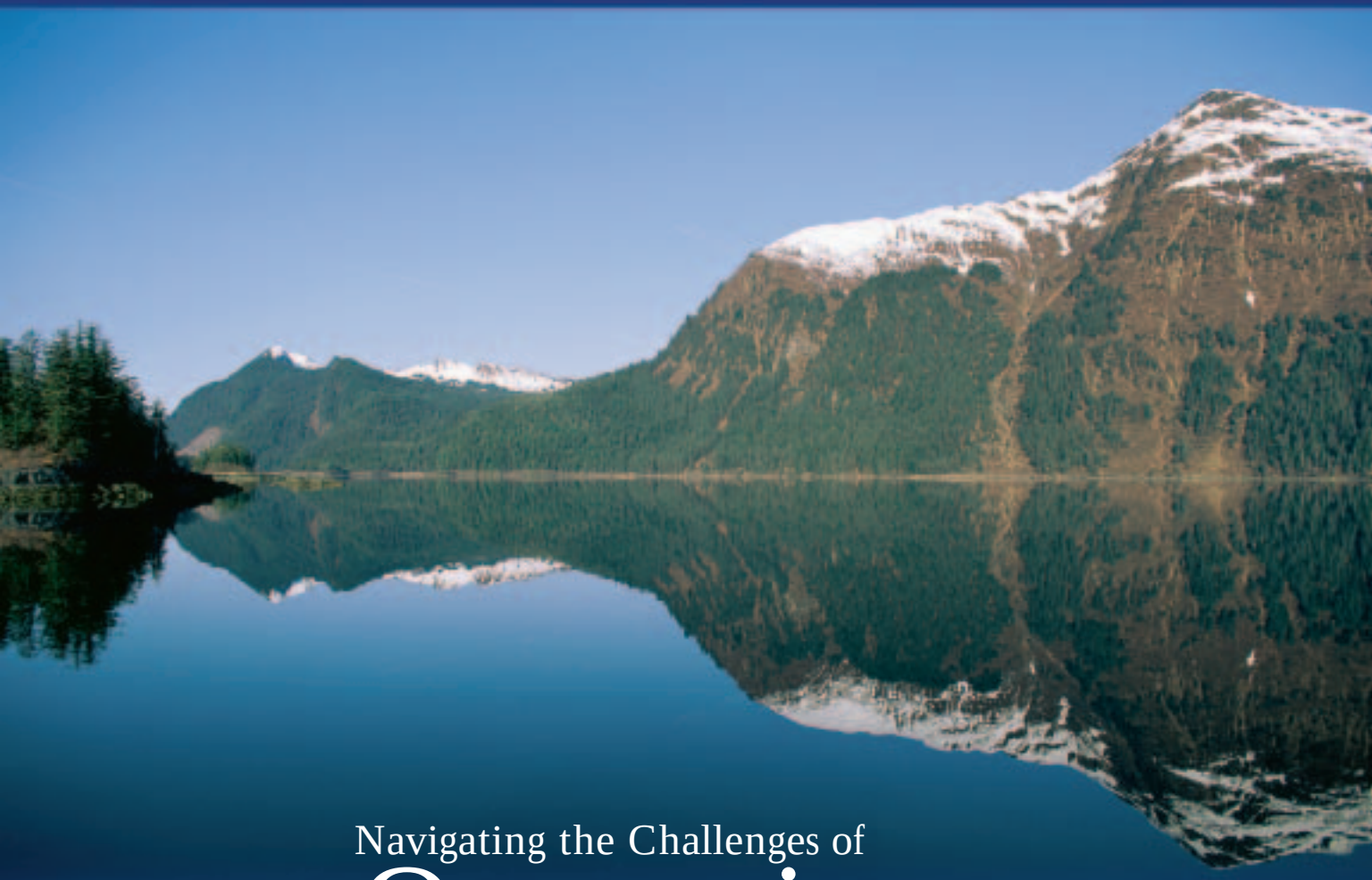
September 2004

A Supplement to

Family Practice Recertification®

A peer-reviewed clinical journal for primary care physicians



Navigating the Challenges of Overactive Bladder: A Primary Care Perspective

Supported by an unrestricted educational grant from

WATSON Pharma, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

An MWC Publication

PUBLISHER'S NOTE: This supplement to *Family Practice Recertification*® is supported by an unrestricted educational grant from Watson Pharma, Inc. The opinions or views expressed in this supplement are those of the authors and do not necessarily reflect the opinions or recommendations of Watson Pharma, Inc., or the publisher or editors of *Family Practice Recertification*®.

Dosages, indications, and methods of use for compounds that are referred to in this supplement by the author may reflect his clinical experience or may be derived from the professional literature or other sources. Because of differences between in vitro and in vivo systems and between laboratory animal models and clinical data in humans, in vitro and animal data may not correlate with clinical results and do not demonstrate clinical safety or efficacy in humans. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested by the author should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturers' product information, and comparison with the recommendations of other authorities.

This supplement may include discussion of treatment indications outside current approved labeling. Consult complete prescribing information before administering any of the drugs discussed.

