



An Overview of Overactive Bladder and Its Pharmacological Management with a Focus on Anticholinergic Drugs

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Educational Objectives

After reviewing the article, the reader should be able to:

- Define overactive bladder (OAB) and its relationship to urinary incontinence.
- Review the basic anatomy, physiology, and pathophysiology of overactive bladder.
- Describe the epidemiology, risk factors, and comorbidities associated with OAB.
- Describe the clinical features of OAB and how they interfere with a patient's lifestyle.
- Describe nonpharmacological and pharmacological treatment options for OAB.
- Counsel, monitor, and educate patients appropriately when dispensing therapeutic agents utilized in the pharmacological management of OAB.

Introduction

Overactive bladder (OAB), a common problem of the urinary tract, can be described as urinary urgency, frequency, or urge urinary incontinence (UI). OAB can present with a constellation of symptoms or as a symptom syndrome, which may include urgency and frequency (voiding more than eight times in a 24-hour period) along with nocturia. Patients may describe a sudden, compelling desire to urinate that may be difficult to defer until a later time.¹⁻³



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Although OAB is often described as being synonymous with UI, most notably urge incontinence, it can occur with or without the features of this disorder. Approximately one third (37%) of patients with OAB have incontinence ("wet" OAB), whereas two thirds (63%) are not incontinent of urine ("dry" OAB).^{4,5}

Urinary incontinence is a complex condition that results from a variety of etiologic mechanisms. In most textbooks, it is characterized by various types or classifications, including urge, stress, overflow, and mixed forms. Patients with OAB may or may not experience UI; within the various UI types, however, the terms OAB and "urge" are often used. A complete review of UI is beyond the scope of this paper.

Table 1 summarizes the various types, causes, common symptoms, and treatments of UI.⁶⁻¹²

Bladder Anatomy and Physiology

The anatomy of the bladder is presented in Figure 1. Certain features of this flexible organ are important in descriptions of the pathophysiology of OAB.^{13,14} The anatomy of the bladder includes the detrusor muscle and the internal and external sphincters. Neurological control of micturition or urination involves the central nervous system (CNS) (the pons), the spinal cord, and the peripheral nerves. Innervation involves the parasympathetic nervous system (PNS), the sympathetic nervous system (SNS), and somatic nervous systems, which must work together for proper bladder control.

In brief, the physiology of the bladder and the micturition process are regulated by the nervous systems. The PNS involves the neurotransmitter acetylcholine and its action on muscarinic or cholinergic receptors. When the PNS is blocked, the terms "antimuscarinic" and "anticholinergic" are often used interchangeably. The SNS involves the neurotransmitters epinephrine or norepinephrine and alpha or beta receptors. Other terms include "alpha-adrenergic" and "beta-adrenergic," which refer to agonists of this system.

Table 1 Overview of Urinary Incontinence

Type of Incontinence	Common Causes	Common Symptoms	Examples of Pharmacological Treatments
Urge incontinence (detrusor overactivity)	<ul style="list-style-type: none"> • Strokes • Alzheimer's disease • Parkinson's disease • Benign prostatic hyperplasia with overflow 	Urgency and frequency occur day or night (nocturia)	Anticholinergic drugs <ul style="list-style-type: none"> • Oxybutynin (Ditropan) • Tolterodine (Detrol)
Stress incontinence (outlet incompetence)	<ul style="list-style-type: none"> • Urological procedures • History of multiple childbirths • Estrogen deficiency 	Small volumes of urine loss with coughing, sneezing, running, or laughing	<ul style="list-style-type: none"> • Topical estrogen • Alpha-agonists • Nonpharmacological
Mixed incontinence	Multiple etiologic factors	Symptoms of urge and/or stress and/or overflow	Treatments typically focus on symptoms that predominate
Overflow incontinence	<ul style="list-style-type: none"> • Benign prostatic hyperplasia • Peripheral neuropathy • Vitamin B₁₂ deficiency • Fecal impaction 	Reduced urinary stream, incomplete voiding, urinary dribbling	Alpha-adrenergic blockers, such as terazosin (Hytrin), tamsulosin (Flomax), others
Atonic bladder	<ul style="list-style-type: none"> • Severe diabetic neuropathy • Stroke 	Complete loss of bladder control	Catheterization
Functional incontinence	<ul style="list-style-type: none"> • Inability to get to the bathroom • Changes in mental status • Urinary tract infections • Medications 	Symptoms of incontinence vary according to type of external cause	Therapy to eliminate the cause

Data compiled from references 6–12.

Bladder control and function can briefly be described as follows (see Figure 1). The bladder fills when SNS control results in a relaxed detrusor muscle and in closed sphincters at the bladder outlet. The SNS also inhibits the PNS during this period, as shown in the figure. When the bladder reaches a certain volume (e.g., from a beverage, 200–400 ml), signals move from the spinal cord to brain centers, resulting in the sensation of urge. At the appropriate time, when a person is ready to void, cholinergic neurons in the PNS system release acetylcholine, which acts on muscarinic receptors in the bladder detrusor smooth muscle to create contractions.

The SNS also allows the internal sphincter to open, and the somatic nervous system (under voluntary control) opens the external sphincter. The result is parasympathetic stimulation of the detrusor muscle, leading to bladder contraction with open sphincters, allowing urine release (micturition) from the bladder.^{2,15,16}

Background of Overactive Bladder

It is thought that OAB is related to changes or dysfunction of the detrusor muscle involving muscarinic receptors, but other mechanisms may also be involved and may include other receptor systems.^{8,10} These changes result in a predisposition

