Constipation occurred in 9.4% of patients receiving trospium XR compared to 1.3% of the placebo group. Central nervous system effects, such as headache, occurred in 1.0% of those given trospium XR compared to 2.6% of patients treated with placebo.
MacDiarmid et al[41] Trospium XR 60 mg QD vs placebo	DB, MC, PC, PG, RCT, SA SA of two previous studies (Dmochowski et al[39] or Staskin et al[40]) of male patient's ≥18 years of age with OAB for ≥6 months who experienced ≥30 voids in three days, ≥1 severe urgency rating in three days and ≥3 UUI episodes	N=176 12 weeks	Primary: Daily number of toilet voids and UUI episodes Secondary: Number of daytime and nocturnal toilet voids, daily urgency severity associated with toilet voids, daily urgency frequency associated with	Primary: In patients treated with trospium XR there was a significantly greater decrease in the mean number of daily toilet voids (-2.5 vs -1.5; *P*<0.05) and daily UUI episodes (-2.3 vs -1.4; *P*<0.05) compared to placebo. Secondary: Significantly greater reductions from baseline occurred with trospium XR compared to placebo with regard to both daytime (-1.7 vs -1.1; *P*<0.05) and nocturnal voids (-0.9 vs -0.5; *P*<0.05). There was no difference in daily urgency severity associated with toilet voids between trospium XR and placebo (*P*=0.22). A significant reduction in daily urgency frequency associated with toilet

