Therapeutic Class Review
Urinary Antispasmodics

Therapeutic Class

- **Overview/Summary:** The urinary antispasmodics are Food and Drug Administration (FDA)-approved for the treatment of overactive bladder (OAB) and include darifenacin (Enablex®), fesoterodine (Toviaz®), 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®).[1-12] The International Continence Society defines OAB as urinary urgency, with or without urge incontinence, usually with frequency and nocturia.[13] 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.[14] These agents act as antagonists of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle in the bladder and decreasing bladder contractions.[1-12] The urinary antispasmodics have a similar safety and efficacy profile and primary 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. Solifenacin and darifenacin are believed to be "uroselective" for the M3 receptor in the bladder; however, the clinical implications of this suggestion have not been established.[15]

  Because of the various muscarinic receptor subtypes and locations in organs throughout the body, these agents 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.[1-12] 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.[16] Trospium, a water soluble compound, has low penetration through the blood brain barrier and the gut; however, clinical studies have not demonstrated a lower incidence of adverse events with trospium compared to others within the class.[9,10,15] Fesoterodine, a prodrug, is metabolized by plasma esterases to 5-hydroxymethyl tolterodine, the same active metabolite as tolterodine.[1,2,12]

Table 1. Current Medications Available in the Class[1-12]

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	a
Oxybutynin (Ditropan®, Ditropan XL®, Gelnique®, Oxytrol®)	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex	Extended-release tablet: 5 mg	a *

	neurogenic bladder, treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition	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 (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: 2 mg 4 mg Tablet: 1 mg 2 mg	a *
Trospium (Sanctura®*, Sanctura XR®)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	Extended-release capsule: 60 mg Tablet: 20 mg	a *

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% 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).[17]
- Solifenacin significant 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 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) in addition to significantly reducing the number of leakage episodes/24 hours (WMD, -0.30; 95% CI -0.53 to -0.08) and urgency

episodes/24 hours (weighted mean difference [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.[17]

- 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 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).[17]
- A meta-analysis comparing oxybutynin IR to tolterodine IR 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 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 (RR, 0.54; 95% CI, 0.48 to 0.61).[18]
- Studies have not consistently demonstrated a lower incidence of adverse events with oxybutynin XL compared to the IR formulation. 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; $P=0.09$). The results from a third study suggest a similar incidence between formulations (68 vs 72%; *P* value not reported).[19-21]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Antimuscarinics may be used in children if there are symptoms that suggest detrusor overactivity. Bladder training is also recommended for children.[13]
  - Antimuscarinic therapy is recommended for male and female patients with overactive bladder symptoms caused by detrusor overactivity with or without urgency incontinence.[13]
  - Antimuscarinic therapy in addition to non-pharmacological therapy may be considered for select cognitively intact elderly patients with urge urinary incontinence.[13]
  - Clinicians should offer oral antimuscarinics including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium as second-line therapy (following behavioral modification), and no single agent is recommended over another.[13,22-25]
  - If both an immediate-release (IR) and an extended-release (ER) formulation are available, the ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth.[23]
  - 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.[13,22-25]
- Other Key Facts:
  - Flavoxate, oxybutynin (IR and XL) and trospium IR have been available generically for many years while tolterodine IR recently became available generically in June 2012.[26]
  - The oral extended-release and transdermal formulations may be associated with a lower incidence of dry mouth compared to the immediate-release products.[1-12]
  - Oxybutynin is the only agent within the class that is available in a transdermal formulation.
  - In April 2012 the FDA-approved a 3% oxybutynin gel, previously only available in 10% strength.[27]

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Overview/Summary

The urinary antispasmodics that are Food and Drug Administration (FDA)-approved for the treatment of overactive bladder (OAB) include darifenacin (Enablex®), fesoterodine (Toviaz®), 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.[1-12] 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.[3,4] The International Continence Society defines OAB as urinary urgency, with or without urge incontinence, usually with frequency and nocturia.[13] 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.[14] In April 2012 the FDA-approved a 3% oxybutynin gel, previously only available in 10% strength. Flavoxate, oxybutynin (IR and XL) and trospium IR have been available generically for many years while tolterodine IR recently became available generically in June 2012.[15,16]

The urinary antispasmodics used for the treatment of urinary incontinence belong to a class of anticholinergic compounds known as muscarinic receptor antagonists.[1-12] These agents act as antagonists of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle in the bladder and decreasing bladder contractions.[1-12] These agents are contraindicated in patients with urinary retention, severe decreases in gastrointestinal motility or uncontrolled narrow-angle glaucoma. All of the urinary antispasmodics 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.[17]

Because of the various muscarinic receptor subtypes and locations in organs throughout the body, these agents 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.[18] 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.[19] No other urinary antispasmodic is available in a topical formulation. Trospium, a water soluble compound, has low penetration through the blood brain barrier and the gut; however, clinical studies have not demonstrated a lower incidence of adverse events with trospium compared to others within the class.[9,10,17] Fesoterodine, a prodrug, is metabolized by plasma esterases to 5-hydroxymethyl tolterodine, the same active metabolite as tolterodine.[1,2,12]

Current clinical practice guidelines recommend urinary antispasmodics as first-line pharmacological therapy of OAB.[13,20-23] According to the National Institute for Health and Clinical Excellence, flavoxate is not recommended for the treatment of urinary incontinence or OAB in women.[20] Head-to-head studies have not consistently demonstrated one urinary antispasmodic agent to be more effective than another. A recent Cochrane systematic review of 86 clinical studies reported that oxybutynin and tolterodine IR formulations are equally effective while tolterodine was better tolerated. Fesoterodine was more effective than tolterodine LA on various patient reported- and clinical outcomes, but at a greater risk of discontinuation due to adverse events. Lastly, solifenacin was found to be more effective and better tolerated compared to tolterodine.[24]

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	a
Oxybutynin (Ditropan®, Ditropan XL®, Gelnique®, Oxytrol®)	Urinary antispasmodic	a *
Solifenacin (Vesicare®)	Urinary antispasmodic	-
Tolterodine (Detrol®, Detrol LA®)	Urinary antispasmodic	a *
Trospium (Sanctura®, Sanctura XR®)	Urinary antispasmodic	a *

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[1-12,18]

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	a *			
Fesoterodine	a *			
Flavoxate				a
Oxybutynin	a * (XL)	a †(XL)	a (IR)	
Solifenacin	a *			
Tolterodine	a *			
Trospium	a *			

ER, LA, XL, XR=extended-release.
***** In patients with symptoms of urge urinary incontinence, urgency, and urinary frequency.
† In pediatric patients ≥6 years of age with symptoms of detrusor overactivity associated with a neurological condition.

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[1-12,18]

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
Oxybutynin	6 (IR) ~9.36 (XL)	<0.1	Desethyloxybutynin	2 to 3 (IR) 13.2 (XL)
Solifenacin	90	69	4R-hydroxy solifenacin	45 to 68

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
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.

Clinical Trials

Although used for urinary incontinence, flavoxate has not consistently demonstrated efficacy in randomized, controlled trials for this condition.[25] 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.[26-65]

In a pooled analysis of three double-blind, multicenter, randomized controlled trials, statistically significant improvements in all overactive bladder (OAB) symptoms (except nocturnal awakenings) occurred with both darifenacin 7.5 mg and 15 mg compared to placebo at 2, 6 and 12 weeks. At 12 weeks, symptoms of incontinent episodes improved from baseline by 69% and 78% for darifenacin 7.5 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).[26] 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).[27] 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 (P<0.05). Darifenacin was comparable to placebo with regard to object-recall while significantly greater memory deterioration was observed with oxybutynin XL compared to placebo (P<0.05).[28]

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 treatment (P<0.0001 for all).[42]

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 (N=896), 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 for patients receiving fesoterodine compared to placebo.[29] 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 treatment was associated with a significantly higher responder rate ("yes" or "no" on treatment benefit scale) compared to patients randomized to placebo (74 vs 45%; P<0.001).[30] 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, and approximately half of the patients in the 4 mg group needed an increase to the 8 mg dose in order to achieve satisfactory control of symptoms.[43] 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).[31] 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).[44] 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).[45]