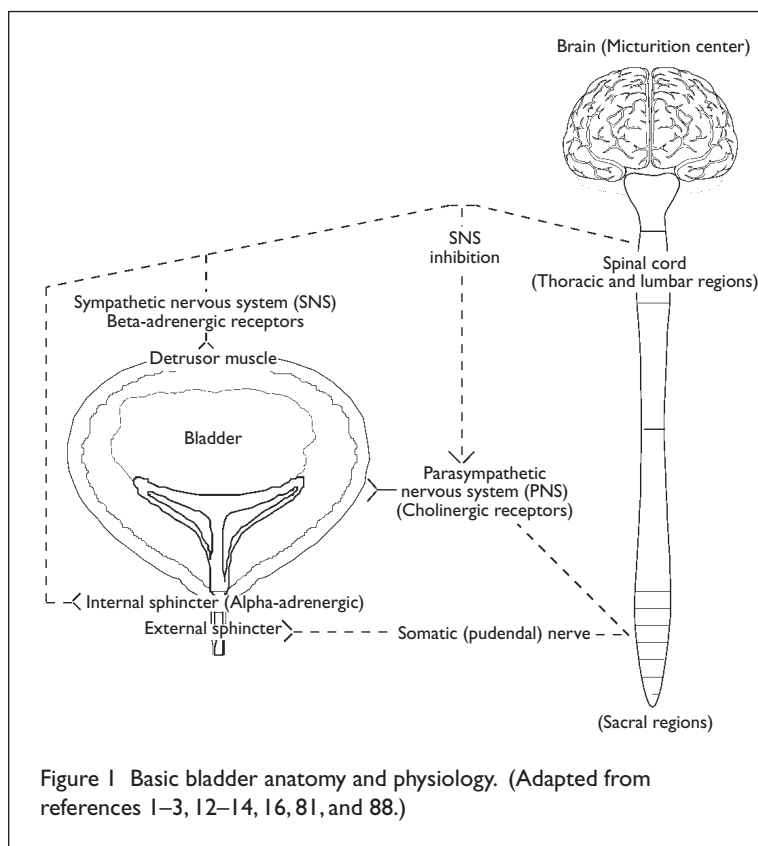


Figure 1 Basic bladder anatomy and physiology. (Adapted from references 1–3, 12–14, 16, 81, and 88.)

toward unstable bladder contractions or overactivity of the detrusor muscle, leading to OAB symptoms. Although the exact mechanism is not completely understood, various mechanisms have been proposed. Most mechanisms focus on CNS involvement, suggesting that increased CNS activity influences or decreases the inhibition of these contractions; others suggest an increased detrusor muscle sensitivity to central stimulation.^{1,2,15-19}

The International Continence Society (ICS) defines OAB as a complex of symptoms that include urinary urgency, with or without UI, and additional features that include frequency and nocturia.¹ Although OAB is common, it remains underdiagnosed and affects approximately 16% of the U.S. population. OAB is not necessarily a disease of only the elderly; it is often observed in people 40 to 64 years of age.^{2,4,5,19}

The National Bladder Evaluation (NOBLE) survey project defined the clinical presentation of OAB without UI as feelings of urgency of at least four times or more over the course of a month, more than eight micturitions daily, or using various coping strategies (e.g., restriction of fluid intake). The project defined OAB with UI as including these features as well as three leakage episodes not related to stress incontinence or other causes such as reversible factors (e.g., metabolic or pathological causes).^{5,17}

The symptoms of OAB are often unreported by patients and are thus under-treated by clinicians. The NOBLE survey reported that OAB affects more than 30 million Americans, with a prevalence of 17% in women and 16% in men. A higher percentage of women report incontinence with OAB (9%) compared with men (3%).^{5,17}

The prevalence of OAB increases with age, especially in patients older than age 75.⁴ In long-term-care facilities, OAB has been reported to affect up to 50% of all residents.^{20,21} OAB imposes significant social, economic, psychological, and physical morbidity on patients, especially women.⁴ It affects quality of life and increases the risk of numerous comorbidities, including urinary tract infections (UTIs), pressure ulcers, falls, and fractures.²²⁻²⁴

As with UI, the causes of and risk factors for OAB are numerous and are not disease-specific (Table 2). Common risk factors include age, especially in the over-65 group; obesity; spinal cord injuries; neuropathies; and neurological diseases, including cerebrovascular events (strokes), Alzheimer's disease, and Parkinson's disease. Reversible risk factors (non-neurogenic causes) may include UTIs, medications, and obstructions.^{2,14,19,25-29}

Complications of OAB include skin ulcerations in patients with concurrent UI, UTIs, and falls and fractures, which are usually related to nocturia.^{23,29} Psychosocial influences, including isolation and depression, affect sleep quality.^{4,5,30} Economic burdens associated with OAB include both direct

costs for diagnosis and treatment and indirect costs related to productivity.^{24,31,32-36} Hospital and nursing-home admissions related to OAB are especially costly.³³ The yearly cost of OAB to society was close to \$13 billion in 2000.^{20,34,35} Data from insurance claims also indicated a five-fold greater rate of spending in patients with OAB.³⁷

Evaluation

OAB may be initially evaluated by the patient's primary care physician, but further evaluation is often required by a urologist. Although OAB is a symptomatic diagnosis, an assessment may include a complete medical history; urination patterns; physical findings; urinalysis; and optional urodynamic studies, cystoscopy, and imaging.^{21,38}

Treatment

The management of OAB includes both nonpharmacological and pharmacological methods. Nonpharmacological methods include simple interventions, such as removing agitators (e.g., caffeine), maintaining adequate hydration, and timing fluid intake, or more invasive procedures may be recommended.³⁹⁻⁴¹

Behavioral modification therapy involves bladder training, timed voiding, and encouragement of gradual increases of the time intervals between voidings. Usually, voiding is started at one-hour to two-hour intervals and is increased from that point. Behavioral modification should be considered before drug therapy is begun and may be more effective and safer for some patients.

Pelvic-floor exercises may also improve detrusor overactivity and can help relieve the symptoms of OAB.⁴²⁻⁴⁴ Various surgical procedures and electrical stimulation with sacral neurostimulation are also used in the treatment of OAB.

