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**Target Audience**

This educational activity is designed for primary care physicians and those physicians who treat patients with overactive bladder.

**Learning objectives:**

Upon completion of this activity, physicians should be able to:

- Assess for symptoms of overactive bladder, including urinary incontinence
- Choose a treatment approach in patients with overactive bladder

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## Recognizing and Managing Overactive Bladder

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### Introduction

Overactive bladder (OAB) is defined as a symptom syndrome suggestive of, although not specific for, lower urinary tract (LUT) dysfunction. Its chief characteristics are urgency with or without urge incontinence, and generally with frequency and nocturia (**Table 1**).<sup>1</sup> OAB may be associated with detrusor muscle (bladder) contractions during bladder filling, called detrusor overactivity.<sup>2</sup> OAB symptoms, however, are not specific for detrusor overactivity or other LUT pathology.

Numerous terms are used to describe urinary symptoms in men and women, such as OAB, urge and stress incontinence, prostatism, benign prostatic hyperplasia (BPH), benign prostatic obstruction, benign prostatic enlargement, and bladder outlet obstruction. Lower urinary tract symptoms (LUTS) is an umbrella term which was introduced in 1994 in an attempt to disassociate urinary symptoms and any specific LUT pathology affecting urination. Although historically BPH and prostatism have been used to describe male LUTS and the term OAB has been reserved mostly for women, these terms no longer accurately describe the range of symptoms presenting in patients. The use of incorrect terminology can lead to confusion among physicians and patients alike, and can result in mismanagement of LUTS.

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Patients usually report that storage symptoms (urgency, urge incontinence, nocturia, frequency) tend to be more bothersome than voiding symptoms (hesitancy when starting to void, slow urine stream, sense of incomplete emptying). Storage symptoms in both sexes may be associated with urinary infections or, more rarely, with other conditions, such as bladder stones, carcinoma of the bladder or prostate, and neurological disease. In men, particularly older men with prostatic enlargement, the traditional assumption by most clinicians has been that these symptoms are due in some way to prostatic obstruction, ignoring the bladder and comorbid conditions as possible etiologies, while in women the identical symptoms have been thought to originate exclusively from the bladder. This concept is being challenged by new data.<sup>3</sup>

The majority of patients with OAB do not seek treatment or go undiagnosed by their health care provider, and of those who are treated many do not experience symptom relief.<sup>4</sup> Health care professionals must increase their awareness of LUTS. Quality care performance measures from the Physician Consortium for Performance Improvement and the Medicare Physician Quality Reporting Initiative now specify routine assessment, characterization, and plan of care for urinary incontinence in women 65 years of age and older.<sup>5</sup> Some patients who seek medical care with complaints of urgency and frequency may be too embarrassed to mention urinary leakage, compounding the need for a clear understanding of the spectrum of symptoms. Screening and detection of LUTS is especially important because OAB has significant personal, social, and economic ramifications (Table 2).

Risk factors for OAB symptoms include age greater than 40, recurrent urinary tract infections, diabetes mellitus, other physical disorders which restrict mobility, any type of pelvic injury, history of hysterectomy, childhood enuresis, obesity, inactivity, neurological disorders (eg, multiple sclerosis, diabetic neuropathy), family history, and trauma (eg, childbirth, prostatectomy, radiation therapy).<sup>6</sup>

### Brief Pathophysiology

The symptoms of OAB are usually associated with involuntary contractions of the detrusor muscle. Detrusor overactivity (DO) may be due to neurogenic or idiopathic causes that result in urgency or urge incontinence depending on the response of the bladder sphincter. However, not all patients with DO will have OAB symptoms. There are a variety of efferent and afferent neural pathways, both central and peripheral, and a wide range of neurotransmitters involved in urine storage and bladder emptying. Acetylcholine is the predominant peripheral neurotransmitter responsible for bladder contraction by interacting with muscarinic receptors on the detrusor muscle.<sup>7</sup> Many factors interfere with the ability of the urinary bladder to function normally including previous surgery, aging-related changes, and underlying neurologic problems. Importantly, LUTS may also be associated with comorbid conditions and medications (Tables 3 and 4).

**Table 1. OAB Clinical Presentation**

**Urinary urgency**

Strong, compelling, sudden desire to void

**Urinary frequency**

Complaint of voiding more than 8 times a day

**Nocturia**

Voiding one or more times/night

**Urge urinary incontinence**

Involuntary urine loss associated with a strong and sudden desire to void

**Table 2. Morbidity from OAB**

Impaired health perception

Decreased quality of life

Depression

Urinary tract infection

Sexual dysfunction

Increased number of outpatient visits

Increased risk of falls and fall-related fracture

## Epidemiology

Two landmark population-based prevalence surveys conducted using telephone interviews in Europe<sup>8</sup> and the United States<sup>9</sup> suggest the prevalence of OAB symptoms in up to 17% of the population over 40 years of age, with a strong age-related increase in both sexes.

A review of the literature demonstrates that incontinence is less common in men than in women, and when it is present, it usually is related to previous prostatic surgery.<sup>10,11</sup> However, the importance of storage symptoms in men with LUTS is clearly emphasized by the landmark studies from the International Continence Society (ICS),<sup>12</sup> which found storage symptoms were the most prevalent and most bothersome in men referred to secondary care centers for prostate surgery.<sup>13</sup> Nevertheless, the age-related prevalence of LUTS in men has been demonstrated by numerous studies, including the Triumph study (TransEuropean Research Into the Use of Management Policies for LUTS suggestive of BPH in Primary Healthcare).<sup>14-16</sup>

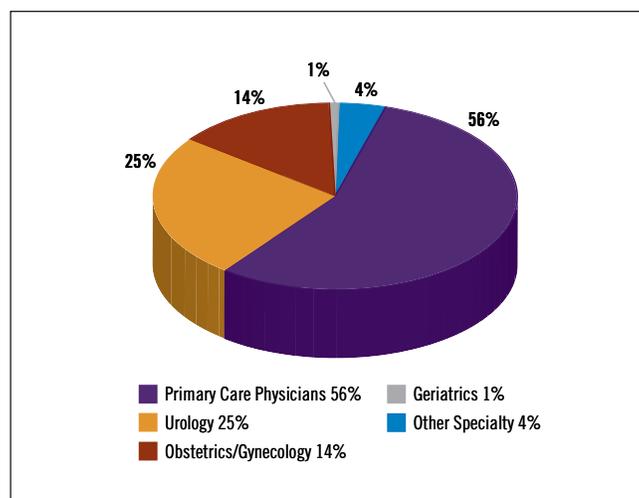
Symptom overlap between storage, voiding and incontinence in both male and female patients is not uncommon, as shown in the large Boston Area Community Health (BACH) study.<sup>17</sup> The BACH study of 5506 men and women aged 30-79 found that 16% of men and women had at least one symptom pattern and 7% had overlapping symptoms. There was no variation in the prevalence of these symptoms by race or ethnicity. Older women had a higher prevalence of LUTS associated with OAB and urinary incontinence. Older men also had a higher prevalence of LUTS with incontinence.