Various studies have compared the safety and efficacy of oxybutynin IR and XL formulations to one another, generally reporting no significant difference in efficacy between the formulations and with dry mouth as the most frequently reported adverse event.[46-48] 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). The results from a third study suggest a similar incidence between formulations (68 vs 72%; *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 an increased the average urine volume per void (*P*=0.0018). Application-site reactions were more common with the gel.[34] The transdermal patch formulation of oxybutynin has been found to have comparable efficacy to oxybutynin IR and tolterodine IR, in separate studies. The results of these trials also demonstrated that the transdermal formulation is associated with a lower incidence of adverse events compared to either oral agent.[35,49]

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).[52] 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).[54,55] Oxybutynin XL and tolterodine LA were directly compared in the OPERA and demonstrated similar improvements in OAB symptoms while dry mouth was more common in patients receiving oxybutynin (*P*=0.02).[56] The results of a subanalysis of OPERA did not show a difference in treatments for patients who had received previous anticholinergic treatment for OAB.[57]

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). A second study comparing oxybutynin and trospium IR formulations demonstrated that trospium was noninferior to oxybutynin 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 noninferiority). Furthermore, the change in micturitions/24 hours, and scores for urgency did not differ significantly between oxybutynin and trospium (*P*>0.05).[58,59] In two, 12-week, randomized, double-blind, placebo-controlled trials, trospium XR was associated with a statistically significant reduction in urinary frequency, incontinence episodes and increases in void 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 frequently reported by patients receiving placebo than trospium XR.[37,38] Two subanalyses in males and patients ≥75, respectively, concluded trospium XR significantly improves OAB symptoms relative to placebo in these patient populations.[39,40]

Mattiasson and colleagues compared solifenacin (5 mg 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).[60] In a 12-week double-blind, randomized controlled trial (N=1,033), patients in solifenacin 5 mg and 10 mg treatment groups 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).[36] 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).[50] In the 12-week STAR study (N=1,177), patients randomized to receive solifenacin experienced statistically significant improvements in 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.[61] In a subanaylsis 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 that there are no significant differences in quality of life, the primary endpoint, 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 when 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).[24]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Khuller et al[26] 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 per week, ≥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 2, 6 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 mg 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 placebo (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 mg and 15 mg compared to placebo (P<0.001 for both). By week two, patients randomized to receive darifenacin 7.5 and 15 mg, respectively, achieved 49 to 69% and 39 to 80% of the final treatment effect observed at week 12 for all symptoms. The greatest percentage of early improvement occurred in the number of UUI episodes/week and incontinence episodes/week. 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 6 and 13.2% with darifenacin 7.5 and 15 mg, respectively, compared to placebo (P≤0.001). At days 9 to 11 and days 12 to 14, darifenacin 7.5 mg reduced incontinence episodes by 4.5 and 7.7%, respectively, while there 15 mg dose reduced these episodes by 11.5 and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 and 15 mg, respectively, compared to placebo (*P*≤0.001 for all). Over the first two weeks of treatment, darifenacin 7.5 mg 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[27] Darifenacin 15 mg QD for two weeks vs darifenacin 30 mg QD for two weeks vs oxybutynin IR 5 mg TID for two weeks vs placebo for two weeks	DB, PC, RCT, XO Patients aged 18 to 85 years, 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 side effects 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 daily 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 daily was associated with a statistically significant reduction in the incidence of dry mouth compared to both darifenacin 30 mg daily 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[28] Darifenacin 7.5 mg QD for	DB, DD, MC, PC, PG, RCT	N=150 3 weeks	Primary: Recall on the name-face association	Primary: In terms of name-face delayed recall, oxybutynin XL therapy was associated with significantly greater memory deterioration compared to both placebo and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
two weeks, titrated up to 15 mg QD vs oxybutynin XL 10 mg QD for one week and titrated up to 15 mg for one week and 20 mg for another week vs placebo	Healthy patients aged >60 years		test, first-last name association test, misplaced objects test at week three and adverse events Secondary: Not reported	darifenacin therapy (P<0.05). In terms of first-last name recall, darifenacin was comparable with placebo 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. Treatment-related adverse events occurred in 26 patients treated with darifenacin, 22 patients taking oxybutynin XL and 16 patients receiving placebo. Secondary: Not reported
Dmochowski et al[29] Fesoterodine 4 mg 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 and rated bladder condition as causing	N=896 12 weeks	Primary: Change from baseline in the mean number of micturitions/24 hours Secondary: Change from baseline in UUI episodes/24 hours, urgency episodes/24 hours, frequency-urgency sum, nocturnal	Primary: At week 12, 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 improved in the fesoterodine treatment group compared to patients receiving placebo (-13.6

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	moderate problems on PPBC		micturitions, nocturnal urgency episodes, OAB-q, PPBC and UPS scores	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). The changes in PPBC and UPS scores significantly favored fesoterodine over placebo throughout the evaluation period at weeks 2, 6 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[30] Fesoterodine 4 mg QD vs fesoterodine 8 mg QD vs placebo	DB, MC, PC, PG, PRO, RCT Men and women ≥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, mean volume voided, number of continent days, number of urgency episodes/24 hours and adverse events	Primary: Compared to placebo, 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 decreases in the mean change in number of nocturnal micturitions (*P*<0.05), urgency episodes (*P*<0.001) and continent days per week (*P*<0.001). Patients in the fesoterodine 8 mg group showed statistically significant changes in mean volume voided per micturition (*P*<0.001), number of urgency episodes (*P*<0.001), number of daytime micturitions (*P*<0.001) and continent days per 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 mg and 8 mg groups at 61 and 69% respectively.
Chapple et al[31] Fesoterodine 4 mg QD	AC, DB, MC, PC, PRO, RCT	N=1,135 12 weeks	Primary: Change in micturitions/24	Primary: Patients in both the fesoterodine and tolterodine LA groups showed statistically significant improvements in micturitions/24 hours (fesoterodine 4

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fesoterodine 8 mg QD vs tolterodine LA 4 mg QD vs placebo	Patients >18 years old with ≥6 months of urinary urgency (≥8 micturitions/24 hours and either ≥6 urgency episodes or ≥3 UUI episodes/24 hours)		hours, number of UUI episodes and treatment response ("yes" or "no") on treatment benefit scale Secondary: Change in mean volume voided per micturition, daytime micturitions/24 hours, nocturnal micturitions/24 hours, urgency episodes/24 hours, continent days per week and adverse events	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%; *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[32] Fesoterodine 4 mg to 8 mg QD	ES, MC, OL Extension study of Chapple et al[31] for patients completing the12-week double-blind 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 HRQOL, bladder-related problems and treatment satisfaction	Primary: Of the patients enrolled in the extension study, 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 open-label 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 event during the open-label 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No clinically significant changes in residual urine volume, vital signs, electrocardiogram measurements, physical, urological or urogynaecological outcomes were reported during the open label-period. Secondary: Compared to baseline of the open-label period, significant improvements were observed at 24 months with fesoterodine for urgency episodes/24 hours, micturitions/24 hours and MVV per micturition (*P*<0.0001 for all). Significant improvements in KHQ domains were reported at 12 and 24 months compared to open-label baseline for all components with the exception of General Health Perception (*P*≤0.02 for all). Similarly, open-label treatment with fesoterodine was associated with significant improvements in ICIQ-SF scores at months 4, 12 and 24 of the open-label period (*P*<0.0001 for all). Subject's assessment of bladder-related problems were significantly improved at months 4, 12 and 24 compared to scores during the open-label baseline period (*P*<0.0001 for all).
Burgio et al[33] Oxybutynin XL 5 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 per day	N=143 8 weeks	Primary: 24-hour post treatment 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 reduction in the mean number of voids per day by 2.2 (-18.8%), while patients receiving oxybutynin XL had 2.09 (-16.9%) fewer voids per day compared to baseline values (*P*<0.001 for both). An equivalence analysis indicated that the post-treatment 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 the behavioral therapy group (*P*=0.007). Greater reductions in urgency scores and lower maximum scores for urgency were reported in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				oxybutynin XL group compared to patients receiving behavior therapy (*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%, 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 Patient Global Ratings for activity restriction (*P*=0.56). At week eight, significantly fewer men who completed behavioral treatment reported bothersome side effects 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[34] Oxybutynin topical gel 1 g applied QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with OAB, urge or mixed UI with predominance of UUI episodes as well as ≥8 urinary voids per day and ≥4 UUI episodes per day	N=789 12 weeks	Primary: Change in mean number of incontinence episodes per day Secondary: Mean change in urinary frequency, urinary volume per void, number of nocturia episodes, percent of patients achieving complete	Primary: Patients receiving oxybutynin gel reported a significantly greater decrease in the mean number of daily incontinence episodes compared to placebo (-3.0 vs -2.5 per day; *P*<0.0001). Secondary: Oxybutynin gel was associated with a significant improvement in the mean number of episodes of urinary frequency (-2.7 vs -2.0 for placebo; *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 per day for oxybutynin gel compared to -0.65 per day for placebo; *P*=0.1372). Complete urinary continence was demonstrated in 27.8% patients receiving

