

Newer Agents for the Management of Overactive Bladder

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The anticholinergics tolterodine and oxybutynin are well established in the management of overactive bladder. However, their activity at muscarinic receptors distant from the target site (i.e., bladder) produces anticholinergic side effects leading to poor tolerability. In 2004, trospium, solifenacin, and darifenacin were approved by the U.S. Food and Drug Administration for the treatment of overactive bladder. Trospium is water soluble and therefore is less likely to enter the central nervous system, and solifenacin and darifenacin are more selective for the bladder than older agents. Although these attributes could improve tolerability, clinical trials comparing relevant agents to validate this are lacking. Trials have shown that these newer agents decrease the frequency of incontinence episodes, the number of voids per day, and the number and severity of urgency episodes compared with placebo. These agents also have been shown to improve quality of life in women with overactive bladder and urinary incontinence. Head-to-head studies of the newer agents and immediate-release oxybutynin and tolterodine have suggested similar effectiveness across the class, although the newer agents are better tolerated. Trospium and darifenacin have not been compared with extended-release formulations of tolterodine or oxybutynin, which are better tolerated than the immediate-release versions. In one study, solifenacin produced a somewhat greater decrease in the number of incontinence episodes than extended-release tolterodine, with no difference in tolerability. In general, the newer agents appear to be at least as effective as their predecessors, although it is unclear whether they are better tolerated. Important pharmacokinetic differences among the agents (e.g., route of elimination) allow for selection of an appropriate agent based on individual factors such as cost and tolerability. (*Am Fam Physician* 2006;74:2061-8. Copyright © 2006 American Academy of Family Physicians.)

Overactive bladder is a clinical syndrome characterized by one or more symptoms of urgency (a difficult-to-defer need to urinate), frequency (greater than eight urinations per 24 hours), nocturia, and incontinence. In persons without overactive bladder, the need to empty the bladder becomes progressively more demanding; in overactive bladder, urgency is characterized by unheralded messages of an immediate need to empty the bladder. These signals are difficult (and sometimes impossible) to delay. The inability to delay urination results in episodes of incontinence in up to 40 percent of patients with overactive bladder.

At present, the only class of drugs with widely accepted clinical effectiveness for the treatment of overactive bladder is the anticholinergics, typified by tolterodine (Detrol; Detrol LA) and oxybutynin (Ditropan; Ditropan XL). However, because these drugs create widespread blockade of cholinergic activity, they may cause anticholinergic adverse effects such as blurred vision, dry

mouth, urinary retention, constipation, and central nervous system (CNS) effects such as somnolence and confusion. These effects are dose dependent but often occur at therapeutic doses. In 2004, three new anticholinergic drugs were approved by the U.S. Food and Drug Administration for the management of overactive bladder: trospium (Sanctura), solifenacin (Vesicare), and darifenacin (Enablex). *Table 1*¹⁻⁹ provides an overview of all five agents; key clinical trials of the newer agents are summarized in *Table 2*.¹⁰⁻¹⁶

Pathophysiology

Normally, during bladder filling the detrusor wall relaxes and the urethral sphincter contracts, promoting urine storage. During the normal voiding process, when threshold bladder volume has been reached, a decrease in urethral pressure and relaxation of the urethral sphincter precedes contraction of the detrusor muscle. At the same time, the pelvic floor muscles relax and the bladder neck forms a funnel. Parasympathetic stimulation of the detrusor muscle, mediated by

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SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Nonpharmacologic therapy is recommended for all patients with overactive bladder.	A	17-19
All available anticholinergic agents effectively decrease the frequency of urgency and incontinence episodes; one should be offered to patients who remain symptomatic despite nonpharmacologic therapy.	A	26, 31
Anticholinergics should be selected on the basis of cost and tolerability.	C	19, 22, 26, 31
Extended-release formulations of oxybutynin (Ditropan) and tolterodine (Detrol) are better tolerated than immediate-release versions.	A	23-31
The lowest effective dose of anticholinergics should be prescribed to avoid dose-dependent adverse effects.	C	26, 31

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 2008 or <http://www.aafp.org/afpsort.xml>.