Each procedure has its place in therapy along with its advantages and disadvantages in addition to cost-related concerns. The appropriate treatment may be determined after a discus-



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Table 2 Risk Factors Associated with Overactive Bladder

Urinary tract infections or obstruction	Cardiac disease (heart failure)
Estrogen deficiency	• Drugs (caffeine, alcohol, diuretics, narcotics, calcium-channel blockers) • Cholinesterase inhibitors
Aging changes, sphincter weakness	Psychological and sleep disorders
Benign prostatic hyperplasia (males)	Constipation
Dementia, Parkinson's disease, stroke, multiple sclerosis, or other neurological diseases or conditions	• Diabetes mellitus and associated complications • Diabetes insipidus
Spinal injuries or diseases	Obesity
Data compiled from references 2, 14, 19, and 24-29.	

sion between patient and clinician.⁴⁵⁻⁴⁹ In some cases, nonpharmacological therapies may be the most successful when combined with pharmacological therapy.^{42,48,50}

Pharmacological Management

Numerous medications have been used in the management of OAB, including traditional agents such as calcium-channel blockers, baclofen (Lioresal, Novartis), intrathecal clonidine (Catapres, Boehringer Ingelheim), intravesical capsaicin, estrogen, and alpha-adrenergic antagonists; however, clinical evidence supporting their utility is limited.⁵¹⁻⁵⁴ Other investigational therapies that might have a future role include duloxetine (Cymbalta, Forest), a mixed serotonergic and SNS-acting agent; serotonergic agonists, botulinum toxin type A (Botox, Allergan), desmopressin, dopamine agonists, potassium-channel transporters, afferent-nerve inhibitors, gamma-aminobutyric acid (GABA) agonists, beta₃ antagonists, and prostaglandin synthesis inhibitors.^{8,10,51,54-58}

Overview of Anticholinergic Drugs

The most effective and commonly used medications for the treatment of OAB have been those with anticholinergic (AC) properties (Table 3).^{59,60} After we present an overview of these AC agents, we will review the potential advantages of each one.

The central cholinergic transmitter and muscarinic receptor systems (the M1 through M5 series) involve a number of organ systems.⁵⁹ These complex multiple receptor systems include the CNS (brain), eyes, cardiac tissue, salivary glands, bladder, ophthalmic tissue, gastrointestinal (GI) tract, and other smooth muscle tissues.

Table 4 describes common organ systems and the muscarinic receptors located within them as well as the effects of AC or antimuscarinic blockage on these organ systems.⁵⁹⁻⁶³

Adverse Effects

The major concern associated with AC drugs, especially because most patients with OAB are elderly, is the side-effect profile. AC agents may be problematic by causing both peripheral and central adverse effects (Table 5).⁶⁴⁻⁶⁷

Influence on Organ Systems

Elderly patients are at an increased risk for developing delirium from AC drugs, especially if they have an underlying mild cognitive impairment or dementia. Central cholinergic transmitter systems are located in the hippocampus and cortex, which are important regions of the brain for memory and learning.

Table 3 Anticholinergic Agents for Overactive Bladder

Older Agents (Rarely Used)	Newer Agents (Commonly Used)
Tricyclic antidepressants: imipramine (Tofranil, Novartis/ Mallinckrodt),* others	<ul style="list-style-type: none"> • Oxybutynin† regular-release (Ditropan, Ortho-McNeil) • Long-acting (Ditropan XL) • Transdermal oxybutynin (Oxytrol, Watson Labs)
Dicyclomine (Bentyl, Aventis)	<ul style="list-style-type: none"> • Tolterodine (Detrol, Pfizer) • Tolterodine LA (Detrol LA)
Hyoscyamine (Levsin, Levsinex, Cystospaz, Schwarz Pharma)	Trospium (Sanctura, Esprit/Indevus)
Propantheline (Pro-Banthine)	Darifenacin (Enablex, Novartis)
Flavoxate (Urispas, Impax/ Ortho-McNeil)	Solifenacin (VESicare, Astellas/GlaxoSmithKline)
<p>* Also increases alpha-adrenergic tone at the internal sphincter. † May also have some direct smooth-muscle relaxant properties. Data from references 14, 51, 65, 77, and 83-92.</p>	

The brain contains all five of these receptor subtypes, but the M1 receptor appears to have the most influence on memory and learning. The M2 receptor may have a similar role, and its blockage may affect cognitive function.

The activities of the M3, M4, and M5 receptors in the CNS are not completely understood. Blocking of these central muscarinic receptors can cause hallucinations, confusion, sedation, delirium, and blurred vision, and may affect memory and learning. Perception, psychomotor speed, attention, and executive function may also be affected.

In the future, the use of AC drugs that are more selective for bladder receptors may result in fewer adverse CNS effects.^{64,66,68-70} Other factors that might influence the CNS

Table 4 Receptor Types and Effects of Anticholinergic Blockage

Organ System	Receptors	Effects of Blockage
Salivary glands	M1, M3, M4	Dry mouth
Cardiac tissue	M2	Tachycardia, palpitations
Eye (ciliary muscle, iris)	M3, M5	Dry eyes, blurred vision
Gastrointestinal tract	M1, M2, M3	Slowing of transit time (constipation), effects on sphincter tone and gastric acid secretion
Central nervous system, brain (cortex and hippocampus)	M1, M2, M3, M4, M5	Effects on memory, cognition and psychomotor speed, confusion, delirium, hallucinations, sleep disruption
Bladder (detrusor muscle)	M2, M3	Decreased contraction, urinary retention
Adapted from references 61-63, 77, 92, and 134.		

Table 5 Adverse Effects of Anticholinergic Drugs

Peripheral Effects	Central Effects
Dry mouth	Sedation
Mydriasis	Confusion/delirium
Constipation	Hallucinations
Urinary retention	Slowed cognitive function
Tachycardia	Sleep disruption
Adapted from references 64–67.	

effects of these agents include their physical properties. Properties that affect penetration into the CNS, including lipophilicity, molecular size, and polarity, may influence the extent to which agents cross the blood–brain barrier.⁷¹

To further complicate the problem, many elderly patients may be taking multiple drugs with AC properties. Many commonly used drugs have AC properties, although they are not always associated with these adverse effects, including histamine-2 (H₂)–receptor blockers and other agents. It is essential that patients be monitored for AC effects, especially if they are taking multiple drugs with AC properties.^{14,72–74}

AC drugs are also associated with the potential for urinary retention, especially in older men with a history of benign prostatic hypertrophy (BPH). Cardiovascular effects may include palpitations, tachycardia, and a prolonged QTc interval. GI tract effects may range from mild constipation to severe obstructions.^{14,65,68}

Contraindications

Contraindications to the use of AC agents include angle-closure or narrow-angle glaucoma, urinary and gastric obstruction, and the need to perform tasks requiring mental alertness. Patients with dementia (mainly the Alzheimer's type) should not take AC drugs because of the potential for exacerbating existing cholinergic deficits.