Family Practice Recertification® is published monthly by Medical World Business Press, Inc., 241 Forsgate Drive, Jamesburg, NJ 08831-0505. Telephone: (732) 656-1140. Periodicals postage is paid at Monroe Township, NJ 08831 and at additional mailing offices. M384

Navigating the Challenges of OAB: A Primary Care Perspective

Karl Luber, MD, Kaiser Permanente, La Jolla, California
David Smith, MD, Texas A&M University, College of Medicine, Brownwood, Texas
Marc Gittelman, MD, South Florida Medical Research, Aventura, Florida

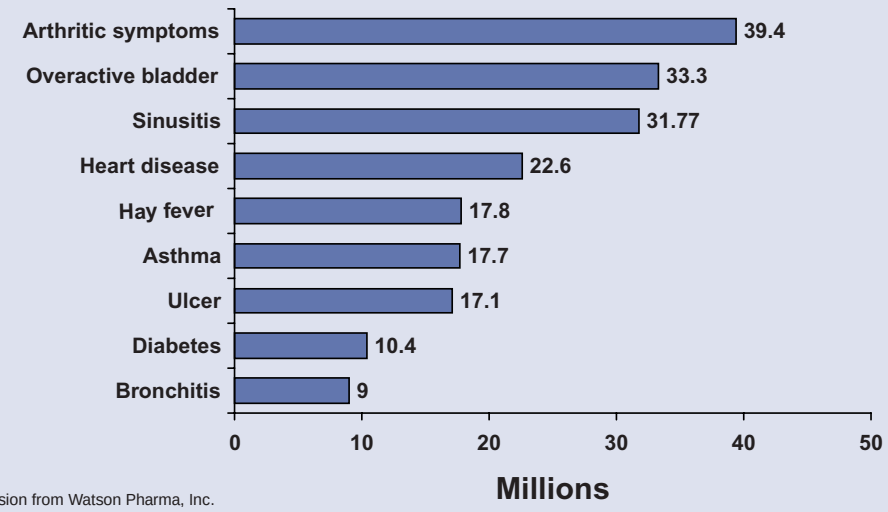
Introduction

Estimated to affect 33 million people in the United States,[1] overactive bladder (OAB) is more prevalent than many other conditions, including long-term sinusitis, heart disease, and diabetes (Figure 1).[1-3] Although millions of people experience symptoms of OAB, the prevalence of this disorder is underestimated because patients often do not report symptoms. Fewer than 60% of patients with OAB inform their health care practitioners that they have OAB symptoms,[4] essentially erecting a barrier to treatment. Additionally, many physicians do not ask patients if they experience OAB symptoms. When primary care physicians (PCPs) do detect incontinence, many may be unaware of the impact this disorder has on their patients' quality of life (QOL) and of the interventions that may be helpful.[5] Results of a recent large, Internet-based survey revealed that only 30% of all patients with OAB symptoms who had discussed their symptoms with a health care provider believe that their providers consider OAB to be a serious medical condition.[6] In another recent study, only 50% of vulnerable older patients were asked about incontinence during an initial visit to a PCP, and fewer than one third received annual continence evaluations. When a patient presented with incontinence, few physicians recorded an incontinence history (19%); treatment options were noted in patients' charts 59% of the time, whereas behavioral treatments were noted in 13% of cases.[7]

With increased longevity and a growing elderly population, the prevalence of OAB is expected to increase. Therefore, more effective strategies, such as practice-based interventions, need to be designed to change physician performance and resultant outcomes, as well as increase patient satisfaction.[8] PCPs, often the first clinicians to see patients with bladder problems, should be educated regarding the screening, detection, and treatment of OAB. They need to clearly understand the definition and symptomology of OAB.

Figure 1

Prevalence of selected long-term conditions in the United States[1,3]



Reprinted with permission from Watson Pharma, Inc.

What Is OAB?

OAB results from involuntary contractions of the detrusor muscle during filling, often without a known cause, which results in sustained high bladder pressure. It encompasses symptoms of urgency (sudden need to urinate), frequency (more than 8 times over 24 hours), and nocturia (waking up one or more times during the night to void), and may include urge incontinence.[9,10] Individuals with OAB often experience urgency at inconvenient and unpredictable times, which may result in an incontinence episode. This compelling need to void may occur, however, with or without urinary incontinence (UI).

The causes of incontinence are multifactorial and may involve factors both within and outside the lower urinary tract. Identifiable causes include nerve damage caused by abdominal trauma, pelvic trauma or surgery, bladder stones, adverse effects of drugs, and neurologic diseases (ie, multiple sclerosis, Parkinson's disease, stroke, or spinal cord lesions).[11] It is not uncommon for individuals to experience more than one type of incontinence simultaneously. Proper diagnosis of the type of incontinence is an essential factor in successful treatment.

Urge urinary incontinence (UUI), also known as detrusor overactivity, is a symptom of OAB. It involves the compelling need to urinate and the inability to prevent leakage long enough to reach a bathroom, representing a failure of the bladder to store urine because of an uninhibited contraction of the detrusor muscle.[12] UI is more common in older adults and has social and hygienic consequences for individuals and their caregivers.[13]

Stress urinary incontinence (SUI) occurs when a rise in intra-abdominal pressure overcomes urethral resistance.[14] Triggered by physical exertion, including sneezing or coughing (Valsalva events), laughing, bending, or lifting, SUI is common in women with obesity or uterine prolapse or following childbirth because of pelvic floor damage.[12,14] Because a Valsalva maneuver can trigger an involuntary contraction of the detrusor, it is often difficult for patients and PCPs to distinguish UUI from SUI.[14]

Mixed UI is a common form of UI and includes symptoms of both UUI and SUI, which may further complicate the diagnosis.[15] Inappropriate bladder contractions and weakened sphincter muscles usually cause this type of incontinence.

Overflow incontinence results in continual leakage of urine because the bladder is full beyond capacity.[12] This failure to empty the bladder may be the result of an underactive or contractile detrusor and is seen in patients with outflow obstruction and/or spinal cord lesions.

Functional UI refers to an individual's inability to use toileting facilities. It is associated with factors other than urinary tract problems, such as long-term physical and/or cognitive impairment.[13]

Transient incontinence often occurs in response to illness or medications that increase the volume of urine or interfere with the normal functioning of the urinary tract.[16]

The Impact of OAB and UI

Both OAB and UI pose a significant economic burden on individuals, their families, and the health care community. For purposes of cost-of-illness estimates, costs are separated into intangible, indirect, and direct expenses.