The EpiLUTS study, a cross-sectional, population-representative web survey conducted in the United States, the United Kingdom, and Sweden to assess prevalence of LUTS, also found that both men and women who reported voiding symptoms were more likely to experience either storage or postmicturition symptoms or both, compared to voiding symptoms.<sup>18</sup> Data from the US study showed that 10.7% of men aged 40 years and older had voiding symptoms, 10.1% experienced both voiding and storage symptoms, and 24.2% experienced voiding, storage, and postmicturition symptoms. Similarly, 5.2%, 14.9%, and 26.3% of women 40 years and older experienced voiding symptoms, voiding and storage symptoms, or voiding, storage and postmicturition symptoms, respectively. To provide the most effective treatment for underlying conditions such as detrusor overactivity, enlarged prostate, and bladder and prostate cancer, and other comorbid conditions, health care providers should assess individual and overlapping storage, voiding, and postmicturition symptoms in both men and women.

## Evaluation of OAB

Primary care physicians treat the majority of patients with OAB and therefore provide the initial evaluation for this condition (Figure 1). However, there is likely to be significant overlap between specialties in the treatment of OAB in women and in managing more difficult cases. This is reflected in the data that shows that collectively PCPs, urologists, and obstetricians/gynecologists manage 95% of all OAB patients.

Patients should be screened for OAB symptoms at least yearly, especially if they are older or have medical or neurological conditions associated with LUTS, such as diabetes, Parkinsonism, multiple sclerosis, stroke, and other CNS disorders. Sample questions include, “Have you had any problems with bladder or urine control?” and if the patient answers no, then the follow-up question, “Do you ever leak urine when you don’t want to?”<sup>19</sup> Because OAB symptoms may reflect underlying diagnoses and/or medications not related to the lower urinary tract, health care providers should always raise the



**Figure 1. Treatment of OAB by Specialty**

Source: IMS Health. Integrated Administrative Claims Data. Time period: 12 months ending December, 2007. Patients diagnosed with OAB include those with an ICD-9 diagnostic code for urinary incontinence (788.3x) and other functional disorders of the bladder (596.5x).

possibility of these health issues through targeted questioning. Such follow-up questions should address sudden onset of OAB symptoms (especially urgency and incontinence), pelvic pain, and hematuria, as these can indicate underlying malignancy or neurological disease. Health care providers should conduct a comprehensive medical history including comorbid conditions associated with LUTS and OAB symptoms (Table 3), surgeries (especially those that impact pelvic function, such as prior anti-incontinence or prostate operations, hysterectomy, rectal, and lumbar/sacral cord surgeries), medications (including over-the-counter) (Table 4) and any impairment in mobility and cognition. Physicians should also inquire about the patient's access to toilets/bathrooms.

**Table 3. Comorbid conditions that may cause or worsen OAB symptoms**

Comorbidity	Effect
<b>Cardiovascular disease</b>	
Arteriovascular disease	Impaired bladder emptying from ischemic myopathy or neuropathy
Heart failure	Nocturnal polyuria and nocturia
<b>Gastrointestinal disease</b>	Impaired bladder emptying from constipation
<b>Metabolic diseases</b>	
Diabetes mellitus	OAB and urge UI; impaired bladder emptying due to neuropathy osmotic diuresis; altered mental status from hyper- or hypoglycemia; impaired bladder emptying and retention from constipation
Hypercalcemia	Diuresis, altered mental status
Vitamin B <sub>12</sub> deficiency	Impaired bladder sensation and emptying from peripheral neuropathy
<b>Musculoskeletal disease</b>	Mobility impairment; urgency and urge UI from cervical myelopathy in rheumatoid arthritis and osteoarthritis
<b>Neurologic conditions</b>	
Cerebrovascular disease, stroke	OAB and urge UI from damage to upper motor neurons; impaired sensation to void from interruption of subcortical pathways; impaired function and cognition
Delirium	Impaired function and cognition
Dementia	OAB and urge UI from damage to upper motor neurons; impaired function and cognition
Multiple sclerosis	OAB and urge UI, areflexia, or sphincter dyssynergia (dependent on level of spinal cord involvement)
Normal-pressure hydrocephalus	OAB and urge UI from compression of frontal inhibitory centers; impaired function and cognition
Parkinsons disease	OAB and urge UI from loss of inhibitory inputs to pontine micturition center; impaired function and cognition; retention and overflow from constipation
Spinal cord injury	OAB and urge UI, areflexia, or sphincter dyssynergia (dependent on level of injury)
Spinal stenosis	OAB and urge UI from damage to detrusor upper motor neurons (cervical stenosis); urge UI or areflexia (lumbar stenosis)
<b>Obstructive sleep apnea</b>	Nocturnal polyuria and impaired sleep
<b>Peripheral venous insufficiency</b>	Nocturnal polyuria
<b>Pulmonary disease</b>	Conditions with chronic cough can worsen stress UI
<b>Psychiatric disease</b>	
Affective and anxiety disorders	Decreased motivation
Alcoholism	Functional and cognitive impairment; rapid diuresis and retention in acute intoxication
Psychosis	Functional and cognitive impairment; decreased motivation

NOTE: LUTS = Lower urinary tract symptoms, OAB = Overactive bladder symptoms, UI = urinary incontinence.

Adapted from: DuBeau CE. Urinary Incontinence. In: *Geriatric Review Syllabus*, 7th edition, American Geriatric Society, 2008 (in press).<sup>20</sup>

**Table 4. Medications that may cause or worsen OAB symptoms**

Medication	Effect on LUTS
Alcohol	Frequency, urgency, sedation, delirium, immobility
$\alpha$ -Adrenergic agonists	Outlet obstruction (men)
Angiotensin-converting enzyme inhibitors	Associated cough worsens stress and possibly urge leakage in persons with impaired sphincter function
Anticholinergics	Impaired emptying, retention, delirium, sedation, constipation, fecal impaction
Antipsychotics	Anticholinergic effects plus rigidity and immobility
Calcium channel blockers	Impaired bladder emptying and retention; the dihydropyridine agents can cause pedal edema, leading to nocturnal polyuria and nocturia
Estrogen	Stress and mixed leakage in women
GABAergic agents (gabapentin, pregabalin)	Pedal edema causing nocturia and nighttime incontinence
Loop diuretics	Polyuria, frequency, urgency
Narcotic analgesics	Urinary retention, fecal impaction, sedation, delirium
Nonsteroidal anti-inflammatory drugs	Pedal edema causing nocturnal polyuria and nocturia
Sedative hypnotics	Sedation, delirium, immobility
Thiazolidinediones	Pedal edema causing nocturnal polyuria and nocturia
Tricyclic antidepressants	Anticholinergic effects, sedation

Adapted from: DuBeau CE. Urinary Incontinence. In: *Geriatric Review Syllabus*, 7th edition, American Geriatric Society, 2008 (in press).<sup>20</sup>

An important component of symptom evaluation is to focus on the frequency, degree of urgency, and associated nocturia and to address incontinence episodes, the quantity of leakage and the impact and bother associated with such leakage on daily living. In women, it is important to differentiate between OAB and stress incontinence since some treatment options differ based on the type of incontinence. Helpful questions include, “Do you lose urine during coughing, sneezing, or lifting (stress UI)?” and “Do you experience such a strong and sudden urge to urinate that you leak before reaching the toilet (urge UI)?” These simple questions are most helpful to diagnose urge UI and slightly less so for stress UI.<sup>21</sup> However, if a woman denies stress leakage, then it is highly unlikely that she has urodynamic stress UI. Simple items such as a bladder diary (see page 14) may be helpful in diagnosing or measuring symptoms or their improvement.