TABLE 1
Overview of Anticholinergic Agents for Treatment of Overactive Bladder

<i>Drug</i>	<i>Availability</i>	<i>Dose</i>	<i>Frequency</i>	<i>Cost per month (generic)*</i>	<i>Uroselective?</i>	<i>Route of elimination</i>
Darifenacin (Enblex)	ER tablet: 7.5, 15 mg	7.5 to 15 mg	Once daily without regard for meals	\$96	Yes	Hepatic (CYP 3A4)
Oxybutynin (Ditropan; Ditropan XL)	IR tablet: 5 mg IR syrup: 5 mg per 5 mL	2.5 to 5 mg 2.5 to 5 mg	Two to four times daily Two to four times daily	(13 to 30) 75 to 113 (24 to 36)	No	Hepatic (CYP 3A4)
Oxybutynin patch (Oxytrol)	ER tablet: 5, 10, 15 mg Transdermal patch: 36 mg	5 to 30 mg 1 patch	Once daily Every three to four days	100 to 112 93		
Solifenacin (Vesicare)	Tablet: 5, 10 mg	5 to 10 mg	Once daily	101	Yes	Hepatic (CYP 3A4)/ Renal
Tolterodine (Detrol; Detrol LA)	IR tablet: 1, 2 mg ER capsule: 2, 4 mg	1 to 2 mg 2 to 4 mg	Twice daily Once daily	112 to 115 97 to 100	No	Hepatic (CYP 2D6/ 3A4)
Trospium (Sanctura)	Tablet: 20 mg	20 mg	Twice daily at least one hour before meals or on an empty stomach	89	No	Renal

ER = extended-release; CYP = cytochrome P450 isoenzymes; IR = immediate-release.

**—Average wholesale cost, based on Red Book, Montvale, N.J.: Medical Economics Data, 2006.*

Information from references 1 through 9.

the interaction between acetylcholine and muscarinic receptors, causes it to contract, and the flow of urine begins. Overactive bladder occurs when the detrusor muscle contracts in the face of submaximal bladder volumes. Anticholinergic drugs suppress such contractions by interfering with the interaction between acetylcholine and muscarinic receptors.

Nonpharmacologic Therapies

Nonpharmacologic intervention is the foundation of treatment for overactive bladder. Pelvic floor muscle training and bladder training have been proven to be effective strategies,¹⁷ and in motivated patients can be more effective than medication.¹⁸ Traditional nonpharmacologic tools and lifestyle modification should be provided consistently as part of a balanced program for improving target symptom control. Reviews of

appropriate behavioral methods and pelvic floor training are available.¹⁹

Older Anticholinergics

Tolterodine and oxybutynin are muscarinic receptor antagonists. Oxybutynin also displays antispasmodic activity in smooth muscle. These agents are recommended for patients with overactive bladder who remain symptomatic despite nonpharmacologic therapy.²⁰⁻²² The introduction of extended-release formulations has improved tolerability without substantively impairing the effectiveness of these drugs.²³⁻²⁷ Completion rates in long-term studies approach 70 percent with extended-release tolterodine, but are as low as 18 percent with immediate-release oxybutynin.²⁸⁻³⁰ On average, anticholinergic therapy reduces weekly urge-incontinence episodes by 70 percent. Dry mouth is the most common adverse event, affecting 20 to 30 percent of patients administered these agents.²⁸⁻³⁰

A Cochrane review of randomized controlled trials comparing anticholinergic drugs with placebo or no treatment in patients with overactive bladder showed that patients treated with anticholinergics were more likely to report cure or improvement in their symptoms than those receiving placebo (60 versus 45 percent; $P < .05$, number needed to treat = 7).³¹ Maximal cystometric capacity increased 54 mL in patients receiving anticholinergics compared with those receiving placebo. Dry mouth was reported significantly more often in the active medication group (32 versus 14 percent; $P < .05$, number needed to harm = 5); however, similar numbers of patients withdrew because of adverse events. Drug therapy resulted in approximately one less episode of leakage and one less void per 48 hours compared with placebo. Because the placebo-adjusted effectiveness of these agents is marginal, the clinical impact must be weighed against the risk of adverse events.

Newer Agents

Head-to-head studies comparing the three newer agents—trospium, solifenacin, and darifenacin—with immediate-release oxybutynin and tolterodine have suggested similar effectiveness across the class.^{10-14,16} Although the attributes of these newer agents in theory could improve tolerability, clinical trials comparing relevant agents to validate this are lacking (*Table 2*).¹⁰⁻¹⁶

TROSPIUM

Trospium, a nonselective anticholinergic agent with antispasmodic properties, is approved for the treatment of overactive bladder with symptoms of urge urinary

Comments

Dose should be decreased in patients with moderate hepatic impairment; not recommended for use in patients with severe hepatic impairment.

No formal recommendations exist for dosing in patients with hepatic impairment, but extensive hepatic elimination warrants caution in this setting.