Intangible Costs

The inability to control urine is one of the more unpleasant problems an individual can endure, both physically and psychologically. Such distress constitutes the intangible costs of OAB and UI and may cause a decrease in QOL, perhaps as severe as that of many long-term diseases.[17] Individuals experience wetness, odor, discomfort, and skin irritation, all of which can cause embarrassment, shame, and damage to one's self-esteem. Some try to cope by limiting their fluid intake. Many fear institutionalization, and not without cause: studies reveal that UI is a major reason given for nursing home admissions.[18] A recent Internet-based survey, involving 898 women

with symptoms of OAB and 330 controls, revealed that most women with OAB symptoms feel a tremendous impact of the disorder on multiple aspects of their work, family, and social lives. They are more likely to believe that they are a burden to family members than are their counterparts who do not have OAB.[19] Patients with UI may limit their physical and recreational activities, routine chores, and social interactions. Additionally, coping mechanisms such as planning ahead to locate public bathrooms (a behavior known as toilet mapping) can cause anxiety.[20] Individuals often avoid sexual intimacy because they fear urine leakage.[21] Other symptoms with psychosocial implications include sleep disruption, diminished self-esteem, and depression.[20]

Indirect Costs

Reduced productivity and lost wages, as well as time spent by friends and family on behalf of the patient, contribute to the indirect costs associated with OAB.[22] In 1995, the toll of unpaid caretaking of individuals with UI totaled $704 million. This unpaid caretaking cost, defined as tending to incidental consequences of UI, such as laundry and cleaning, was estimated as 10 minutes per day at $5.50 per hour.[22] In 2000, the total loss in productivity attributable to OAB was $841 million.[23] Indirect costs can continue to increase if OAB remains undetected or undertreated.

Direct Costs

Direct costs associated with OAB include the costs of diagnostics, treatments, routine care, rehabilitation, and direct consequences of incontinence. Treatment costs comprise outpatient visits, surgery, home care, and pharmacologic therapy.[23] Consequential costs associated with OAB include injuries and fractures from falls, often occurring during nighttime trips to the bathroom (Table 1). In 2000, the overall direct cost for OAB amounted to approximately $11 billion, with $1.2 billion spent by women on pharmacologic treatments.[23]

Table 1

Direct costs of overactive bladder in women[23]

Contributing items	Estimated annual direct cost
Diagnostic procedures, treatment, routine care	$3.9 billion
Nursing home stays	$1.47 billion
Urinary tract infections	$1.19 billion
Falls and fractures	$306.9 million
Extended hospital stays	$49.1 million
Skin conditions	$38.4 million

Clinical Challenges for PCPs

Despite the prevalence of OAB and recommendations in *Urinary Incontinence in Adults: Acute and Chronic Management*,[18] guidelines developed to improve reporting, diagnosis, and treatment, the condition remains widely underdiagnosed and underreported. Many individuals do not seek medical help and, therefore, fail to receive the appropriate screening, evaluation, and treatment for the condition. In a survey of women with UI symptoms (N = 1970), fewer than half reported discussions with a physician about incontinence.[24] Historically, physicians are trained to respond to the complaints of their patients; however, many patients with OAB do not initiate discussions about their symptoms, which adds a barrier to implementing treatment. Compounding the problem, many physicians do not query their patients regarding OAB and many clinicians consider the disorder to be a low priority. Yet PCPs are in a strategic position to address these symptoms and to improve the QOL of patients with OAB by meeting the challenges of early screening, detection, and treatment.

Screening for OAB

The most immediate clinical challenge in managing OAB is improving communication between PCPs and their patients to better screen for symp-

toms of the disorder. The first step in screening for OAB is identifying those at risk for UI (see *Risk factors for UI*). The next step includes incorporating routine diagnostic questions (see *Suggested assessment questions*) into annual patient visits, along with obtaining a urinary history and performing a physical examination and laboratory evaluation. Questions about OAB symptoms, particularly UI, urgency, and frequency of urination, can be added to routine questioning about gastrointestinal (GI) symptoms and bowel habits or, alternatively, in the form of a standardized symptom questionnaire.[25] A self-administered questionnaire given to patients in the waiting room or a nurse-administered questionnaire in the examination room can minimize the practitioner's screening time.

Risk factors for UI[14]

- Menopause
- Medications
- Nerve damage
- Cognitive dysfunction
- Immobility
- Fecal impaction

Diagnosing OAB

If the screening results are positive, the PCP should then complete a more detailed evaluation. This should include the duration of symptoms, the timing and volume of voids, the precipitants, associated symptoms, daily fluid and caffeine intake, and medications currently being taken (see *Agents that mimic OAB or affect bladder control*), as well as a review of the patient's medical history.

A physical examination should include the abdomen, prostate, and genitalia for men, internal pelvic and external genital area for women, and rectal and neurologic exams for both.[12] Mental and functional status should also be evaluated. For patients with symptoms, a urinalysis provides information on the presence or absence of an infection, glycosuria, proteinuria, or hematuria. The Agency for Health Care Policy and Research has recommended an estimation of postvoid urine residual (PVR) in its clinical practice guideline as a secondary measure for assessing treatment outcomes in studies of UI.[18] However, PVR is the subject of controversy because of the lack of normative data, the variability in measurements, and the increase in residual urine that may occur with pharmacologic treatment of UI.[9,26] In one clinical study,[27] it was observed that voiding difficulty (feelings of incomplete emptying, the need to strain, or urinary hesitancy), pelvic organ prolapse, and absence of SUI symptoms were predictive of an elevated PVR in 82% of cases. However, only 10% of women with UUI had elevated PVRs. Therefore, PVRs may not be useful as a routine diagnostic procedure for OAB in female patients. Formal urodynamics are unnecessary for most incontinent patients but may be useful in clarifying the diagnosis of OAB in complicated cases or when empiric therapy is unacceptable or has failed.[29] In general, urodynamics are of limited benefit when administered routinely because they have not yet been shown to be reproducible over

Suggested assessment questions[28]

- How often must you use the bathroom to empty your bladder during waking hours?
- How often do you awaken during the night to empty your bladder?
- During the last week, have you leaked urine on your way to the bathroom?
- During the last week, have you had a wetting accident?
- Do you use pads, tissues, or cloth in your underwear to catch leaking urine?
- Have you had an urgent sense of needing to empty your bladder?
- Do you avoid places that may not have a nearby restroom?
- Does a frequent need to urinate interfere with your activities?