## Physical exam

The physical examination should focus on the status of comorbid conditions, the genitourinary exam and, in older persons, functional status. Particular areas of emphasis are:

- In the genitourinary exam: perineal masses, lesions, and sensation
- In the rectal examination: rectal tone, assessment for masses, and in men, prostate consistency (prostate size cannot be accurately assessed on digital rectal exam)
- In the pelvic exam: vaginal mucosal changes, any prolapse (cystocele, rectocele, uterine prolapse), masses, and pelvic floor strength (by having the patient contract her pelvic muscles around the examiner’s finger, without contracting the buttocks, thighs, or abdomen).

Patients with symptoms of stress urinary incontinence should have a cough stress test. While the patient has a full bladder, have them stand upright with a pad available to catch any leakage, and have them give a single, vigorous cough. A positive stress test is helpful to make the diagnosis of stress UI, but a negative test does not rule it out.<sup>21</sup>

### Laboratory testing

The only laboratory test necessary in the initial evaluation is urinalysis, specifically looking for glucose and hematuria. Should a urinary tract infection be suspected because of bacteriuria, pyuria, or positive nitrite and leukocyte esterase in the setting of relative new onset of symptoms, dysuria, or suprapubic discomfort, it is mandatory to perform a urine culture. It is important to remember that 20% of women over age 65 have asymptomatic bacteriuria, with or without pyuria, which is neither associated with OAB or incontinence nor should it be treated with antibiotics. Therefore, a diagnosis of urinary tract infection in such patients should not be based solely on culture results, but also the presence of other supporting symptoms such as dysuria, suprapubic or flank pain, or fever. More invasive testing, such as urodynamic evaluation and cystoscopy to rule out intravesical lesions, is not routinely required or recommended.

### Differential diagnosis

In addition to the comorbid conditions and medications listed in Tables 3 and 4, the differential diagnosis of OAB includes UTIs, interstitial cystitis (if there is associated pain preceding or relieved by voiding), bladder outlet obstruction, and impaired detrusor contractility. It should always be kept in mind that nocturia may be due to sleep disorders and high night-time urine output.

Stress (effort related) urinary incontinence (SUI) in women is usually due to impaired urethral support, often related to parity and associated pelvic floor weakness, and in men it is most commonly due to sphincter damage from radical prostatic surgery. SUI may co-exist with urgency incontinence, resulting in mixed urinary incontinence (MUI), or with urgency alone (no incontinence).<sup>1,22</sup> Pelvic floor disorders including both urge urinary incontinence, SUI and MUI, are highly prevalent in older women and their frequency increases with age. The 2005-2006 National Health and Nutritional Survey (NHANES) found that prevalence of pelvic floor disorders in women was approximately 24% with 15.7% of women experiencing urinary incontinence.<sup>23</sup>

Disorders of lower urinary tract and pelvic sensation also affect storage, and pelvic pain in particular can be associated with the development of urgency-like symptoms. Pain associated with voiding is the primary symptom of painful bladder syndrome, also called interstitial cystitis (PBS/IC). Frequency is present in both PBS and OAB, but urgency-related incontinence is a symptom only of OAB.<sup>24</sup> Although PBS/IC is more common in women, men may also develop similar symptoms of pelvic discomfort without infection; in the past, such men were usually considered to have “abacterial prostatitis” (prostatodynia), but the correct diagnosis now would be PBS/IC.

Reasons for primary care physicians to consider an immediate specialty referral for patients with OAB symptoms include the presence of hematuria, pelvic pain, marked pelvic floor prolapse, suspicion of PBS/IC, history of urinary retention, recurrent urinary tract infections, recent pelvic surgery, previous pelvic radiation, a history of suspected neurogenic bladder, suspected fistula, and failure to respond to initial empiric treatment.

### Management Options

The goal of OAB management is the reduction or elimination of LUTS experienced by the patient. Treatment of OAB requires ongoing management that begins with remediation of any contributing comorbidity and lifestyle factors. As necessary, this should be followed by behavioral treatment, and then pharmacotherapy. Patients with urgency and urge incontinence refractory to these interventions may require more invasive strategies. Behavioral therapy combined with pharma-

cotherapy may provide the best benefit for many patients. It is crucial to discuss the patient's goals for management, particularly the most important or bothersome aspects of their target symptom(s). In the case of urge incontinence complete control may be the goal, and in other patients reduction of the symptoms of urgency, nocturia, and frequency may be sufficient.<sup>4</sup>

### Lifestyle modifications

Two important lifestyle factors associated with OAB symptoms and incontinence are physical inactivity and obesity.<sup>25</sup> Several epidemiological studies in men suggest that increased physical activity offers a protective effect against LUTS. Using the Health Professionals' Follow-up Study, investigators found that physical activity was inversely related with LUTS in men, even after controlling for relevant confounding factors.<sup>26</sup> Walking was the most prevalent activity, and patients who walked 2 to 3 hr per week had a 25% lower risk of total LUTS. Similarly, results from the Massachusetts Male Aging Study showed that community-based enrollees with higher levels of physical activity had a reduced risk of LUTS.<sup>27</sup> An analysis of NHANES III found that all levels of moderate and vigorous activity were inversely associated with male LUTS, whereas men who reported no leisure-time physical activity had a greater odds (ie, 2.06) of LUTS.<sup>28</sup>

Physical activity is also important in women with LUTS and OAB, but with particular regard to incontinence, the effectiveness of pelvic muscle exercises has been well established. Intervention studies in women have shown that exercises to increase pelvic muscle strength in combination with behavioral treatment significantly improved incontinence symptoms of OAB.<sup>29</sup>

Obesity is epidemic in the US, with persons with a BMI >30 comprising >30% of the adult population in a vast majority of states.<sup>30</sup> There is evidence that weight loss in obese women decreases incontinence. Lifestyle changes involving weight loss and increased physical activity decreased the prevalence of weekly SUI among obese women (mean BMI 35 kg/m<sup>2</sup>) participating in the Diabetes Prevention Program trial.<sup>31</sup> The decrease in incontinence was almost entirely attributable to weight loss (mean -3.4 kg). In a smaller randomized study of incontinent obese women participating in a liquid diet program, weight reduction of 10% to 20% was associated with a 50% decrease in incontinence.<sup>32</sup>

Fluid and diet management may also help some patients. Clearly, simple evaluation of the patient's intake of fluid volumes and beverage types (caffeinated and alcohol) may partly explain urgency, frequency, and nocturia which may dominate OAB complaints. These contributing causes can be addressed by restricting the amount, timing or type of fluid intake.