Dose should be decreased in patients with moderate hepatic or severe renal impairment; not recommended for use in patients with severe hepatic impairment.

Approximately 15 percent is eliminated unchanged in the urine.

Lowest dose should be used in patients with severe hepatic or renal impairment who are taking CYP 3A4 inhibitors.

Tolterodine has a lesser effect at the salivary gland than oxybutynin.

May have functional selectivity

Administer once daily in patients with severe renal impairment.

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TABLE 2
Key Clinical Trials of Newer Antimuscarinic Agents for Treatment of Overactive Bladder

<i>Study</i>	<i>Agent(s)</i>	<i>Design (no. of participants)</i>	<i>Outcomes</i>
Placebo-controlled studies			
Chapple, et al., 2005 ¹⁰	Darifenacin (Enablex) 7.5 to 15 mg per day versus placebo	Pooled analysis of three RCTs (1,059)	Decrease in incontinence episodes per day: -1.25 (7.5 mg), -1.5 (15 mg) versus -0.99 placebo ($P < .004$) Decreases in frequency and severity of urgency, leakage, voids per day, and nocturnal awakenings
Cardozo, et al., 2004 ¹¹	Solifenacin (Vesicare) 5 to 10 mg per day versus placebo	RCT (911)	Decrease in incontinence episodes per day: -1.63 (5 mg), -1.57 (10 mg) versus -1.25 placebo ($P = .002$) Decreases in voids per day, urgency episodes, and nocturia; increase in bladder capacity
Zinner, et al., 2004 ¹²	Trospium (Sanctura) 40 mg per day versus placebo	RCT (523)	Decrease in incontinence episodes per day: -2.0 versus -1.3 placebo ($P < .001$) Complete dryness in 21% versus 11% placebo Decreases in frequency and severity of urgency, leakage, voids per day, and nocturnal awakenings
Active-comparator studies			
Zinner, et al., 2005 ¹³	Darifenacin 15 to 30 mg per day versus oxybutynin IR (Ditropan) 5 mg per day or placebo	RCT crossover (76)	Incontinence episodes per week: 10.9 (15 mg), 8.8 (30 mg) versus 9.5 oxybutynin, 14.6 placebo ($P < .05$)
Chapple, et al., 2004 ¹⁴	Solifenacin 5 to 10 mg per day versus tolterodine IR (Detrol) 2 mg per day or placebo	RCT (1,081)	Decrease in incontinence episodes per day: -1.42 (5 mg), -1.45 (10 mg) versus -1.14 tolterodine, -0.76 placebo Decreases in voids per day and urgency episodes; increase in bladder capacity
Chapple, et al., 2005 ¹⁵	Solifenacin 5 to 10 mg per day versus tolterodine ER (Detrol LA) 4 mg per day	RCT (1,177)	Decrease in incontinence episodes per day: -1.60 (10 mg) versus -1.11 tolterodine ($P < .0001$) Significant decrease in urgency episodes with solifenacin ($P < .05$)
Halaska, et al., 2003 ¹⁶	Trospium 40 mg per day versus oxybutynin IR 10 mg per day	RCT (358); unblinded	Similar changes in urodynamic parameters

NOTE: Differences were not statistically significant or were not tested for significance unless otherwise noted.

RCT = randomized controlled trial; IR = immediate-release; ER = extended-release.

Information from references 10 through 16.

Adverse effects

Dry mouth: 20.2 to 35.3% versus 8.2% placebo ($P < .05$)
 Constipation: 14.8 to 21.3% versus 6.2% placebo ($P < .05$)
 Dyspepsia: 2.7 to 8.4% versus 2.6% placebo ($P < .05$)

Dry mouth: 7.7% (5 mg), 23.1% (10 mg), 2.3% placebo
 Constipation: 3.7% (5 mg), 9.1% (10 mg), 2.0% placebo
 Blurred vision: 4.0% (5 mg), 5.9% (10 mg), 2.3% placebo

Dry mouth: 21.8% versus 6.5% placebo ($P < .05$)
 Constipation: 9.5% versus 3.8% placebo ($P < .05$)
 Abdominal pain: 3.1% versus 1.1% placebo

Dry mouth: 13.1% (15 mg), 34.4% (30 mg) versus
 36.1% oxybutynin, 4.9% placebo
 Constipation: 9.8% (15 mg), 21.3% (30 mg) versus
 8.2% oxybutynin, 3.3% placebo