Agents that mimic OAB or affect bladder control[11]

- Anticholinergics (antidepressants, antipsychotics, narcotics)
- Antihypertensives (alpha-blockers, beta-blockers, calcium channel blockers)
- Rosiglitazone
- Alcohol
- Diuretics (Rx and caffeine)

a period of several years, even within individual patients.[29,30] To assist with the diagnostic process, patients may be instructed to use a bladder diary, which can help identify triggers and provide a more complete clinical picture of a patient's bladder control problems.

Bladder Diaries

Bladder diaries provide a format for recording the number of diurnal and nocturnal voids and the intervals between voids as well as the number of UI episodes that occur. Diaries also provide a record of absorbent pad use, fluid and caffeine intake patterns, circumstances associated with incontinence, and void volumes (Figure 2).[20] Bladder diaries can also enhance patients' awareness of their bladder habits, including leakage patterns, and may reduce incontinence episodes, possibly decreasing urge accidents. Once it is confirmed that a patient has OAB, treatment may be initiated.

Figure 2

Sample page from a bladder diary

NAME		DATE			
TIME	**FLUIDS**	**URINATION**		**ACCIDENTS**	
Hours	**Type and amount of fluid intake**	**Strong urge to urinate (Y, N)**	**Amount urinated in toilet (S, M, L)**	**Amount of leakage (S, M, L)**	**Activity preceding leakage**
EXAMPLE	**1 glass milk**	**Y**	**S**	**S**	**Walking dog**
6-9 AM					
9 AM-12 PM					
12-3 PM					
3-6 PM					
6-9 PM					
9 PM-12 AM					
12-3 AM					
3-6 AM					

Treating OAB: An Integrated Approach

Treating patients with OAB is always challenging and it is important for physicians to set realistic goals. Because a cure is rarely achieved, the most effective goal is symptom management. Two of the major categories of treatment—behavioral interventions and pharmacologic therapy—will be discussed in this supplement. Although each category is shown to be effective in managing OAB symptoms, reasonably convincing data suggest that using both methods together is better than using either alone for some patients.[31,32] One study[31] revealed that after 8 weeks of treatment with behavioral therapy alone, there was a 57% reduction in UI episodes; when drug therapy was added for an additional 8 weeks, there was a further reduction in UI episodes (88% compared with baseline). Conversely, after 8 weeks, drug therapy alone reduced UI episodes by 73%, increasing to 84% compared with baseline when behavioral therapy was added for an additional 8 weeks. A treatment plan should be tailored to each patient individually, including factors such as age, emotional stability, and physical and mental comorbidities.

Teaching patients behavioral techniques provides them with the skills necessary to improve bladder control. Such interventions involve altering a patient's behavior, environment, or contributory activities.[20,33] The following techniques range from simple to complex and require patients to have good cognitive functioning and caregiver assistance:

Lifestyle changes. These changes assist in management of symptoms by altering one's normal habits. Such alterations include smoking cessation, weight reduction, and the adequate management of fluid and food intake.

Bladder training (also referred to as bladder retraining). This method utilizes scheduled voiding and the systematic delay of voiding, meaning that the patient extends the time between each void to increase the intervals between episodes. It is recommended for patients with OAB and mixed UI, but may also benefit patients with SUI.[11]

Pelvic floor muscle (also referred to as Kegel exercises). Muscle-toning exercises help to strengthen the pelvic floor muscles and increase the patient's bladder control. These exercises are recommended for patients with SUI and OAB.[11]

Biofeedback. This method is often used with pelvic floor muscle exercises and is recommended for bladder training. A visual or audio device is used to alert patients when the appropriate bladder muscles are being contracted as recommended.

Electric stimulation. This course of action involves direct electrical stimulation of the pelvic floor. It is recommended for women with SUI and for both men and women with OAB or mixed UI.

Devices. By supporting areas of organ prolapse, devices such as pessaries are often used to reduce leakage that may occur because of uterine prolapse or cystocele and the resultant SUI.[34]

Pharmacologic Options

When a patient's QOL is severely compromised by OAB, or if a patient fails to or cannot comply with behavioral strategies, physicians may consider medication. Although pharmacologic therapies used to treat OAB include antimuscarinics, estrogen (for postmenopausal women with atrophic vaginitis), and alpha-adrenergic antagonists (for men with benign prostatic hypertrophy), only oxybutynin (OXY), tolterodine (TOL), and trospium, all antimuscarinic agents and competitive inhibitors of acetylcholine at muscarinic receptors, have been approved for this indication. OXY and TOL are associated with a wealth of clinical experience. Both agents have demonstrated efficacy in reducing OAB symptoms in several placebo-controlled, double-blind clinical trials.[35-39] OXY and TOL control detrusor hyperactivity by altering autonomic tone of the bladder and relaxing smooth-muscle spasms.[40,41] However, all antimuscarinics can have bothersome anticholinergic-related side effects, such as dry mouth, dry eyes,

blurred vision, constipation, and drowsiness, which often limit dosing and decrease patient adherence. In fact, several studies have demonstrated that adherence with oral antimuscarinics is generally poor, mainly because of intolerability and, in some cases, lack of efficacy.[42,43] Because of the long-term nature of this disorder, the problem of intolerability presents another clinical challenge.