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			urinary continence (no episodes logged in bladder diary) and safety	oxybutynin gel patients compared to 17.3% of patients randomized to the placebo group (*P* value not reported). Compared to placebo, oxybutynin 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[35] Oxybutynin transdermal patch applied twice weekly vs tolterodine LA 4 mg QD vs placebo	DB, RCT Patients ≥18 years of age with OAB and ≥4 UUI episodes, with either pure urge or a predominance of urge episodes, ≥24 voids, and an average urinary void volume ≤350 mL	N=361 12 weeks	Primary: Change in the number of daily urinary incontinence episodes, proportion of patients achieving complete continence, frequency of daily micturitions, average urinary volume per void, quality of life and adverse events Secondary: Not reported	Primary: The oxybutynin transdermal patch was associated with a statistically significant reduction in the number of urinary incontinence episodes per day from baseline compared to placebo (75 vs 50%; *P*=0.0137). The therapeutic effect was observed after two weeks of therapy and was maintained for the duration of the study. Tolterodine LA was associated with a statistically significant reduction in the number of urinary incontinence episodes per day from baseline compared to placebo (75 vs 50%; *P*=0.0011). Patients randomized to receive the oxybutynin transdermal patch or tolterodine LA experienced comparable reductions from baseline in the number of urinary incontinence episodes per day (*P*=0.216). A greater proportion of patients randomized to either oxybutynin patch or tolterodine experienced complete continence compared to placebo (39 and 38 vs 22%; *P*=0.014). Both treatment groups experienced comparable reductions from baseline in the frequency of micturitions per day (*P*=0.276). Both treatment groups experienced comparable improvements from baseline in the average urinary volume per void (*P*=0.769). Both treatments increased urinary volume per void compared to placebo (*P*<0.01). Both treatment groups were associated with comparable improvements from baseline in the overall Global Assessment of Disease State scores (*P*=0.186). Both therapies led to statistically significant improvements from baseline in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Global Assessment of Disease State scores compared to placebo ($P \leq 0.01$). More treatment-related adverse events occurred with tolterodine LA compared to the transdermal oxybutynin therapy (*P* value not reported). The most common treatment-related adverse events in the transdermal oxybutynin group were application site reactions, including erythema and pruritus. Anticholinergic adverse events (i.e. dry mouth, constipation) were the most common treatment-related adverse events reported in association with tolterodine LA therapy. Secondary: Not reported
Chapple et al[36] Solifenacin 5 mg QD vs solifenacin 10 mg QD vs tolterodine IR 2 mg BID vs placebo	DB, MC, RCT Patients ≥18 years of age with symptoms of OAB for ≥3 months, ≥8 daily voids and ≥3 daily urgency or incontinence episodes during three-day voiding diary period	N=1,033 12 weeks	Primary: Change in the mean number of urgency episodes and all incontinence and UUI episodes Secondary: Change in the mean number of voids/24 hours, volume voided per void and adverse events	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 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 mg and 10 mg was associated with statistically significant reductions 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%; $P=0.112$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 mean volume voided per each void were reported 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* value 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).
Dmochowski et al[37] 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 mean number of daily toilet voids and the number of UUI episodes Secondary: Urgency severity, volume voided per void, dry rate (defined as no UUI episodes during the diary collection period), responder	Primary: Treatment with trospium XR resulted in a significant reduction from baseline in the mean number of toilet voids per day compared to placebo at week 12 (19.3 vs 13.1%; *P*<0.05). At week 12, patients treated with trospium XR experienced a statistically significant reduction from baseline in daily UUI episodes compared to patients randomized to 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 at week 12 (*P*<0.001). Treatment with trospium XR resulted in a significant increase in the mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			rate (≤8 toilet voids/day and no UUI episodes) and adverse events	volume voided per void from baseline compared to placebo at week 12 (*P*<0.01). A significantly greater proportion of patients treated to trospium XR were "dry" during the diary collection period compared to patients randomized to placebo (*P*<0.05). A significantly greater proportion of patients treated with trospium XR responded to therapy compared to patients randomized to 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. Central nervous system effects, such as headache, occurred in 1.8% of those given trospium XR and 2.1% in the placebo group.
Staskin et al[38] Trospium XR 60 mg QD vs placebo	DB, OL, RCT Patients ≥18 years of age with symptoms of OAB ≥6 months	N=601 12 weeks; 9 months OL phase	Primary: Calculated changes in daily urinary frequency and daily UUI episodes Secondary: Normalization rate (defined as no UUI episodes and a daily void frequency ≤8), urgency severity, volume voided per void, the number of urgency voids per day and adverse events	Primary: Treatment with trospium XR resulted in a significant improvement in daily urinary frequency from baseline compared to placebo at week 12 (*P*<0.01). Treatment with trospium XR resulted in a significant reduction in daily UUI episodes from baseline compared to placebo at week 12 (*P*<0.001). Subjects treated with trospium XR experienced an average decrease in daily voids from 12.8 per day at baseline to fewer than 10.0 per day at week 12 (*P*<0.001). Participants treated with trospium XR experienced an average decrease from 4.1 UUI episodes per day 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)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Treatment with trospium XR resulted in a significant improvement in daily urgency severity, volume voided per void and the number of urgency voids per day 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% in 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[39] Trospium XR 60 mg QD vs placebo	DB, MC, PC, PG, RCT, SA Subanalysis of Dmochowski et al[37] and Staskin et al[38] 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 in three days	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 toilet voids, volume voided per toilet void and OAB-SCS	Primary: In male patients treated with trospium XR there was a significantly greater decrease from baseline in the mean number of daily toilet voids compared to placebo (-2.5 vs -1.5; *P*<0.05) and daily UUI episodes (-2.3 vs -1.4; *P*<0.05). 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 (-0.9 vs -0.5; *P*<0.05) voids at week 12. There was no difference in daily urgency severity associated with toilet voids between trospium XR and placebo at 12 weeks (*P*=0.22). A significant reduction in daily urgency frequency associated with toilet voids was reported in patients treated with trospium XR compared to placebo (*P*=0.007). At week 12, trospium XR significantly increased the mean volume voided 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 the placebo group (-10.4 vs -6.3; *P*=0.010).
Sand et al[40] Trospium XR 60 mg QD	DB, MC, OL, PC, PG, RCT, SA	N=143 21 weeks	Primary: Change in the average number of	Primary: At 12 weeks, trospium XR was associated with significantly greater reductions in the mean number of toilet voids per day compared to placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	Subanalysis of Dmochowski et al[37] and Staskin et al[38] 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	(12 weeks DB, 9 weeks OL)	toilet voids per day and frequency of UUI episodes per day at 12 weeks Secondary: Urgency severity associated with toilet voids, volume voided per toilet void, frequency of nocturnal toilet voids and frequency of toilet voids associated with urgency, quality of life measures, safety and tolerability	(-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 volume voided per toilet void was achieved with trospium XR treatment group compared to 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). 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 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 differences were only significant for the average change in severity measures.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 to be 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[41] (Cohort 1): Oxybutynin IR 2.5 mg TID vs darifenacin IR* 2.5 mg TID (Cohort 2): oxybutynin IR 5 mg TID vs darifenacin ER 15 mg QD (Cohort 3): oxybutynin IR mg TID vs	DB, DD, RCT, XO Patients 18 to 75 years of age, with detrusor overactivity within six months, either idiopathic or neurogenic (secondary to a neurological lesion present for ≥12 months), with ≥2 associated symptoms (average of ≥7 micturitions/day, ≥7 episodes of urgency/week, ≥1	N=65 21 days	Primary: Ambulatory urodynamics, responder rate (patients achieving 25 to 30% improvement), salivary flow and adverse events Secondary: Not reported	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 darifenacin ER 30 mg therapy (*P* value not reported). Dry mouth and constipation were the most frequently reported adverse events. Within each of the three cohorts, patients receiving oxybutynin IR reported dry mouth more frequently than patients on darifenacin therapy (*P* value not reported). In contrast, constipation was reported more often by patients taking darifenacin therapy. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
darifenacin ER 30 mg QD	UUI episode/week necessitating change of clothing or pads)			
Zinner et al[42] Darifenacin 7.5 to 15 mg QD	OL, MC Patients ≥18 years of age with OAB symptoms for ≥6 months prior to randomization with a baseline score of ≥2 on the PPBC questionnaire at screening and were naïve to darifenacin, but 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 and PSTB scores, 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, and 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 -2.8; *P*=0.0296). The mean change in 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%,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[43] 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" on 12 question treatment satisfaction questionnaire Secondary: Change form baseline in nocturnal micturitions, severe micturition-related urgency episodes and frequency-urgency sum/24 hours and reported adverse events	Primary: Patients experienced a decrease 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%) 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[44]	DD, DB, MC, PC, RCT	N=1,712	Primary: Change from	Primary: Over 12 weeks of treatment, the mean reduction in UUI episodes/24 hours

