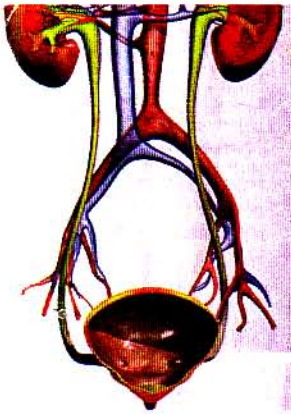

IN ASSOCIATION WITH *CONTEMPORARY OB/GYN*

OVERACTIVE BLADDER (OAB) SYNDROME:

BRIDGING THE CLINICAL GAP

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FACULTY

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COURSE DESCRIPTION
"Overactive Bladder (OAB) Syndrome: Bridging the Clinical Gap" provides medical professionals with a clear understanding of the pathophysiology of OAB, which is becoming a more common presenting condition as the population ages. The quality-of-life impact of this condition poses an increasing health care problem as assessing, screening, and distinguishing the type of incontinence are key to correct diagnosis and effective treatment. This article will review the basics of diagnosing and treating the female patient with OAB complaints, and will offer an algorithm for patient care, including a review of when referral to a subspecialist is appropriate.

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EDUCATIONAL OBJECTIVES
After completing this activity, the participant should be better able to:
- Discuss the epidemiology and pathophysiology of OAB to provide an overview of the prevalence and mechanisms that govern this clinical condition
- Appraise the methods and tools employing the diagnostic algorithm for the effective treatment and management of OAB in the clinical practice setting
- Discuss the clinician's role in counseling patients who exhibit complicated clinical histories or cases of refractory OAB with appropriate alternative options

Introduction

Overactive bladder (OAB) syndrome is an increasingly common condition presenting to the obstetrician-gynecologist for various reasons. Over the last decade, there has been improved understanding of the pathophysiology of the condition as well as the various treatment options. Newer and more effective treatment options have been introduced in the last five years. In addition, the quality-of-life (QOL) impact of OAB has become increasingly important to both men and women, especially as the population ages. Finally, there has been significant direct-to-consumer marketing of various OAB drugs, with a related increase in public awareness of the condition and treatment options. The diagnosis and management of OAB are straightforward and can easily be offered by the general obstetrician-gynecologist with only few patients requiring subspecialty referral.

Recent assessment of practicing clinicians has identified a serious practice gap between the desire and ability to effectively diagnose and treat OAB and urinary incontinence. Most will agree this is an increasing problem with significant health care and QOL effects. Common reasons cited for not being able to assess patients and implement treatment include lack of general knowledge, lack of patient assessment tools to appropriately screen, inability to distinguish between the types of incontinence, and confusion over pharmaceutical options and appropriate drug choice. In addition, clinicians are often unsure of the best treatment algorithm and how to handle patients who do not respond to first-line treatment, or when to refer to a subspecialist. The following article will review the basics of diagnosing and treating the female patient with OAB complaints and specifically address some of these critical practice gaps.

Definitions

Previously described as urge incontinence associated with detrusor instability, OAB is a more descriptive symptom-based term adopted by the International Continence Society (ICS) and defined as "urgency, with or without urge incontinence, usually with frequency and nocturia in the absence of local or metabolic factors explaining these symptoms." ICS has further defined urgency as "the complaint of a sudden compelling desire to pass urine which is difficult to defer." Urge urinary incontinence is "the complaint of involuntary leakage accompanied by or immediately preceded by urgency."[1] The most common symptoms of OAB include frequency, defined as voiding eight or more times in a 24-hour period, and nocturia, defined as waking one or more times at night to void. Patients with OAB typically complain of frequent urination during the day and/or night. They may also complain of a sudden urge to void with or without associated urinary leakage. Some patients may present with suprapubic discomfort and/or post-void fullness due to detrusor spasms.