Oxybutynin

OXY has been prescribed for OAB and associated UUI for many years in doses ranging from 5 to 15 mg daily.[14] OXY is available in orally administered immediate-release (OXY-IR) and extended-release (OXY-ER) forms, as well as in a transdermal patch (OXY-TDS).

OXY-IR is effective for treating neurogenic and non-neurogenic overactivity of the detrusor muscle with UI and has reduced incontinent episodes by >50% in approximately 60% to 80% of patients.[18,41,44] OXY-IR also decreases urinary frequency and increases void volume.[18,40,41,44] Although the efficacy of OXY-IR is well documented, it is limited by anticholinergic side effects, primarily dry mouth and constipation. Anticholinergic adverse events (AEs) associated with OXY are thought to be linked to high plasma concentrations of the active metabolite N-desethyloxybutynin (N-DEO), which appears in the serum after first-pass metabolism of the parent compound in the gut wall and in the liver.[38,45,46]

Similar to studies of OXY-IR, studies of OXY-ER also report significant reductions in episodes of UI and urinary frequency in patients with symptoms of OAB.[40,47-50] With this formulation, absorption of OXY occurs mostly in the colon, thereby avoiding the first-pass metabolism that occurs early in the small intestine with the IR formulation. Compared with the IR formulation, OXY-ER appears to be more tolerable, demonstrating a lower incidence of anticholinergic AEs, including dry mouth.[40,41]

OXY-TDS has recently become available for the treatment of OAB and UI. OXY-TDS, a thin, flexible, clear patch, is applied twice weekly to the abdomen, buttock, or hip for controlled delivery of 3.9 mg/day of OXY. In clinical trials, the use of OXY-TDS has resulted in significant reductions in incontinence episodes and urinary frequency.[35,51,52] OXY-TDS has also demonstrated a tolerability profile similar to placebo. In a clinical study comparing OXY-TDS with placebo, there was no significant difference in anticholinergic-mediated AEs, including dry mouth between OXY-TDS and placebo (Table 2).[35] Fewer than 10% of patients receiving OXY-TDS in clinical trials reported dry

Table 2

Transdermal oxybutynin and long-acting tolterodine vs placebo: Most common adverse events[35]

Adverse event	OXY-TDS (%) (n = 121)	Placebo (%) (n = 117)	TOL-LA (%) (n = 123)
Dry mouth	4.1	1.7	7.3
Constipation	3.3	1.7	5.7
Abnormal vision	2.5	0.9	0.8
Dizziness	0.8	0.9	2.4
Application-site pruritus	14	4.3	2.4
Application-site erythema	8.3	1.7	0.8

OXY-TDS = oxybutynin transdermal delivery system; TOL-LA = long-acting tolterodine.
Reprinted with permission from Watson Pharma, Inc.

Table 3

Adverse events: Transdermal oxybutynin vs placebo[53]

	Study 1		Study 2	
Adverse event	OXY-TDS (%) (n = 125)	Placebo (%) (n = 132)	OXY-TDS (%) (n = 121)	Placebo (%) (n = 117)
Application-site pruritus	16.8	6.1	14.0	4.3
Dry mouth	9.6	8.3	4.1	1.7
Application-site erythema	5.6	2.3	8.3	1.7
Constipation	–	–	3.3	–
Diarrhea	3.2	2.3	–	–
Abnormal vision	–	–	2.5	–
Application-site vesicles	3.2	–	–	–
Application-site macules	–	–	2.5	–
Application-site rash	–	–	3.3	0.9
Dysuria	2.4	–	–	–

OXY-TDS = oxybutynin transdermal delivery system.
Reprinted with permission from Watson Pharma, Inc.

mouth, the most common AE associated with antimuscarinics.[35,52] In one randomized, double-blind, phase 3 study with 361 patients, the most common AEs associated with OXY-TDS included pruritus (14%) and erythema (8.3%) at the site of application. However, the majority of occurrences were mild to moderate in nature (Table 3).[53] The decrease in anticholinergic AEs associated with OXY-TDS has been hypothesized to be because of the pharmacokinetics of OXY associated with this delivery method.

The transdermal route of administration maintains long-lasting, consistent drug delivery of OXY over a 96-hour treatment period, with marked reduction in the plasma concentrations of N-DEO relative to oral OXY-IR. This reduction occurs because transdermal delivery bypasses first-pass metabolism in the GI tract and hepatic tissue.[45,54] This factor provides the likely explanation for the relatively low incidence of dry mouth and constipation in clinical trials involving OXY-TDS.[35,55,56]

Tolterodine

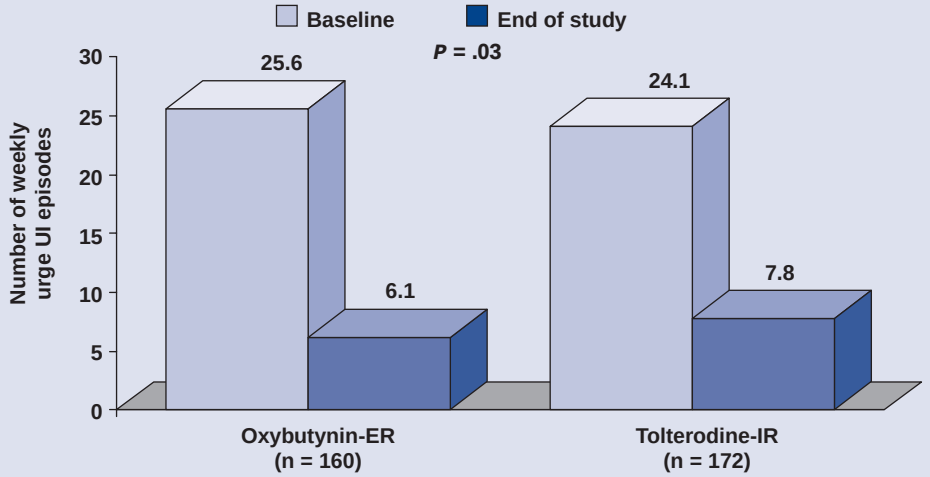
TOL, another widely used antimuscarinic, has also been shown in clinical evaluations to be effective in the treatment of OAB. TOL is available in both immediate-release (TOL-IR) and long-acting (TOL-LA) formulations.