Early discontinuation: 10.0% (5 mg), 7.1% (10 mg) versus
 9.9% tolterodine, 12.0% placebo
 Dry mouth: 14.0% (5 mg), 21.3% (10 mg) versus
 18.6% tolterodine, 4.9% placebo
 Constipation: 7.2% (5 mg), 7.8% (10 mg) versus
 2.6% tolterodine, 1.9% placebo
 Blurred vision: 3.6% (5 mg), 5.6% (10 mg) versus
 1.5% tolterodine, 2.6% placebo

Early discontinuation: 3.5% versus 3.0% tolterodine
 Dry mouth: 30.0% versus 24.0% tolterodine
 Constipation: 6.4% versus 2.5% tolterodine
 Blurred vision: 0.7% versus 1.7% tolterodine

Early discontinuation (< 52 weeks): 25.0% versus
 26.7% oxybutynin
 Dry mouth: 33.0% versus 50.0% oxybutynin
 Constipation: 7.0% versus 4.0% oxybutynin

incontinence, urgency, or frequency. It has been in use in Europe for more than 20 years. Unlike other anticholinergics, trospium is water soluble and crosses the blood-brain barrier poorly.⁹ Although it has been suggested that this feature might minimize centrally mediated events such as drowsiness, nervousness, dizziness, and cognitive impairment, the limited clinical trial data do not support this.

In a prospective, randomized, controlled trial comparing trospium with immediate-release oxybutynin in patients with detrusor instability, there were fewer overall adverse events with trospium (mainly because of a lower incidence of dry mouth).¹⁶ However, there was no difference in CNS adverse effects. Another study evaluated the impact of trospium on somnolence and daytime sleepiness. Trospium did not increase sleepiness or produce other CNS adverse effects; however, the lack of an active comparator arm hinders interpretation of this study.³²

In one placebo-controlled study that enrolled patients experiencing approximately 30 episodes of urinary incontinence per week, trospium significantly reduced the number of voids and episodes of urge urinary incontinence compared with placebo (*Table 2*¹⁰⁻¹⁶).¹² After 12 weeks, patients treated with trospium experienced between 1.5 and 4.0 fewer incontinence episodes per week than those treated with placebo and had a greater improvement in quality of life. However, these modest results were tempered by an increased incidence of anticholinergic adverse events. In addition, patients enrolled in this study were highly symptomatic, and thus a favorable effect on quality of life is not surprising.¹² Whether these results can be extrapolated to other populations is debatable.

Trospium was compared with immediate-release oxybutynin in several randomized, double-blind clinical trials.^{16,33,34} These studies reported similar improvements in detrusor contractions, maximal cystometric bladder capacity, and bladder volume at first sensation with both agents. However, trospium was better tolerated because of fewer reports of dry mouth.

Collectively, these data suggest that trospium effectively reduces symptoms of overactive bladder and is better tolerated than immediate-release oxybutynin.^{16,33,34} Trospium has not been compared with extended-release forms of oxybutynin or tolterodine.

SOLIFENACIN

Solifenacin is a selective M₃ muscarinic receptor antagonist approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, or frequency. Selectivity for the M₃ receptor may confer

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TABLE 3
Factors Affecting Selection of Anticholinergic Agents for Treatment of Overactive Bladder

<i>Factor</i>	<i>Agent to consider</i>	<i>Comments</i>	<i>References</i>
Anticholinergic adverse effects	Darifenacin (Enablex), solifenacin (Vesicare), tolterodine ER (Detrol LA), oxybutynin ER (Ditropan XL)	ER products and drugs with uroselectivity may offer enhanced tolerability.	15, 27, 31
CNS adverse effects	Trospium (Sanctura)	Trospium may be less likely to cross the blood-brain barrier (unproven benefit).	31
Cost	Oxybutynin IR	ER and newer agents may be more expensive; generics are available for oxybutynin IR.	22
Drug-drug interactions	Trospium	Agents other than trospium are metabolized by CYP 3A4 or 2D6, which are responsible for elimination of hepatically metabolized drugs.*	9
Effectiveness	Oxybutynin	Nonselectivity may offer more complete suppression of detrusor overactivity. Head-to-head studies of tolterodine and oxybutynin have suggested improved efficacy with oxybutynin.	27
Pregnancy	Oxybutynin	Oxybutynin is pregnancy risk category B whereas all other agents are class C.	2
Severe hepatic impairment	Trospium	Trospium is eliminated renally whereas all other agents undergo extensive hepatic metabolism.*	5, 16, 22, 35
Severe renal impairment	Oxybutynin, tolterodine, darifenacin, solifenacin	Avoid trospium because it is eliminated renally.	9

ER = extended-release; CNS = central nervous system; IR = immediate-release; CYP = cytochrome P450 isoenzyme.