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In contrast to OAB, which results from spasms of the detrusor muscle, stress urinary incontinence (SUI) results from weakness of the bladder neck continence mechanism and is "the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing".[1] These patients typically complain of small amounts of urine leakage with activity, exercise, coughing, and sneezing. As the severity of stress incontinence worsens, patients may complain of urinary leakage with simple events, including standing or bending. Many patients may present with a combination of OAB and SUI symptoms, and these patients are considered to have mixed incontinence with treatment being focused on the more predominant complaint. It is important to note that, in these women, voiding frequently will reduce the impact and severity of stress incontinence by reducing bladder volumes and thus reducing the amount of stress-related leakage. There can be significant overlap in a patient's symptoms, and it is important that the practicing clinician have a basic understanding of the various types and symptoms of incontinence prior to initiating treatment.

Epidemiology

The exact prevalence and incidence of OAB are unknown and most probably underreported. Recent studies include the National Overactive Bladder Evaluation (NOBLE) computer-aided phone survey that evaluated 11,740 respondents in the United States.[2] The overall prevalence of OAB from that study was 16.9% in women and 16.0% in men. Extrapolated to the U.S. population, more than 33 million adults may suffer from OAB. More importantly, only one-third of the respondents had associated urge incontinence classified as OAB wet, while the remaining two-thirds had no significant associated urinary leakage, classified as OAB dry. This is an important point, as the commonly asked question, "Do you have any problem with urinary leakage?" might not capture the majority of patients with clinically significant OAB symptoms such as sensory urgency, daytime frequency, and nocturia. The prevalence of OAB symptomatology increased with age in both men and women, rising from less than 10% in the 25- to 34-year age group to 30% in the greater than 75-year age group. This is likely due to prolapse and vaginal atrophy in women compared with prostatic hypertrophy/neoplasm in men. Aging and neurologic decompensation is common to both women and men. Women typically had a greater percentage of OAB wet compared with men (9.3% vs 2.6%). Notably, the likelihood of OAB wet in women appeared to increase markedly between the ages of 35 and 44 years and then significantly after age 55.[2]

Pathophysiology

The exact etiology of OAB is not completely understood; however, both neurogenic and myogenic hypotheses have been proposed. Control of bladder storage and voiding involves a complex interplay of the parasympathetic, sympathetic, and somatic neurons; pelvic floor musculature; and the detrusor muscle. The neurogenic hypothesis of OAB suggests reduction in peripheral and/or central inhibition as the cornerstone of the condition. This results in increased activity of the micturition reflex with development of inhibition-resistant bladder reflexes. These are thought to be mediated by afferent C-fibers that are pathologically active in patients with OAB.[3] The myogenic hypothesis suggests alteration in detrusor myocyte activity as the basis for OAB. During storage, myocyte activity with associated detrusor contraction is latent and activated only during voiding. In patients with OAB, it is proposed that increased myocyte cell-to-cell communication and coupling exist that allow local overactivity of the detrusor muscle.[4]

Normally, bladder contractions are induced with parasympathetic activation of muscarinic receptors on the detrusor muscle. Acetylcholine binding to the receptor triggers smooth muscle contraction. Five subtypes of the muscarinic receptors have been reported in the bladder and other parts of the body, with M2 and M3 receptors concentrated in the bladder. Although M2:M3 concentration in the bladder is nearly 3:1, the M3 receptor is thought to play the primary role in regulating bladder contractions. M3 receptors are also present in the salivary glands, mediating secretions and saliva volume; in the gastrointestinal (GI) tract, mediating motility; and in the eye, mediating contractility.[5] OAB pharmacotherapy is designed to affect these muscarinic receptors to overcome the pathologic neurogenic and/or myogenic alterations previously described. Recent attention has been given to drug specificity of the specific muscarinic receptors of the bladder, but the quantitative differences and outcome and side effects are currently unclear.

Diagnosis

Diagnosis of OAB is easily made in the office based on patient history, physical exam, and basic bladder testing. Those patients with a complicated picture (Table 1) may need subspecialty referral to urology or urogynecology for further evaluation. Treatment can often be implemented after one to two office visits to assess the patient's symptoms and initial baseline status. The key to effective treatment is correct diagnosis, with the primary goal to differentiate overactive bladder, stress urinary incontinence, and mixed incontinence.