The TOL-IR tablet was the first available formulation of TOL, requiring twice-daily administration. In a pooled analysis, TOL-IR (1 or 2 mg twice daily) was superior in tolerability to OXY-IR (5 mg 3 times daily), particularly regarding dry mouth.[57] Although associated with a lower incidence of AEs relative to OXY-IR, the tolerability of TOL could likely be improved by reducing the fluctuations in serum concentrations associated with twice-daily administration of the compound.[58]

TOL-LA (4 mg once daily) has demonstrated an improved safety profile, a result of the lower serum peak concentrations following sustained release of the drug over 24 hours. This formulation of TOL has shown significant improvement in symp-

Figure 3

Comparative efficacy of oxybutynin-ER and tolterodine-IR: Reduction in weekly urge incontinence episodes in the OBJECT trial[33,50]



ER = extended release; IR = immediate release; OBJECT = Overactive Bladder: Judging Effective Control and Treatment; UI = urinary incontinence.

toms of OAB compared with placebo and appears to be more effective than TOL-IR, with a lower frequency of dry mouth.[58]

Tolterodine vs Oral Oxybutynin

The safety and efficacy of TOL and oral OXY have been compared in 2 large clinical trials. The Overactive Bladder: Judging Effective Control and Treatment (OBJECT) trial was a prospective, randomized, multicenter, double-blind, parallel study in 378 patients with OAB that compared OXY-ER 10 mg once daily with TOL-IR 2 mg twice daily.[50] OXY-ER was significantly more effective than TOL-IR in reducing each of the main outcome measures: weekly UUI episodes (P = .03) (Figure 3), total incontinence episodes (P = .02), and urinary frequency (P = .02). Both treatment groups had similar rates of dry mouth and other anticholinergic-related AEs.[50] The Overactive Bladder: Performance of Extended Release Agents (OPERA) trial[59] was a multicenter, randomized, double-blind, active-control study in 790 women with OAB symptoms that compared OXY-ER 10 mg daily with TOL-LA 4 mg daily. Reductions in weekly UUI and total incontinence episodes were similar with both ER formulations. However, OXY-ER was significantly more effective than TOL-LA in reducing urinary frequency (P = .003), and 23% of women taking OXY-ER reported no episodes of UI compared with 16.8% of women taking TOL-LA (P = .03). Although dry mouth was more common with OXY-ER compared with TOL-LA (29.7% vs 22.3%, respectively, P = .02), tolerability was otherwise comparable between the 2 treatment groups. The findings of these 2 studies support the notion that OXY may be more effective in reducing UI episodes. However, the tolerability of TOL, at least with respect to dry mouth, appears to be superior to that of oral OXY.[59]

Transdermal Oxybutynin vs Tolterodine

The safety and efficacy of OXY-TDS were com-

pared with that of TOL-LA in a 12-week, double-blind, placebo-controlled, randomized trial in patients with urge or mixed UI who had been previously treated for OAB.[35] The reduction in UI episodes was similar with both agents. However, dry mouth and constipation were commonly reported with TOL-LA. Dry mouth occurred in 7.3% of patients who received TOL-LA (P = .0379 vs placebo) compared with 4.1% of those who received OXY-TDS (P = .0268 vs placebo) and 1.7% of those who received placebo. Therefore, the incidence of dry mouth did not differ statistically between OXY-TDS and placebo, although it did between TOL-LA and placebo. The incidence of constipation was 5.7% with TOL-LA and 3.3% with OXY-TDS.

The most common treatment-related AEs in the OXY-TDS group were application-site reactions, including erythema (8.3% vs 1.7% with placebo) and pruritus (14% vs 4.3% with placebo). AEs resulted in treatment discontinuation by 13 patients in the OXY-TDS group (10.7%) vs 2 patients (1.6%) in the TOL-LA group. Owing to its several advantages, such as fewer side effects, as well as its convenience (twice-weekly administration), OXY-TDS is an innovative, appealing addition to the OAB drug armamentarium available to physicians.

Trospium

Trospium chloride is a unique anticholinergic agent recently approved in the United States for the treatment of OAB. It is recommended to be administered at a dosage of 20 mg given twice daily.[60,61] Unlike TOL or OXY, trospium has a quaternary amine structure that inhibits the ability of the drug to easily cross the blood-brain barrier, thus potentially decreasing the incidence of central nervous system effects typically associated with anticholinergic agents.[62-64] Unlike other antimuscarinic agents, however, administration of trospium with high-fat meals significantly reduces absorption (yielding area under the curve and maximum serum concentration values 70%-80% lower than those in the fasting state). Therefore, trospium must be given on an empty stomach 1 hour before or 2 to 3 hours after meals.[65] In a head-to-head comparison of trospium 20 mg twice daily and oral OXY-IR 5 mg twice daily, both drugs were equivalent in decreasing urinary voiding frequency.[60] Trospium, however, demonstrated a more favorable dry mouth AE profile compared with OXY. In a recent multicenter, parallel, randomized, double-blind, placebo-controlled trial, 523 patients with OAB symptoms were treated with either trospium or placebo.[61] Overall, by the end of week 1, patients treated with trospium averaged significantly fewer voids ($P \leq .001$) compared with patients receiving placebo and sustained this improvement throughout the study. At the end of the study, trospium-treated patients experienced a significant average decrease of >2 incontinent episodes (60%) per 24 hours from baseline compared with a decrease of 1.3 episodes (44.2%) in the placebo group ($P \leq .0001$). The most common AEs were dry mouth and constipation. No studies have yet been conducted comparing trospium with OXY-TDS.