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	in three days		toilet voids, MVV/void and OAB-SCS	voids was reported in patients treated with trospium XR compared to placebo (*P*=0.007). Trospium XR significantly increased the MVV compared to placebo (18.6 vs 1.0 mL; *P*=0.036). Improvements in OAB-SCS were significantly greater for patients randomized to receive trospium XR compared to patients in receiving placebo (-10.4 vs -6.3; *P*=0.010).
Sand et al[42] Trospium XR 60 mg QD vs placebo	DB, MC, OL, PC, PG, RCT, SA SA of two previous studies (Dmochowski et al, 2008 and Staskin et al, 2007) of patients ≥75 years of age with OAB for ≥6 months who experienced ≥30 voids in three days, ≥1 severe urgency rating in three days and ≥3 UUI episodes in three days	N=143 21 weeks (12 weeks DB, 9 weeks OL)	Primary: Change in the number of daily toilet voids and daily frequency of UUI episodes at 12 weeks Secondary: Urgency severity associated with toilet voids, MVV/void, frequency of nocturnal toilet voids and frequency of toilet voids associated with urgency, QOL measures, safety and tolerability	Primary: At 12 weeks, trospium XR was associated with significantly greater reductions in the mean number of daily toilet voids compared to placebo (-2.15 vs -0.37; *P*=0.0008). The number of UUI episodes was also significantly reduced for patients randomized to receive trospium XR compared to placebo (-1.77 vs -0.54; *P*=0.003). Secondary: The change from baseline in average urgency severity associated with toilet voids did not differ significantly between the trospium XR and placebo treatment groups (-0.28 vs -0.20, respectively; *P*=0.33). A significantly greater increase in the MVV/void was achieved with trospium XR treatment compared to treatment with placebo (30.73 vs 3.10 mL; *P*=0.001). Compared to placebo, trospium XR significantly improved the mean number of nocturnal toilet voids (those occurring from bedtime to arising) over 12 weeks of treatment (-0.76 vs -0.08; *P*<0.01). In patients ≥75 years of age, trospium XR was associated with a significant improvement in the frequency of voids associated with urgency compared to patients randomized to receive placebo (-2.53 vs -0.61; *P*=0.004).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A higher proportion of subjects receiving trospium XR considered their outcome to be "very much" or "much" improved on the OAB-PGA scale compared to those receiving placebo, with regard to frequency of toilet voids (38.3 vs 22.4%; *P*=0.004), accidental urge leaks (37.0 vs 24.1%; *P*=0.032), urge to urinate (38.3 vs 19.0%; *P*=0.012) and overall OAB condition (42.0 vs 25.9% *P*=0.027). Improvements in KHQ scores at week 12 were numerically greater for patients receiving trospium XR compared to placebo on most domains, although the difference was only significant for the average change in severity measures. Increases from baseline in OAB-q scores were numerically greater in the trospium XR group compared to placebo on all subscales, and the difference between the groups was significant for the concern/worry subscale (*P*=0.02). Significantly greater improvements were achieved with trospium XR on most items of the symptom-bother scale, including frequent urination during daytime hours, night-time urination and urine loss associated with a strong desire to urinate (*P*<0.05 for all). The most commonly reported adverse events considered treatment-related included dry mouth and constipation. During the treatment period, nine and 22 patients in the placebo and trospium XR groups, respectively, experienced a treatment-related adverse event. No central nervous system adverse events were reported. There was no change in laboratory outcomes between the trospium XR and placebo treatment groups.
Chapple et al[43] (Cohort 1): Oxybutynin IR 2.5 mg TID vs darifenacin IR 2.5 mg	DB, DD, RCT, XO Patients 18 to 75 years of age with detrusor overactivity for ≤6 months idiopathic or neurogenic (secondary to a	N=65 21 days	Primary: Ambulatory urodynamics, responder rate (patients achieving 25 to 30% improvement), salivary flow and adverse events	Primary: All treatment groups experienced a significant improvement in urodynamic pressure parameters (*P* value not reported). There was no statistically significant difference between groups in the percentage of patients responding to therapy (*P* value not reported). Oxybutynin IR treatment groups experienced a greater decrease in salivary flow compared to patients receiving darifenacin ER 15 daily (*P*<0.001) or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
TID (Cohort 2): oxybutynin IR 5 mg TID vs darifenacin ER 15 mg QD (Cohort 3): oxybutynin IR 5 mg TID vs darifenacin ER 30 mg QD	neurological lesion present for ≥12 months), with ≥2 associated symptoms (average of ≥7 micturitions/day, ≥7 episodes of urgency/week, ≥1 UUI episode/week necessitating change of clothing or pads)		Secondary: Not reported	darifenacin ER 30 mg therapy (*P* value not reported). Patients receiving oxybutynin IR reported dry mouth more frequently than patients did on darifenacin therapy (*P* value not reported). In contrast, constipation was reported more often by patients taking darifenacin therapy. Secondary: Not reported
Zinner et al[44] Darifenacin 7.5 to 15 mg QD	OL, MC Patients ≥18 years of age with OAB symptoms for ≥6 months with a baseline score of ≥2 on the PPBC questionnaire and received ≥1 week of treatment with oxybutynin ER or tolterodine LA within the previous year	N=500 12 weeks	Primary: Change from baseline in PPBC, micturition frequency, urgency, UUI, tolerability and safety Secondary: Not reported	Primary: In patients dissatisfied with previous OAB treatment, darifenacin significantly reduced PPBC scores from baseline over 12 weeks (-1.4; *P*<0.0001). Improvements in PPBC scores were similar regardless of previous OAB therapy or whether patients were receiving treatment at baseline. Improvements in PPBC scores were observed as early as week six of treatment (*P*<0.0001). Treatment with darifenacin resulted in statistically significant improvements in micturition frequency, urgency episodes and UUI episodes compared to baseline, in both the overall study population and after stratification by prior treatment (*P*<0.0001 for all). The micturition frequency was reduced by 19.5% compared to baseline with darifenacin treatment (*P*<0.0001). Similarly, urgency episodes were reduced by 61.6% with treatment compared to placebo. Patients previously treated with tolterodine LA experienced greater reductions in urgency episodes compared to patients previously receiving oxybutynin XL (-3.2 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				-2.8; *P*=0.0296). The mean number of UUI episodes/week was decreased by 10.8 at week 12 compared to baseline (*P*<0.0001). Darifenacin was associated with significantly greater decreases in UUI episodes/week among patients previously treated with tolterodine LA compared to previous treatment with oxybutynin XL (-11.5 vs -9.9; *P*<0.0001). The most commonly reported adverse events occurring with darifenacin treatment were dry mouth (20.1%) and constipation (14.1%). Both were reported less frequently in patients who previously received oxybutynin XL (16.1 and 11.0%, respectively) compared to tolterodine LA (23.3 and 16.5%, respectively). Discontinuation due to adverse events occurred in 4.6% and 4.3% of patients previously treated with oxybutynin XL or tolterodine LA. No deaths were reported during the study and no changes in laboratory parameters or vital signs occurred. Secondary: Not reported
Wyndaele et al[45] Fesoterodine 4 mg QD vs fesoterodine 8 mg QD Patients started on 4 mg of fesoterodine had an opportunity to increase to 8 mg after four weeks of treatment.	FD, MC, OL, SA Men and women ≥18 years old with ≥3 months of OAB symptoms	N=516 12 weeks	Primary: Mean change from baseline in number of micturitions, UUI episodes, urgency episodes/24 hours and number of subjects reporting treatment response of “very satisfied” or “somewhat satisfied” Secondary: Change form baseline in	Primary: Patients experienced significant decreases from baseline in all primary endpoints including mean number of micturitions/24 hours (-3.0), UUI episodes/24 hours (-1.7) and urgency episodes/24 hours (-5.0; *P*<0.001 for all). Approximately 80% of the subjects responded with a response of “very satisfied” or “somewhat satisfied” on the treatment questionnaire. Secondary: Patients experienced a decrease from baseline of all secondary endpoints including mean number of nocturnal micturitions/24 hours (-8.0), and severe micturition-related urgency episodes/24 hours (-0.8; *P*<0.001 for all). The most commonly reported adverse events included dry mouth (23%)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			nocturnal micturitions, severe micturition-related urgency episodes, frequency-urgency sum/24 hours and adverse events	and constipation (5%). Only two cases of serous urinary retention were reported. Fifty-three percent of patients opted to increase the dose of fesoterodine from 4 mg to 8 mg at four weeks.
Herschorn et al[46] Fesoterodine 8 mg QD vs tolterodine LA 4 mg QD vs placebo	DB, DD, MC, PC, RCT Patients ≥18 of age with symptoms of OAB for ≥3 months and ≥1 UUI episode/24 hours and ≥8 voids/24 hours reported in a three day bladder diary	N=1,712 12 weeks	Primary: Change from baseline in UUI episodes/24 hours Secondary: MVV/void, voids, nocturnal voids, urgency episodes, frequency-urgency sum, PPBC, UPS and OAB-q scores	Primary: The mean reduction in UUI episodes/24 hours was significantly reduced with fesoterodine treatment compared to tolterodine LA and placebo (-1.72 vs -1.61 and-1.46, respectively; *P*<0.05 for both comparisons). The improvement with tolterodine LA compared to placebo was also statistically significant. Secondary: Patients receiving treatment with fesoterodine experienced significantly greater increases in MVV/void compared to patients in the tolterodine LA and placebo groups (32.9 vs 23.5 and 16.8 mL, respectively; *P*<0.05 for both comparisons). The difference in mean void volume between tolterodine LA and placebo was not statistically significant (*P*=0.103). No difference in voids/24 hours was reported between fesoterodine and tolterodine LA (-2.2 vs -2.1; *P* value not reported); however, both treatments were significantly more effective compared to placebo (*P*<0.05 for both comparisons). There was no improvement in nocturnal voids for patients who received fesoterodine (*P*=0.327) or tolterodine LA (*P*=0.506) compared to those who received placebo. Both fesoterodine and tolterodine LA reduced urgency episodes/24 hours compared to placebo (-3.5 and -3.1 vs -2.0, respectively; *P*<0.05 for both); however, there was no difference between fesoterodine and tolterodine LA (*P*=0.054).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The frequency-urgency sum (all voids over 24 hours) was numerically lower with fesoterodine compared to tolterodine LA; however, the difference was not significant (-13.2 vs -12.1; *P*=0.105). Treatment with either agent was associated with significant improvements in frequency-urgency sum compared to placebo (*P*<0.05 for both comparisons). The change in PPBC scores from baseline showed a significantly greater improvement in the fesoterodine group compared to the tolterodine LA and placebo groups (*P*<0.001 for both comparisons). Changes between tolterodine LA and placebo were also significant (*P*<0.001). The proportion of patients reporting only "some minor problems" or better on the PPBC at week 12 was higher with fesoterodine compared to tolterodine LA and placebo (55 vs 45 and 33%, respectively; *P*<0.001 for both comparisons). The improvement observed in the tolterodine LA group was also statistically significant compared to placebo (*P*<0.001). Significant improvements on the UPS scale were reported for patients with fesoterodine compared to tolterodine LA and placebo (*P*<0.05). The percentage of patients who reported 'I am usually able to finish what I am doing before going to the toilet (without leaking)' at week 12 was higher in the fesoterodine group (31%) compared to tolterodine LA (23%; *P*=0.002) and placebo (15%; *P*=0.001). The difference between the tolterodine LA and placebo groups was also significant (*P*=0.003). In a post-hoc analysis, significant improvements on the OAB-q questionnaire occurred with fesoterodine compared to tolterodine LA with regard to symptom bother (*P*<0.001), concern (*P*=0.008), coping (*P*=0.002) and social interaction (*P*=0.019).
Kaplan et al[47] Fesoterodine 8 mg QD vs tolterodine LA 4 mg QD	DB, DD, MC, PC, PG, RCT Patients ≥18 years of age with OAB symptoms for ≥3 months, ≥1 UUI	N=2,411 12 weeks	Primary: Change from baseline in UUI episodes Secondary: Change from	Primary: The median percentage reduction in UUI episodes at week 12 was 100% in all three treatment groups. The percent reduction in UUI episodes was significantly greater with fesoterodine compared to tolterodine LA (*P*=0.0093), and placebo (*P*=0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	episode and ≥8 micturitions/24 hours in a three-day bladder diary		baseline in 24-hour micturitions, nocturnal micturitions, urgency episodes, severe urgency episodes, frequency-urgency sum, three-day diary-dry rate, and MVV/void	Patients randomized to the fesoterodine treatment group experienced a greater reduction in micturition frequency compared to tolterodine LA and placebo (-23.5 vs -20.8 and -19.2%, respectively; *P*<0.05 for all comparisons). In addition, greater improvements in micturition frequency occurred with tolterodine LA compared to placebo (*P*<0.05). Nocturnal micturition frequency was significantly improved with fesoterodine compared to placebo (-33 vs -27.3%; *P*<0.05), but not compared to tolterodine LA (-33.3 vs -33.3%; *P*=0.1661). Treatment with fesoterodine significantly improved urgency episodes/24 hours compared to tolterodine LA and placebo (-45.5 vs -37.5 and -31.0%, respectively; *P*<0.05 for both). Urgency episodes were not significantly improved with tolterodine LA compared to placebo (*P*<0.05). A significant reduction in severe urgency episodes/24 hours occurred with fesoterodine compared to tolterodine LA and placebo (-79.3 vs -69.2 and -61.0%; *P*<0.05). There was no statistically significant difference between tolterodine LA and placebo (*P*>0.05). Treatment with fesoterodine significantly reduced the mean frequency-urgency sum from baseline to week 12 compared to treatment with both tolterodine LA and placebo (*P*<0.05 for both). No significant differences were reported between tolterodine LA and placebo. Treatment with fesoterodine and tolterodine LA significantly increased diary dry-rates compared to placebo (*P*<0.05 for both). Moreover, patients randomized to fesoterodine achieved higher diary dry-rates compared to those randomized to tolterodine LA (*P*<0.05). No significant differences were reported between fesoterodine and tolterodine LA with regard to the MVV/void; however, both treatment groups experienced statistically significant improvements relative to placebo (*P*<0.05 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Anderson et al[48] Oxybutynin XL 5 mg to 30 mg QD vs oxybutynin IR 5 mg QD to QID	AC, DB, MC, PG, RCT Patients 34 to 76 years of age with urge incontinence or mixed incontinence with a primary urge component, ≥6 urge incontinence episodes weekly and previously responsive to oxybutynin therapy	N=105 Duration not specified	Primary: Change in the number of weekly UUI episodes Secondary: Proportion of patients achieving resolution of UUI episodes, number of incontinence episodes, proportion of those patients achieving continence, total void frequency and adverse events	Primary: The number of weekly UUI episodes decreased from 27.4 to 4.8 with oxybutynin XL and from 23.4 to 3.1 with oxybutynin IR therapy (*P*=0.56). Secondary: Fifty-two percent of patients randomized to oxybutynin XL and 51% of patients randomized to oxybutynin IR experienced resolution of urge incontinence (*P*=0.70). The total number of incontinence episodes decreased from 29.3 to 6.0 with oxybutynin XL treatment and from 26.3 to 3.8 with oxybutynin IR treatment (*P*=0.6). Continence was achieved in 41% of the oxybutynin XL group and 40% of the oxybutynin IR group (*P*=0.90). Normal void frequency was increased by 54% in the oxybutynin XL treatment group compared to 17% in the oxybutynin IR group (*P*<0.001). Dry mouth of any severity was reported by 68% of patients receiving oxybutynin XL and 87% of the oxybutynin IR group (*P*=0.04). Moderate or severe dry mouth occurred in 25% and 46% of patients, respectively (*P*=0.03). Both regimens were associated with comparable incidences of somnolence, blurred vision, constipation, dizziness, impaired urination, nervousness and nausea (*P*>0.05).
Barkin et al[49] Oxybutynin XL 15 mg QD vs oxybutynin IR 5 mg TID Patients in either	AC, DB, MC, RCT Patients ≥18 years of age with UUI	N=125 9 weeks	Primary: Change in the number of weekly incontinence episodes, voluntary micturitions, volume of urine voided/void, frequency and severity of urgency and adverse events	Primary: There was no statistically significant difference between the two treatment groups in the number of incontinence episodes weekly (*P*=0.404), voluntary micturitions (*P*=0.286), volume of urine voided/void (*P*=0.533), frequency of urgency (*P*=0.116) or severity of urgency (*P*=0.255). Both oxybutynin XL and IR treatment groups exhibited statistically significant improvements from baseline in the number of mean weekly incontinence episodes, voluntary micturition, frequency and severity of urgency (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treatment arm could titrate the dose by 5 mg in weekly increments to patient response and tolerability.			Secondary: Not reported	Dry mouth was reported by 68% of patients receiving oxybutynin XL and 72% of the oxybutynin IR group (*P* value not reported). Headache was reported by 12% of patients receiving oxybutynin XL compared to 22% of patients receiving oxybutynin IR (*P* value not reported). Secondary: Not reported
Versi et al[50] Oxybutynin XL 5 mg QD vs oxybutynin IR 5 mg QD The dose could be titrated up in 5 mg increments weekly to a maximum of 20 mg QD.	DB, MC, PG, RCT Patients 59.2 years of age on average, with 7 to 45 UUI episodes weekly, ≥4 days of incontinence/ week and prior response to an antimuscarinic agent	N=226 ≤7 weeks	Primary: Change in the number of weekly incontinence episodes, proportion of patients reporting the absence of urge incontinence and adverse events Secondary: Not reported	Primary: Both oxybutynin XL and IR regimens were associated with significant weekly reductions from baseline in UUI episodes (83 vs 76%; *P*=0.36). At equal doses, comparable proportions of patients in both treatment groups reported the absence of urge incontinence (*P*=0.85). The incidence of dry mouth increased as the dose increased in both groups. There was no difference in the rate of dry mouth between the oxybutynin XL and IR groups (47.7 vs 59.1%; *P*=0.09). Secondary: Not reported
Davila et al[51] Oxybutynin transdermal patch, two to four patches applied twice weekly vs oxybutynin IR 2.5 mg, two capsules administered BID to TID	DB, MC, RCT Patients ≥18 years of age with a history of urge or mixed urinary incontinence with a predominance of urge symptoms, >3 UUI episodes	N=76 6 weeks	Primary: Change in the number of daily incontinence episodes, and adverse events Secondary: Not reported	Primary: Both the oxybutynin transdermal patch and oral IR formulations were associated with statistically significant reductions in the number of daily incontinence episodes from baseline (66 vs 72%; *P*<0.0001). There was no statistically significant difference between the treatment groups (*P*=0.90). Dry mouth occurred more frequently in the oral oxybutynin IR group compared to patients treated with the oxybutynin transdermal patch (94 vs 38%; *P*<0.001). Of patients randomized to the oxybutynin transdermal patch, 67% reported a reduction in dry mouth severity compared to previous oral therapy. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Herschorn et al[52] Oxybutynin IR 5 mg TID vs solifenacin 5 mg QD	DB, DD, MC, RCT Patients ≥18 years of age with OAB symptoms (≥1 urgency episode/24 hours and ≥8 micturitions/24 hours)	N=132 8 weeks	Primary: Incidence and severity of dry mouth and treatment-emergent adverse events Secondary: Changes in urgency, incontinence, frequency, nocturia and MVV/void	Primary: Significantly fewer patients randomized to receive solifenacin experienced dry mouth compared to oxybutynin IR (35 vs 83%; *P*<0.0001). In patients treated with solifenacin who experienced dry mouth, the severity was significantly lower compared to the patients treated with oxybutynin IR (*P*=0.001). The incidence of dry mouth occurred within two weeks in 96% of oxybutynin IR-treated patients compared to 75% of patients receiving solifenacin. Discontinuation rates were not significantly different between the treatment groups (*P*=0.081). Overall, significantly fewer solifenacin patients compared to oxybutynin IR patients experienced one or more adverse events during the study (72 vs 92%; *P*=0.003). In addition, more adverse events with solifenacin compared to oxybutynin IR were rated as mild or moderate (84 vs 70%; *P*=0.009). Secondary: Patients in both treatment groups experienced improved bladder urgency, incontinence, frequency, nocturia and MVV/void from baseline (*P* value s not reported). Both solifenacin and oxybutynin IR significantly improved patient reported outcomes on questionnaires for PPBC and OAB symptoms with no differences between groups (*P* values not reported).
Mallone-Lee et al[53] Oxybutynin IR 2.5 mg to 5 mg BID vs tolterodine IR 2 mg BID	DB, MC, PG, RCT Patients ≥50 years of age, with symptoms of urinary frequency with urgency, and/or UUI episodes	N=378 10 weeks	Primary: Adverse events Secondary: Voids/24 hours, UUI episodes/24 hours, MVV/void, pads used in 24 hours	Primary: Oxybutynin IR treatment was associated with a greater incidence of adverse events compared to tolterodine IR treatment (81 vs 69%; *P*=0.01). Oxybutynin IR treatment was associated with a greater incidence of dry mouth compared to tolterodine IR treatment (61 vs 37%; *P*=0.01). Significantly more patients in the oxybutynin IR group experienced severe