Table 1. Indication for Subspecialty Referral Based on Physician Experience and Resources

Unsuccessful Prior Surgery	Unsuccessful Prior Treatment
Neurologic Problem	Radical Pelvic Surgery
Advanced Prolapse	Unclear Diagnosis
Prior to Prolapse Surgery	Difficulty in Emptying
Recurrent UTI	Hematuria

Patient-Assisted Tools

Prior to the initial history and physical exam, patient education and survey tools may be of great benefit to help the clinician make a diagnosis and assess treatment outcomes. One of several validated questionnaires completed prior to assessing patient history and the physical exam may help in the definitive diagnosis. Traditionally, the short-form Incontinence Impact Questionnaire (IIQ-7), a seven-question instrument, has been used to determine type of incontinence and its effect on social relationships, independence, and emotional health (Form 1).[6] More recently, Brown and colleagues have introduced a simple three-question instrument, the 3IQ, to differentiate between urge and stress incontinence (Form 2).[7] For diagnosing urge incontinence, the 3IQ has been shown to be 75% sensitive, 77% specific, and had a positive likelihood ratio of 3.29.[7] The Overactive Bladder Validated 8-Question Screener (OAB-V8) has been specifically designed to assess the impact of OAB on a patient based on a bother scale.[8]

Form 1. Incontinence Impact Questionnaire – Short Form (IIQ-7)[6]

Some people find that accidental urine loss may affect their activities, relationships, and feelings. The questions below refer to areas in your life that may have been influenced or changed by your problem. For each question, circle the response that best describes how much your activities, relationships, and feelings are being affected by urine leakage.

Has urine leakage affected your...

	Not at All	Slightly	Moderately	Greatly
1. Ability to do household chores (cooking, housecleaning, laundry)?	0	1	2	3
2. Physical recreation such as walking, swimming, or other exercise?	0	1	2	3
3. Entertainment activities (movies, concerts, etc)?	0	1	2	3
4. Ability to travel by car or bus more than 30 minutes from home?	0	1	2	3
5. Participation in social activities outside your home?	0	1	2	3
6. Emotional health (nervousness, depression, etc)?	0	1	2	3
7. Feeling frustrated?	0	1	2	3

Items 1 and 2 = physical activity

Items 3 and 4 = travel

Item 5 = social/relationships

Items 6 and 7 = emotional health

Scoring. Item responses are assigned values of 0 for "not at all," 1 for "slightly," 2 for "moderately," and 3 for "greatly." The average score of items responded to is calculated. The average, which ranges from 0 to 3, is multiplied by 33⅓ to put scores on a scale of 0 to 100.

Form 2. 3IQ[7]

1. During the last 3 months, have you leaked urine?
- ❑ Yes
- ❑ No

If no, no need to proceed.

2. During the last 3 months, did you leak urine: (Check all that apply)
- ❑ a. When you were performing a physical activity such as coughing, sneezing, lifting, or exercise?
- ❑ b. When you had the urge or need to empty your bladder, but could not get to the toilet fast enough?
- ❑ c. Without physical activity and without a sense of urgency?

3. During the last 3 months, did you leak urine most often: (Check only one)
- ❑ a. When you were performing a physical activity?
- ❑ b. When you had the urge or the feeling that you needed to empty your bladder?
- ❑ c. Without physical activity and without a sense of urgency?
- ❑ d. About equally as often with physical activity as with a sense of urgency?

Score by response to question 3:
- a = stress or stress dominant
- b = urge or urge dominant
- c = other causes
- d = mixed

In addition to these validated questionnaires, a 24- or 48-hour bladder diary is particularly helpful in the initial evaluation of the OAB or incontinence patient. This is a self-administered tool that the patient completes at home, keeping track of the number and amount of voids, the number and severity of leakage episodes, and the association of leakage with urgency or physical activity. In addition, patients record the amount and type of fluid intake. Increased fluid intake and consumption of bladder irritants, which include caffeine and alcohol, are monitored and documented. Typically, the OAB patient will demonstrate frequent small-volume voids during the day and/or night. Patients with frequent large-volume voids may be consuming excessive fluid or have an endocrine abnormality. Patients with only daytime symptoms may be affected by daytime fluid/caffeine intake or may be exhibiting a learned response, treatable with simple behavioral modification and bladder retraining. The bladder diary is an important tool in assessing patients' symptoms to objectively correlate with presenting complaints. It is also an excellent follow-up tool to assess progress after intervention or treatment. A variety of bladder diaries are available for download on the Internet and can be given or mailed to the patient to complete prior to the initial visit. If provided at the initial visit, it may also be helpful to give the patient a voiding hat to precisely measure and record void amounts.