AC agents should be used with caution in patients with ulcerative colitis, myasthenia gravis, and cardiac disease, especially patients with arrhythmias and coronary heart disease, because of the potential for QTc prolongation.^{14,65}

Drug Interactions

The most troubling interaction with AC agents is an additive response with other AC agents, resulting in an increased anticholinergic load. A noteworthy interaction in patients taking acetylcholinesterase inhibitors for dementia is their influence on clinical efficacy as a result of the antagonism between these two classes of medications.

AC agents may also alter the absorption of other drugs as a result of decreased GI mobility. Individual drug interactions with the various AC drugs used in OAB are discussed in the following sections.^{14,75,65}

Rationale for the Use of Anticholinergic Drugs in Overactive Bladder

The major mechanism of AC drugs is their ability to antagonize the effect of acetylcholine on muscarinic receptors, in the cholinergically innervated bladder detrusor muscle. The result is a decrease in the contractions of the detrusor smooth mus-

cle of the bladder and suppression of or a reduction in the intensity of urgency symptoms.^{55,76,77}

Of the five muscarinic receptors, M3 and, to a lesser extent, M2 appear to have the most influence on bladder detrusor muscle activity. Animal trials suggest that M2 and M3 are involved in bladder contraction. The M3 receptor appears to have the most involvement in direct bladder contraction; the M2 receptor is indirectly involved by opposing beta-receptor activity.⁷⁸ M2 and M3 receptors appear to work synergistically to control the micturition process.^{54,55,78}

As discussed earlier, the future role of agents with greater selectivity for the bladder with primary effects on the M3 and M2 receptor types may result in a more tolerable side-effect profile.^{54,55,78} All current AC drugs lack true specificity for the bladder muscarinic receptors, although one newer agent, darifenacin (Enablex, Novartis), is being promoted as an M3-selective agent, with claims of selectivity to the bladder as compared with other organ systems; however, clinical trials have not validated this claim or clinical advantage.⁷⁹ The reported binding affinity of these agents does not always correlate with clinical efficacy and tolerability. At present, the muscarinic receptor system remains the main target in the treatment of OAB and is the basis for the mechanism of action of these drugs.

Oxybutynin (Ditropan, Ortho-McNeil) may have additional effects on relaxing the smooth muscle of the bladder.⁸⁰ The complexity of the receptor systems involved and their relationship to bladder function continue to challenge researchers. In the future, it may be possible to develop agents with an optimal muscarinic receptor profile to target drug therapy for OAB. Beta-receptor–mediated bladder relaxation along with muscarinic antagonist activity may offer an effective combination for treating OAB.

Other receptor systems, neurotransmitters, and substances may also be involved in the pathophysiology of OAB. Further investigation is ongoing to define more specific targets for pharmacotherapy.^{51,54,55,62,81–88}

Clinical Trials

A number of AC drugs have been used in the treatment of OAB (see Table 3). A review that evaluated 32 placebo-controlled trials in approximately 7,000 subjects reported clinical efficacy with all of the available agents.⁸⁹ Propantheline (Pro-Banthine), dicyclomine (Bentyl), and flavoxate (Urispas, Impax/McNeil), although still available, are rarely used because of their limited efficacy and side-effect profiles.^{77,83,84–87}

Tricyclic antidepressants (TCAs), including imipramine (Tofranil, Novartis/Mallinckrodt), have been used in OAB and in mixed urinary incontinence. Imipramine controls detrusor contractions (through its antimuscarinic effects) and sphincter laxity (through its alpha-adrenergic effects). This dual mechanism of action offers an option for patients with a mixed urge and/or OAB and stress incontinence. The use of TCAs in elderly patients is limited by their significant anticholinergic side-effect profile, cardiac conduction abnormalities, and slow onset of action.^{14,51,65,77,83–89}

Over the past five to 10 years, oxybutynin chloride (Ditropan) and tolterodine (Detrol, Pfizer) have been the mainstays of AC therapy for OAB. Compared with the older agents

(e.g., propantheline), these newer agents have been studied more extensively and appear to be better tolerated.^{85,89} Three agents entered the U.S. market in 2004—trospium chloride (Sanctura, Esprit/Indevus), darifenacin (Enblex), and solifenacin (VESIcare, Astellas Pharma US/GlaxoSmithKline)—along with a transdermal formulation of oxybutynin (Oxytrol, Watson).

In one review of published clinical trials, the use of AC agents in the treatment of OAB had a significant effect on frequency of micturition and the number of incontinence episodes, and it offered at least partial relief for most patients.⁸⁹

A large meta-analysis, published in 2005, reviewed clinical trial data for oxybutynin, tolterodine, darifenacin, and solifenacin versus placebo. Similar efficacy was noted for each of these agents, when compared with placebo.⁶⁰ These agents may differ in their muscarinic receptor activity, dosing formulations, pharmacokinetic profiles, and tolerability, and they may offer additional options for some patients.^{60,89}

Following is a comparison of the potential differences in the common agents used in treating OAB. Head-to-head trials with these agents are limited. Most of the trials have compared oxybutynin with tolterodine and, in a few cases, some of the newer agents.⁹⁰⁻⁹²

Older Drugs

Oxybutynin Chloride

Oxybutynin chloride (OBC, Ditropan) is one of the oldest agents for patients with OAB.^{80,85} Originally available in regular-release (RR) tablets administered up to three times daily, newer formulations include extended-release (ER) tablets and, most recently, a twice-weekly applied transdermal patch (Oxytrol) (Table 6).