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fesoterodine 8 mg QD vs tolterodine LA 4 mg QD vs placebo	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	12 weeks	baseline in UUI episodes/24 hours Secondary: Mean void volume, voids, nocturnal voids, urgency episodes, frequency-urgency sum/24 hours, PPBC, UPS and OAB-q scores	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 mean void volumes (mL) 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 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, no difference was reported between fesoterodine and tolterodine LA (*P*=0.054). The sum of all voids over 24 hours (frequency-urgency sum) 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 tolterodine LA and placebo (*P*<0.001 for both comparisons). Changes between tolterodine LA and placebo were also significant (*P*<0.001). The proportion of patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[45] Fesoterodine 8 mg QD vs tolterodine LA 4 mg QD vs placebo	DB, DD, PC, PG, MC, RCT Patients ≥18 years of age with OAB symptoms for ≥3 months, ≥1 UUI episode and ≥8 micturitions/24 hours in a three-day bladder diary	N=2,411 12 weeks	Primary: Change from baseline in UUI episodes Secondary: Change from baseline in 24-hour micturitions, nocturnal micturitions, urgency episodes, severe urgency episodes, frequency-urgency sum, three-day diary-dry rate, and mean voided	Primary: The median percentage reduction in UUI episodes at week 12 was 100% in all three treatment groups. The treatment difference between fesoterodine and tolterodine LA treatment was statistically significant (*P*=0.0093), as well as when compared to placebo (*P*=0.0001). Secondary: 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 improved with fesoterodine compared to placebo after 12 weeks (-33 vs -27.3%; *P*<0.05), but not compared to tolterodine LA (-33.3 vs -33.3%; *P*=0.1661).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			volume per micturition	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). Urgency episodes did not significantly improve with tolterodine LA compared to placebo (*P*<0.05). Following 12 weeks of treatment, 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 both tolterodine LA and placebo (*P*<0.05 for both). No significant differences were reported between tolterodine LA and placebo. At 12 weeks, 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 the tolterodine LA treatment group (*P*<0.05). No significant differences were reported between fesoterodine and tolterodine LA with regard to the mean voided volume per micturition; however, both treatment groups experienced statistically significant improvements relative to placebo (*P*<0.05 for both).
Anderson et al[46] Oxybutynin XL 5 mg QD, titrated up in 5 mg increments 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	N=105 Duration not specified	Primary: Change in the number of mean weekly UUI episodes Secondary: Proportion of patients achieving resolution of UUI episodes, number of	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 in the oxybutynin IR group experienced resolution of urge incontinence (*P*=0.70). The total number of incontinence episodes decreased from 29.3 to 6.0 with oxybutynin XL and from 26.3 to 3.8 with oxybutynin IR therapy (*P*=0.6).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	urge incontinence episodes weekly (not on medication), previously responsive to oxybutynin therapy		incontinence episodes, proportion of those patients achieving continence, total void frequency and adverse events	Continence was achieved in 41% of the oxybutynin XL and 40% of the oxybutynin IR group (*P*=0.90). Normal void frequency was significantly 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[47] Oxybutynin XL 15 mg QD, titrated up in 5 mg increments vs oxybutynin IR 5 mg TID, titrated up in 5 mg increments	AC, DB, MC, RCT Patients ≥18 years of age with UUI	N=125 9 weeks	Primary: Change in the number of mean weekly incontinence episodes, voluntary micturitions, volume of urine voided per micturition, frequency and severity of urgency and adverse events Secondary: Not reported	Primary: There was no statistically significant difference between the two treatment groups in the number of incontinence episodes per week (*P*=0.404), voluntary micturitions (*P*=0.286), volume of urine voided per micturition (*P*=0.533), frequency of urgency (*P*=0.116) or severity of urgency (*P*=0.255). Both oxybutynin XL and IR 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). 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 the oxybutynin IR group (*P* value not reported). Secondary: Not reported
Versi et al[48] Oxybutynin XL 5 mg QD, titrated up in 5 mg increments weekly to a	DM, MC, PG, RCT Patients 59.2 years of age on	N=226 ≤7 weeks	Primary: Change in the number of mean weekly incontinence episodes, proportion	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
maximum of 20 mg QD vs oxybutynin IR 5 mg QD, titrated up in 5 mg increments weekly to a maximum of 20 mg QD	average, with 7 to 45 UUI episodes per week, ≥4 days of incontinence/ week and prior response to an antimuscarinic agent		of patients reporting the absence of urge incontinence and side effects Secondary: Not reported	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[49] 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 UI with a predominance of urge symptoms, >3 UUI episodes, and experienced symptomatic improvement after six weeks of oral oxybutynin therapy	N=76 6 weeks	Primary: Change in the number of daily incontinence episodes, and adverse events Secondary: Not reported	Primary: Both oxybutynin transdermal 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 the transdermal treatment group (94 vs 38%; *P*<0.001). Of patients randomized to the transdermal oxybutynin therapy, 67% reported a reduction in dry mouth severity compared to previous oral therapy. Secondary: Not reported
Herschorn et al[50] 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	N=132 8 weeks	Primary: Incidence and severity of dry mouth and treatment-emergent adverse events Secondary: Changes in urgency, incontinence,	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 oxybutynin IR treatment group (*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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hours)		frequency, nocturia and volume voided per micturition	Overall, significantly fewer solifenacin patients compared to oxybutynin IR-treated patients experienced one or more adverse events during the study (72 vs 92%; *P*=0.003) and 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 diary-documented urgency, incontinence, frequency, nocturia and volume voided per micturition from baseline (*P* value s not reported). Both solifenacin and oxybutynin IR significantly improved patient reported outcomes on questionnaires for PPBC and Overactive Bladder symptoms with no differences between treatment groups (*P* values not reported).
Mallone-Lee et al[51] Oxybutynin IR 2.5 mg BID titrated up 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, voided volume per micturition, pads used in 24 hours	Primary: Oxybutynin IR treatment was associated with a greater incidence of one or more adverse events compared to tolterodine IR (81 vs 69%; *P*=0.01). Oxybutynin IR treatment was associated with a greater incidence of dry mouth compared to tolterodine IR (61 vs 37%; *P*=0.01). Significantly more patients in the oxybutynin IR group experienced severe 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 in each void (*P*=0.90). At 10 weeks, both treatment groups were associated with comparable improvements from baseline in the number of pads used per day (*P*=0.43).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 mean voided volume per micturition was achieved within four weeks in both treatment groups. The maximal effect on voiding frequency occurred within 4 to 10 weeks in each treatment group.
Harvey et al[52] Oxybutynin IR 2.5 to 5 mg TID vs tolterodine IR 1 to 2 mg BID	MA of 4 RCT, DB 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 mean voided volume per micturition 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; *P* value not reported). 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; *P* value not reported). Oxybutynin IR was associated with a statistically significant increase from baseline in the volume voided per micturition compared to tolterodine IR (WMD, 8.24; 95% CI, 2.38 to 14.11; *P* value not reported). 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; *P* value not reported). 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; *P* value not reported).
Kilic et al[53] Oxybutynin IR 0.4 mg/kg, divided TID vs	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:	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tolterodine IR 1 mg BID; patients <5 years of age received 0.1 mg/kg daily, divided BID			Not reported	(*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
Sand et al[54] Oxybutynin XL 10 mg QD vs tolterodine IR 2 mg BID	DB, MC, PG, RCT Patients (average age of 58) with OAB and 7 to 50 UUI episodes per week and ≥10 voids/24 hours; patients with mixed incontinence were eligible if urge episodes predominated	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 (*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[55]	DB, MC, PG, RCT	N=378	Primary: Change in the	Primary: At 12 weeks, oxybutynin XL was significantly more effective at reducing the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
OBJECT Study Oxybutynin XL 10 mg QD vs tolterodine IR 2 mg BID	Patients ≥18 years of age with OAB and 7 to 50 UUI episodes per week and ≥10 voids/24 hours; patients with mixed incontinence were eligible if urge episodes predominated	12 weeks	number of UUI episodes Secondary: Change in the number of total incontinence episodes, micturition frequency and adverse events	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 comparisons). 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 compared to the 33.2% in the tolterodine IR treatment group (*P*=0.32).