Patient History

A careful patient history can provide valuable insight into the etiology, impact, and concurrent conditions of OAB. The patient should be questioned regarding the duration, severity, and type of OAB symptoms as well as how it impacts activities of daily living and emotional/social health. Any coexisting incontinence—either stress or overflow—should also be thoroughly reviewed. Many patients self-induce daytime frequency in order to keep their bladders empty and reduce the risk of symptomatic stress or overflow incontinence. Although more common in men, any symptoms of voiding dysfunction or incomplete bladder emptying should be noted. A careful medical and surgical history with particular inquiries regarding diabetes, neurologic conditions, endocrine abnormalities, back injury, or pelvic surgery is recommended. Sleep apnea has recently been associated with nocturia and incontinence,[9] and suspected patients may benefit from a sleep study. Any previous prolapse or incontinence surgery should be discussed in detail. Review of any special diets or exercise programs is also helpful, as these may be associated with significant fluid or caffeine intake. Concurrent medications should be reviewed, as various medications, including diuretics, antidepressants, antihypertensives, and antipsychotics, can be associated with significant urinary side effects. A baseline QOL questionnaire such as the Short Form-36 (SF-36) may be helpful in assessing the extended impact of OAB on patients.

Physical Exam

A thorough physical exam with particular emphasis on the abdomen and vagina should be performed at the time of the initial visit. The vaginal exam should consist of inspection and palpation. The perineal skin should be examined for signs of irritation and breakdown associated with chronic urinary incontinence. Estrogenation of the external genitalia and vaginal mucosa should be assessed during inspection. With a half speculum retracting the posterior vaginal wall, the anterior vaginal wall should be assessed for suburethral mass suggestive of a urethral diverticulum and/or significant cystocele. The exam should be performed with the patient at rest and during Valsalva. OAB can often be associated with advanced cystocele, resulting in a bladder outlet obstruction due to urethral kinking. The half speculum should then be removed and reinserted, retracting the anterior vaginal wall to assess for posterior vault prolapse, including rectocele and enterocele. A vaginal bimanual exam should be performed to assess uterine size and position as well as presence of pelvic masses or uterine fibroids, as these can compress the bladder, simulate OAB, and reduce bladder capacity. Pelvic muscle tone and appropriate recruitment of muscles, upon request of pelvic muscles squeeze, should be assessed during bimanual exam. Two fingers are placed in the vagina and the patient is asked to squeeze her pelvic muscles. Correct contraction and baseline strength can be assessed. A standing exam with inspection and palpation with the patient performing Valsalva is particularly helpful in order to assess prolapse. Finally, a cotton swab test should be performed to assess urethral hypermobility. (A cotton swab test is

somewhat controversial among practitioners.) Although associated predominantly with stress incontinence, it has been suggested that patients with urethral hypermobility may have "urethral funneling", allowing urine to "leak" into the proximal urethra and induce a reflex detrusor contraction that initiates sensory urgency and urge incontinence. This may be the mechanism by which a loosely placed sling that provides urethral support, not obstruction, may improve both stress and urge symptoms.

Bladder Testing

Bladder testing for OAB can be routinely performed in the office by the primary care physician or obstetrician-gynecologist. The basic panel consists of a urinalysis/urine culture to rule out infection and measurement of a postvoid residual via urethral catheterization or bladder ultrasonography. Secondary testing, also easily performed in the office setting, involves uroflow and simple cystometrogram. With the patient presenting with a full bladder, she is asked to void into a special commode for a uroflow. The volume voided, max flow rate, and time to void are recorded. The patient's bladder is then catheterized with a red rubber catheter for postvoiding residual (PVR) and urine sample for culture or cytology. With the red rubber catheter in place, a 50-cc catheter tip old syringe with the bulb removed is attached to the distal end of the catheter. The bladder is slowly backfilled with room temperature normal saline or sterile water. During filling, the patient's bladder volumes for first sensation to void, first urge to void, and strong urge to void are recorded. Normal capacities are 100-200 cc, 200-400 cc, and 400-600 cc, respectively. Patients with OAB typically exhibit smaller bladder capacities with earlier sensations. They may also exhibit a detrusor contraction during filling that presents as a "hiccup" or backup in the water line during filling. Patients with significantly larger bladder capacities with delayed sensation should be suspected to have neurogenic bladder with associated overflow incontinence. These patients require further urodynamic evaluation and possible neurology consultation. Once the patient reaches maximum capacity, the catheter is removed and the patient is asked to cough in the standing position. Patients who exhibit large amounts of spontaneous urinary leakage while getting in the standing position are most likely having urge incontinence associated with detrusor contractions. Demonstration of small amounts of urinary leakage during provocation (cough or strain) in the standing position is more consistent with the diagnosis of stress incontinence.