### Behavioral treatment

Behavioral interventions have been shown to reduce OAB symptoms, particularly urge incontinence. While these interventions are safe and relatively effective, they do require a commitment on the part of both the clinician and patient in terms of patient education and time. For this reason, along with the misperception that behavioral interventions are ineffective compared with pharmacotherapy, behavioral therapy has been underutilized.<sup>4</sup>

The most common behavioral treatment for OAB is bladder training, which addresses voiding habits and bladder function, and often includes pelvic muscle exercises. Bladder training employs two principles: 1) frequent voluntary voiding to keep bladder volume low, and 2) urgency suppression using central nervous system and pelvic mechanisms. The initial toileting frequency can be every 2 hours or individualized using the patient's bladder diary (page 14). Urgency suppression involves not responding to urgency with running to the bathroom, but standing or sitting still, performing several pelvic muscle contractions, and concentrating on decreasing urgency (eg, by taking a deep breath and letting it out slowly, or visualizing the urgency as a wave that peaks and then falls). Once patients feel more in control, they then walk to a bathroom and void. After 2 days without leakage, the time between scheduled voids can be increased by 30 to 60 minutes; this process is continued until the patient is satisfied with his/her symptom control, or is dry with a normal voiding interval of about every 4 hours. Successful bladder training usually takes several weeks, and patients need reassurance to proceed despite any initial failure.

Patients with OAB who have cognitive impairment can be treated with a related therapy, prompted voiding. A caretaker monitors the patient and encourages them to report any need to void; prompts the patient to toilet on a regular schedule during the day (usually every 2-3 hours) and leads them to the bathroom; and praises them with positive feedback when they toilet. Toileting routines without prompting, such as just using a set schedule are not effective.

Pelvic muscle exercises (PME) which strengthen the muscular components of urethral support are effective for OAB, as well as urge, mixed, and stress UI. To perform PME, the patient learns to contract the pelvic muscles in isolation, without involving buttocks, abdomen, or thighs. The patient holds the contraction for 6 to 8 seconds (only shorter durations may be initially possible), then relaxes, and repeats a set of 8 to 12 contractions, relaxing the pelvis between each contraction. Initially, patients should complete three sets of contractions 3 to 4 times a week, and over time should try to increase the intensity and duration of the contraction, perform PME in various positions (sitting, standing, walking), and alternate fast and slower contractions. PME should be continued for at least 15 to 20 weeks.

Biofeedback can help patients learn both bladder training and PME. Patients can be referred for biofeedback to physical therapists or urology/gynecology nurses. Medicare covers biofeedback for patients who do not improve after 4 weeks with conventional instruction. Other behavioral methods, including vaginal electrical stimulation and the magnetic chair, have not been proven to be effective.

### Pharmacotherapy

The use of antimuscarinic agents for the treatment of OAB symptoms is founded on the premise that detrusor contractions are primarily regulated by parasympathetic stimulation of acetylcholine muscarinic receptors in bladder smooth muscle. There is some evidence now that these medications actually work primarily during the storage phase. There are currently six antimuscarinic agents available with well established efficacy for the treatment of OAB and urge UI: oxybutynin (immediate-release, extended-release, and topical forms), tolterodine (immediate-release, extended-release), trospium (immediate-release; extended-release), solifenacin, darifenacin, and the recently FDA-approved fesoterodine fumarate (extended release). Other anticholinergic medications, such as flavoxate and tricyclic antidepressants, are either ineffective or limited by marked anticholinergic and cardiac effects.

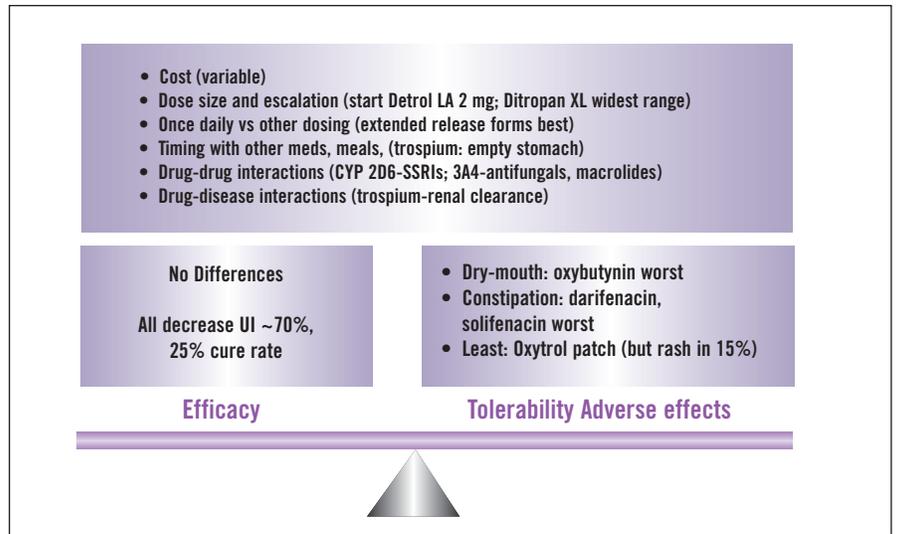
Antimuscarinic Agents for OAB	Brand Names	Available Preparations	Dosage
darifenacin	Enablex	7.5, 15 mg extended release tablets	7.5 mg once daily, increasing to 15 mg once daily after 2 weeks
fesoterodine	Toviaz	4, 8 mg extended release tablets	4 mg once daily, increasing to 8 mg once daily
oxybutynin	Ditropan XL	5, 10, 15 mg extended release tablets	5 mg once daily (up to maximum of 30 mg/d)
	Ditropan, generic	1, 2 mg tablets	2 mg BID, dosage can be lowered to 1 mg BID
oxybutynin transdermal system	Oxytrol	3.9 mg/d patch (39 cm <sup>2</sup> system containing 36 mg oxybutynin)	Twice weekly
solifenacin	VESIscare	5, 10 mg tablets	5 mg once daily, increasing to 10 mg once daily
tolterodine	Detrol LA	2 mg extended release capsules	4 mg once daily with liquids
	Detrol	1 mg, 2 mg tablets	2 mg BID
trospium	Sanctura	20 mg tablets	20 mg BID on empty stomach
	Sanctura XR	60 mg extended release capsules	60 mg once daily on empty stomach

The key question for physicians in their approach to selecting pharmacotherapy for OAB is: do the antimuscarinic agents differ in their effectiveness and in their adverse effect profile? A review of the clinical trial literature on drugs used in the treatment of OAB indicated that the five antimuscarinic agents mentioned previously are equally effective in reducing the symptoms of OAB.<sup>33</sup> With similar effectiveness among antimuscarinic agents for OAB, the selection of one agent over another may be made on differences in side effect profiles and other considerations provided in **Figure 2**.