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				adverse events compared to the tolterodine IR group (28 vs 13%; *P*=0.0004). Secondary: At 10 weeks, both treatment groups were associated with comparable improvements from baseline in the number of daily voids (*P*=0.97). At 10 weeks, both treatment groups were associated with comparable improvements from baseline in the number of daily UUI episodes (*P*=0.065). At 10 weeks, both treatment groups were associated with comparable improvements from baseline in the volume voided/void (*P*=0.90). At 10 weeks, both treatment groups were associated with comparable improvements from baseline in the number of pads used daily (*P*=0.43). There was no difference in the time to onset of action between the treatment groups (*P* value not reported). The maximal treatment effect on UUI episodes and MMV/void was achieved within four weeks in both treatment groups. The maximal effect on voiding frequency occurred within four to 10 weeks in each treatment group.
Harvey et al[54] Oxybutynin IR 2.5 mg to 5 mg TID vs tolterodine IR 1 mg to 2 mg BID	MA of 4 studies Patients ≥18 years of age with UUI or frequency (>8 times daily), and urgency or diagnosed with detrusor instability	N=not specified Duration not specified	Primary: Change in the number of incontinence episodes/24 hours, number of daily micturitions, and MVV/void Secondary: Adverse events	Primary: Oxybutynin IR was associated with a statistically significant reduction from baseline in the number of incontinence episodes/24 hours compared to tolterodine IR (WMD, 0.41; 95% CI, 0.04 to 0.77). There was no statistically significant difference between the two regimens in the reduction of micturition frequency from baseline (WMD, 0.0; 95% CI, -0.38 to 0.38). Oxybutynin IR was associated with a statistically significant increase from baseline in the MVV/void compared to tolterodine IR (WMD, 8.24; 95% CI, 2.38 to 14.11).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Tolterodine IR treatment was associated with a statistically significant reduction in the risk of dry mouth compared to oxybutynin IR (RR, 0.54; 95% CI, 0.48 to 0.61). Tolterodine IR therapy was associated with a statistically significant reduction in the risk of withdrawing from the study secondary to adverse events compared to oxybutynin IR therapy (RR, 0.63; 95% CI, 0.46 to 0.88).
Kilic et al[55] Oxybutynin IR 0.4 mg/kg, divided TID vs tolterodine IR 1 mg BID; patients <5 years of age received 0.1 mg/kg daily, divided BID	RCT Children, 3 to 13 years of age with evidence of detrusor instability	N=60 6 months	Primary: Change in bladder capacity, bladder compliance, and detrusor pressure Secondary: Not reported	Primary: Patients treated with oxybutynin IR experienced significant improvements in bladder capacity, bladder compliance and depressor pressure from baseline (P<0.001). Tolterodine IR therapy was associated with a significant improvement in bladder capacity, bladder compliance, and detrusor pressure from baseline (P<0.001). There were no significant differences between treatment groups with regard to the change from baseline in bladder capacity or bladder compliance (P value not reported). There were no significant differences between treatment groups in the recovery from detrusor instability (P value not reported). There were no significant differences between treatment groups in clinical response to therapy (P>0.05). Tolterodine IR therapy was associated with a lower incidence of adverse events compared to oxybutynin IR therapy (P=0.027). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Sand et al[56] Oxybutynin XL 10 mg QD vs tolterodine IR 2 mg BID	AC, DB, MC, PG, RCT Patients (average age of 58) with OAB and 7 to 50 UUI weekly episodes and ≥10 voids/ 24 hours	N=315 12 weeks	Primary: Change in UUI episodes, total incontinence episodes, micturition frequency and adverse events Secondary: Not reported	Primary: At 12 weeks, oxybutynin IR treatment was associated with a statistically significant reduction from baseline in UUI and total incontinence episodes compared to tolterodine IR treatment (*P*=0.03). At 12 weeks, both treatment groups were associated with comparable improvements from baseline in micturition frequency episodes (*P*=0.272). The incidences of adverse events were not significantly different between the two treatment groups (*P*>0.05). Secondary: Not reported
Appell et al[57] (OBJECT Study) Oxybutynin XL 10 mg QD vs tolterodine IR 2 mg BID	AC, DB, MC, PG, RCT Patients ≥18 years of age with OAB and 7 to 50 UUI weekly episodes and ≥10 voids/ 24 hours	N=378 12 weeks	Primary: Change in the number of UUI episodes Secondary: Change in the number of total incontinence episodes, micturition frequency and adverse events	Primary: At 12 weeks, oxybutynin XL was significantly more effective at reducing the number of UUI episodes from baseline compared to tolterodine IR (*P*=0.03). Secondary: At 12 weeks, oxybutynin XL was significantly more effective compared to tolterodine IR in reducing the number of total incontinence episodes from baseline (*P*=0.02). At 12 weeks, oxybutynin XL was significantly more effective than tolterodine IR for reducing the mean weekly micturition frequency from baseline (*P*=0.02). Both drugs were associated with statistically significant improvements in symptoms of OAB from baseline (*P*<0.001 for both). Overall, 96.2 and 95.3% of patients on oxybutynin XL and tolterodine IR, respectively, experienced fewer incontinence episodes at week 12 compared to baseline. Dry mouth was reported by 28.1% of patients in the oxybutynin XL group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to 33.2% in the tolterodine IR treatment group (*P*=0.32).
Diokno et al[58] (OPERA Study) Oxybutynin XL 10 mg QD vs tolterodine LA 4 mg QD	DB, MC, PG, RCT Women ≥18 years of age with OAB and 21 to 60 UUI weekly episodes and ≥10 voids/24 hours	N=790 12 weeks	Primary: Change in the number of weekly UUI episodes Secondary: Change in the number of total incontinence episodes, percentage of patients reporting complete continence, micturition frequency and adverse events	Primary: The oxybutynin XL and tolterodine LA treatment groups experienced a comparable weekly reduction from baseline in the number of UUI episodes (*P*=0.13). Secondary: The oxybutynin XL and tolterodine LA treatment regimens were associated with comparable reductions from baseline in the number of total incontinence episodes (*P*=0.08). A significantly greater proportion of patients treated with oxybutynin XL reported no UUI episodes at last observation from baseline, compared to the tolterodine LA group (23.0 vs 16.8%; *P*=0.03). The oxybutynin XL and tolterodine LA regimens were associated with a comparable reduction from baseline in micturition frequency (*P*=0.05); however, when a weekly analysis was performed, oxybutynin XL was more effective compared to tolterodine LA in decreasing mean weekly micturition frequency (*P*<0.05). Dry mouth was the most frequently reported adverse event in each group and was reported more often by patients in the oxybutynin XL group compared to the tolterodine LA group (29.7 vs 22.3%; *P*=0.02).
Anderson et al[59] (OPERA Study) Oxybutynin XL 10 mg QD vs tolterodine LA 4 mg QD	DB, MC, PG, RCT, SA SA (Diokno et al[58]) evaluating the safety and efficacy in patients with and without a history of prior antimuscarinic use	N=790 12 weeks	Primary: Change in the number of weekly UUI episodes Secondary: Change in the number of total incontinence episodes, percentage of	Primary: Among patients previously treated with anticholinergic therapy, oxybutynin XL and tolterodine LA regimens were associated with a comparable weekly reduction from baseline in the number of UUI episodes (*P*=0.306). Among patients not previously treated with anticholinergic therapy, oxybutynin XL and tolterodine LA regimens were associated with a comparable weekly reduction from baseline in the number of UUI episodes (*P*=0.663). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			patients reporting complete continence, micturition frequency and adverse events	Among patients previously treated with anticholinergic therapy, oxybutynin XL and tolterodine LA regimens were associated with comparable improvements from baseline in the number of total incontinence episodes (*P*=0.086). Among patients not previously treated with anticholinergic therapy, oxybutynin XL and tolterodine LA regimens were associated with a comparable reduction from baseline in the number of total incontinence episodes (*P*=0.886). Among patients who had previously been treated with anticholinergic therapy, a significantly greater proportion of patients receiving oxybutynin XL reported no UUI episodes compared to the tolterodine LA (23.6 vs 15.1%; *P*=0.038). Among patients not previously treated with anticholinergic therapy, the proportion of patients with no UUI episodes was comparable between patients in the oxybutynin XL and tolterodine LA groups (29.4 vs 26.4%; *P*=0.495). Among patients previously treated with anticholinergic therapy, oxybutynin XL and tolterodine LA regimens were associated with a comparable reduction from baseline in mean weekly micturition frequency (26 vs 23%; *P*=0.052). Among patients not previously treated with anticholinergic therapy, oxybutynin XL was associated with a statistically significant reduction from baseline in mean weekly micturition frequency compared to tolterodine LA (33 vs 29%; *P*=0.035). Dry mouth was the most frequently reported adverse event in each group. Among patients previously treated with anticholinergic therapy, dry mouth was reported more frequently in the oxybutynin XL group compared to the tolterodine LA treatment group (32.2 vs 19.2%; *P*=0.004). The incidence of other adverse events was similar between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Zellner et al[60] Oxybutynin IR 2.5 to 5 mg TID vs trospium IR 15 to 30 mg TID	AC, DB, MC, NI, PG, RCT Patients ≥18 years of age with documented urinary frequency (≥8 micturitions/24 hours) plus UUI (≥5 episodes/ week)	N=1,659 12 weeks	Primary: Reduction in weekly UUI episodes Secondary: Absolute reductions in micturitions/24 hours, intensity of urgency, MVV/void, qualitative symptoms changes, scores on VAS, KHQ, SF-36 and adverse events	Primary: The absolute reduction in the number of UUI episodes weekly was 11 in both groups in the per-protocol population. In the full analysis, the reduction in urinary UUI episodes was 10.42 with trospium IR compared to 10 with oxybutynin IR. NI of trospium IR compared to oxybutynin IR was supported by the treatment difference and the corresponding 95% CI (per protocol: [95% CI, -1.00 to 1.00]; full analysis: [95% CI, -1.00 to 0.83]) because the upper bound of the 95% CI was below the NI margin of 3.5 weekly UUI episodes. Secondary: After 12 weeks, the reduction in micturitions/24 hours was similar between the trospium IR and oxybutynin IR treatment groups (-2.22 vs -2.35, respectively; *P*=0.3853). There were no statistically significant differences between trospium IR and oxybutynin IR formulations with regard to scores for urge intensity (*P*=0.12) or increase in micturition volume (*P*=0.0881). The change from baseline in VAS score was -33 mm with trospium IR compared to -32 mm reported with oxybutynin IR (*P*=0.796). Similarly, there was no significant difference between the two treatment groups with respect to the change in KHQ domain scores at 12 weeks (-16.17 vs -15.76, respectively; *P*=0.744). With regard to the SF-36 questionnaire, there was no apparent difference between treatment groups, as 45.4% of trospium IR and 46.9% oxybutynin IR-treated patients experienced improvement (*P* value not reported). Treatment-related adverse events occurred in 13.9% of patients receiving trospium IR and 18.3% of patients treated with oxybutynin IR. Adverse events reported as “mild” occurred in 6.2% of patients treated with trospium IR and 5.5% of patients receiving oxybutynin IR. Adverse events rated as “moderate” occurred in 10.7 and 13.4% of patients receiving trospium IR and oxybutynin IR, respectively. Severe adverse events