- Multichannel urodynamic evaluation and cystoscopy are most commonly performed by the subspecialist and requires specialized equipment and trained personnel. They are not required for first-line evaluation and treatment of OAB. Multichannel urodynamic testing allows precise measurement or calculation of intravesical, intraurethral, and intra-abdominal pressure during filling (storage) and emptying (voiding). Although some patients with OAB may demonstrate spontaneous detrusor contractions and reduced bladder compliance during filling, the majority of patients only exhibit reduced maximum bladder capacity and early bladder sensations. Cystoscopy is often normal but may sometimes reveal significant trabeculations. The clinical significance of these findings is unclear but may represent reduced bladder compliance associated with frequent voiding. Cystoscopy for OAB should also evaluate for abnormal masses or lesions consistent with bladder cancer as well as bladder stones, which may present with OAB or urinary incontinence.

Treatment

The management of OAB is best accomplished by simultaneously implementing a variety of treatment options, including behavioral modification, pelvic floor exercises, and pharmacotherapy. This treatment plan acts synergistically on both the neuromuscular and psychosocial levels. It often requires the patient to be proactive and dedicated, which can be challenging. Encouragement and positive reinforcement with frequent visits for reassessment may be helpful in select patients. Patient education is vital, and this portion of the treatment can be time consuming for the busy clinician. Access to knowledgeable and experienced nurses and/or physician extenders who can often manage the OAB patient with physician supervision is helpful. Patient education materials are also helpful and readily available. Neuromodulation and alternative therapies are best reserved for patients who do not respond to conservative measures. A sample treatment algorithm is shown in Figure.