Diokno et al[56] 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 episodes per week and ≥10 voids/24 hours; patients with mixed incontinence were eligible if urge episodes predominated	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	Primary: The oxybutynin XL and tolterodine LA treatment groups experienced comparable weekly reduction from baseline in the number of UUI episodes (*P*=0.13). Secondary: 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). Oxybutynin XL and tolterodine LA regimens were associated with a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			frequency and adverse events	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[57] OPERA Study Oxybutynin XL 10 mg QD vs tolterodine LA 4 mg QD	DB, MC, PG, RCT, SA Subanalysis of the OPERA study[43], 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 patients reporting complete continence, micturition frequency and adverse events	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: 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%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Zellner et al[58] 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, mean voided volume, qualitative symptoms changes, scores on VAS, KHQ, SF-36 and adverse events	Primary: The absolute reduction in the number of UUI episodes per week 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. Noninferiority 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 noninferiority margin of 3.5 UUI episodes per week. 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 (-0.585 vs -0.620, respectively; *P*=0.12) or increase in micturition volume (*P*=0.0881).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				At the final visit, 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). For 38.5% of the trospium IR group and 36.1% of the oxybutynin IR group, there was no difference in health transition (*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, and severe adverse events 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[59] 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	N=358 52 Weeks	Primary: Maximum cystometric bladder capacity Secondary: Change in the volume at the first sensation to void, volume at first	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	neurological condition		unstable contraction, micturition frequency, subjective physician appraisal of efficacy and adverse events	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 the trospium IR treatment group (*P*<0.01). The weekly risk of experiencing an adverse event was 0.027 with trospium IR and 0.045 with oxybutynin IR therapy.
Mattiasson et al[60] Solifenacin 5 mg to 10 mg QD vs solifenacin 5 mg 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 mean number of micturitions/24 hours at eight weeks Secondary: Change from baseline to week 16 in mean number of micturitions/24 hours, mean urgency frequency/24 hours, mean number of incontinence and urgency incontinence	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 lower for patients receiving combination therapy with 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 significantly lower UUI episodes compared to solifenacin monotherapy (-1.38 vs -1.13, respectively; *P*=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			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	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 combination treatment 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 discontinuation occurred in 5.3% of patients, with the most common being gastrointestinal in nature. No clinically relevant changes in physical examination were reported.
Chapple et al[61] STAR Study Solifenacin 5 mg QD, offered to titrate up to 10 mg QD after four weeks of therapy vs tolterodine LA 4 mg daily	DB, DD, 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, mean volume voided per	Primary: Solifenacin therapy was associated with a statistically significant reduction in micturition frequency from baseline compared to tolterodine LA (*P*=0.004). Secondary: Solifenacin therapy was associated with a statistically significant reduction in the number of urgency episodes from baseline compared to tolterodine LA (*P*=0.035). Solifenacin therapy was associated with a statistically significant reduction in the number of UUI episodes from baseline compared to tolterodine LA (*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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			micturition, incontinence pad utilization and adverse events	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 therapy was associated with a statistically significant increase in the mean volume voided per micturition compared to tolterodine LA (*P*=0.01). Solifenacin therapy was associated with a statistically significant reduction in incontinence pad utilization from baseline compared to tolterodine LA (*P*=0.0023). 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 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[62] STAR Study Solifenacin 5 mg QD vs tolterodine LA 4 mg QD	DB, DD, PG, PRO, RCT, SA Present study is a subanalysis of Chapple et al[61] for 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	Primary: At week four, both solifenacin and tolterodine LA therapies 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 therapies resulted in comparable reductions in the number of urgency episodes from baseline (-1.98 vs -1.67; *P*>0.05). At week four, both solifenacin and tolterodine LA therapies resulted in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			episodes, nocturia episodes, complete continence, mean volume voided per micturition, incontinence pad utilization and adverse events	comparable reductions in the number of UUI episodes from baseline (-1.22 vs -0.91; *P*>0.05). At week four, solifenacin therapy was associated with a significant 44.4% reduction in the number of overall incontinence episodes from baseline compared to tolterodine LA (-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 percentage of patients randomized to solifenacin experienced complete continence compared to tolterodine LA-treated patients (39 vs 34%; *P*>0.05). At week four, both solifenacin and tolterodine LA therapies resulted in comparable increases from baseline in the mean volume voided per micturition (*P*>0.05). At week four, both solifenacin and tolterodine LA therapies 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 incidence of constipation was 3.0 and 1.2% and blurred vision was reported in 0.2 and 1.2% of patients receiving solifenacin and tolterodine LA, respectively. The rates of 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[63] Solifenacin 5 mg QD	OL, PRO, RCT, SA Subanalysis of	N=48 12 weeks	Primary: Change in PBC, TVV, VVPM, micturition	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs tolterodine LA 4 mg QD	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		frequency, urgency, incontinence, nocturia/24 hours and adverse events Secondary: Not reported	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 observed 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 tolterodine LA improved micturition frequency at the final visit (*P*<0.05), but not the first two. No difference in improvement was reported between solifenacin and tolterodine LA treatment (*P*=0.87). Patients receiving solifenacin experienced an improvement in urgency at 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 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 the tolterodine LA group (*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,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				constipation and palpitations were the most frequently reported adverse events among patients in both treatment groups.
Armstrong et al[64] Oxybutynin XL 10 mg QD vs tolterodine LA 4 mg QD vs tolterodine IR 2 mg BID	MA Present study is a MA of the OPERA and OBJECT studies[55,56]	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 digestive system 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). Approximately 10% of all patients experienced a nervous system adverse event. 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). 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 in oxybutynin XL, tolterodine LA and tolterodine IR groups, respectively (*P* value not reported). Secondary: Not reported
Madhuvrata et al[24] Fesoterodine 4 mg to 8 mg QD vs oxybutynin IR 2.5 to 5 mg	MA of 86 studies Patients with a symptomatic diagnosis of OAB syndrome with or without a urodynamic	N=31,249 Up to 52 weeks	Primary: Condition-specific QOL, generic QOL and psychosocial measures Secondary: Patient	Primary: There was no significant difference between tolterodine and oxybutynin with regard to quality of life (SMD, -0.00; 95% CI, -0.18 to 0.18). The results from three studies reported a statistically significant improvement in quality of life for patients treated with solifenacin compared to tolterodine (SMD, -0.12; 95% CI, -0.23 to -0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
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 QD vs trospium IR 20 mg BID vs solifenacin 5 mg to 10 mg QD vs placebo	diagnosis of detrusor overactivity		observations, quantification of symptoms, clinician's measures, socioeconomics, other events	Treatment with fesoterodine was associated with a significant improvement in quality of life 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 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) as well 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 with solifenacin compared to tolterodine (WMD, -0.30; 95% CI, -0.53 to -0.08). Similarly, solifenacin significantly reduced urgency episodes/24 hours 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 treatment with tolterodine LA, patients taking fesoterodine reported significantly fewer 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 (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). Similar improvements in leakage episodes and micturitions/24 hours were reported for 1 mg, 2 mg and 4 mg doses of tolterodine IR administered twice-daily. There was a higher incidence of dry mouth both the 2 and 4 mg doses relative to the lower doses of tolterodine IR. When the 10 mg dose of solifenacin was compared to the 5 mg dose, there was a lower incidence of urinary frequency and urgency with the 10 mg compared to 5 mg; however a higher incidence of dry mouth was reported with the 10 mg dose. Fesoterodine 8 mg was associated with a greater clinical efficacy (patient reported cure, leakage episodes, micturition per 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 caused more 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 IR formulations; however, no significant differences in cure, improvement, leakage episodes, micturitions/24 hours, or withdrawal events were reported between the two treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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[65] Darifenacin 7.5 mg to 15 mg QD vs fesoterodine 4 mg to 8 mg QD vs 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	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) and oxybutynin oral and transdermal formulations (P≤0.01 for both). Oxybutynin IR 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 side effects compared to oxybutynin IR. The risk of adverse events were 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 side effect 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 patch, tolterodine LA, tolterodine IR and trospium (P value not reported). Secondary: A significantly greater proportion of patients treated with antimuscarinics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs tolterodine LA 2 to 4 mg QD vs trospium IR 20 mg BID vs solifenacin 5 to 10 mg QD vs placebo				returned to continence compared to placebo (*P*<0.01). There were no statistically significant differences between antimuscarinic agents. No data were available for fesoterodine for this measurement. Antimuscarinics were significantly more effective compared to placebo with regard to the change in the number of incontinence episodes per day. 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 micturitions per day 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 the number or urgency episodes per day. 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 volume voided per micturition 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).