Conclusion

The current clinical challenge that PCPs face in the treatment of OAB is threefold: screening, detection, and treatment. Many individuals assume that both UI and OAB are signs of "old age" and therefore unavoidable. As a result, they refrain from discussing symptoms with their PCPs. On the other hand, although the primary care setting is ideal for the screening, detection, basic evaluation, and initial management of OAB, most PCPs fail to ask patients about this condition. Consequently, the disorder goes undiagnosed and undertreated, despite advancements in behavioral therapy and medical treatment options. The understanding and management of OAB needs to evolve. Improving patient-provider communication regarding OAB is

imperative in increasing the proportion of patients who receive effective treatment for their symptoms. Once the lines of communication between patients and providers about bladder problems are open, most cases of OAB can be managed using currently available treatments for OAB, either behavioral, pharmacologic, or often a combination of both. Currently available drug delivery systems include OXY-IR, OXY-ER, TOL-IR and TOL-ER, OXY-TDS, and trospium.

References

1. Wein AJ, Rovner ES. Definition and epidemiology of overactive bladder. *Urology*. 2002;60:7-12.
2. Stewart WF, Van Rooyan JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20:327-336.
3. Pleis JR, Coles R. Summary Health Statistics for US Adults: National Health Interview Survey, 1998. National Center for Health Statistics. *Vital Health Stat*. 2002;10(209).
4. Ricci JA, Baggish JS, Hunt TL, et al. Coping strategies and health care-seeking behavior in a US national sample of adults with symptoms suggestive of overactive bladder. *Clin Ther*. 2001;23:1245-1259.
5. Knowledge, attitudes, and practices of physicians regarding urinary incontinence in persons aged ≥65 years—Massachusetts and Oklahoma, 1993. *Morb Mortal Wkly Rep*. 1995;44:747,753-754.
6. Newman DK, Dmochowski R. Patient-provider communication: a barrier to effective overactive bladder treatment? Presented at the 36th Annual Meeting of the Wound Ostomy and Continence Nurses Society. June 5-9, 2004, Tampa, Fla.
7. Wenger NS, Solomon DH, Roth CP, et al. The quality of medical care provided to vulnerable community-dwelling older patients. *Ann Intern Med*. 2003;139:740-747.
8. Davis DA, Thomson MA, Oxman AD, et al. Changing physician performance. A systematic review of the effect of continuing medical education strategies. *JAMA*. 1995;274: 700-705.
9. Davila GW. Management of urinary incontinence: existing and emerging therapies. *Manag Care Consultant*. 2002;2:13-23.
10. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21:167-178.
11. Crespi Lofton J. Managing adult bladder control problems. *J Am Pharm Assoc*. 2001;41(suppl):S3-S17.
12. Diokno AC, Atassi O. Urinary incontinence. *Compr Ther*. 1996;22:592-597.
13. Merkelj I. Urinary incontinence in the elderly. *South Med J*. 2001;94:952-957.
14. Miller SW. Management and treatment of overactive bladder in the elderly. *J Am Soc Consult Pharm*. 1999;14(suppl 4):S1-S11.
15. Wein AJ. Overactive bladder: defining the disease. *Am J Manag Care*. 2000;6:S559-S564.
16. Smith DA. Urinary incontinence: epidemiology, demographics, and costs. *Director*. 2003;11:115-118.
17. Hu TW. The economic impact of urinary incontinence. *Clin Geriatr Med*. 1986;2:673-687.
18. The Agency for Health Care Policy and Research. Urinary incontinence in adults: acute and chronic management. Clinical Practice Guideline Number 2. March 1996; publication number 96-0682.
19. Newman DK, Dmochowski RR. Multiple aspects of the social impact of overactive bladder: results from a national survey. Presented at the Society for Urodynamics and Female Urology. March 26-30, 2004, San Antonio, Tex.
20. Newman DK, Giovannini D. The overactive bladder: a nursing perspective. *Am J Nurs*. 2002;102:36-45.
21. Rogers RG, Kammerer-Doak D, Villarreal A, et al. A new instrument to measure sexual function in women with urinary incontinence or pelvic organ prolapse. *Am J Obstet Gynecol*. 2001;184:552-558.
22. Wagner TH, Hu TW. Economic costs of urinary incontinence in 1995. *Urology*. 1998;51:355-361.
23. Hu T, Wagner TH, Bentkover JD, et al. Estimated economic costs of overactive bladder in the United States. *Urology*. 2003;61:1123-1128.
24. Kinchen KS, Burgio K, Diokno A, et al. Factors associated with women's decisions to seek treatment for urinary incontinence. *J Womens Health*. 2003;12:687-698.
25. Newman DK. New treatment options for overactive bladder and incontinence. *Director*. 2002;10:74-76.
26. Goode PS, Locher JL, Bryant RL, et al. Measurement of postvoid residual urine with portable transabdominal bladder ultrasound scanner and urethral catheterization. *Int Urogynecol J Pelvic Floor Dysfunct*. 2000;11:296-300.
27. Fitzgerald MP, Jaffar J, Brubaker L. Risk factors for an elevated postvoid residual urine volume in women with symptoms of urinary urgency, frequency and urge incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*. 2001;12:237-239.
28. Bladder Health Council. *Overactive Bladder Screening Initiative*. Baltimore, Md: American Foundation for Urology Disease; 2003.
29. Klausner AP, Vapnek JM. Urinary incontinence in the geriatric population. *Mt Sinai J Med*. 2003;70:54-61.
30. Sōrensen S, Gregersen H, Sorensen SM. Long term reproducibility of urodynamic investigations in healthy fertile females. *Scand J Urol Nephrol*. 1988;(suppl 114):35-41.
31. Burgio K, Locher JL, Goode PS. Combined behavioral and drug therapy for urge incontinence in older women. *J Am Geriatr Soc*. 2000;48:370-374.
32. DuBeau CE. The continuum of urinary incontinence in an aging population. *Geriatrics*. 2002;57:12-17.
33. Ouslander JG. Management of overactive bladder. *N Engl J Med*. 2004;350:786-799.
34. Clemons JL, Aguilar VC, Tillinghast TA, et al. Patient satisfaction and changes in prolapse and urinary symptoms in women who were fitted successfully with a pessary for pelvic organ prolapse. *Am J Obstet Gynecol*. 2004;190:1025-1029.
35. Dmochowski RR, Sand PK, Zinner NR, et al.

Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology*. 2003;62:237-242.
36. Van Kerrebroeck EVA, Serment G, Dreher E. Clinical efficacy and safety of tolterodine compared to oxybutynin in patients with overactive bladder. *Neurourol Urodyn*. 1997;16 (suppl):478-479.
37. Millard R, Tuttle J, Moore K, et al. Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity. *J Urol*. 1999;161:1551-1555.
38. Thuroff JW, Bunke B, Ebner A, et al. Randomized, double-blind, multicenter trial on treatment of frequency, urgency and incontinence related to detrusor hyperactivity: oxybutynin versus propantheline versus placebo. *J Urol*. 1991;145: 813-816.
39. Tapp A, Fall M, Norgaard J, et al. Terodiline: a dose titrated, multicenter study of the treatment of idiopathic detrusor instability in women. *J Urol*. 1989;142:1027-1031.
40. Anderson RU, Mobley D, Blank B, et al. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence: OROS Oxybutynin Study Group. *J Urol*. 1999;161:1809-1812.
41. Yarker YE, Goa KL, Fitton A. Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. *Drugs Aging*. 1995; 6:243-262.
42. Lawrence M, Guay DR, Benson SR, et al. Immediate-release oxybutynin versus tolterodine in detrusor overactivity: a population analysis. *Pharmacotherapy*. 2000;20:470-475.
43. Kelleher CJ, Cardozo LD, Khullar V, et al. A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. *Br J Obstet Gynaecol*. 1997;104:988-993.
44. Yoshimura N, Chancellor MB. Current and future pharmacological treatment for overactive bladder. *J Urol*. 2002;168:1897-1913.
45. Waldeck K, Larsson B, Andersson KE. Comparison of oxybutynin and its active metabolite, N-desethyl-oxybutynin, in the human detrusor and parotid gland. *J Urol*. 1997;157: 1093-1097.
46. Zobrist RH, Schmid B, Feick A, et al. Pharmacokinetics of the R- and S-enantiomers of oxybutynin and N-desethyl-oxybutynin following oral and transdermal administration of the racemate in healthy volunteers. *Pharm Res*. 2001;18:1029-1034.
47. Burgio KL, Locher JL, Goode PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. *JAMA*. 1998;280:1995-2000.
48. Gleason DM, Susset J, White C, et al. Evaluation of a new once-daily formulation of oxybutynin for the treatment of urinary urge incontinence. Ditropan XL Study Group. *Urology*. 1999;54:420-423.
49. Birns J, Lukkari E, Malone-Lee JG. A randomized controlled trial comparing the efficacy of controlled-release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets (5 mg twice daily) in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. *BJU Int*. 2000;85:793-798.
50. Appell RA, Sand P, Dmochowski R, et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT study. *Mayo Clin Proc*. 2001;76:358-363.
51. Dmochowski R, Kell S, Staskin D. Oxybutynin chloride: alterations in drug delivery and improved therapeutic index. *Expert Opin Pharmacother*. 2002;3:443-454.
52. Dmochowski RR, Davila GW, Zinner NR, et al. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. *J Urol*. 2002;168:580-586.
53. Oxytrol [package insert]. Corona, Calif: Watson Pharma, Inc.; 2003.
54. Zobrist RH, Quan D, Thomas HM, et al. Pharmacokinetics and metabolism of transdermal oxybutynin: in vitro and in vivo performance of a novel delivery system. *Pharm Res*. 2003;20:103-109.
55. Davila GW, Daugherty CA, Sanders SW. A short-term, multicenter, randomized double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. *J Urol*. 2001;166:140-145.
56. Dmochowski RR, Davila GW, Sanders SW. Transdermal oxybutynin and controlled-release oral tolterodine in patients with positive treatment effect to anticholinergic therapy for overactive bladder [abstract]. *Neurourol Urodyn*. 2002;21:380.
57. Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. *Urology*. 1997;50:90-96.
58. Van Kerrebroeck P, Kreder K, Jonas U, et al. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology*. 2001;57:414-421.
59. Diokno A, Appell RA, Sand PK, et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. *Mayo Clin Proc*. 2003;78:687-695.
60. Halaska M, Ralph G, Wiedemann A, et al. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World J Urol*. 2003;20:392-399.
61. Zinner N, Gittelman M, Harris R, et al. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol*. 2004;171:2311-2315.
62. Pietzko A, Dimpfel W, Schwantes U, et al. Influences of trospium chloride and oxybutynin on quantitative EEG in healthy volunteers. *Eur J Clin Pharmacol*. 1994;47:337-343.
63. Todorova A, Vonderheid-Guth B, Dimpfel W. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. *J Clin Pharmacol*. 2001;41:636-644.
64. Uckert S, Stief CG, Odenthal KP, et al. Responses of isolated normal human detrusor muscle to various spasmolytic drugs commonly used in the treatment of the overactive bladder. *Arzneimittelforschung*. 2000;50:456-460.
65. Sanctura [package insert]. East Hanover, NJ/Lexington, Mass: Odyssey Pharmaceuticals, Inc and Indevus Pharmaceuticals, Inc; 2004.