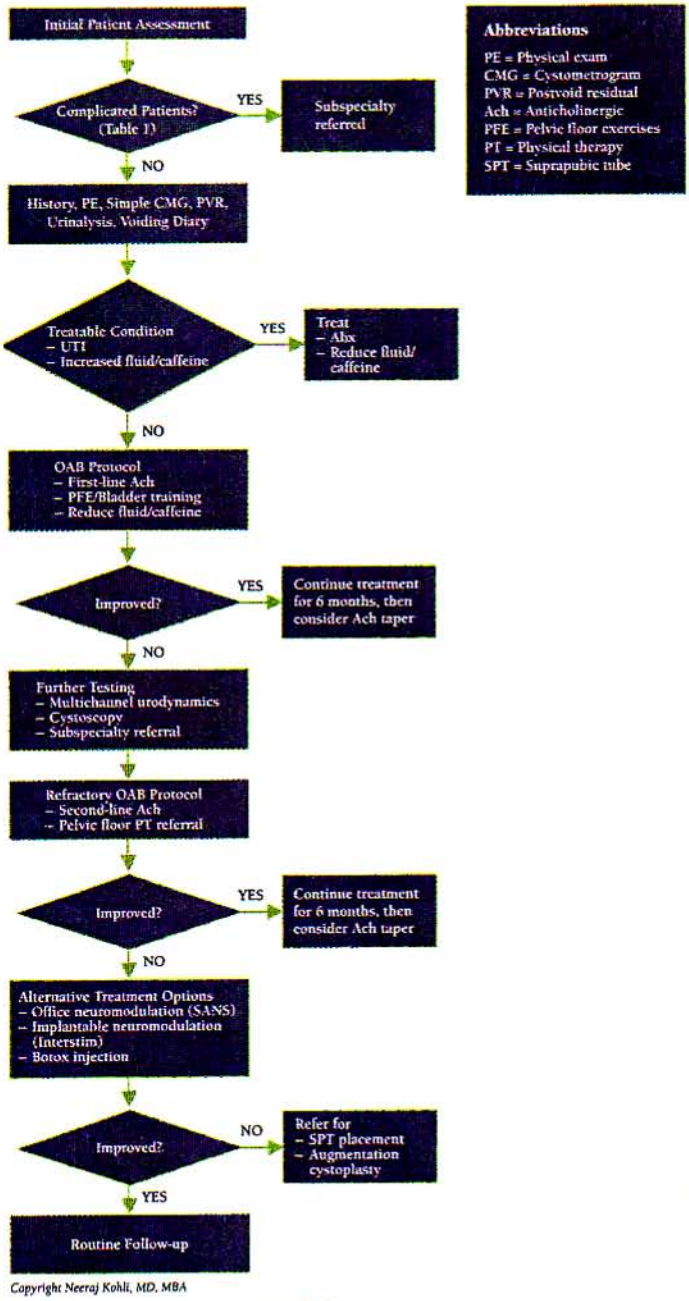


Figure. Treatment algorithm for OAB.

Behavioral Modification

Dietary and behavioral modification can often result in significant improvement in OAB without the side effects associated with pharmacotherapy. Unfortunately, patients may not experience significant improvement for some time given the gradual effect of these changes.

Reduction of fluid and caffeine or alcohol intake can result in significant improvement in micturition frequency, sensory urgency, and urge incontinence. A voiding diary specifically detailing the amount and type of intake is helpful in identifying those patients who would benefit most from dietary changes. Bladder retraining, where the patient voids daily at a set interval and then gradually increases the interval to increase bladder capacity, is very effective although sometimes difficult to implement depending on a patient's work schedule. Developing coping strategies, which may include prompted voiding and toilet mapping, can also help to reduce the social impact of OAB and should be encouraged, especially early during the treatment process.

Pelvic Floor Exercises/Physical Therapy

Pelvic floor or Kegel exercises have been shown to be beneficial in the treatment of pelvic prolapse, urinary incontinence, and OAB. When done properly and regularly, they can effectively reduce acute episodes of urgency by inducing detrusor relaxation during pelvic floor contraction. In fact, results have been comparable to medical therapy. The variable rates of response previously reported are mostly due to variations in patients' neuromuscular integrity, failure of patients to perform the exercises properly, and poor long-term compliance.[10] Most clinicians implement a pelvic floor exercise program based on use of a patient hand-out. This results in many patients performing the exercises incorrectly and deriving little benefit. Verbal "biofeedback" at the time of pelvic exam, confirming the appropriate contraction and evaluating strength of the pelvic floor during vaginal manual exam, is easy, convenient, and effective. Response to pelvic floor exercises can take up to three to four months of continued therapy, so both short- and long-term compliance are necessary for patient success. For those patients who have difficulty performing the exercises correctly or remaining compliant, pelvic floor physical therapy referral may be indicated.

Pelvic floor physical therapists routinely employ a variety of techniques in order to improve patients' ability to correctly perform the exercises. These include detailed instruction and counseling, visual and auditory biofeedback, vaginal cones, and electrical stimulation. Although much of this can be implemented by the physician, the role of the physical therapist expands to that of a cheerleader for the patient, with considerable time spent on offering encouragement and counseling. Previous studies have shown no significant additional benefit to electrical stimulation and biofeedback compared with properly performed pelvic floor exercises.[11] However, these additional therapies may be helpful in the noncompliant or refractory patient. A variety of "gadgets and gizmos" has been marketed directly to consumers to help with pelvic floor exercises, including "The Kegelmaster". There are no clinical data regarding the efficacy of these products compared with simple verbal biofeedback, yet they may have merit in inducing patients to remain compliant. With regard to pelvic floor physical therapy and available devices, it is important to remember the associated costs and limited availability for some patients. In addition, patients with altered mental state and limited mobility may not be able to implement behavioral modification or a pelvic floor exercise program.