*Not available in the United States.
Drug regimen abbreviations: ER/LA/XL/XR=extended-release, IR=immediate-release
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, DM=double-masked, FD= flexible dose, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SA=subanalysis, WMD=weighted mean difference, 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, 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, SMD=standardized mean difference, TVV=total voided volume, UI=urinary incontinence, UPS=urgency perception scale, USS=urinary sensation scale, VAS=visual analog scale, VVPM=volume voided per micturition

Special Populations

Table 5. Special Populations[1-12,18]

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	Safety and	Safety and	B	Unknown

	efficacy in children <12 years of age have not been established.	efficacy in patients with renal insufficiency have not been established.	efficacy in patients with hepatic insufficiency have not been established.		
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
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	Renal dose adjustment is required; for creatinine clearances of <30 mL/min, 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.	C	Unknown

	established.		Not recommended for use in patients with severe hepatic impairment (Child-Pugh C).		
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/min, a dose of 2 mg and dosing frequency of once-daily is recommended (LA). Not recommended for use in patients with a CrCl <10 mL/min (LA).	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 impairment (Child-Pugh C).	C	Unknown
Trospium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients (IR).*	Renal dose adjustment is recommended; for creatinine clearances of <30 mL/min, a dose of 20 mg and dosing frequency of once-daily is	Use with caution in patients with moderate to severe hepatic dysfunction.	C	Unknown

	Safety and efficacy in children have not been established.	recommended. Not recommended for use in patients with severe renal impairment (XR)			

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

Adverse Drug Events

The following table presents the most common adverse events reported with urinary antispasmodics in clinical trials. The most frequently reported adverse events with oral agents were dry mouth, constipation, blurred vision, dizziness, and headache.[1-12,18] Application site reaction was commonly reported in association with the oxybutynin gel and transdermal oxybutynin formulations.[6,7]

Table 6. Adverse Drug Events (%)[1-12,18]

Adverse Event	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin IR	Oxybutynin XL			Solifenacin	Tolterodine IR	Tolterodine LA	Trospium IR	Trospium XR
					Tablet	Patch	Gel					
Cardiovascular												
Blood pressure decreased	-	-	-	a	a	-	-	-	-	-	-	-
Blood pressure increased	-	-	-	a	a	-	-	-	-	-	-	-
Chest pain	-	-	-	-	-	-	-	-	2	-	a	a
Hypertension	a	-	-	-	a	-	-	<1.4	-	-	-	-
Hypertensive crisis	-	-	-	-	-	-	-	-	-	-	a	a
Palpitations	a	a	a	a	-	-	-	-	a	a	a	a
Peripheral edema	a	0.7 to 1.2	-	a	a	-	-	a	a	-	-	-
QT prolongation	-	-	a	-	-	-	-	a	-	-	-	-
Tachycardia	-	-	a	-	-	-	-	-	a	a	a	a
Torsades de Pointes	-	-	-	-	-	-	-	a	-	-	-	-
Sinus arrhythmia	-	-	-	a	-	-	-	-	-	-	-	-
Supraventricular tachycardia	-	-	-	-	-	-	-	-	-	-	a	a
Central Nervous System												
Anxiety	-	-	-	-	-	-	-	-	-	1	-	-
Confusion	a	-	a	a	a	-	-	-	a	a	-	-
Delirium	-	-	-	-	-	-	-	-	-	-	a	a
Depression	-	-	-	-	a	-	-	0.8 to 1.2	-	-	-	-
Disorientation	-	-	-	-	-	-	-	-	a	a	-	-
Hallucinations	a	-	-	-	-	-	-	a	a	a	a	a
Insomnia	-	0.4 to 1.3	-	5.5	a	-	-	-	-	-	-	-
Memory impairment	-	-	-	-	-	-	-	-	a	a	-	-
Nervousness	-	-	a	6.5	a	-	-	-	-	-	-	-
Somnolence	a	-	a	14	2 to 12	-	-	a	3	3	-	a
Syncope	a	-	-	-	-	-	-	-	-	-	a	a
Vertigo/dizziness	0.9 to 2.1	-	a	16.6	4 to 6	-	-	1.8 to 1.9	5	2	-	-
Dermatological												

Adverse Event	Darifen-acin	Fesoter-odine	Flavo-xate	Oxybut-ynin IR	Oxybutynin XL			Solifen-acin	Toltero-dine IR	Toltero-dine LA	Trosp-ium IR	Trosp-ium XR
					Tablet	Patch	Gel					
Anaphylactic reaction	a	-	-	-	-	-	-	-	a	a	a	a
Angioedema	a	a	-	-	-	-	-	a	a	a	a	a
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	a	-	-	a	a	-	-	-	1	-	a	a
Exfoliative dermatitis	-	-	-	-	-	-	-	a	-	-	-	-
Erythema multiforme	a	-	-	-	-	-	-	a	-	-	-	-
Pruritus	a	a	-	a	a	-	-	a	-	-	-	-
Rash	a	0.7 to 1.1	-	-	-	a	-	a	-	-	-	a
Stevens-Johnson syndrome	-	-	-	-	-	-	-	-	-	-	a	a
Urticaria	-	a	a	-	-	-	-	a	-	-	-	-
Gastrointestinal												
Abdominal distension	-	-	-	-	-	-	-	-	-	-	a	1
Abdominal pain	2.4 to 3.9	05 to 1.1	-	a	a	a	-	1.2 to 1.9	5	4	1.5	1.4
Constipation	14.8 to 21.3	4.2 to 6.0	-	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	-	-	a	7 to 9	3.2	-	-	4	a	-	-
Dry mouth	18.7 to 35.3	18.8 to 34.6	a	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	-	6	5 to 7	-	-	1.4 to 3.9	4	3	1.2	1.2
Eructation	-	-	-	a	a	-	-	-	-	-	-	-
Flatulence	-	-	-	a	a	a	-	-	-	-	1.2	1.6
Gastritis	-	-	-	-	-	-	-	-	-	-	a	a
Loose stools	-	-	-	a	a	-	-	-	-	-	-	-
Nausea	1.5 to 3.7	0.7 to 1.9	a	11.6	2 to 9	-	-	1.7 to 3.3	-	-	-	1.4
Hardened feces	-	-	-	-	-	-	-	-	-	-	-	a
Vomiting	a	-	a	a	a	a	-	<1.1	-	-	a	-
Genitourinary												
Cystitis	-	-	-	a	a	-	-	-	-	-	-	-