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				occurred in 5.8 and 7.6% of these patients, respectively. The most common adverse events determined to be related to the study drugs were dry mouth, constipation and nausea. No deaths during the study were reported, and no changes in laboratory parameters or vital signs occurred.
Halaska et al[61] Oxybutynin IR 5 mg BID vs trospium IR 20 mg BID	DB, MC, RCT Patients ≥18 years of age with urge syndrome, UUI as a component of mixed incontinence, or UUI due to a neurological condition	N=358 52 Weeks	Primary: Maximum cystometric bladder capacity Secondary: Change in the volume at the first sensation to void, volume at first unstable contraction, micturition frequency, subjective physician appraisal of efficacy and adverse events	Primary: Both treatment groups experienced a significant improvement in the maximum cystometric bladder capacity from baseline (*P*=0.001). The change in bladder capacity was comparable between treatment groups (*P* value not reported). Secondary: There were no statistically significant differences between groups in the volume at the first sensation to void, volume at first unstable contraction or micturition frequency (*P* value not reported). After 52 weeks of treatment, trospium IR and oxybutynin IR formulations were associated with "cure" by 29 and 17% of physicians, respectively (*P* value not reported). Dry mouth occurred in 33% of patients treated with trospium IR compared to 50% of those receiving oxybutynin IR. Gastrointestinal adverse events occurred in 39% trospium IR-treated patients compared to 51% in the oxybutynin IR group. Central nervous system effects occurred in 4% of those given trospium IR and 9% of patients taking oxybutynin IR. Treatment-related adverse events occurred more frequently in patients receiving oxybutynin IR therapy compared to those receiving trospium IR (*P*<0.01). The weekly risk of experiencing an adverse event was 0.027 with trospium IR and 0.045 with oxybutynin IR therapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mattiasson et al[62] Solifenacin 5 to 10 mg QD vs solifenacin 5 to 10 mg QD plus simplified bladder training	MC, OL, PG, PRO, RCT Patients ≥18 years of age with OAB symptoms who were capable of completing a simplified bladder training regimen correctly and were willing and able to complete a voiding diary correctly	N=693 16 weeks	Primary: Change in the number of micturitions/24 hours at eight weeks Secondary: Change from baseline to week 16 in number of micturitions/24 hours, urgency frequency/24 hours, number of incontinence and urgency incontinence episodes/24 hours, number of pads used, and the percentage of patients requiring an increase in dose at eight weeks, PBC score, VAS to measure treatment satisfaction, I-QOL questionnaire, safety and tolerability	Primary: There was a greater reduction in micturition frequency/24 hours after eight weeks for patients who received solifenacin plus bladder training compared to solifenacin alone (-2.87 vs -2.18; *P*<0.001). Secondary: At 16 weeks, micturition frequency/24 hours remained significantly reduced for patients receiving solifenacin plus bladder training compared to solifenacin monotherapy (-3.11 vs -2.42; *P*<0.005). The mean number of urgency episodes/24 hours at week 16 was numerically lower with solifenacin plus bladder training compared to solifenacin alone; however, the difference was not statistically significant (-2.5 vs -2.2, respectively; *P*=NS). Patients treated with solifenacin plus bladder training did not experience a significant reduction in UUI episodes compared to solifenacin monotherapy (-1.38 vs -1.13, respectively; *P*=NS). There was no statistically significant difference between the two treatments with regard to the number of pads used/24 hours (*P*=0.28), PBC score (*P*=0.61) or I-QOL score (*P*=0.57). Treatment satisfaction (VAS) favored solifenacin plus bladder training over solifenacin monotherapy (*P*=0.025). At week eight, 42.3% of patients receiving solifenacin monotherapy requested a dosage increase compared to 39.1% of patients receiving solifenacin plus bladder training (*P* value not reported) Treatment-emergent adverse events occurred in 46.5% of patients. The most frequently reported adverse events were dry mouth, constipation and dyspepsia. Adverse events leading to treatment discontinuation occurred in 5.3% of patients, with the most common being gastrointestinal in nature. No clinically relevant changes in physical examination were reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chapple et al[63] (STAR Study) Solifenacin 5 mg QD vs tolterodine LA 4 mg QD	DB, DD, MC, PG, PRO, RCT Patients ≥18 years of age, with symptoms of OAB for ≥3 months with ≥8 daily micturitions or ≥1 daily urgency episodes during three-day voiding diary period	N=1,177 12 weeks	Primary: Change in the number of daily micturitions Secondary: Change in the number of urgency episodes, UUI episodes, overall incontinence episodes, nocturia episodes, ≥50% resolution of incontinence episodes, complete continence, MVV/void, incontinence pad utilization and adverse events	Primary: Solifenacin treatment was associated with a statistically significant reduction in micturition frequency from baseline compared to tolterodine LA (*P*=0.004). Secondary: Solifenacin treatment was associated with a statistically significant reduction in the number of urgency episodes from baseline compared to tolterodine LA treatment (*P*=0.035). Solifenacin treatment significantly reduced in the number of UUI episodes from baseline compared to tolterodine LA treatment (*P*=0.001). Solifenacin significant reduced in the number of overall incontinence episodes from baseline compared to tolterodine LA (*P*=0.006). Both treatment groups were associated with comparable reductions in nocturia episodes from baseline (*P*=0.73). Of those patients who were incontinent at baseline, approximately 74% and 67% solifenacin- and tolterodine LA-treated patients, respectively, experienced ≥50% resolution of their incontinence episodes (*P*=0.021). A greater percentage of patients randomized to solifenacin experienced complete continence compared to tolterodine LA-treated patients (59 vs 49%; *P*=0.006). Solifenacin treatment was associated with a statistically significant increase in the mean VVPM compared to tolterodine LA treatment (*P*=0.01). Solifenacin treatment was associated with a statistically significant reduction in incontinence pad utilization from baseline compared to tolterodine LA treatment (*P*=0.0023).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The most frequently reported adverse events in both groups were dry mouth, constipation and blurred vision. Severe dry mouth occurred in 1.7% of solifenacin-treated patients and 1.5% of patients receiving treatment with tolterodine LA (*P* value not reported). The rates of discontinuation due to adverse events in the solifenacin and tolterodine LA groups were comparable (3.5 vs 3.0%, respectively; *P* value not reported).
Chapple et al[64] STAR Study Solifenacin 5 mg QD vs tolterodine LA 4 mg QD	DB, DD, MC, PG, PRO, RCT, SA SA (Chapple et al[63])of patients choosing to remain on the lower treatment dose	N=1,177 4 weeks	Primary: Change in the number of daily micturitions Secondary: Change in the number of urgency episodes, UUI episodes, overall incontinence episodes, nocturia episodes, complete continence, MVV/void, incontinence pad utilization and adverse events	Primary: At week four, both solifenacin and tolterodine LA treatments resulted in comparable reductions in micturition frequency from baseline (-1.71 vs -1.47; *P*>0.05). Secondary: At week four, both solifenacin and tolterodine LA treatments resulted in similar improvements in the number of urgency episodes from baseline (-1.98 vs -1.67; *P*>0.05). Both solifenacin and tolterodine LA treatments resulted in comparable improvements in the number of UUI episodes from baseline (-1.22 vs -0.91; *P*>0.05). Solifenacin treatment was associated with a significant reduction in the number of overall incontinence episodes from baseline compared to tolterodine LA treatment (-1.30 vs -0.90; *P*=0.0181). Both treatment groups were associated with comparable reductions in nocturia episodes from baseline (*P*>0.05). A greater proportion of patients randomized to solifenacin experienced complete continence compared to tolterodine LA-treated patients (39 vs 34%; *P*>0.05). Both solifenacin and tolterodine LA treatments resulted in comparable increases from baseline in the MVV/void (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Solifenacin and tolterodine LA treatments were associated with a comparable reduction from baseline in incontinence pad utilization (-1.21 vs -0.80; *P*>0.05). The most frequently reported adverse events in both groups were dry mouth, constipation and blurred vision. Dry mouth occurred in 18.2% of solifenacin-treated patients and 14.5% of tolterodine LA-treated patients (*P* value not reported). The rate of treatment discontinuation due to adverse events in the solifenacin and tolterodine LA groups were comparable (3.0 vs 2.8%; *P* value not reported).
Hsiao et al[65] Solifenacin 5 mg QD vs tolterodine LA 4 mg QD	OL, PRO, RCT, SA SA of females ≥18 years of age with ≥3 month history of OAB symptoms including urgency, urinary frequency, nocturia, or UUI in addition to ≥8 micturitions/24 hours	N=48 12 weeks	Primary: Change in PBC, TVV, VVPM, micturition frequency, urgency, incontinence, nocturia/24 hours and adverse events Secondary: Not reported	Primary: Following initiation of solifenacin treatment, improvements in PBC were observed at all visits (two through four) compared to baseline (*P*<0.01 for all visits). Similar improvements were reported with tolterodine LA with regard to PBC all time points (*P*<0.05 for all visits). There was no significant difference between the solifenacin and tolterodine LA treatment groups with regard to change in PBC scores (*P*=0.87). Neither treatment group improved TVV compared to baseline values, and no between-group differences were reported (*P*=0.82). Patients treated with solifenacin experienced improvements in VVPM at the third and fourth visits (*P*<0.05), while patients in the tolterodine LA group improved at all follow-up visits (*P*<0.05). No between-group differences were reported between patients receiving solifenacin or tolterodine (*P*=0.88). There was an improvement in micturition frequency at all visits for patients receiving solifenacin (*P*<0.05), while patients receiving tolterodine LA improved micturition frequency at the final visit (*P*<0.05), but not the first two. No difference was reported between solifenacin and tolterodine LA treatment (*P*=0.87). Patients receiving solifenacin experienced an improvement in urgency at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the second and fourth visit (*P*<0.05), while no improvement in urgency occurred in patients treated with tolterodine LA. There was no significant difference in urgency episodes/24 hours between the solifenacin and tolterodine LA treatment groups (*P*=0.62). Patients receiving treatment with solifenacin achieved a statistically significant reduction in incontinence episodes/24 hours at the second and fourth visit (*P*<0.05), while no significant improvement was noted in patients receiving tolterodine LA (*P*=0.64). The frequency of nocturnal incontinence did not significantly improve with solifenacin treatment; however, patients receiving tolterodine LA had fewer episodes of nocturnal incontinence at the third and fourth visit (*P*<0.05). No significant differences were reported between the treatment groups (*P*=0.56). The incidence of adverse events was not significantly different among patients receiving solifenacin or tolterodine LA (*P*=0.23). Dry mouth, constipation and palpitations were the most frequently reported adverse events among patients in both treatment groups. Secondary: Not reported
Armstrong et al[66] Oxybutynin XL 10 mg QD vs tolterodine LA 4 mg QD vs tolterodine IR 2 mg BID	MA of 2 studies Present study is a MA of the OPERA and OBJECT studies (Appell et al[57]and Diokno et al[58])	N=1,168 12 weeks	Primary: Adverse events Secondary: Not reported	Primary: Gastrointestinal adverse events occurred in 41.8, 36.3 and 45.1% of patients receiving oxybutynin XL, tolterodine LA and tolterodine IR therapy, respectively (*P* value not reported). The most common adverse event was dry mouth, occurring in 29.3, 22.3 and 33.2% of patients receiving oxybutynin XL, tolterodine LA and tolterodine IR therapy, respectively (*P* value not reported). The incidence of nervous system adverse events in the oxybutynin XL, tolterodine LA, and tolterodine IR groups was comparable (10.2 vs 8.3 vs 10.9%, respectively; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Most adverse events were mild or moderate in intensity. Severe drug-related adverse events occurred in 4.3, 1.5 and 2.6% of patients in the oxybutynin XL, tolterodine LA and tolterodine IR groups, respectively. The most common adverse event resulting in early discontinuation from the study was dry mouth, with 1.2, 1.0 and 1.6% of patients discontinuing treatment with oxybutynin XL, tolterodine LA and tolterodine IR, respectively (*P* value not reported). Secondary: Not reported
Madhuvrata et al[67] Fesoterodine 4 to 8 mg QD vs oxybutynin IR 2.5 to 5 mg BID to QID vs oxybutynin XL 5 to 20 mg QD vs tolterodine IR 1 to 2 mg BID vs tolterodine LA 2 to 4 mg	MA of 86 studies Patients with a symptomatic diagnosis of OAB syndrome with or without a urodynamic diagnosis of detrusor overactivity	N=31,249 Up to 52 weeks	Primary: Condition-specific QOL and psychosocial measures Secondary: Patient observations, quantification of symptoms, clinician's measures, socioeconomics	Primary: There was no significant difference between tolterodine and oxybutynin with regard to QOL (SMD, -0.00; 95% CI, -0.18 to 0.18). The results from three studies reported a statistically significant improvement in QOL for patients treated with solifenacin compared to tolterodine (SMD, -0.12; 95% CI, -0.23 to -0.01). Treatment with fesoterodine was associated with a significant improvement in QOL compared to tolterodine LA (SMD, -0.20; 95% CI, -0.27 to -0.14). Secondary: There was no statistically significant difference between tolterodine and oxybutynin with regard to the proportion of patients reporting a symptomatic cure or improvement (RR, 1.01; 95% CI, 0.93 to 1.11), fewer leakage episodes or voids over 24 hours (WMD, 0.33; 95% CI, -0.08 to 0.73). There was no difference in patient reported cure or improvement between patients receiving oxybutynin or trospium (RR, 1.00; 95% CI, 0.90 to 1.11). Moreover, there was no significant difference between the treatments with regard to cystometric capacity or residual bladder volume. Trospium was associated with fewer treatment withdrawals (RR, 0.66; 95% CI, 0.48 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD vs trospium IR 20 mg BID vs solifenacin 5 to 10 mg QD vs placebo				0.91) and a lower risk of dry mouth compared to oxybutynin (RR, 0.64; 95% CI, 0. 52 to 0.77). Compared to oxybutynin, tolterodine was associated with significantly lower rates of withdrawal due to adverse events (RR, 0.52; 95% CI, 0.40 to 0.66) and a lower incidence of dry mouth (RR, 0.65; 95% CI, 0.60 to 0.71). Treatment with solifenacin was associated with a higher patient report of cure or improvement compared to tolterodine (RR, 1.25; 95% CI, 1.13 to 1.39). There was a statistically significant reduction in the number of leakage episodes/24 hours (WMD, -0.30; 95% CI, -0.53 to -0.08 and urgency episodes/24 hours with solifenacin compared to tolterodine (WMD, -0.43; 95% CI, -0.74 to -0.13). Withdrawal rates due to adverse events and the incidence of dry mouth were similar between solifenacin and tolterodine; however, following the exclusion of one study with tolterodine LA, dry mouth rates were significantly lower with solifenacin compared to tolterodine LA (RR, 0.69; 95% CI, 0.51 to 0.94). Fesoterodine treatment was associated with a higher rate of patient reported cure or improvement compared to tolterodine LA (RR, 1.11; 95% CI, 1.06 to 1.16). Compared to tolterodine LA, patients taking fesoterodine reported significant reductions in leakage episodes (WMD, -0.19; 95% CI, -0.30 to -0.09), frequency (WMD, -0.27; 95% CI, -0.47 to -0.06) and urgency episodes/24 hours (WMD, -0.44; 95%CI, -0.72 to -0.16). Patients receiving treatment with fesoterodine had a higher risk of withdrawal due to adverse event compared to tolterodine LA treatment (RR, 1.45; 95% CI, 1.07 to 1.98) and higher risk of dry mouth (RR, 1.80; 95% CI, 1.58 to 2.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Similar improvements in leakage episodes and micturitions/24 hours were reported for 1 mg, 2 mg and 4 mg doses of tolterodine IR administered BID. There was a higher incidence of dry mouth with both the 2 and 4 mg doses relative to the lower doses of tolterodine IR. Fesoterodine 8 mg was associated with a greater clinical efficacy (patient reported cure, leakage episodes, micturition/24 hours) compared to the 4 mg fesoterodine. There was no difference in efficacy between the 4 mg and 12 mg doses, although higher dose was associated with a greater incidence of dry mouth. The 8 mg strength was also associated with a higher risk of dry mouth compared to fesoterodine 4 mg. Both tolterodine LA and oxybutynin XL were associated with a lower risk of dry mouth compared to their respective IR formulations; however, no significant differences in cure, improvement, leakage episodes, micturitions/24 hours, or withdrawal events were reported between. There was a lower risk of dry mouth with tolterodine LA compared to oxybutynin XL (RR, 0.75; 95% CI, 0.59 to 0.95). There was no difference in the incidence of dry mouth between transdermal oxybutynin and tolterodine LA, although there was a higher withdrawal rate with transdermal oxybutynin due to a skin reaction at the transdermal patch site at 12 weeks.
Chapple et al[68] Darifenacin 7.5 to 15 mg QD vs fesoterodine 4 to 8 mg QD vs	MA of 73 studies Patients ≥18 years of age, with idiopathic OAB, detrusor overactivity, UI, mixed incontinence with predominantly urge incontinence, or UUI	N=not reported 2 weeks to 18 months	Primary: Total withdrawals and adverse events Secondary: Efficacy measures	Primary: Only oxybutynin IR was associated with a significantly increased risk of treatment withdrawal due to any cause compared to placebo (*P*<0.05). Compared to oxybutynin IR therapy, oxybutynin XL and tolterodine therapies were associated with lower risks of early therapy discontinuation (*P* value not reported). Tolterodine LA was the only agent associated with a significantly lower risk of withdrawal due to an adverse event compared to placebo (*P*=0.02), oxybutynin IR oral and transdermal patch (*P*≤0.01 for both). Oxybutynin IR