Although RR tablets are poorly absorbed with a reported bioavailability of 2% to 11%, the controlled-release (CR) product has improved absorption and is associated with fewer fluctuations in concentration. The CR formulation is an osmotic delivery system with a laser-drilled delivery device, which may remain intact and is seen in the feces.⁹⁴⁻⁹⁶

OBC is metabolized by the liver, specifically the cytochrome P450 (CYP 450) 3A4 system (see Drug Interactions earlier), and is eliminated in the feces and urine. One active metabolite, desethyl oxybutynin (DES), has antimuscarinic activity similar to that of its parent. OBC is a tertiary amine compound; it is reported to be a lipophilic chemical with a small molecular size and neutral polarity, suggesting increased CNS penetration compared with other agents.^{71,93,96}

The mechanism of action appears to be primarily a result of anticholinergic (antimuscarinic) effects on the bladder detrusor muscle. OBC may affect M1, M2, and M3 receptors, and it may have a greater effect on M3, compared with M2, on the bladder detrusor muscle.^{97,98} Other data suggest that it may have a greater selectivity for M3 and M1.^{99,100}

Additional effects that may be unique to this drug involve direct smooth muscle-relaxing properties, through a direct spasmolytic action at higher doses on the detrusor muscle mediated by calcium antagonism.^{80,101}

In clinical trials, OBC was efficacious in reducing incontinence, increasing bladder capacity, and improving symptoms. In some trials, it was more efficacious than tolterodine; the

regular-release (RR) form was the least well tolerated.^{60,102-105}

The adverse effects of OBC may be problematic, especially in older patients, and appear to be dose-related. Dry mouth has been reported in 50% to 70% of patients treated with RR OBC and is probably caused by a high affinity for parotid gland muscarinic receptors.

The RR product is associated with a greater incidence of dry mouth than the ER form.⁹⁴ An eight-fold greater receptor binding affinity to the parotid gland with OBC versus tolterodine has been reported.^{80, 106-108} Other adverse effects included blurred vision, impaired urination, and nervousness, reported in about 10% of patients.^{80,85,109,110}

Discontinuation rates for RR OBC were approximately 25% because of adverse effects.¹⁰⁹ Quantitative topographical electroencephalography (EEG) indicated more CNS side effects with OBC than with tolterodine (Detrol) and trospium (Sanctura). Patient questionnaire data also reported more side effects with RR OBC than with tolterodine and trospium.⁷¹

The controlled-release (CR) formulation of oxybutynin was developed as an attempt to improve tolerability by reducing concentration-dependent adverse events and by producing less conversion of the parent drug to its active metabolite. This product offers an ER effect by using an osmotic system that negates or diminishes the first pass through the liver, resulting in less accumulation of DES, and may result in more tolerable side effects.^{95,114}

The newly released transdermal system (Oxytrol), which results in less first-pass metabolism, also forms a less active DES metabolite and provides improved tolerability. The patch is similar in efficacy to, and is better tolerated than, oral OBC.^{95,116}

A study comparing transdermal oxybutynin with long-acting (LA) tolterodine reported similar efficacy, with a trend toward a higher incidence of dry mouth with tolterodine LA.¹¹⁷ Local reactions reported with the patch include skin erythema and pruritus in up to 17% of patients.^{96,108,115-117}

Drug interactions may involve the CYP 450 system, specifically 3A4 and 2D6. Drugs that inhibit this system may increase the levels of OBC and the risk of side effects.⁹⁶ Increased AC effects may also occur when OBC is used concurrently with other drugs having AC properties.^{64,65}

Tolterodine

Tolterodine (Detrol, Detrol LA) entered the market in the 1990s and has been used extensively in the treatment of OAB. This product is available in RR tablets dosed twice daily and also as a once-daily, long-acting (LA) product designed as a capsule containing microspheres. This microsphere system enables the product to be ingested or sprinkled on food.

The bioavailability of tolterodine varies, ranging from 30% to 90%, and is dependent on the CYP 2D6 phenotype. The product is less bioavailable in patients who are more "extensive metabolizers," but the opposite is true with "poor metabolizers."

Tolterodine is extensively bound to plasma proteins (93%) mainly the alpha₁-glycoprotein. The drug is metabolized by the liver, and its primary metabolic pathway is the CYP 2D6 pathway. The extent of metabolism and excretion (urine or feces) also depends on the CYP 2D6 phenotype. Patients with the poor oxidizer phenotype excrete more drug into the urine

Table 6 Antimuscarinic Drugs Commonly Used in the Treatment of Overactive Bladder

	Oxybutynin (Ditropan, Ditropan XL, Oxytrol)	Tolterodine (Detrol, Detrol LA)	Tropium (Sanctura)	Solifenacin (VESIcare)	Darifenacin (Enablex)
<i>Chemical structure</i>	Tertiary amine	Tertiary amine	Quaternary amine	Tertiary amine	Tertiary amine
<i>Receptor binding</i>	Nonselective	Nonselective	Nonselective	Nonselective	May be more M3-selective
<i>Oral bioavailability</i>	Poor (2%–15%)	Good (75%)	Poor (<10%); taken on an empty stomach	Good (90%)	Poor (15%–20%)
<i>Metabolism</i>	Metabolized by CYP 3A4	Metabolized by CYP 2D6	Minimal, if any, CYP 450 metabolism	Metabolized by CYP 3A4	Metabolized by CYP 2D6 and 3A4
<i>Excretion</i>	Less than 5% of active compound in urine	Less than 5% of active compound in urine	Tubular secretion; 80% of parent com- pound in urine	Less than 15% of parent compound in urine	3% of active compound in urine
<i>Half-life</i>	About 2 hours • Extended-release, 13 hours • Patch, 7–8 hours	About 2 hours; • Extended-release, 8.5 hours	12–20 hours	45–68 hours	13–19 hours
<i>Dosing</i>	• Regular-release: 5 mg two to three times/day • XL: 5–30 mg once daily • Transdermal sys- tem, 3.9 mg twice weekly (hips, abdomen, or buttock)	1–2 mg twice daily LA: 2–4 mg once daily	• 20 mg twice daily • 20 mg daily if elderly or if there is renal impairment	5–10 mg daily	7.5–15 mg once daily
CYP = cytochrome P450; LA = long-acting; M = muscarinic receptor subtypes (M1–M3); XL = extended-release. Adapted from references 71, 79, 85, 133, 134, and 135.					

than patients with the extensive oxidizer phenotype; for these patients, more drug is eliminated in the feces. One active metabolite (the 5-hydroxymethyl metabolite), has antimuscarinic activity similar to that of the parent compound. It is not known whether tolterodine crosses the placenta or is excreted in breast milk.⁹⁶