Adverse Event	Darifen-acin	Fesoter-odine	Flavo-xate	Oxybut-ynin IR	Oxybutynin XL			Solifen-acin	Toltero-dine IR	Toltero-dine LA	Trosp-ium IR	Trosp-ium XR
					Tablet	Patch	Gel					
Dysuria	-	1.3 to 1.6	a	a	a	2.4	-	-	2	1	-	-
Pollakiuria	-	-	-	a	a	-	-	-	-	-	-	-
Urinary hesitation	-	-	-	8.5	-	-	-	-	-	-	-	-
Urinary retention	-	1.1 to 1.4	-	6	-	-	-	1.4	-	-	1.2	a
Urinary tract infection	3.0 to 4.7	2.8 to 2.5	-	6.5	5	-	-	2.8 to 4.8	-	-	-	1.2 to 7.3
Infections												
Fungal infection	-	-	-	a	-	-	-	-	-	-	-	-
Infection	-	-	-	-	-	-	-	-	1	-	-	-
Influenza	<3	-	-	-	-	-	-	0.9 to 2.2	3	-	-	2.2
Upper respiratory tract infection	-	1.8 to 2.5	-	-	-	-	-	-	-	-	-	-
Musculoskeletal												
Arthralgia	a	-	-	a	a	-	-	-	2	-	-	-
Back pain	a	0.9 to 2.0	-	a	a	a	-	-	-	-	-	a
Dysphagia	-	-	-	a	a	-	-	-	-	-	-	-
Flank pain	-	-	-	a	a	-	-	-	-	-	-	-
Headache	6.7	-	a	7.5	6 to 10	a	-	a	7	6	-	4.2
Pain (not specified)	-	-	-	-	4 to 7	-	-	-	-	-	-	-
Pain in extremity	-	-	-	a	a	-	-	-	-	-	-	-
Pharyngolaryngeal pain	-	-	-	a	a	-	-	-	-	-	-	-
Rhabdomyolysis	-	-	-	-	-	-	-	-	-	-	a	a
Ophthalmic												
Abnormal vision	a	-	-	-	-	2.5	-	-	-	1	a	a
Accommodation abnormal	-	-	-	-	-	-	-	-	2	-	-	-
Blurred vision	-	a	a	9.6	1 to 8	-	-	3.8 to 4.8	-	-	a	a
Eye irritation	-	-	-	a	-	-	-	-	-	-	-	-
Increased ocular tension	-	-	a	-	-	-	-	-	-	-	-	-
Keratoconjunctivitis sicca	-	-	-	a	-	-	-	-	-	-	-	-
Xerophthalmia	1.5 to 2.1	1.4 to 3.7	-	-	3 to 6	-	-	<1.6	3	3	-	1.6
Other												
Accidental injury	<3	-	-	-	-	-	-	-	-	-	-	-
ALT increased	-	0.5 to 1.2	-	-	-	-	-	-	-	-	-	-

Adverse Event	Darifen-acin	Fesoter-odine	Flavo-xate	Oxybut-ynin IR	Oxybutynin XL			Solifen-acin	Toltero-dine IR	Toltero-dine LA	Trosp-ium IR	Trosp-ium XR
					Tablet	Patch	Gel					
Aptyalism	-	-	-	a	-	-	-	-	-	-	-	-
Asthenia	1.5 to 2.7	-	-	a	3 to 7	-	-	-	-	-	-	-
Blood glucose increased	-	-	-	a	a	-	-	-	-	-	-	-
Dysgeusia	-	-	-	a	a	-	-	-	-	-	a	-
Facial edema	-	a	-	-	-	-	-	-	-	-	-	-
Falls	-	-	-	a	a	-	-	-	-	-	-	-
Fatigue	-	-	-	a	a	a	-	<2.1	4	2	1.9	-
Fluid retention	-	-	-	a	-	-	-	-	-	-	-	-
Flushing	-	-	-	a	-	a	-	-	-	-	-	-
GGT increased	-	0.4 to 1.2	-	-	-	-	-	-	-	-	-	-
Hoarseness	-	-	-	a	a	-	-	-	-	-	-	-
Hyperpyrexia	-	-	a	-	-	-	-	-	-	-	-	-
Interstitial granuloma annulare	a	-	-	-	-	-	-	-	-	-	-	-
Leukopenia	-	-	a	-	-	-	-	-	-	-	-	-
Lower limb edema	-	-	-	-	-	-	-	<1.1	-	-	-	-
Sinus headache	-	-	-	a	-	-	-	-	-	-	-	-
Thirst	-	-	-	a	a	-	-	-	-	-	-	-
Tongue coated	-	-	-	a	-	-	-	-	-	-	-	-
Weight gain	a	-	-	-	-	-	-	-	1	-	-	-
Respiratory												
Asthma	-	-	-	a	a	-	-	-	-	-	-	-
Airway obstruction	a	a	-	-	-	-	-	a	-	-	-	-
Bronchitis	a	-	-	a	a	-	-	-	-	-	-	-
Cough	-	0.9 to 1.6	-	a	a	-	-	<1.1	-	-	-	-
Dry throat	-	0.9 to 2.3	-	a	a	-	-	-	-	-	a	-
Nasal congestion	-	-	-	a	-	-	-	-	-	-	-	-
Nasal dryness	-	-	-	a	a	-	-	-	-	-	-	1
Nasopharyngitis	-	-	-	a	a	-	-	-	-	-	-	2.9
Pharyngitis	a	-	-	-	-	-	-	<1.1	-	-	-	-
Rhinitis	a	-	-	-	2 to 6	-	-	-	-	-	-	-
Sinus congestion	-	-	-	a	a	-	-	-	-	-	-	-
Sinusitis	a	-	-	-	a	-	-	-	-	2	-	-

ER, LA, XL, XR=extended-release.
-Event not reported.
a Percent not specified.

Contraindications

Table 7. Contraindications[1-12,18]

Contraindications	Darifen-acin	Fesote-rodine	Flavo-xate	Oxybut-ynin IR	Oxybutynin XL			Solifen-acin	Toltero-dine IR	Toltero-dine LA	Trosp-ium IR	Trosp-ium XR
					Tablet	Patch	Gel					
Achalasia	-	-	a	-	-	-	-	-	-	-	-	-
Gastric retention	a	a	-	a	a	a	a	a	a	a	a	a
Gastrointestinal hemorrhage	-	-	a	-	-	-	-	-	-	-	-	-
Hypersensitivity to active ingredients	-	a	-	a	a	-	a	a	a	a	a	a
Hypersensitivity to fesoterodine fumarate	-	-	-	-	-	-	-	-	a	a	-	-
Hypersensitivity to tolterodine tartrate	-	a	-	-	-	-	-	-	-	-	-	-
Obstructive intestinal lesions or ileus	-	-	a	-	-	-	-	-	-	-	-	-
Obstructive uropathies of the lower urinary tract	-	-	a	-	-	-	-	-	-	-	-	-
Pyloric or duodenal obstruction	-	-	a	-	-	-	-	-	-	-	-	-
Severe decreased gastrointestinal motility	-	-	-	a	a	a	-	-	-	-	-	-
Uncontrolled narrow angle glaucoma	a	a	-	a	a	a	a	a	a	a	a	a
Urinary retention	a	a	-	a	a	a	a	a	a	a	a	a

ER, LA, XL, XR=extended-release

Warnings/Precautions

Table 8. Warnings and Precautions[1-12,18]

Warning/Precaution	Darifen-acin	Fesoter-odine	Flavo-xate	Oxybut-ynin IR	Oxybutynin XL			Solifen-acin	Toltero-dine IR	Toltero-dine LA	Trosp-ium IR	Trosp-ium LA
					Tablet	Patch	Gel					
Alcohol should not be consumed within two hours of administration.	-	-	-	-	-	-	-	-	-	-	a	a
Anticholinergic central nervous system adverse events; monitor patients for symptoms within the	-	-	-	a	a	-	-	-	-	-	-	-

Warning/Precaution	Darifen-acin	Fesoter-odine	Flavo-xate	Oxybut-ynin IR	Oxybutynin XL			Solifen-acin	Toltero-dine IR	Toltero-dine LA	Trosp-ium IR	Trosp-ium LA
					Tablet	Patch	Gel					
first few months of treatment.												
Cardiac arrhythmias; symptoms may be aggravated with use.	-	-	-	a	-	-	-	-	-	-	-	-
Case reports of angioedema	a	a	-	a	a	a	a	a	-	a	a	a
Central nervous system adverse events; Patients should not drive or operate heavy machinery until they know how the medication affects them.	a	-	-	a	-	-	-	a	-	-	-	-
Congenital or acquired QT prolongation; use caution in these patients.	-	-	-	-	-	-	-	a	a	a	-	-
Congestive heart failure symptoms may be aggravated with use.	-	-	-	a	-	-	-	-	-	-	-	-
Controlled narrow angle glaucoma	a	a	-	-	-	-	a	a	a	-	a	a
Coronary heart disease symptoms may be aggravated with use.	-	-	-	a	-	-	-	-	-	-	-	-
CYP3A4 inhibitors; Use of lower doses with strong CPY 3A4 inhibitors is recommended.	-	a	-	-	-	-	-	-	-	-	-	-
Decreased gastrointestinal motility; use with caution in patients with gastrointestinal obstructive disorders.	a	a	-	a	a	a	a	a	a	-	a	a
Dementia; use caution in patients treated with cholinesterase inhibitors due to the aggravation of symptoms.	-	-	-	a	a	-	-	-	-	-	-	-
Flammable gel; avoid open fire or smoking.	-	-	-	-	-	-	a	-	-	-	-	-
Frail, elderly patients; use caution in these patients.	-	-	-	a	-	-	-	-	-	-	-	-
Gastroesophageal reflux disease; use with caution when administering other drugs that may	-	-	-	a	a	a	a	-	-	-	-	-