Anticholinergic Medication

Anticholinergic medication has long been the mainstay for treatment of OAB and should be used in conjunction with the nonpharmacologic therapies described above. This approach can be integrated from the first visit or following an initial trial of behavioral modification and pelvic floor exercises. Traditionally, long-term compliance has been challenging because of significant co-existing side effects. Introduction of newer drugs has improved outcomes by reducing side effects and increasing efficacy. The currently approved and commonly used drugs include oxybutynin in immediate-release (IR) (Ditropan), extended-release (ER) (Ditropan XL), and transdermal patch (Oxytrol) formulations, tolterodine IR (Detrol), tolterodine ER (Detrol LA), solifenacin (Vesicare), darifenacin (Enablex), and trospium chloride (Sanctura). The drugs are all muscarinic receptor antagonists and have demonstrated comparable efficacy with varying dosing schedules, side-effect profiles, and biochemical properties, which may affect selection for various patient subgroups. With their primary effect on the M3 receptor found in the bladder, these anticholinergic medications have been thought to act by blocking the effect of acetylcholine and impairing bladder contraction during the voiding phase. However, studies have shown little effect on bladder contractions during voiding. Few patients develop voiding dysfunction due to anticholinergic agents, but this class should be used with caution in patients with pre-existing incomplete bladder emptying or urinary retention. Recent theories suggest these agents may, in fact, work primarily during the storage phase, increasing bladder capacity and decreasing urge, by blocking acetylcholine released from the urothelium or nerves during storage, resulting in reduced bladder tone.

Side effects occur because of the blockade of M3 and other muscarinic receptors (M1-M5) in various other parts of the body, including the salivary glands, GI tract, eyes, brain, and heart. Side effects may vary based on physical properties of the molecule (ie, size and lipid solubility affecting passage through the blood-brain barrier) and M3 bladder selectivity. Side effects of nonbladder muscarinic receptor action include dry mouth (salivary glands), constipation (GI tract), visual changes (eyes), cognitive dysfunction (brain), and tachycardia and prolongation of the QT interval (heart).

For decades, oxybutynin has been the prototypical anticholinergic, antimuscarinic medication used for OAB and urge incontinence. Oxybutynin is mildly M3 and M1 bladder selective and has been associated with tachycardia and reported to increase the QT interval in older patients. It has long been available in an IR formulation that is now on generic formulary. The IR formulation has been associated with the greatest amount of dry mouth compared with other agents available, with up to 40% of patients discontinuing medication due to this side effect in clinical trials. The ER formulation (Ditropan XL) and the transdermal patch (Oxytrol) may provide the patient with such additional benefits as more convenient dosing, prolonged steady-state, improved bioavailability, and reduced side effects. The ER formulation can be titrated up from 5 mg to 10 mg to 15 mg, based on patient response and side effects. In a recent head-to-head comparison of oxybutynin ER with tolterodine ER, oxybutynin ER was noted to have greater effect in reducing weekly micturition frequency and urinary urge incontinence with comparable tolerability except for slightly higher dry mouth in the oxybutynin group.[12] The transdermal formulation is unique in allowing greater bioavailability by avoiding the first-pass effect of hepatic metabolism associated with oral drug administration. In addition, avoiding the first-pass effect reduces concentrations of N-desethyloxybutynin, which has been associated with the high incidence of anticholinergic side effects. Convenient twice-weekly dosing is also beneficial for patients and improves compliance. In two previous pivotal studies, both dry mouth and constipation were shown to be significantly less with the transdermal formulation compared with the oral formulation.[13] Unique side effects of the patch include skin irritation, erythema, and pruritus, which can be minimized by alternating the site of application.[13]

Tolterodine (Detrol) was one of the first drugs to be specifically marketed for the treatment of OAB and is thus one of the most well studied. It is a nonselective muscarinic antagonist that has been shown to have some cardiac effect, including tachycardia. Available in IR and ER formulations and ranging from 2-mg to 4-mg daily dosage, tolterodine has been shown to be effective within 1 week of dosing. The prescribing information recommends the 4-mg daily

dosage with titration *down* if the patient reports significant side effects. There is no increased titration dose in patients who do not have response at the 4-mg daily dose. The ER formulation has been shown to have greater efficacy and fewer side effects compared with the IR formulation.[14]