The drug's mechanism of action is similar to that of OBC, but it appears to lack the antispasmodic effects on the smooth muscle of the bladder. Animal data suggest that tolterodine might be more selective for the bladder than OBC is.¹¹⁸ Tolterodine may also have less affinity for salivary gland muscarinic receptors, suggesting improved tolerability.^{119,120}

Despite the suggested differences in receptor affinities, tolterodine and OBC have similar efficacy and tolerability. A recent meta-analysis reported some nonsignificant trends, such as fewer incontinence episodes with extended-release (XL) OBC versus tolterodine LA; however, OBC RR was reported to be the least well tolerated.⁶⁰

Other trials have noted similar efficacy but improved tolerability and a lower incidence of dry mouth with tolterodine than

with OBC.^{97,120–122} These differences in tolterodine's tolerability may be a result of greater bladder selectivity or less CNS penetration, attributable to its less lipophilic nature.^{71,124–128}

A small trial of EEG effects with tolterodine, OBC, and tropium supported these findings.^{71,124,125} The more recent addition of ER and transdermal formulations of OBC may offer similar efficacy and comparable tolerability.^{108,115,117}

Tolterodine is metabolized by the CYP 450 system, specifically by 2D6 and 3A4. Numerous drugs may inhibit its metabolism and may lead to increased levels and adverse effects. Drugs such as cimetidine (Tagamet, GlaxoSmithKline), fluconazole (Diflucan, Pfizer), erythromycin (Ery-Tab, Abbott), nefazodone (Serzone, Bristol-Myers Squibb), fluoxetine (Prozac, Eli Lilly), and others can interact with this agent, although the clinical significance is not known at this time.

Other agents with AC properties should be used with care to avoid an excessive AC load. Patient monitoring and reviewing the patient's medication profile are important when tolterodine is prescribed with other agents.^{74,96,129,130}

Newer Agents (Approved in 2004)

In an effort to improve quality of life as well as patient compliance, research has focused on the need for more selective and tolerable agents in the treatment of OAB. Improved tolerability may help patient compliance, as reported in some studies.^{85,131,132}

This search for agents with bladder specificity led to the development, approval, and release of three drugs during 2004 (trospium, solifenacin, and darifenacin). Properties of several older and newer OAB drugs are compared in Table 6. Initial claims for OBC and tolterodine indicated similar efficacy and an improved tolerability profile because of their greater selectivity for bladder muscarinic receptors.

Few studies have compared OBC and tolterodine with these newer agents, but a few clinical trials will be discussed. It is not clear, without more comparison trials, whether these more recently approved antimuscarinic agents have clinical advantages over OBC and tolterodine.^{60,85,133-135}

Trospium Chloride

Trospium (Sanctura), the first of the three agents to enter the U.S. market in 2004, has been available in Europe for more than 20 years. It is taken twice daily and differs from other antimuscarinic agents in that its chemical structure is a quaternary amine. This structure results in less CNS penetration and a potential for fewer side effects.¹²⁴

The limiting consequence of the drug's hydrophilic chemical structure is a reduced oral bioavailability; therefore, it should be taken one hour before or two hours after meals.¹³⁴ Metabolism is limited, with fewer than 5% to 10% of these metabolites excreted in the urine.

At normal doses, CYP 450 system involvement is minimal. Excretion is primarily renal via tubular secretion and involves the parent compound. Other drugs may compete for this elimination mechanism (e.g., metformin, digoxin), resulting in increased levels of either trospium or the coadministered drug. It has been proposed that this tubular secretion mechanism is a therapeutic advantage because of the high bladder concentration, which ensures efficacy at the target tissue and, possibly, improved tolerability.^{92,124}

The half-life of trospium is approximately 12 to 20 hours. For older patients and those with severe renal impairment (a creatinine clearance [CrCl] < 30 ml/minute), the dose should be reduced to 20 mg daily. Caution is recommended in patients with moderate-to-severe liver disease.^{92,124}

Trospium's muscarinic receptor-binding profile has been described as having high affinity and specificity for M1, M2, and M3 receptors. Further evaluation is necessary to assess the clinical significance of this receptor profile in reducing side effects as contrasted with other AC agents. Trospium is also reported to have smooth muscle-relaxant properties.^{92,110,134,136-138}

Placebo-controlled trials report efficacy in treating OAB, although comparative trials with other AC agents are limited. Trials comparing trospium with OBC and tolterodine report greater tolerability with tolterodine than with OBC.^{138,139}

Adverse effects of trospium appear to be similar to those of tolterodine and OBC, although CNS side effects may be fewer as a result of reduced CNS penetration secondary to its quaternary amine structure.^{71,142}

Other data reported minimal effects on rapid eye move-

ment (REM) sleep, suggesting improved sleep hygiene.⁹² Safety and tolerability studies with trospium suggested dose-related side-effect profiles, although tolerability was seen with a wide range of doses.¹⁴³ Another potential advantage of trospium, compared with OBC or TD, is minimal CYP 450 metabolism and thus a reduced potential for drug interactions. Higher doses may inhibit the CYP 2D6 enzyme system, and careful monitoring is necessary.^{134,144-146}

Contraindications have been discussed on page 466. A pregnancy category C warning suggests that trospium be used only if the potential benefits outweigh the risks.⁹²

Solifenacin

Solifenacin (VESIcare), another new AC agent, is dosed at 5–10 mg daily, and it has excellent bioavailability. It is widely distributed with extensive hepatic metabolism, the primary pathway involving CYP 450 3A4, with at least one pharmacologically active metabolite reported.

The half-life is approximately 50 hours because of its extensive distribution and slow elimination, which allow once-daily dosing. This half-life may be increased in patients with hepatic impairment; therefore, a dosage adjustment, for a maximum of 5 mg daily, is recommended in patients with moderate hepatic impairment (class Child-Pugh B). The drug should be avoided in cases of severe hepatic impairment (class Child-Pugh C).