Warning/Precaution	Darifen-acin	Fesoter-odine	Flavo-xate	Oxybut-ynin IR	Oxybutynin XL			Solifen-acin	Toltero-dine IR	Toltero-dine LA	Trosp-ium IR	Trosp-ium LA
					Tablet	Patch	Gel					
exacerbate esophagitis.												
Hiatal hernia symptoms may be aggravated with use.	-	-	-	a	-	-	-	-	-	-	-	-
Hypertension symptoms may be aggravated with use.	-	-	-	a	-	-	-	-	-	-	-	-
Hyperthyroidism symptoms may be aggravated with use.	-	-	-	a	-	-	-	-	-	-	-	-
Intestinal atony; use caution in these patients.	-	-	-	a	a	a	-	-	-	-	-	-
Myasthenia gravis; use caution in these patients.	-	a	-	a	a	a	a	-	a	a	-	-
Preexisting severe gastrointestinal narrowing (pathologic or iatrogenic)	-	-	-	-	a	-	-	-	-	-	-	-
Prostatic hypertrophy symptoms may be aggravated with use.	-	-	-	a	-	-	-	-	-	-	-	-
Reduced hepatic function; caution should be used in this patient population.	a	a	-	-	a	a	-	a	a	a	-	-
Reduced renal function; use caution in these patients.	-	-	-	-	a	a	-	-	a	-	-	-
Severe renal impairment; use caution in these patients.	-	a	-	-	-	a	-	a	-	a	a	a
Suspected glaucoma; use with caution.	-	-	a	-	-	-	-	-	-	-	-	-
Tachycardia symptoms may be aggravated with use.	-	-	-	a	-	-	-	-	-	-	-	-
Transfer of oxybutynin to another person through skin-to-skin contact.	-	-	-	-	-	-	a	-	-	-	-	-
Ulcerative colitis; use caution in these patients.	-	-	-	a	a	a	-	-	-	-	-	-
Urinary retention; use with caution in patients with clinically significant bladder obstruction.	a	a	-	a	a	a	a	a	a	a	a	a

ER, LA, XL, XR=extended-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[1-12,18]

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.
Darifenacin	CYP2D6 Substrates (e.g., flecainide, thioridazine and tricyclic antidepressants)	Darifenacin may increase the pharmacologic and adverse events of these agents through inhibition of CYP2D6 metabolism.
Trospium	Metformin	Concurrent use of metformin and trospium may result in decreased plasma concentrations of trospium.

Dosage and Administration

Oxybutynin, tolterodine and trospium extended-release (LA, XL, XR) formulations as well as darifenacin, fesoterodine 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[1-12,18]

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 pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis and urethrocystitis/urethrotrigonitis: Tablet: 100 mg to 200 mg TID or QID	Safety and efficacy in children <12 years of age have not been established.	Tablet: 100 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

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)
The American College of Obstetricians and Gynecologists (ACOG): **ACOG Practice Bulletin: Urinary Incontinence in Women (2005)**[20]	· Behavioral therapy may help to improve symptoms of urge and mixed incontinence. · Anticholinergic medications, oxybutynin and tolterodine, have been shown in randomized controlled clinical trials to exert a small beneficial effect in patients with urge incontinence. · No significant difference between anticholinergic agents has been reported. · The most common adverse event with anticholinergic therapy is dry mouth. Other adverse events are blurred vision, constipation, nausea, dizziness and headache.
National Institute for Health and Clinical Excellence (NICE): **Urinary Incontinence: The Management of Urinary Incontinence in Women (2006)**[21]	· Generic immediate-release (IR) oxybutynin should be offered to women with overactive bladder or mixed urinary incontinence as first-line therapy. · If patients cannot tolerate generic IR oxybutynin, darifenacin, solifenacin, tolterodine, trospium, or an extended-release or transdermal oxybutynin formulation should be considered. · Patients should be counseled on associated adverse events common with anticholinergic drug therapy. · Flavoxate is not recommended for the treatment of urinary incontinence or overactive bladder in women. · Imipramine is not recommended for the treatment of urinary incontinence or overactive bladder 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.

Clinical Guideline	Recommendation(s)
	· Desmopressin should be considered for the reduction of nocturia in women with urinary incontinence of overactive bladder. · Systemic hormone replacement is not recommended for the treatment of urinary incontinence or overactive bladder in women. · Intravaginal estrogens are recommended for the treatment of overactive bladder symptoms in postmenopausal women with vaginal atrophy.
European Association of Urology (EAU): **Guidelines on Neurogenic Lower Urinary Tract Dysfunction (2008)**[22]	· Anticholinergic agents are the most effective therapy for detrusor overactivity. · Anticholinergic agents are used to reduce detrusor overactivity and to improve bladder compliance. · Oxybutynin, tolterodine and trospium are safe and effective agents. · Due to different tolerability profiles, patients experiencing an adverse event or inadequate efficacy with one anticholinergic agent may be switched to another. · Darifenacin and solifenacin have limited clinical data in patients with neurogenic bladder overactivity.
International Scientific Committee: **Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse and Fecal Incontinence (2009)**[13]	· Antimuscarinics may be used in children if there are symptoms that suggest detrusor overactivity. Bladder training is also recommended for children. · If initial treatment is unsuccessful for enuresis or daytime symptoms, referral for a specialist's advice recommended after 8 to 12 weeks. · Antimuscarinic therapy is recommended for male patients with overactive bladder symptoms caused by detrusor overactivity with or without urgency incontinence. These agents may be used in combination with an α-blocker. · If incontinence is associated with bladder outlet obstruction, surgical treatment is recommended to relieve obstruction. α-blockers and/or 5-α reductase inhibitors may be a treatment option. There is increased evidence for the safety of antimuscarinics for overactive bladder symptoms in men, chiefly in combination with an α-blocker. · Antimuscarinic therapy is recommended for female patients with overactive bladder with or without urgency incontinence. Duloxetine may be considered for stress urinary incontinence. The initial treatment regimen should be maintained for 8 to 12 weeks before reassessing. · Antimuscarinic therapy in addition to non-pharmacological therapy may be considered for select cognitively intact elderly patients with urge urinary incontinence. Medication should be initiated at a low dose and titrated up cautiously. · α-blockers may be cautiously considered in frail men with suspected prostatic outlet obstruction. All drugs should be started at the lowest dose and titrated with cautiously. · Vasopressin has a high risk of severe hyponatremia in frail persons and should not be used. · Antimuscarinic therapy in adjunction to behavioral therapy is recommended for patients with neurogenic incontinence.
American Urological Association: **Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults**	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.

Clinical Guideline	Recommendation(s)
(2012)[23]	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 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 intradetrusor 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.

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.[13] 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.[14] The urinary antispasmodics are a class of anticholinergic compounds known as muscarinic receptor antagonists and include darifenacin (Enablex®), fesoterodine (Toviaz®), oxybutynin (Ditropan®) solifenacin (Vesicare®), tolterodine (Detrol®) and trospium (Sanctura®). These agents antagonize the

effects of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle tissue in the bladder and consequently decreasing bladder contractions. In an effort to reduce frequency of dosing and incidence of adverse events, extended-release (LA, XL, and XR) formulations are available for oxybutynin (Ditropan XL®), tolterodine (Detrol LA®) and trospium (Sanctura XR®). Oxybutynin is the only agent that is 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. Flavoxate, oxybutynin (IR and XL), trospium IR and tolterodine IR 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. 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 urinary one urinary antispasmodic is recommended over another; however, ER formulations should be used when available due to lower rates of dry mouth.

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