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oxybutynin IR 2.5 to 5 mg BID to QID vs oxybutynin XL 5 to 20 mg QD vs oxybutynin transdermal patch vs tolterodine IR 1 to 2 mg BID vs tolterodine LA 2 to 4 mg QD vs trospium IR 20 mg BID vs solifenacin 5 to 10 mg QD vs				and solifenacin significantly increased the risk of withdrawal due to an adverse event compared to placebo (P<0.05 for both). Tolterodine IR was associated with lower withdrawals due to adverse events compared to oxybutynin IR. The risk of adverse events was significantly lower with tolterodine IR compared to oxybutynin IR and XL (P<0.01), while trospium had a lower incidence of adverse events compared to oxybutynin IR (P=0.02). Dry mouth was the most frequently reported adverse event with all drugs. Mild to moderate dry mouth occurred significantly more frequently with oxybutynin, solifenacin and tolterodine compared to placebo. Oxybutynin IR was associated with a greater incidence of dry mouth compared to oxybutynin XL, oxybutynin transdermal patch, tolterodine LA, tolterodine IR and trospium (P value not reported). Secondary: A significantly greater proportion of patients treated with antimuscarinics returned to continence compared to placebo (P<0.01). Antimuscarinics were significantly more effective compared to placebo with regard to the change in the number of daily incontinence episodes. Data for trospium was not reported. Fesoterodine was considered more effective compared to tolterodine LA (P=0.03); however, the basis for this analysis was based on a single study. No other significant differences were reported between treatments. Antimuscarinic treatments significantly improved the number of daily micturitions compared to placebo. Data was not reported for trospium. Solifenacin significantly improved micturition frequency compared to tolterodine IR (P=0.01). There were no differences between the other treatments. Fesoterodine, solifenacin and tolterodine were significantly more effective compared to placebo with regard to reductions in daily urgency episodes.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				Data for oxybutynin and trospium were not reported. Solifenacin treatment was associated with greater improvements compared to tolterodine IR therapy (*P*<0.01). There were no differences between the other treatments. The change in MVV/void was significantly higher with active treatment compared to placebo. Data for trospium was not reported. Both oxybutynin IR and solifenacin increased voided volume compared to tolterodine IR, while fesoterodine increased volume compared to tolterodine LA (*P*<0.05 for all).

Drug regimen abbreviations: BID=twice daily, ER/LA/XL/XR=extended-release, IR=immediate-release, QD=once daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, FD= flexible dose, MA=meta-analysis, MC=multicenter, NI=non inferiority, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SA=subanalysis, XO=crossover
Other abbreviations: GPI=global perception of improvement, ICIQ-SF=international consultation on incontinence questionnaire-Short Form, I-QOL=incontinence quality of life scale, KHQ=King's health questionnaire, LS=least squares, MVV=mean voided volume, OAB=overactive bladder , OAB-PGA=overactive bladder patients global assessment, OAB-q=overactive bladder questionnaire, OAB-SCS=overactive bladder symptom composite score, PPBC or PBC=perception of bladder condition, PSQ=patient satisfaction questionnaire, QOL=quality of life, SF-36=short-form, SMD=standardized mean difference, TVV=total voided volume, UUI=urge urinary incontinence, UPS=urgency perception scale, VAS=visual analog scale, VVPM=volume voided per micturition, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[3-16]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Darifenacin	No dosage adjustment required in elderly patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in patients with mild hepatic impairment (Child-Pugh A). Hepatic dose adjustment is required in patients with moderate hepatic impairment (Child-Pugh B); a maximum dose of 7.5 mg and a once-daily dosing schedule is recommended. Not recommended for use in patients with severe hepatic impairment (Child-Pugh C).	C	Unknown
Fesoterodine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required in patients with mild or moderate renal impairment. Daily dose should not exceed 4 mg in patients with severe renal insufficiency (creatinine clearance <30 mL/ minute).	No dosage adjustment required in patients with mild or moderate hepatic impairment. Not recommended for use in patients with severe hepatic impairment.	C	Unknown
Flavoxate	Safety and efficacy in children <12 years of age	Safety and efficacy in patients with renal	Safety and efficacy in patients with hepatic insufficiency have	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	have not been established.	insufficiency have not been established.	not been established.		
Mirabegron	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for severe renal impairment (creatinine clearance <30 mL/minute), a dose of 25 mg and dosing frequency of once-daily is recommended.	Hepatic dose adjustment is required in patients with moderate hepatic impairment (Child-Pugh B); a dose of 25 mg and dosing frequency of once-daily is recommended.	C	Unknown
Oxybutynin	Dose adjustment is recommended; a dose of 2.5 mg and a two or three times daily dosing schedule is recommended in frail elderly patients due to a prolonged elimination half-life (IR only). FDA-approved for use in children >5 years of age (IR) and >6 years of age (XL). The safety and efficacy in of oxybutynin gel and transdermal patches in children have not been established.	Use with caution. Safety and efficacy of oxybutynin gel and transdermal patches in patients with renal insufficiency have not been established.	Use with caution. Safety and efficacy of oxybutynin gel and transdermal patches in patients with hepatic insufficiency have not been established.	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Solifenacin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances of <30 mL/minute, a dose of 5 mg and dosing frequency of once-daily is recommended.	Hepatic dose adjustment is required in patients with moderate hepatic impairment (Child-Pugh B); a maximum dose of 5 mg and a dosing frequency of once-daily are recommended. Not recommended for use in patients with severe hepatic impairment (Child-Pugh C).	C	Unknown
Tolterodine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for patients with significantly reduced renal function, a dose of 1 mg and dosing frequency of twice-daily is recommended (IR). Renal dose adjustment is recommended; for creatinine clearances of 10 to 30 mL/minute, a dose of 2 mg and dosing frequency of once-daily is recommended (LA). Not recommended for use in patients with a creatinine	Hepatic dose adjustment is required in patients with significantly reduced hepatic function; a maximum dose of 1 mg and a dosing frequency of twice-daily are recommended. Hepatic dose adjustment is required in patients with mild to moderate hepatic dysfunction (Child-Pugh A or B); a maximum dose of 2 mg and a dosing frequency of once-daily is recommended (LA). Not recommended for use in patients with severe hepatic	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		clearances <10 mL/minute (LA).	impairment (Child-Pugh C).		
Trospium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients (IR).* Safety and efficacy in children have not been established.	Renal dose adjustment is recommended; for creatinine clearances of <30 mL/minute, a dose of 20 mg and dosing frequency of once-daily is recommended. Not recommended for use in patients with severe renal impairment (XR)	Use with caution in patients with moderate to severe hepatic dysfunction.	C	Unknown

* Higher incidence of adverse events reported in patients >65 years of age.
ER, LA, XL, XR=extended-release, IR=immediate release.

