Newer Agents for the Management of Overactive Bladder

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Abstract

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.

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Introduction

Overactive bladder is a clinical syndrome characterised 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 characterised 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 (Detrusitol® SR) and oxybutynin (Ditropan®, Lenditro®, Merck-Oxybutynin®, Sandoz-oxybutynin®, Urihexal®). 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 (Uricon®), solifenacin (Vesicare®), and darifenacin (Enablex®). *Table 1* provides an overview of all five agents; key clinical trials of the newer agents are summarised in *Table 2*.

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 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.

Non-pharmacologic therapies

Non-pharmacologic 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 non-pharmacologic tools and lifestyle modification should be provided consistently as part of a balanced program for improving target symptom control. Reviews of

SORT: Key Recommendations for Practice		
Clinical recommendation	Evidence rating	References
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

Drug	Availability	Dose	Frequency	Cost per month (generic)*	Uroselective?	Route of elimination	Comments
Darifenacin (Enablex®)	ER tablet: 7.5, 15 mg	7.5 to 15 mg	Once daily without regard for meals	$96	Yes	Hepatic (CYP 3A4)	Dose should be decreased in patients with moderate hepatic impairment; not recommended for use in patients with severe hepatic impairment.
Oxybutynin (Ditropan®; Ditropan XL®)	IR tablet: 5 mg	2.5 to 5 mg	Two to four times daily	(13 to 30)	No	Hepatic (CYP 3A4)	No formal recommendations exist for dosing in patients with hepatic impairment, but extensive hepatic elimination warrants caution in this setting.
	IR syrup: 5 mg per 5 mL	2.5 to 5 mg	Two to four times daily	75 to 113 (24 to 36)			
	ER tablet: 5, 10, 15 mg	5 to 30 mg	Once daily	100 to 112			
Oxybutynin patch (Not in RSA)	Transdermal patch: 36 mg	1 patch	Every three to four days	93			
Solifenacin (Vesicare®)	Tablet: 5, 10 mg	5 to 10 mg	Once daily	101	Yes	Hepatic (CYP 3A4)/ Renal	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.
Tolterodine (Detrusitol®)	IR tablet: 1, 2 mg	1 to 2 mg	Twice daily	112 to 115	No	Hepatic (CYP 2D6/ 3A4)	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.
	ER capsule: 2, 4 mg	2 to 4 mg	Once daily	97 to 100			
Trospium (Sanctura)	Tablet: 20 mg	20 mg	Twice daily at least one hour before meals or on an empty stomach	89	No	Renal	May have functional selectivity Administer once daily in patients with severe renal impairment.

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.

appropriate behavioural 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 non-pharmacologic 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 epi-

sodes 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 randomised 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 (Uricon®)

Trospium, a non-selective anticholinergic agent with antispasmodic proper-

Table 2: Key Clinical trials of newer antimuscarinic agents for treatment of overactive bladder

Study	Agent(s)	Design (no. of participants)	Outcomes	Adverse effects
Placebo-controlled studies				
Chapple, et al., 2005[10]	Darifenacin 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	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 ($P < .05$)
Cardozo, et al., 2004[11]	Solifenacin 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	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
Zinner, et al., 2004[12]	Trospium 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	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
Active-comparator studies				
Zinner, et al., 2005[13]	Darifenacin 15 to 30 mg per day versus oxybutynin IR 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 ($P < .05$)	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
Chapple, et al., 2004[14]	Solifenacin 5 to 10 mg per day versus tolterodine IR 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	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
Chapple, et al., 2005[15]	Solifenacin 5 to 10 mg per day versus tolterodine ER 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 ($P < .05$)	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
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	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

ties, is approved for the treatment of overactive bladder with symptoms of urge urinary 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 favourable 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 (Vesicare®)

Solifenacin is a selective M_3 muscarinic receptor antagonist approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, or frequency. Selectivity for the M_3 receptor may confer improved tolerability given the preferential location of this receptor subtype on the detrusor wall. However, M_3 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 2*[10-16]*)*.[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 (Enablex®)

Similar to solifenacin, darifenacin is a muscarinic receptor antagonist with enhanced specificity for the M_3 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 anticholinegic 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.

Acknowledgement

Members of various family medicine depart-

Table 3: Factors Affecting Selection of Anticholinergic Agents for Treatment of Overactive Bladder

Factor	Agent to consider	Comments	References
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 (Uricon®)	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(Uricon®)	Agents other than trospium are metabolized by CYP 3A4 or 2D6, which are responsible for elimination of hepatically metabolized drugs.*	9
Effectiveness	Oxybutynin	Non-selectivity 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(Uricon®)	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.

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Propiverine hydrochloride (Detrunorm®)

Detrunorm tablets are indicated for the treatment of urinary frequency and unstable bladder conditions.

Detrunorm's active ingredient propiverine hydrochloride is a product of original research by APOGEPHA Arzneimittel GmbH, and has been marketed in Europe for many years.

Propiverine has a dual mode of action (it causes a dosage dependent decrease of the intravesical pressure and an increase in bladder capacity) by the following mechanisms :

- Inhibition of calcium influx and modulation of the intracellular calcium in urinary bladder smooth muscle cells causing musculotropic spasmolysis. And
- Inhibition of the efferent neurotransmission of the nervus pelvicus due to anti-cholinergic action.

The effect is based on the sum of the pharmacological properties of propiverine and its three active metabolites which are directly musculotropic and anticholinergic.

Madersbacher and Mürtz in the review entitled "Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic), makes the following statement : ***"Propiverine hydrochloride is a compound that has neurotropic and musculotropic effects on the urinary bladder smooth muscle. Controlled clinical trials have shown its effectiveness in treating detrusor hyperreflexia and in treating patients with symptoms of an overactive bladder."***[1]

The International Consultation of Urological Diseases classes propiverine hydrochloride as a Class 1/A product the highest grade, which confirms evidence of efficacy.[2]

Detrunorm is well-tolerated with the commonest side effects being dry mouth and constipation. However, with continued use of the product the side effects lessen.

Madersbacher and Mürtz in the same review state : ***"Propiverine is well tolerated. It is better tolerated than oxybutinin (particularly in regard to frequency and severity of dryness of mouth)."***[1]

After oral administration of Detrunorm® propiverine hydrochloride is rapidly absorbed from the gastrointestinal tract. Maximal plasma concentrations are reached after 2.3 hours as an average after a single dose of one coated tablet. The average absolute bioavailability of Detrunorm® is 40.5%. (arithm. Mean value for AUC o-∞(p.o.)/AUC 0-∞ (i.v.)).

Propiverine is already intensively metabolized pre-systemically. After repeated application (15 mg two to three times a day) steady state is reached after four to five days at a higher concentration level than after single dose application (C average = 61 ng/ml). The substance has a high first pass effect.

Detrunorm is currently available as a tablet containing 15 mg propiverine hydrochloride. The usual dose is one tablet once or twice daily.

For further information please contact Pharmafrica at 0800 601 098.

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