Solifenacin and its metabolites are excreted in urine (70%) and in feces (25%). In a case of severe renal impairment (CrCl < 30 ml/minute), doses should be limited to 5 mg daily.^{91,133,135}

The drug is approximately 95% protein-bound, primarily to alpha₁-glycoprotein, which has minimal clinical significance. Little information is available involving its specific binding affinity. Although solifenacin is more selective for the bladder, no clinical evidence has supported this potential advantage.¹⁴⁷

In clinical trials, solifenacin was more effective than placebo. More than 99% of patients found it to be well tolerated and "acceptable" or "satisfactory." Reductions in episodes of urgency, incontinence, frequency, and increased volume per void were reported to be significantly improved compared with placebo.^{91,148-153}

In a trial comparing solifenacin 5 and 10 mg with tolterodine 2 mg twice daily, no statistical differences between the treatment arms were observed; however, this trial was not powered to detect differences between the treatment groups.¹³³ Another trial comparing solifenacin 5 and 10 mg and tolterodine LA 4 mg twice daily showed similar efficacy in OAB, measured as reductions in nocturia episodes.¹⁵⁵

The effect of solifenacin on cardiac electrophysiology was significant at a dose of three times the maximum recommended dose. At normal therapeutic doses of 5 to 10 mg, no clinically significant effect on QTc prolongation was reported. This observation should be considered if solifenacin is used with other drugs that prolong the QTc interval or if the patient has a history of QTc prolongation.⁹¹

Like OBC and tolterodine, solifenacin is a substrate of the CYP 450 enzymes, specifically the CYP 3A4 pathway. The dose should be limited to 5 mg daily when the drug is used concurrently with CYP 3A4 inhibitors such as ketoconazole (Nizoral, Janssen), fluconazole, and erythromycin.⁹¹

Contraindications are similar to those of other AC drugs. A pregnancy category C warning suggests that solifenacin be used during pregnancy only if the benefits justify the risks. It is not known whether solifenacin is excreted in breast milk. Whether or not nursing mothers should continue therapy depends on an assessment of the risks and benefits of continued use.⁹¹

Darifenacin

Darifenacin is given once daily as a 7.5- or a 15-mg CR tablet. As with trospium, it has poor oral bioavailability (15% to 25%).

Metabolism occurs via the CYP 450 system, and 2D6 and 3A4 are the primary pathways. Because of darifenacin's extensive first-pass metabolism and because some patients metabolize CYP 2D6 pathway drugs poorly, the drug may have greater bioavailability with these patients. The drug's metabolism may occur more extensively via the CYP 3A4 pathway in patients who are considered poor metabolizers. Excretion occurs via both urine and feces. The elimination half-life is about 15 hours.

Doses should not exceed 7.5 mg in patients with moderate hepatic impairment (class Child-Pugh B) or when the drug is given with CYP 3A4 inhibitors. Renal dysfunction has minimal, if any, influence on clearance, but caution is recommended for patients with renal disease.^{90,156}

According to the manufacturer, Novartis, darifenacin has a higher affinity for the M3 receptor than for other muscarinic receptors.⁹⁰ Although Novartis suggests that this may offer improved tolerability, the presence of M3 receptors in the salivary glands, GI tract, and iris of the eye may still lead to the common AC side effects (Table 5).^{90,130,135}

Compared with placebo, darifenacin reduced the number of weekly incontinence episodes, daily micturitions, and nocturnal awakenings. Trial doses ranged from 7.5 to 15 mg and were titrated up or down to 7.5 mg or 30 mg, respectively, based on efficacy and tolerability. Side effects were dry mouth and constipation, and these were related to the dose.^{135,156,158,159} Some trials reported similar cardiac and CNS effects with darifenacin versus placebo.^{130,156}

Like other newer antimuscarinics, comparative data on other agents in the class are limited. A trial comparing darifenacin 15 mg daily with OBC IR 5 mg three times per day reported similar efficacy but a higher rate of dry mouth and blurred vision with OBC.¹⁵⁸ In a trial comparing darifenacin 15 mg with tolterodine 2 mg twice daily, efficacy and side-effect profiles were similar.^{90,159} Adverse events, including dry mouth, CNS effects, and cardiac effects, were similar to those associated with placebo, suggesting support for darifenacin's claim of M3 bladder receptor selectivity.^{79,135}

The drug-interaction profile of darifenacin is similar to that of OBC and tolterodine in terms of involvement of the CYP 450 3A4 and 2D6

enzyme systems. The darifenacin dose should be reduced when it is used with inhibitors of the CYP 450 3A4 system such as ketoconazole, clarithromycin (Biaxin, Abbott), and others. Similarly, patients taking potent CYP 450 2D6 inhibitors such as paroxetine (Paxil, GlaxoSmithKline) may also need dose reductions.

Other reported drug interactions included slight increases in the concentration of digoxin and midazolam (Versed, Roche) when used concurrently with darifenacin, in addition to the potential additive AC effects when it is used with other AC agents.

Contraindications to the use of darifenacin are similar to those for other AC drugs. The pregnancy category C warning suggests that darifenacin should be used only if the benefits outweigh the risks.

It is not known whether darifenacin is excreted in breast milk. Decisions as to whether to continue therapy in nursing mothers should be based on an assessment of the risks and benefits of continued use.^{90,156}

Darifenacin may have advantages because of its bladder M3 selectivity, but clinical evidence supporting this is lacking in humans.^{79,156} This concept is complicated by the fact the M3 receptors are also located in other organ systems (the CNS, salivary glands, and the GI tract). The research also suggests a role for the M2 receptor in bladder contractility.^{79,161,162}

Table 7 Counseling Points for Patients with Overactive Bladder

1. Explain the basic role of the medication and how it works on the bladder.
2. Explain the long-acting and short-acting versions (do not crush extended-release tablets).
3. Discuss missing doses (do not double up the next day).
4. Trospium should be taken one hour before or two hours after meals.
5. Suggest adequate fluid intake while patients are taking these agents.
6. Because these medications may cause drowsiness, blurred vision, or dizziness, recommend caution if the patient must drive.
7. Advise a balanced diet or a dietary consultation if constipation occurs. Patients should consult their physician or go to the emergency department if they experience severe abdominal pain.
8. Patients should report unusual reactions (visual changes, headache, stomach problems, itching, difficulty breathing) to their physician or pharmacist.
9. It might be prudent to obtain a brief medical history, because these agents are contraindicated in patients with narrow-angle glaucoma, myasthenia gravis, ulcerative colitis, and some liver diseases.
10. If dispensing the drug in the summertime, mention that decreased sweating may occur and may contribute to hyperthermia.
11. Although most patients receiving these agents are older, these drugs are classified as pregnancy category C except for oxybutynin (category B). Inform women of childbearing age that they should be certain that their physician knows whether they are pregnant or breast-feeding.
12. Advise that medications should always be stored away from heat, moisture, and direct light.
13. Patients should be advised to wash their hands before applying the oxybutynin (Oxytrol) patch. They should leave the patch in its sealed wrapper until it is ready to use. They should not apply the patch over an old patch, and they should never place the patch over burns, cuts, or irritated skin.
14. Patients should follow dosing instructions or consult their pharmacist or health care provider if they have questions.