Adverse Drug Events

The following table presents the most common adverse events reported with urinary antispasmodics in clinical trials.

Table 6. Adverse Drug Events (%)[3-16]

Adverse Event	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin IR	Oxybutynin XL			Solifenacin	Tolterodine IR	Tolterodine LA	Trospium IR	Trospium XR
						Tablet	Patch	Gel					
Cardiovascular													
Atrial fibrillation	-	-	-	0.2	-	-	-	-	-	-	-	-	-
Blood pressure decreased	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Blood pressure increased	-	-	-	<1	✔	✔	-	-	-	-	-	-	-
Cerebrovascular accident	-	-	-	0.4	-	-	-	-	-	-	-	-	-
Chest pain	-	-	-	-	-	-	-	-	-	2	-	✔	✔
Hypertension	✔	-	-	7.5 to 11.3	-	✔	-	-	<1.4	-	-	-	-
Hypertensive crisis	-	-	-	-	-	-	-	-	-	-	-	✔	✔
Palpitations	✔	✔	✔	<1	✔	-	-	-	-	✔	✔	✔	✔
Peripheral edema	✔	0.7 to 1.2	-	-	✔	✔	-	-	✔	✔	-	-	-
QT prolongation	-	-	✔	-	-	-	-	-	✔	-	-	-	-
Tachycardia	-	-	✔	1.2 to 1.6	-	-	-	-	-	✔	✔	✔	✔
Torsades de Pointes	-	-	-	-	-	-	-	-	✔	-	-	-	-
Sinus arrhythmia	-	-	-	-	✔	-	-	-	-	-	-	-	-
Supraventricular tachycardia	-	-	-	-	-	-	-	-	-	-	-	✔	✔
Central Nervous System													
Anxiety	-	-	-	-	-	-	-	-	-	-	1	-	-
Confusion	✔	-	✔	-	✔	✔	-	-	-	✔	✔	-	-
Delirium	-	-	-	-	-	-	-	-	-	-	-	✔	✔
Depression	-	-	-	-	-	✔	-	-	0.8 to 1.2	-	-	-	-
Disorientation	-	-	-	-	-	-	-	-	-	✔	✔	-	-
Hallucinations	✔	-	-	-	-	-	-	-	✔	✔	✔	✔	✔
Insomnia	-	0.4 to 1.3	-	-	5.5	✔	-	-	-	-	-	-	-

Adverse Event	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin IR	Oxybutynin XL			Solifenacin	Tolterodine IR	Tolterodine LA	Trospium IR	Trospium XR
						Tablet	Patch	Gel					
Memory impairment	-	-	-	-	-	-	-	-	-	✔	✔	-	-
Nervousness	-	-	✔	-	6.5	✔	-	-	-	-	-	-	-
Somnolence	✔	-	✔	-	14	2 to 12	✔	✔	✔	3	3	-	✔
Syncope	✔	-	-	-	-	-	-	-	-	-	-	✔	✔
Vertigo/dizziness	0.9 to 2.1	-	✔	2.7	16.6	4 to 6	-	-	1.8 to 1.9	5	2	-	-
Dermatological													
Anaphylactic reaction	✔	-	-	-	-	-	-	-	-	✔	✔	✔	✔
Angioedema	✔	✔	-	-	-	-	-	-	✔	✔	✔	✔	✔
Application site erythema	-	-	-	-	-	-	5.6	3.7	-	-	-	-	-
Application site macules	-	-	-	-	-	-	2.5	3.3	-	-	-	-	-
Application site pruritus	-	-	-	-	-	-	14.0 to 16.8	-	-	-	-	-	-
Application site rash	-	-	-	-	-	-	3.3	-	-	-	-	-	-
Application site vesicles	-	-	-	-	-	-	3.2	-	-	-	-	-	-
Dry skin	✔	-	-	-	✔	✔	-	-	-	1	-	✔	✔
Exfoliative dermatitis	-	-	-	-	-	-	-	-	✔	-	-	-	-
Erythema multiforme	✔	-	-	-	-	-	-	-	✔	-	-	-	-
Leukocytoclastic vasculitis	-	-	-	<1	-	-	-	-	-	-	-	-	-
Pruritus	✔	✔	-	<1	✔	✔	-	-	✔	-	-	-	-
Purpura	-	-	-	<1	-	-	-	-	-	-	-	-	-
Rash	✔	0.7 to 1.1	-	<1	-	-	✔	-	✔	-	-	-	✔
Stevens-Johnson syndrome	-	-	-	-	-	-	-	-	-	-	-	✔	✔
Urticaria	-	✔	✔	<1	-	-	-	-	✔	-	-	-	-
Gastrointestinal													
Abdominal distension	-	-	-	<1	-	-	-	-	-	-	-	✔	1

Adverse Event	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin IR	Oxybutynin XL			Solifenacin	Tolterodine IR	Tolterodine LA	Trospium IR	Trospium XR
						Tablet	Patch	Gel					
Abdominal pain	2.4 to 3.9	05 to 1.1	-	0.6 to 1.4	✔	✔	✔	-	1.2 to 1.9	5	4	1.5	1.4
Constipation	14.8 to 21.3	4.2 to 6.0	-	1.6 to 2.8	15.1	7 to 13	3.3	-	5.4 to 13.4	7	6	9.6	8.5 to 9.0
Constipation aggravated	-	-	-	-	-	-	-	-	-	-	-	1.4	1.2
Diarrhea	0.9 to 2.1	-	-	1.2 to 1.5	✔	7 to 9	3.2	-	-	4	✔	-	-
Dry mouth	18.7 to 35.3	18.8 to 34.6	✔	2.8	71.4	29 to 61	4.1 to 9.6	12.1	10.9 to 27.6	35	23	20.1	10.7 to 11.1
Dyspepsia	2.7 to 8.4	1.6 to 2.3	-	<1	6	5 to 7	-	-	1.4 to 3.9	4	3	1.2	1.2
Eructation	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Flatulence	-	-	-	-	✔	✔	✔	-	-	-	-	1.2	1.6
Gastritis	-	-	-	<1	-	-	-	-	-	-	-	✔	✔
Loose stools	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Nausea	1.5 to 3.7	0.7 to 1.9	✔	-	11.6	2 to 9	-	-	1.7 to 3.3	-	-	-	1.4
Hardened feces	-	-	-	-	-	-	-	-	-	-	-	-	✔
Vomiting	✔	-	✔	-	✔	✔	✔	-	<1.1	-	-	✔	-
Genitourinary													
Bladder pain	-	-	-	<1	-	-	-	-	-	-	-	-	-
Cystitis	-	-	-	2.1	✔	✔	-	-	-	-	-	-	-
Dysuria	-	1.3 to 1.6	✔	-	✔	✔	2.4	-	-	2	1	-	-
Nephrolithiasis	-	-	-	<1	-	-	-	-	-	-	-	-	-
Pollakiuria	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Urinary hesitation	-	-	-	-	8.5	-	-	-	-	-	-	-	-
Urinary retention	-	1.1 to 1.4	-	✔	6	-	-	-	1.4	-	-	1.2	✔
Urinary tract infection	3.0 to 4.7	2.8 to 2.5	-	2.9 to 5.9	6.5	5	-	-	2.8 to 4.8	-	-	-	1.2 to 7.3
Vulvovaginal pruritus	-	-	-	<1	-	-	-	-	-	-	-	-	-
Infections													
Fungal infection	-	-	-	-	✔	-	-	-	-	-	-	-	-
Infection	-	-	-	-	-	-	-	-	-	1	-	-	-
Influenza	<3	-	-	2.6	-	-	-	-	0.9 to 2.2	3	-	-	2.2
Upper respiratory tract infection	-	1.8 to 2.5	-	1.5 to 2.1	-	-	-	-	-	-	-	-	-

Adverse Event	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin IR	Oxybutynin XL			Solifenacin	Tolterodine IR	Tolterodine LA	Trospium IR	Trospium XR
						Tablet	Patch	Gel					
Vaginal infection	-	-	-	<1	-	-	-	-	-	-	-	-	-
Musculoskeletal													
Arthralgia	✔	-	-	1.3 to 2.1	✔	✔	-	-	-	2	-	-	-
Back pain	✔	0.9 to 2.0	-	2.8	✔	✔	✔	-	-	-	-	-	✔
Dysphagia	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Flank pain	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Headache	6.7	-	✔	2.1 to 4.1	7.5	6 to 10	✔	-	✔	7	6	-	4.2
Osteoarthritis	-	-	-	0.2	-	-	-	-	-	-	-	-	-
Pain (not specified)	-	-	-	-	-	4 to 7	-	-	-	-	-	-	-
Pain in extremity	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Pharyngolaryngeal pain	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Rhabdomyolysis	-	-	-	-	-	-	-	-	-	-	-	✔	✔
Ophthalmic													
Abnormal vision	✔	-	-	-	-	-	2.5	-	-	-	1	✔	✔
Accommodation abnormal	-	-	-	-	-	-	-	-	-	2	-	-	-
Blurred vision	-	✔	✔	-	9.6	1 to 8	-	-	3.8 to 4.8	-	-	✔	✔
Eye irritation	-	-	-	-	✔	-	-	-	-	-	-	-	-
Glaucoma	-	-	-	<1	-	-	-	-	-	-	-	-	-
Increased ocular tension	-	-	✔	-	-	-	-	-	-	-	-	-	-
Keratoconjunctivitis sicca	-	-	-	-	✔	-	-	-	-	-	-	-	-
Xerophthalmia	1.5 to 2.1	1.4 to 3.7	-	-	-	3 to 6	-	-	<1.6	3	3	-	1.6
Other													
Accidental injury	<3	-	-	-	-	-	-	-	-	-	-	-	-
Alanine transaminase increased	-	0.5 to 1.2	-	<1	-	-	-	-	-	-	-	-	-
Aspartate aminotransferase	-	-	-	<1	-	-	-	-	-	-	-	-	-

Adverse Event	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin IR	Oxybutynin XL			Solifenacin	Tolterodine IR	Tolterodine LA	Trospium IR	Trospium XR
						Tablet	Patch	Gel					
increased													
Aptyalism	-	-	-	-	✔	-	-	-	-	-	-	-	-
Asthenia	1.5 to 2.7	-	-	-	✔	3 to 7	-	-	-	-	-	-	-
Blood glucose increased	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Dysgeusia	-	-	-	-	✔	✔	-	-	-	-	-	✔	-
Facial edema	-	✔	-	-	-	-	-	-	-	-	-	-	-
Falls	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Fatigue	-	-	-	1.2 to 1.4	✔	✔	✔	-	<2.1	4	2	1.9	-
Fluid retention	-	-	-	-	✔	-	-	-	-	-	-	-	-
Flushing	-	-	-	-	✔	-	✔	-	-	-	-	-	-
Gamma-glutamyl transpeptidase increased	-	0.4 to 1.2	-	<1	-	-	-	-	-	-	-	-	-
Hoarseness	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Hyperpyrexia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Leukopenia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Lip edema	-	-	-	<1	-	-	-	-	-	-	-	-	-
Lower limb edema	-	-	-	-	-	-	-	-	<1.1	-	-	-	-
Prostate cancer	-	-	-	0.2	-	-	-	-	-	-	-	-	-
Sinus headache	-	-	-	-	✔	-	-	-	-	-	-	-	-
Thirst	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Tongue coated	-	-	-	-	✔	-	-	-	-	-	-	-	-
Weight gain	✔	-	-	-	-	-	-	-	-	1	-	-	-
Respiratory													
Asthma	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Airway obstruction	✔	✔	-	-	-	-	-	-	✔	-	-	-	-
Bronchitis	✔	-	-	-	✔	✔	-	-	-	-	-	-	-
Cough	-	0.9 to 1.6	-	-	✔	✔	-	-	<1.1	-	-	-	-
Dry throat	-	0.9 to 2.3	-	-	✔	✔	-	-	-	-	-	✔	-
Nasal congestion	-	-	-	-	✔	-	-	-	-	-	-	-	-
Nasal dryness	-	-	-	-	✔	✔	-	-	-	-	-	-	1

Adverse Event	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin IR	Oxybutynin XL			Solifenacin	Tolterodine IR	Tolterodine LA	Trospium IR	Trospium XR
						Tablet	Patch	Gel					
Nasopharyngitis	-	-	-	3.5 to 3.9	✔	✔	-	-	-	-	-	-	2.9
Pharyngitis	✔	-	-	-	-	-	-	-	<1.1	-	-	-	-
Rhinitis	✔	-	-	<1	-	2 to 6	-	-	-	-	-	-	-
Sinus congestion	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Sinusitis	✔	-	-	<2.7	-	✔	-	-	-	-	2	-	-

ER, LA, XL, XR=extended-release, IR=immediate release.
-Event not reported.
✔ Percent not specified.