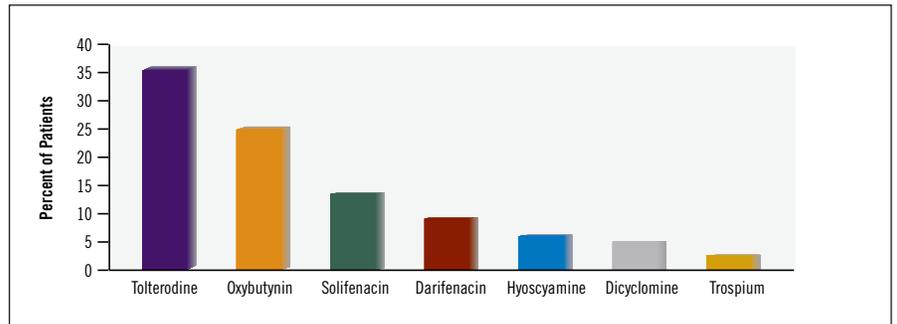
**Figure 3** provides an overview of which anticholinergic/antimuscarinic agents are currently being used in the treatment of over 2 million patients (male and female) diagnosed with OAB (based on ICD-9 codes that include all forms of urinary incontinence and overactive bladder). By a significant margin, tolterodine and oxybutynin are the most commonly used antimuscarinic agents. Of note, hyoscyamine and dicyclomine which are less effective for OAB, are used in more than 12% of patients with this condition.

**Figure 4** illustrates the use of these agents by age group and shows the expected increase in the percentage of patients treated with antimuscarinic therapy as a function of increasing age.

Medications should be started at the lowest dose, and titrated at 4-6 week intervals until symptoms are satisfactorily improved or adverse effects become intolerable. Common side effects include dry mouth, blurred vision, and constipation. Physicians should discuss these side effects with their patients as well as the possibility of cognitive disturbances. There is no consistent compelling evidence that potential cognitive effects outweigh the potential benefit of treatment in individual older patients. The combination of behavioral and drug therapy may offer better outcomes than drug treatment alone, particularly regarding quality of life.<sup>37</sup>

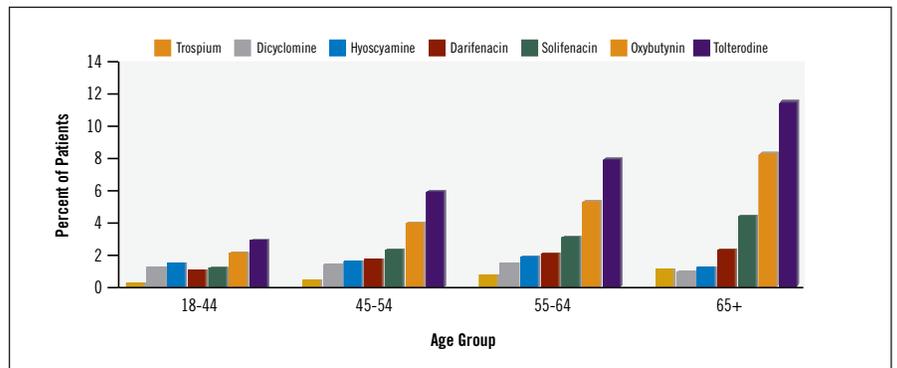


**Figure 2. Considerations When Choosing an Antimuscarinic Agent.**<sup>34-36</sup>



**Figure 3. Patients Diagnosed with OAB (females and males >18) - Treated with Pharmacologic Therapy.** Data excludes those with OAB ICD-9 code and treated with tricyclic antidepressants, flavoxate and propantheline. No data are available on the recently FDA-approved, fesoterodine fumarate.

Source: IMS Health. Integrated Administrative Claims Data. Time period: 12 months ending December, 2007. Patients diagnosed with OAB include those with an ICD-9 diagnostic code for urinary incontinence (788.3x) and other functional disorders of the bladder (596.5x).



**Figure 4. Patients Diagnosed with OAB (females and males >18) - Treated with Pharmacologic Therapy.** Data excludes those with OAB ICD-9 code and treated with tricyclic antidepressants, flavoxate and propantheline. No data are available on the recently FDA-approved, fesoterodine fumarate.

Source: IMS Health. Integrated Administrative Claims Data. Time period: 12 months ending December, 2007. Patients diagnosed with OAB include those with an ICD-9 diagnostic code for urinary incontinence (788.3x) and other functional disorders of the bladder (596.5x).

Antimuscarinics are not used in men with OAB to the same degree as in women (Figure 5), probably because of the perception that there is potential risk for causing urinary retention in men with OAB symptoms and BPH. Several recent studies have demonstrated that antimuscarinics in this group of men are safe, with urinary retention exceedingly rare with usual clinical doses. This risk was addressed in a study in which 221 men with urodynamically confirmed bladder outlet obstruction and detrusor overactivity were randomized to tolterodine or placebo for 12 weeks.<sup>38</sup> Post-void residual volume increased to a significantly greater extent in the tolterodine group relative to placebo, but only by 25 mL, and was not accompanied by an increase in adverse events. In men with predominant OAB symptoms and only a partial response to the alpha 1-blocker, the addition of an antimuscarinic is supported by several studies.<sup>39</sup> The use of combination therapy with an alpha 1-blocker and an antimuscarinic agent will be discussed further in case study #3.

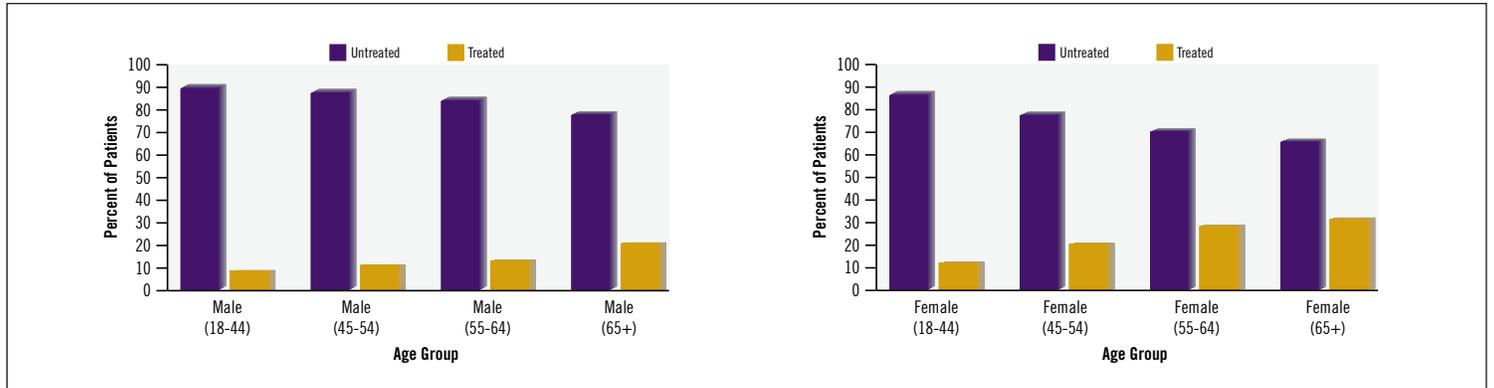


Figure 5. Men and Women age >18 years, with OAB: Treated vs Untreated with Pharmacological Therapy.