*—The overall correlation between hepatic function and drug disposition is poor.

Information from references 2, 5, 9, 15, 16, 22, 27, 31, and 35.

improved tolerability given the preferential location of this receptor subtype on the detrusor wall. However, M₃ receptors also are present on smooth muscles in the gastrointestinal tract, salivary glands, eyes, and brain. For this reason, common adverse effects include constipation, dry mouth, blurred vision, fatigue, and cognitive impairment.⁵

Results from several 12-week, double-blind, placebo-controlled studies involving patients with approximately 20 urinary incontinence episodes per week showed that solifenacin reduced urinary frequency by approximately two voids per day compared with a decrease of approximately one void per day with placebo (Table 2¹⁰⁻¹⁶).^{5,11,35} Solifenacin also significantly improved urgency, nocturia, and bladder emptying. Compared with immediate-release tolterodine, solifenacin resulted in greater decreases in urgency and incontinence episodes but produced anticholinergic side effects at a similar frequency.^{14,36} One possible explanation for these findings is that trials of solifenacin used doses up to the maximum of 10 mg, whereas the dose of tolterodine was capped at 2 mg. Solifenacin improved health-related quality of life in patients with overactive bladder and urinary incontinence.³⁶

Another study compared 5 to 10 mg of solifenacin daily with 4 mg of extended-release tolterodine daily.¹⁵ In this study, patients treated with solifenacin had better symptom control but experienced more adverse events. Again, however, the dosing strategy may explain these findings: patients treated with solifenacin initially were given 5 mg daily and could request an increase in dosage after four weeks; 48 percent of patients requested such increase and subsequently were treated with 10 mg daily. In the tolterodine arm, 51 percent of patients requested a dosage increase, but they already were receiving the maximal dosage.

DARIFENACIN

Similar to solifenacin, darifenacin is a muscarinic receptor antagonist with enhanced specificity for the M₃ receptor subtype. It is approved for the management of overactive bladder, and improves overactive bladder symptomatology to an extent similar to that of other agents (Table 2).¹⁰⁻¹⁶ One unique parameter that has been examined with darifenacin is “warning time”: the time from the first sensation of urgency to the time of

voluntary urination or incontinence.³⁷ An increase in this duration may permit more patients to experience or maintain continence. Darifenacin increased warning time by 4.3 minutes compared with placebo ($P = .003$), and 47 percent of patients treated with darifenacin experienced a 30 percent or greater increase in mean warning time compared with only 20 percent of patients treated with placebo ($P = .009$).³⁷

In a crossover study with immediate-release oxybutynin, the incidence of dry mouth was significantly lower with darifenacin 15 mg than with oxybutynin (13 versus 36 percent, respectively; $P < .05$) but not with darifenacin 30 mg (34 versus 36 percent).¹³ Constipation was more common in patients given darifenacin 30 mg (21 versus 8 percent with oxybutynin; $P < .05$) but not in those given 15 mg (10 percent). Effectiveness was similar for patients receiving either dose of darifenacin and those receiving oxybutynin. Comparisons of darifenacin with extended-release oxybutynin or tolterodine are lacking.

Selecting Pharmacologic Agents for Overactive Bladder

The availability of three newer anticholinergic drugs increases the pharmacologic armamentarium for the treatment of overactive bladder. Caution is required with each of these agents, particularly in patients with contraindications to anticholinergic therapy (e.g., untreated open-angle glaucoma, constipation, urinary retention, gastrointestinal disease). A careful evaluation of the balance between benefits and harms, with special attention paid to quality of life, is warranted when considering use of these agents. Appropriately conducted trials are needed to determine the clinical value of functional, structural, and pharmacokinetic nuances. The pharmacokinetic differences among anticholinergic agents allow for the selection of agents based on individual factors (Table 3).^{2,5,9,15,16,22,27,31,35} In the absence of definitive comparative data, a reasonable strategy is to select a therapy according to the individual patient and to try alternative agents if the first is not effective or cannot be tolerated.

Members of various family medicine departments develop articles for "Clinical Pharmacology." This is one in a series coordinated by Allen F. Shaughnessy, Pharm.D., and Andrea E. Gordon, M.D., Tufts University Family Medicine Residency, Malden, Mass.

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