Contraindications

Table 7. Contraindications[3-16]

Contraindications	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin IR	Oxybutynin XL			Solifenacin	Tolterodine IR	Tolterodine LA	Trospium IR	Trospium XR
						Tablet	Patch	Gel					
Achalasia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Gastric retention	✔	✔	-	-	✔	✔	✔	✔	✔	✔	✔	✔	✔
Gastrointestinal hemorrhage	-	-	✔	-	-	-	-	-	-	-	-	-	-
Hypersensitivity to active ingredients	-	✔	-	-	✔	✔	-	✔	✔	✔	✔	✔	✔
Hypersensitivity to fesoterodine fumarate	-	-	-	-	-	-	-	-	-	✔	✔	-	-
Hypersensitivity to tolterodine tartrate	-	✔	-	-	-	-	-	-	-	-	-	-	-
Obstructive intestinal lesions or ileus	-	-	✔	-	-	-	-	-	-	-	-	-	-
Obstructive uropathies of the lower urinary tract	-	-	✔	-	-	-	-	-	-	-	-	-	-
Pyloric or duodenal obstruction	-	-	✔	-	-	-	-	-	-	-	-	-	-
Severe decreased gastrointestinal motility	-	-	-	-	✔	✔	✔	-	-	-	-	-	-
Uncontrolled narrow angle glaucoma	✔	✔	-	-	✔	✔	✔	✔	✔	✔	✔	✔	✔
Urinary retention	✔	✔	-	-	✔	✔	✔	✔	✔	✔	✔	✔	✔

ER, LA, XL, XR=extended-release, IR=immediate release.

Warnings/Precautions

Table 8. Warnings and Precautions[3-16]

Warning/Precaution	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin IR	Oxybutynin XL			Solifenacin	Tolterodine IR	Tolterodine LA	Trospium IR	Trospium LA
						Tablet	Patch	Gel					
Alcohol should not be consumed within two hours of administration.	-	-	-	-	-	-	-	-	-	-	-	✔	✔
Anticholinergic central nervous system adverse events; monitor patients for symptoms within the first few months of treatment.	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Cardiac arrhythmias; symptoms may be aggravated with use.	-	-	-	-	✔	-	-	-	-	-	-	-	-
Case reports of angioedema	✔	✔	-	-	✔	✔	✔	✔	✔	-	✔	✔	✔
Central nervous system adverse events; Patients should not drive or operate heavy machinery until they know how the medication affects them.	✔	✔	-	-	✔	✔	✔	✔	✔	✔	✔	✔	✔
Congenital or acquired QT prolongation; use caution in these patients.	-	-	-	-	-	-	-	-	✔	✔	✔	-	-
Congestive heart failure symptoms may be aggravated with use.	-	-	-	-	✔	-	-	-	-	-	-	-	-
Controlled narrow angle glaucoma	✔	✔	-	-	-	-	-	✔	✔	✔	-	✔	✔
Coronary heart disease symptoms may be aggravated with use.	-	-	-	-	✔	-	-	-	-	-	-	-	-
CYP3A4 inhibitors; Use of lower doses with strong CYP 3A4 inhibitors is recommended.	-	✔	-	-	-	-	-	-	-	-	-	-	-
Decreased gastrointestinal motility; use with caution in patients with gastrointestinal obstructive disorders.	✔	✔	-	-	✔	✔	✔	✔	✔	✔	-	✔	✔
Dementia; use caution in patients treated with cholinesterase inhibitors due to the aggravation of symptoms.	-	-	-	-	✔	✔	-	-	-	-	-	-	-
Drugs metabolized by CYP2D6; mirabegron may increase systemic exposure to these drug via inhibition of CYP2D6	-	-	-	✔	-	-	-	-	-	-	-	-	-
Flammable gel; avoid open fire or smoking.	-	-	-	-	-	-	-	✔	-	-	-	-	-

Warning/Precaution	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin IR	Oxybutynin XL			Solifenacin	Tolterodine IR	Tolterodine LA	Trospium IR	Trospium LA
						Tablet	Patch	Gel					
Frail, elderly patients; use caution in these patients.	-	-	-	-	✔	-	-	-	-	-	-	-	-
Gastroesophageal reflux disease; use with caution when administering other drugs that may exacerbate esophagitis.	-	-	-	-	✔	✔	✔	✔	-	-	-	-	-
Hiatal hernia symptoms may be aggravated with use.	-	-	-	-	✔	-	-	-	-	-	-	-	-
Hypertension symptoms may be aggravated with use.	-	-	-	-	✔	-	-	-	-	-	-	-	-
Hyperthyroidism symptoms may be aggravated with use.	-	-	-	-	✔	-	-	-	-	-	-	-	-
Increased blood pressure; not recommended for use in patients with severe uncontrolled hypertension (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg)	-	-	-	✔	-	-	-	-	-	-	-	-	-
Intestinal atony; use caution in these patients.	-	-	-	-	✔	✔	✔	-	-	-	-	-	-
Myasthenia gravis; use caution in these patients.	-	✔	-	-	✔	✔	✔	✔	-	✔	✔	-	-
Preexisting severe gastrointestinal narrowing (pathologic or iatrogenic)	-	-	-	-	-	✔	-	-	-	-	-	-	-
Prostatic hypertrophy symptoms may be aggravated with use.	-	-	-	-	✔	-	-	-	-	-	-	-	-
Reduced hepatic function; caution should be used in this patient population.	✔	✔	-	-	-	✔	✔	-	✔	✔	✔	-	-
Reduced renal function; use caution in these patients.	-	-	-	-	-	✔	✔	-	-	✔	-	-	-
Severe renal impairment; use caution in these patients.	-	✔	-	-	-	-	✔	-	✔	-	✔	✔	✔
Suspected glaucoma; use with caution.	-	-	✔	-	-	-	-	-	-	-	-	-	-
Tachycardia symptoms may be aggravated with use.	-	-	-	-	✔	-	-	-	-	-	-	-	-
Transfer of oxybutynin to another person through skin-to-skin contact.	-	-	-	-	-	-	-	✔	-	-	-	-	-
Ulcerative colitis; use caution in these patients.	-	-	-	-	✔	✔	✔	-	-	-	-	-	-
Urinary retention; use with caution in patients with clinically significant bladder obstruction.	✔	✔	-	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

ER, LA, XL, XR=extended-release, IR=immediate release.

Drug Interactions

All urinary antispasmodics, except for trospium, are metabolized by the cytochrome P450 (CYP450) 3A4/2D6 isoenzyme system. Consequently, inhibitors of CYP450 may decrease urinary antispasmodic metabolism potentially leading to increased pharmacological and toxic effects. Since trospium is excreted by the kidneys via tubular secretion and glomerular filtration, agents competing with trospium for tubular secretion may increase its plasma concentration and risk of toxicity. Moreover, specific drug interaction studies have not been performed with the transdermal and topical oxybutynin gel products. Significant drug interactions with the urinary antispasmodics are listed in Table 9.

Table 9. Drug Interactions[3-16]

Generic Name	Interacting Medication or Disease	Potential Result
Urinary antispasmodics (all)	Potent CYP3A4 inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin)	Potent CYP3A4 inhibitors may increase the pharmacologic and adverse events of urinary antispasmodics. Patients receiving potent CYP3A4 inhibitors may require the urinary antispasmodic dose to be adjusted.
Urinary antispasmodics (solifenacin, tolterodine)	Drugs known to cause QT prolongation (amiodarone, propafenone, quinidine)	Drugs known to cause QT prolongation may lead to additive, potentially life-threatening QT interval prolongation if used concurrently with tolterodine and solifenacin.
Trospium	Metformin	Concurrent use of metformin and trospium may result in decreased plasma concentrations of trospium.
Darifenacin, mirabegron	CYP2D6 Substrates (e.g., flecainide, thioridazine and tricyclic antidepressants)	Darifenacin and mirabegron may increase the pharmacologic and adverse events of these agents through inhibition of CYP2D6 metabolism.

Dosage and Administration

Oxybutynin, tolterodine and trospium extended-release (ER, LA, XL, XR) formulations as well as darifenacin, fesoterodine mirabegron and solifenacin are approved for once-daily dosing. Tolterodine immediate-release (IR) tablets are dosed twice-daily; while, flavoxate and oxybutynin IR tablets may be used up to four times daily. The usual dosing regimens for the urinary antispasmodics are summarized in Table 10.

Table 10. Dosing and Administration[3-16]

Generic Name	Adult Dose	Pediatric Dose	Availability
Darifenacin	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Extended-release tablet: initial, 7.5 mg QD; maintenance, 7.5 mg to 15 mg QD	Safety and efficacy in children have not been established.	Extended-release tablet: 7.5 mg 15 mg
Fesoterodine	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Extended-release tablet: initial, 4 mg QD; maintenance, 4 mg to 8 mg QD	Safety and efficacy in children have not been established.	Extended-release tablet: 4 mg 8 mg
Flavoxate	Symptomatic relief of dysuria, urgency, nocturia, suprapubic	Safety and efficacy in children <12 years of	Tablet: 100 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis and urethrocystitis/urethrotrigonitis: Tablet: 100 mg to 200 mg TID or QID	age have not been established.	
Mirabegron	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet: initial, 25 mg QD; maintenance, 25 mg to 50 mg QD	Safety and efficacy in children have not been established.	Extended-release tablet: 25 mg 50 mg
Oxybutynin	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder: Tablet: maintenance, 5 mg BID or TID; maximum, 5 mg QID; a lower starting dose of 2.5 mg BID or TID is recommended for the frail elderly. Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency: Extended-release tablet: initial, 5 mg to 10 mg QD; maximum, 30 mg QD Transdermal patch: maintenance, one patch applied twice-weekly (every three to four days) 3% Gel: maintenance, three pumps applied QD to dry, intact skin. 10% Gel: maintenance, apply contents of one sachet QD to dry, intact skin.	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder in children >5 years of age: Tablet: maintenance, 5 mg BID; maximum, 5 mg TID Treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition: Extended-release tablet: initial, 5 mg QD; maximum, 20 mg QD The safety and efficacy in of oxybutynin gel and transdermal patches in children have not been established.	Extended-release tablet: 5 mg 10 mg 15 mg Gel: 3% (pump) 10% (sachet) Syrup: 5 mg/5 mL Tablet: 5 mg Transdermal patch: 3.9 mg/ 24 hours
Solifenacin	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency: Tablet: initial 5 mg QD; maintenance, 10 mg QD	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Tolterodine	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency: Tablet: initial, 2 mg BID; maintenance 1 mg to 2 mg BID Extended-release capsule: initial, 4 mg QD; maintenance, 2 mg to 4 mg QD; however, there is limited efficacy data available for the 2 mg dose.	Safety and efficacy in children have not been established.	Extended-release capsule: 2 mg 4 mg Tablet: 1 mg 2 mg
Trospium	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency: Tablet: maintenance, 20 mg BID Extended-release capsule: maintenance, 60 mg QD in the morning	Safety and efficacy in children have not been established.	Extended-release capsule: 60 mg Tablet: 20 mg