Source: IMS Health. Integrated Administrative Claims Data. Time period: 12 months ending December, 2007.

Methods: The category of diagnosed, untreated is defined as patients with a diagnostic claim for OAB (ie, those with an ICD-9 diagnostic code for urinary incontinence (788.3x) and other functional disorders of the bladder (596.5x) between January 2007 and December 2007 who did not fill a prescription for their OAB in the last 12 months of the study period. Treated and untreated refers to pharmacologic management.

Figure 5 shows the increasing percentage of men and women with OAB treated with antimuscarinics as a function of age, and the large portion of patients who receive no pharmacologic treatment. This is likely to be due to a number of reasons including response to other treatment (lifestyle modification, behavioral therapy, addressing comorbidity), lack of symptom bother, moderate symptom severity, discontinuation of medication due to side effects, or by virtue of physician or patient preference. It is also interesting to note the relatively young age of women receiving this diagnostic code. The large percentage of untreated male patients with OAB may also be a consequence of the treatment approach to LUTS in men that focuses on prostatic enlargement and not OAB. The data demonstrate that men in all age groups are less likely to receive antimuscarinic medications for OAB symptoms than women.

### Further approaches

In patients who fail to respond to behavioral and medication therapy, newer alternatives include sacral neuromodulation (an invasive procedure involving placement of a sacral nerve electrical lead) and botulinum toxin injection therapy. When injected into the bladder submucosa or smooth muscle, botulinum-A toxin (BTX-A) is thought to induce selective denervation and subsequent ablation of overactive contractions by blocking the release of acetylcholine at the neuromuscular junction as well as in autonomic neurons. Relatively short term trials suggest that BTX-A injected into the bladder can relieve refractory urgency and urge UI.<sup>40</sup> Some patients develop urinary retention after injection, and the optimal dosing and injection to avoid this complication is under study. The effects of denervation wear off in approximately 6 months as new axons develop, and repeat treatment would be necessary. Although BTX-A is promising, it does not have FDA-approval for this indication.

Prostatectomy may be an additional consideration for men whose OAB symptoms fail medical treatment and who demonstrate prostatic obstruction on urodynamic testing.

### OAB CASE STUDIES

The following case studies provide a context for the discussion of the role of lifestyle, behavioral approaches and pharmacotherapy in managing the symptoms of OAB. Data on prescribing patterns will provide insight into the use of different agents. Surgical interventions are beyond the scope of this newsletter and will not be covered.

#### **Case Study 1**

*A 55-year-old woman complains of daytime urinary frequency, urgency, and nocturia. She describes urgency incontinence that requires changing protective pads twice a day. She wears the pad for fear of leakage but most of the time she makes it to the bathroom in time (OAB without urge incontinence). She denies any leakage with coughing, sneezing, straining or any abdominal activity. She denies any suprapubic pain or discomfort associated with her urinary complaints. Her only medical problem is mild hypertension controlled with diet and exercise. Her neurologic and abdominal pelvic examination is normal as is her urinalysis.*

*A history of her fluid intake can be helpful, but completion of a bladder diary may be more revealing. She is asked to fill out a 3-day bladder diary recording the amounts and times of all fluids and liquid based foods consumed and, the amount and time of each urination and the activity at each event (eg, lifting, sleeping, walking, sitting, coughing). She returns 2 weeks later with the bladder diary in hand revealing a large volume of caffeinated beverages consumed throughout the day and early evening. This corresponds to an appropriately large urine output (eg, 2000 ml/day). She is counseled to reduce her caffeinated beverage consumption. At follow-up she reports marked improvement of her OAB symptoms.*

#### **• Interpretation**

It is clear that this woman has OAB symptoms, which do not appear to be related to any contributing medical problem or medication. Her symptoms are not likely related to stress incontinence as she reports no stress related leakage. Interstitial cystitis seems unlikely given her lack of associated pain complaints, especially suprapubic pain. The bladder diary reveals a behavior related etiology, high caffeine intake, which should be addressed before other therapies are initiated. Should lifestyle intervention fail to decrease her symptoms, then next therapies to consider are behavioral, followed by antimuscarinic medication as needed.

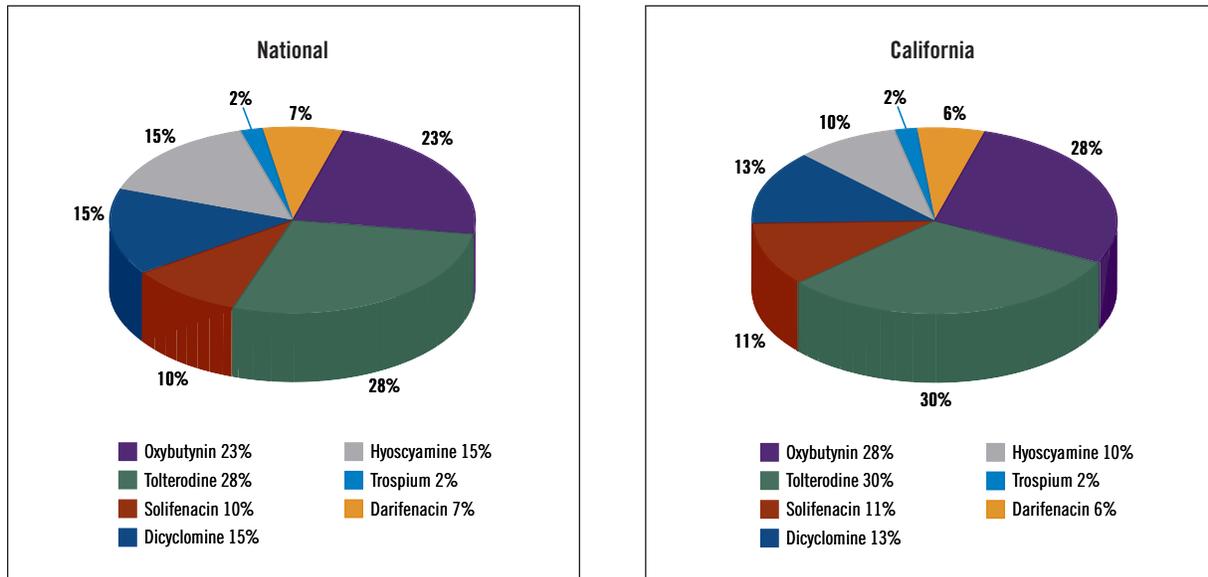
#### **Case Study 2**

*A 65-year-old man presents with bothersome complaints of urgency and frequency, with as many as 10 episodes/day. He also complains of worsening nocturia of 2-3 episodes/night. The patient reports progressively worse symptoms over the past several months. He drinks two cups of coffee in the morning only, and a small glass of water with dinner. His past medical history includes well-controlled COPD, and he uses only an albuterol inhaler and occasional acetaminophen. Physical examination reveals a well-developed, well-nourished man in no apparent distress, with normal vital signs. He has no peripheral edema. His rectal sphincter tone is intact, and his prostate is smooth. His urinalysis is negative.*

#### **• Interpretation**

It is clear from this patient's complaint that he has LUTS which are extremely bothersome to him. There is no clear medical cause for his symptoms. Because OAB symptoms may coexist with BPH, or bladder outlet obstruction without being caused by prostatic conditions, treatment with agents that target the prostate and not the bladder, such as alpha 1-blockers and 5 alpha-reductase inhibitors, may not fully alleviate LUTS in men.