Adapted from references 90–92 and 115.

Conclusion

The antimuscarinic agents used in the treatment of OAB include eight chemical entities, seven oral forms, and one transdermal formulation. All of these forms differ somewhat in their pharmacokinetic properties, dosing, and side-effect profiles (see Table 6). Differences in muscarinic receptor affinity have also been reported, but the clinical advantage among these variations is not known at this time.^{85,111,133,134,135}

The clinical efficacy of each formulation appears to be similar, as reported in clinical trials. All these agents bring about improved responses, when compared with placebo, and when they are used in combination with various behavioral interventions, there may be additional benefits.^{42-44, 50,163-165}

At present, it is difficult to suggest that one of the newer agents (trospium, solifenacin, darifenacin, or the patch) has an advantage over the older agents (oxybutynin and tolterodine) except for some differences in tolerability. Trospium, with its significant dependence on a tubular secretion mechanism for elimination, suggests a more favorable target effect on the bladder than on other body systems, but the clinical significance of this property is not clear. In addition, trospium's highly charged quaternary ammonium group suggests little or no penetration across the blood-brain barrier and may be associated with fewer CNS effects, compared with IR oxybutynin in healthy volunteers.^{71,142} This may be an important advantage and may have utility in some (elderly) patients who have difficulty tolerating other agents within the class.^{138,139,143}

The selective blockage of the M3 receptor by darifenacin may also have a theoretical advantage in its more selective effect on the bladder.¹⁵⁶ This concept is complicated by the fact that M3 receptors are also located in other organ systems in addition to the suggested role of the M2 receptor in bladder contractility.^{79,161-162} Tolerability may be the decisive factor in the selection of a preferred agent.

Whether it is through decreased CNS penetration or decreased affinity for the M1 muscarinic receptors in the brain, the newer agents demonstrate a potential for improved side-effect profiles over IR OBC and, possibly, tolterodine.^{124,130,134,147,155-158} Further clinical evidence is needed in order to determine the best option for the treatment of OAB, and an individual approach is recommended. Future agents will focus on targeting other receptor systems and will possibly be used in combination with existing therapies.

Although pharmacological therapies have been effective in the treatment of OAB, side-effect profiles and a lack of patient counseling may result in poor compliance and ineffective management. Pharmacists can play a major role in counseling patients on the various antimuscarinic agents used in OAB, educating them about their proper use, and encouraging them to maintain compliance with their regimens (Table 7).

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Conflict-of-Interest (COI) Statement

Dr. DeMaagd has disclosed that he is on the Speaker's Bureau for Forest Pharmaceuticals. Dr. Geibig has no relationships to disclose. The content of this article has been reviewed under Jefferson's Continuing Medical Education COI policy.

Continuing Education Questions for Physicians and Pharmacists

P&T® 2006;31(8):462-474

ACPE Program #079-999-06-018-H01

Expiration Date: August 31, 2007

TOPIC: An Overview of Overactive Bladder and Its Pharmacological Management with a Focus on Anticholinergic Drugs

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Continuing Education Questions for Physicians and Pharmacists

TOPIC: An Overview of Overactive Bladder and Its Pharmacological Management with a Focus on Anticholinergic Drugs

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Multiple Choice

Select the one correct answer.

1. **Which of the following is a complication of OAB?**
 - a. urinary tract infection
 - b. skin ulceration
 - c. falls
 - d. all of the above
2. **What is the estimated total yearly cost of OAB?**
 - a. \$1 million
 - b. \$5 million
 - c. \$13 billion
 - d. \$20 million
3. **According to the NOBLE survey project, OAB affects approximately how many Americans?**
 - a. 15 million
 - b. 20 million
 - c. 25 million
 - d. 30 million
4. **Which of the following drugs reportedly has the most M3 selectivity?**
 - a. oxybutynin
 - b. tolterodine
 - c. solifenacin
 - d. darifenacin
5. **Which of the following drugs has the longest half-life (45 to 68 hours)?**
 - a. tolterodine
 - b. trospium
 - c. solifenacin
 - d. darifenacin
6. **Which of the following drugs, when used orally, should be taken on an empty stomach (e.g., one hour before or two hours after meals)?**
 - a. oxybutynin
 - b. tolterodine
 - c. trospium
 - d. darifenacin
7. **Which of the following drugs is available in a transdermal dosage form?**
 - a. oxybutynin
 - b. tolterodine
 - c. trospium
 - d. solifenacin
8. **Which of the following muscarinic receptors is located on the bladder?**
 - a. M1
 - b. M3
 - c. M4
 - d. M5
9. **All of the following are central side effects of anticholinergic drugs except:**
 - a. mydriasis.
 - b. sedation.
 - c. confusion.
 - d. sleep disruption.
10. **Anticholinergic agents are contraindicated in all of the following except:**
 - a. glaucoma.
 - b. urinary and gastric obstructive disorders.
 - c. arthritis.
 - d. performing tasks that require mental alertness.

CE Registration and Evaluation Form

Date of publication: August 2006

Title: **An Overview of Overactive Bladder and Its Pharmacological Management with a Focus on Anticholinergic Drugs**

Authors: **George DeMaagd, PharmD, BCPS, and Jeffrey D. Geibig, PharmD**

Submission deadline: **August 31, 2007**

ACPE Program #079-999-06-018-H01

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