QD=once-daily, BID=twice-daily, TID=three times daily

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Urological Association: **Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults (2012)**[21]	First-Line Treatments • Behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) are considered first-line treatment in all patients with overactive bladder (OAB) • Behavioral therapies may be combined with antimuscarinic therapies. Second-Line Treatments • Clinicians should offer oral antimuscarinics including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium as second-line therapy. No one agent is recommended over another. • If both an immediate-release (IR) and an extended-release (ER) formulation are available, then ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth. • Transdermal oxybutynin (patch or gel) may be offered. • If a patient experiences an inadequate response or unacceptable adverse events with one antimuscarinic medication, then a dose reduction or a switch to a different antimuscarinic medication is indicated. • Antimuscarinics should not be used in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist. In addition, antimuscarinics should be used with extreme caution in patients with impaired gastric emptying or a history of urinary retention. • Clinicians should manage constipation and dry mouth before abandoning effective antimuscarinic therapy. Management may

Clinical Guideline	Recommendation(s)
	include bowel management, fluid management, dose modification or alternative antimuscarinics. • Caution should be used in prescribing antimuscarinics to patients who are using other medications with anticholinergic properties. • Clinicians should use caution in prescribing antimuscarinics in the elderly, frail OAB patient. • Patients who are not responsive to behavioral and medical therapy should be referred to a specialist if they desire additional therapy. Third-line Treatments • Sacral neuromodulation may be considered a third-line treatment in a carefully selected patient population characterized by severe refractory OAB symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure. • Peripheral tibial nerve stimulation may be considered as third-line treatment in a carefully selected patient population. • Clinicians may offer intra detrusor onabotulinumtoxinA as third-line treatment in carefully-selected and thoroughly-counseled patients who are refractory to first- and second-line OAB treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary.
European Association of Urology: **Guidelines on Assessment and Nonsurgical Management of Urinary Incontinence (2013)**[22]	Antimuscarinic drugs • Offer IR or ER formulations of antimuscarinic drugs as initial drug therapy for adults with urgency urinary incontinence (UUI). • If IR formulations of antimuscarinic drugs are unsuccessful for adults with UUI, offer ER formulations or longer-acting antimuscarinic agents. • Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth. • Evaluate efficacy and any adverse events for patients on antimuscarinic medication for UUI in the first 30 days. • When prescribing antimuscarinic drugs to elderly patients, be aware of the risk of cognitive adverse events, especially in those receiving cholinesterase inhibitors. • Avoid using oxybutynin IR in patients who are at risk of cognitive dysfunction. • Consider use of trospium chloride in patients known to have cognitive dysfunction. Use solifenacin, tolterodine and darifenacin with caution in patients with cognitive dysfunction. • Check mental function in patients on antimuscarinic medication if they are at risk of cognitive dysfunction. Adrenergic drugs: • Offer mirabegron extended-release to patients with UUI depending on local licensing arrangements. Duloxetine • Duloxetine should not be offered to patients who are seeking a cure for incontinence. • Duloxetine can be offered to patients who are seeking temporary improvement in incontinence symptoms. • Duloxetine should be initiated using dose titration because of high

Clinical Guideline	Recommendation(s)
	adverse event rates. Intravaginal estrogen • Offer post-menopausal women with urinary incontinence local estrogen therapy, although the ideal duration of therapy and best delivery method are unknown. Desmopressin • Desmopressin may be used in patients requiring occasional short-term relief from urinary incontinence; however, this use is off-label. • Do not use desmopressin for long-term control of urinary incontinence. Intravesical injection of botulinum toxin A • Offer botulinum toxin A intravesical injections to patients with UUI refractory to antimuscarinic therapy. • Check the botulinum toxin brand before injection, as units among the available brands are not interchangeable. • Offer onabotulinumtoxinA 100 units as initial dose to minimize the risk of urinary retention and urinary tract infection. • Warn patients of the limited duration of response, the possible prolonged need to self-catheterize (ensure that they are willing and able to do so) and the associated risk of urinary tract infection. • Patients should also be informed that long-term adverse events, although improbable, remain uncertain.
European Association of Urology: **Guidelines on Neurogenic Lower Urinary Tract Dysfunction (2011)**[69]	Drug treatment • Antimuscarinic therapy for neurogenic detrusor overactivity (NDO) is safe and effective for long-term use. • Outcomes for NDO can be maximized by considering a combination of antimuscarinic agents. • Alternative ways of administration of antimuscarinic agents (transdermal and intravesical) should be considered to reduce adverse events. • α-blockers may help to decrease bladder outlet resistance and may be a preventive measure in spinal cord injury to prevent autonomic dysreflexia. • The mainstay of treatment for overactive detrusor is antimuscarinic drug therapy. • Lower urinary tract rehabilitation may be effective in selected cases (patients not suffering from a complete spinal cord lesion). • Any method of assisted bladder emptying should be used with the greatest caution. Intravesical drug treatment • Botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce NDO. • Sphincterotomy is the standard treatment for detrusor-sphincter dyssynergia. • Bladder neck incision is effective in a fibrotic bladder neck.
National Institute for Health and Clinical Excellence: **Management of Lower**	Behavioral treatment • For patients with neurogenic lower urinary tract dysfunction, behavioral management programs should be considered (e.g., timed voiding, bladder retraining or habit retraining).

Clinical Guideline	Recommendation(s)
Urinary Tract Dysfunction in Neurological Disease (2012)[70]	• When choosing a behavioral management program, take into account that prompted voiding and habit retraining are particularly suitable for people with cognitive impairment. Antimuscarinics • Antimuscarinic drugs should be offered to patients with spinal cord disease (e.g., spinal cord injury or multiple sclerosis) who have symptoms of OAB such as increased frequency, urgency and incontinence. • In patients with conditions affecting the brain (e.g., cerebral palsy, head injury or stroke) with symptoms of an OAB, antimuscarinic drugs should be considered. • Antimuscarinic drug treatment should be considered in patients with urodynamic investigations showing impaired bladder storage. • Residual urine volume should be monitored in patients not using intermittent or indwelling catheterization after beginning treatment. • Antimuscarinic treatment can reduce bladder emptying, which may increase the risk of urinary tract infections and may precipitate or exacerbate constipation. Botulinum toxin A • Bladder wall injection with botulinum toxin A should be offered to adult patients with spinal cord diseases (e.g., spinal cord injury or multiple sclerosis) and symptoms of OAB and an inadequate response to or poorly tolerated antimuscarinic drugs. • Bladder wall injection with botulinum toxin A may be considered for children and young people with spinal cord disease and symptoms of OAB for who antimuscarinic drugs were ineffective or poorly tolerated. • Bladder wall injection with botulinum toxin A may be considered in adults with spinal cord disease with urodynamic investigations showing impaired bladder storage for whom antimuscarinic drugs were ineffective or poorly tolerated. • Consider bladder wall injection with botulinum toxin A for children and young people with spinal cord disease with urodynamic investigations showing impaired bladder storage and for whom antimuscarinic drugs were ineffective or poorly tolerated. • A catheterization regimen is needed in most people with neurogenic lower urinary tract dysfunction after botulinum toxin A treatment. The patient must be able and willing to manage such a regimen should urinary retention develop after the treatment. • Monitor residual urine volume in patients who are not using a catheterization regimen during treatment with botulinum toxin A. • Monitor upper urinary tract in patients at risk of renal complications (e.g., those with high intravesical pressures on filling cystometry) during treatment. • People should be offered repeated botulinum toxin A injections and have prompt access to repeat injections when symptoms return.
National Institute for Health and Clinical Excellence (NICE): **Urinary Incontinence: The Management of Urinary Incontinence in**	• Generic oxybutynin IR should be offered to women with OAB or mixed urinary incontinence as first-line therapy. • If patients cannot tolerate generic IR oxybutynin, darifenacin, solifenacin, tolterodine, trospium, or an ER or transdermal oxybutynin formulation should be considered. • Patients should be counseled on associated adverse events common

Clinical Guideline	Recommendation(s)
Women (2006)[23]	with anticholinergic drug therapy. • Flavoxate is not recommended for the treatment of urinary incontinence or OAB in women. • Imipramine is not recommended for the treatment of urinary incontinence or OAB in women. • Duloxetine is not recommended for first-line treatment of stress urinary incontinence. It may be offered as a second-line therapy for women who are not candidates for or are opposed to surgical treatment of stress urinary incontinence. • Desmopressin should be considered for the reduction of nocturia in women with urinary incontinence of OAB. • Systemic hormone replacement is not recommended for the treatment of urinary incontinence or OAB in women. • Intravaginal estrogens are recommended for the treatment of OAB symptoms in postmenopausal women with vaginal atrophy.

Conclusions

The urinary antispasmodics are approved by the Food and Drug Administration (FDA) for the management of overactive bladder (OAB), defined by urinary urgency, with or without urge incontinence, usually with frequency and nocturia.[1] In the absence of treatment, urinary incontinence has been show to greatly reduce quality of life in areas such as physical and social functions as well as mental and general health.[2] The urinary antispasmodics include the muscarinic receptor antagonists (darifenacin [Enablex®], fesoterodine [Toviaz®], oxybutynin [Ditropan®], solifenacin [VESIcare®], tolterodine [Detrol®] and trospium [Sanctura®] and beta-3 adrenergic receptor agonists (mirabegron [Myrbetriq®]) . The antimuscarinics 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 frequency of dosing and incidence of adverse events, extended-release (ER, LA, XL, and XR) formulations are available. Oxybutynin is the also available in a topical gel (Gelnique®) and transdermal patch (Oxytrol®). Both fesoterodine and tolterodine are metabolized to the active metabolite 5-hydroxymethyl tolterodine; however fesoterodine is not dependant of cytochrome P450 2D6 for metabolism. Mirabegron acts on the beta-3 adrenergic receptor to increase bladder capacity via relaxation of the detrusor smooth muscle. This novel mechanism may improve tolerability compared to other urinary antispasmodics.[19] Several of the muscarinic receptor antagonists are available generically.

The results from clinical studies have demonstrated each of the urinary antispasmodics to be more effective compared to placebo with regard to improvements in micturition frequency, urgency and urge incontinence episodes. Head-to-head studies with agents within the class have not consistently found one agent to be “superior” to other agents within the class. A large Cochrane review by Madhuvrata et al reported that IR formulations of oxybutynin, tolterodine and trospium have a similar efficacy, but oxybutynin was associated with more adverse events. In addition, solifenacin improved symptoms of OAB more so than tolterodine IR, while fesoterodine was more effective than tolterodine LA. Current consensus guidelines recommend the use of urinary antispasmodics in patients with OAB symptoms caused by detrusor overactivity with or without urgency incontinence.[67] The American Urological Association recommends the use of behavioral therapies as first-line treatment (e.g., 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. No one urinary antispasmodic is recommended over another; however, ER formulations should be used when available due to lower rates of dry mouth.[21,22]

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