Antimuscarinic medications for presumptive detrusor overactivity are reasonable additions to the prostate-specific agents, and may also be tried as first line agents. National and state prescription data for antimuscarinic agents are presented in **Figure 6**. Included with the antimuscarinics with FDA-approved labeling for the treatment of OAB (*ie*, oxybutynin, tolterodine, darifenacin, solifenacin, trospium) are two other additional agents, dicyclomine and hyoscyamine. These latter 2 agents were shown to be used in patients with OAB based on claims data (Figure 3).



**Figure 6. Proportion of OAB Prescriptions at Retail Pharmacies Nationally and in the state of California. No data are available on the recently FDA-approved, fesoterodine fumarate.**

Source: IMS Health. National Retail Prescription Data. Time period: 12 months ending June 2008.

### Case Study 3

The patient is a 60-year-old man who complains of a long history of LUTS manifested primarily by bothersome frequency and urgency. He has little complaint of sensation of incomplete emptying or diminished force of stream. He has been treated with an alpha 1-blocker, doxazosin, for his LUTS but has shown little improvement after an initial 6-week trial at the maximum dose of 8 mg/day.

His past medical history is non-contributory. Physical examination reveals a well-developed, well-nourished man in no apparent distress. His vital signs are stable. His rectal sphincter tone is normal as is his neurologic exam. His urinalysis is normal showing no red cells, no white cells, and no bacteria.

#### • Interpretation

This patient is being treated with a maximum dose of doxazosin for his LUTS without improvement in his symptoms. Given his primary complaint of bothersome urinary frequency and urgency, addition of an anti-muscarinic agent with his doxazosin therapy may be beneficial. This approach is generally safe for men with mild to moderate symptoms, but men with severe symptoms should be referred to a urologist so that post-void residual (PVR) can be measured and followed. Clinical trials of OAB medications in men excluded those with an elevated PVR (>250-300 ml) at baseline or during treatment. It is therefore not clear what the relative risk is of anti-muscarinics as monotherapy or combined with alpha 1-blockers in men with a PVR above this level.

The rationale for the combination of an alpha 1-blocker and an antimuscarinic agent is to exploit the beneficial effects of each class of agents in relieving OAB-related LUTS<sup>41</sup>. Antimuscarinics work primarily on urgency and detrusor overactivity. Because detrusor overactivity is thought to contribute to symptoms in 40% to 70% of patients with bladder outlet obstruction, it is reasonable to expect that combination therapy with an alpha blocker and an antimuscarinic would alleviate LUTS and improve quality of life.<sup>42,43</sup> Combination therapy has been studied in a number of clinical trials (Table 5) which have demonstrated the effectiveness of this approach.

**Table 5. Summary of Trials with Alpha 1-Blocker/Antimuscarinic Combination Therapy**

Combination	N	Duration	Primary outcome	Combination therapy efficacy vs. alpha 1-blocker alone
Tamsulosin (0.4 mg/d) and Tolterodine (2 mg/d) <sup>27</sup>	50	3 mos	<ul style="list-style-type: none"> <li>Quality of life questionnaire</li> <li>Urodynamic studies</li> </ul>	<ul style="list-style-type: none"> <li>Improved quality of life scores</li> <li>Improvement in some urodynamic variables</li> </ul>
Doxazosin CR (4 mg/d) and Propiverine CR (20 mg/d) <sup>28</sup>	211	8 wks	<ul style="list-style-type: none"> <li>Urinary frequency</li> <li>Urodynamic studies</li> <li>Patient satisfaction rates</li> </ul>	<ul style="list-style-type: none"> <li>Improved urinary frequency</li> <li>Improved average micturition volume</li> <li>Improved storage symptoms</li> <li>Improved urgency severity</li> </ul>
Tamsulosin (0.4 mg/d) and Tolterodine ER (4 mg/d) <sup>23</sup>	879	12 wks	<ul style="list-style-type: none"> <li>Bladder diaries</li> </ul>	<ul style="list-style-type: none"> <li>Improved urgency incontinence</li> </ul>
Terazosin (2 mg/d) and Tolterodine (2 mg BID) <sup>29</sup>	191	6 wks	<ul style="list-style-type: none"> <li>IPSS score</li> <li>Peak urinary flow rate</li> <li>Post-void residual volume</li> </ul>	<ul style="list-style-type: none"> <li>Reduced IPSS score</li> </ul>

*N=number of men; mos=months; wks=weeks; CR=controlled release; ER=extended release; IPSS=International Prostate Symptom Score*

### Case Study 4

A 65-year-old woman complains of urgency and frequency that began one month ago. She denies any incontinence. She has no previous history of LUTS, stress incontinence, or urinary tract infections. She denies any dysuria, fever, suprapubic pain, or discomfort associated with her urination complaints. Her past medical history is remarkable for a 40 pack year history of smoking, and she currently smokes 1.5 packs per day. Her neurologic and pelvic examination is normal. Her laboratory studies include a urinalysis showing microscopic hematuria with 15 red cells/hpf, no nitrate or leukocyte esterase, and no bacteria. A repeat urinalysis two weeks later again demonstrates microscopic hematuria. Because of the patient's persistent unexplained microscopic hematuria and her history of smoking, she is referred for cystoscopy, which reveals carcinoma in situ of the bladder wall.

#### • Interpretation

This patient presents with OAB symptoms. However, her symptoms were sudden in onset, which is unusual for patients with common causes of OAB symptoms, and should raise suspicion of underlying malignancy or neurological disease. In this case, the additional presence of microscopic hematuria made cystoscopic and upper tract imaging mandatory. It would be inappropriate to treat such patients with behavioral or antimuscarinic therapy for OAB without evaluation for possible underlying malignancy.

## Summary/Conclusion

Overactive bladder (OAB) is defined as a symptom syndrome suggestive of lower urinary tract dysfunction, whose chief characteristics are urgency with or without urge incontinence, and generally with frequency and nocturia. OAB symptoms are extremely prevalent among both female and male patients in primary care, but nearly half may never mention them to their provider. Therefore, it is very important for primary care clinicians to actively screen for OAB in all patients. Office-based evaluation and noninvasive treatment is feasible and appropriate for most persons with OAB. Furthermore, because OAB symptoms may be caused or worsened by comorbid conditions and medications, and many patients will respond to noninvasive therapies, primary care physicians are well suited to initiate evaluation and treatment.

Simple questions are effective in distinguishing between OAB symptoms and stress incontinence in women. Besides history and physical examination, the initial evaluation of OAB involves only a urinalysis. Treatment should proceed step-wise, beginning by addressing lifestyle factors such as obesity and fluid intake, and any contributing comorbid conditions and medications. Next, behavioral therapies such as bladder training and pelvic muscle exercises should be added. For patients whose symptoms continue to be bothersome, antimuscarinic agents can be added. Antimuscarinics are safe and effective to use in older men with coexistent BPH, either alone or in addition to alpha 1-blocker therapy. Options for patients with OAB and urge incontinence refractory to medications include sacral neuromodulation and possibly botulinum toxin (the latter currently not FDA-approved for this indication).

### Bladder Diary (“Uro-Log”)

Complete one form for each day for four days before your appointment with a healthcare provider. In order to keep the most accurate diary possible, you’ll want to keep it with you at all times and write down the events as they happen. Take the completed forms with you to your appointment.

Your Name: \_\_\_\_\_

Date: \_\_\_\_\_

TIME	FLUIDS		FOODS		DID YOU URINATE?		ACCIDENTS		
	What kind?	How much?	What kind?	How much?	How many times?	How much? (sm, med, lg)	Leakage How much? (sm, med, lg)	Did you feel an urge to urinate?	What were you doing at the time? Sneezing, exercising, etc.
Sample	Coffee	1 cup	Toast	1 slice		med	sm	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Running
6-7 am								Yes <input type="checkbox"/> No <input type="checkbox"/>	
7-8 am								Yes <input type="checkbox"/> No <input type="checkbox"/>	
8-9 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	
9-10 am								Yes <input type="checkbox"/> No <input type="checkbox"/>	
10-11 am								Yes <input type="checkbox"/> No <input type="checkbox"/>	
11-12 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	
12-1 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	
1-2 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	
2-3 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	
3-4 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	
4-5 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	
5-6 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	
6-7 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	
7-8 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	
8-9 pm								Yes <input type="checkbox"/> No <input type="checkbox"/>	

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## Self-Assessment Questions

You may receive your CME certificate online by going to [www.ama-assn.org/go/therapeuticinsights](http://www.ama-assn.org/go/therapeuticinsights) and completing the self-assessment and program evaluation. Alternatively, you may use the answer sheet provided with the AMA Therapeutic Insights newsletter to record your answers, and either fax to 312-464-4849 or mail to:

Healthcare Education Products  
Therapeutic Insights—OAB  
American Medical Association  
515 N State Street  
Chicago, IL 60654

If completing online, you will be able to print your CME certificate.  
If faxing or mailing, you will receive your CME certificate in 3-4 weeks.  
Please select the single best answer for each question.

1. Which of the following is not typically considered an increased risk factor or comorbidity for OAB?
  - a. increased risk of hip fracture
  - b. increased risk of sexual dysfunction
  - c. increased risk of depression
  - d. increased risk from diabetes mellitus
  - e. increased risk of bladder malignancy
2. Which of the following are the cardinal symptoms of OAB?
  - a. hematuria, nocturia and bladder pain
  - b. urgency with or without urge incontinence, frequency and nocturia
  - c. stress incontinence
  - d. mixed urge and stress incontinence
  - e. suprapubic pain and urinary tract infections
3. Community-based prevalence surveys reveal which of the following concerning OAB?
  - a. storage symptoms are present in up to 17% of the population over 40 years of age
  - b. suprapubic pain is the most bothersome symptom
  - c. age-related decrease in both sexes
  - d. age-related increase in females only
  - e. age-related decrease in males only
4. What is the physiological rationale for using anti-muscarinics to treat OAB?
  - a. to reduce bladder outlet resistance to allow unobstructed flow of urine
  - b. to counteract the influence of the alpha-1 adrenergic tone of the bladder detrusor
  - c. to improve bladder perfusion and reduce ischemia
  - d. to decrease parasympathetically mediated bladder contractility
  - e. to bind to and thus activate smooth muscle adenylyl cyclase
5. Which of the following is true regarding men with bothersome LUTS predominated by urgency symptoms which are only partially relieved with alpha-1 blockers?
  - a. an immediate surgical approach (*ie*, TURP) should be used
  - b. a trial of anticholinergics are contraindicated because of the high risk of urinary retention secondary to BPH
  - c. a trial combination of alpha-1 blockers and anti-muscarinics may improve symptoms
  - d. an empiric trial of antibiotics may improve urinary frequency
  - e. a trial of antidiuretic hormone (vasopressin) should be used

## Program Evaluation

1. As a result of participating in this activity, I am better able to assess for symptoms of OAB, including urinary incontinence.
2. As a result of participating in this activity, I am better able to choose a treatment approach in patients with OAB.
3. As a result of participating in this educational activity it is unlikely that I will change my management of OAB.
4. The program was free of commercial bias.
5. Overall, the program effectively met my educational needs.
6. As a result of participating in this educational activity I plan to change my management of OAB.
7. Based on the information in this program, what likely changes do you anticipate making in your management of OAB? If no changes are planned, why not? (eg, currently managing OAB as described or not currently practicing).

### Self-Assessment Responses

(Please circle your response, one response per question)

- Q.1      a          b          c          d          e
- Q.2      a          b          c          d          e
- Q.3      a          b          c          d          e
- Q.4      a          b          c          d          e
- Q.5      a          b          c          d          e

Name: \_\_\_\_\_

Address: \_\_\_\_\_

City/State/Zip \_\_\_\_\_

Phone: \_\_\_\_\_ Fax: \_\_\_\_\_

E-mail address: \_\_\_\_\_

\*M.E.# \_\_\_\_\_

### Evaluation Responses *(Please circle)*

- |     | <i>Strongly<br/>Agree</i> |   | <i>Agree</i> |   | <i>Strongly<br/>Disagree</i> |
|-----|---------------------------|---|--------------|---|------------------------------|
| Q.1 | 1                         |   | 2            |   | 3                            |
|     |                           | 4 |              | 5 |                              |
| Q.2 | 1                         |   | 2            |   | 3                            |
|     |                           | 4 |              | 5 |                              |
| Q.3 | 1                         |   | 2            |   | 3                            |
|     |                           | 4 |              | 5 |                              |
| Q.4 | 1                         |   | 2            |   | 3                            |
|     |                           | 4 |              | 5 |                              |
| Q.5 | 1                         |   | 2            |   | 3                            |
|     |                           | 4 |              | 5 |                              |
| Q.6 | 1                         |   | 2            |   | 3                            |
|     |                           | 4 |              | 5 |                              |
| Q.7 | _____                     |   |              |   |                              |

\*The Medical Education (ME) number is an 11-digit number assigned to every physician in the US by the AMA for identification and recording of basic information. If you are an AMA member, this number is found on your AMA membership card. If you do not have your ME number, you can obtain this number by calling the AMA at 1-800-262-3211. If this is not possible, please identify your date of birth, medical school, and year of graduation so that AMA staff can look up your ME number and accurately record credits.

Date of Birth: \_\_\_\_\_  
Mo/day/year

Medical School: \_\_\_\_\_

Yr. Graduation: \_\_\_\_\_

Hours of participation claimed (not to exceed 1): \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

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515 North State Street  
Chicago, IL 60654

Additional Comments \_\_\_\_\_

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