The newer agents recently approved for use in the United States—solifenacin, darifenacin, and trospium chloride—have been studied with greater scrutiny with regard to adverse effects. Solifenacin had moderate selectivity for the M3 receptor with no significant reported cardiac effects. The drug is available in 5-mg and 10-mg doses, with titration based on patient response and side effects.[15] The significantly long half-life of the drug, 50 hours, allows convenient dosing but may also be related to prolonged side effects. The long half-life does allow patients to miss a dose without significantly decreasing blood drug levels. In a recent head-to-head comparison of solifenacin with the standard, tolterodine ER 4 mg po daily, solifenacin was shown to be "noninferior" to tolterodine with 24-hour micturition frequency as the primary endpoint. Statistically significant improvement was noted in terms of urge incontinence episodes and sensory urgency.[16]

Darifenacin (Enablex) is highly selective for the M3 receptor with affinity almost 60 times that of M2 and M4. Available in 7.5-mg and 15-mg daily doses, the drug has been shown to have no significant effect on QT prolongation or tachycardia.[17] Previous trials have shown significant dose-related improvement in incontinence episodes, duration frequency, and sensory urgency. In phase 3 studies, the most common adverse effect was dry mouth. Given its high M3 bladder selectivity, it has less cognitive side effects and memory deterioration than oxybutynin, which can have significant effects due to its effects on the M1 receptor and physical properties that favor crossing the blood-brain barrier.[18]

Trospium chloride (Sanctura) has long been available in Europe and recently has been approved for use in the United States. Previous European trials have compared the drug with oxybutynin and tolterodine and found substantial differences in volume of first detrusor contraction as well as a decrease in micturition frequency.[19] Trospium is a nonselective muscarinic receptor antagonist with only 1 dose given twice a day. The dosage schedule and inability to titrate may limit its use in some patients. Trospium is not metabolized by hepatic cytochrome P450; it is excreted relatively unchanged in the kidneys and, therefore, may have an additional local effect on the bladder. In addition, interaction with other medications that are metabolized in the liver is reduced. There is no association of prolonged QT interval with the drug and only mild tachycardia has been noted in select trials. Because of its quaternary amine structure, it is less likely to cross the blood-brain barrier and, therefore, has decreased potential for cognitive side effects.

It is important to note that some patients may not respond or may develop side effects to one anticholinergic medication versus another (Table 2). Typically, the clinician will try one anticholinergic medication and then refer out if the patient does not respond or because of poor tolerability. Although this referral pattern is reasonable, an alternative treatment option would be to titrate the dose up, if there is no effect, or down, if tolerability is poor. Also, trying an alternative second- or even third-line drug can result in clinical response in many patients. It is difficult to assess which patients will respond to which medications, and an "adequate trial" of at least 8 weeks, with or without behavioral modification, should be attempted before switching medications for poor response. Alternate medications can be considered sooner in patients who have significant side effects prior to the completion of 8 weeks of therapy.

Neuromodulation

Neuromodulation may be helpful in certain cases of refractory OAB. The technology has previously been used with good results for conditions that include Parkinson disease and epilepsy. The technique employs mild electrical stimulation of the pelvic nerves (S3 nerve root) via peripheral acupuncture techniques or a central implant. Although the exact mechanism of action is incompletely understood, it is postulated that sacral neuromodulation stimulates the somatic afferent inhibition of sensory processing of the bladder within the spinal cord. This is mediated by unmyelinated C-fibers and myelinated A-fibers. Pudendal nerve stimulation can induce the two guarding reflexes that reduce incontinence as well as block ascending sensory pathways.

The only available technique for office-based neuromodulation is the Urgent PC Neuromodulation System, which employs acupuncture electrical stimulation of the tibial nerve. This provides ascending effect to the pelvic nerve plexus. The procedure is performed in the office with each session lasting 30 minutes. Treatment is recommended every 7 to 10 days, with 8 to 12 treatments total. Variable response has been reported. Benefits of the treatment include its noninvasive technique and ease-of-use, with a short learning curve. Disadvantages include variable response, spotty insurance coverage, and the need for frequent visits.[24]

The only available option for surgical neuromodulation is the use of the Interstim and Interstim II implant devices, which employ an implanted unilateral or bilateral lead attached to a small pacemaker placed with a subdermal pocket in the buttock region. The procedure involves a staged technique with two brief outpatient surgeries. The initial surgery is performed with the patient in the supine position; two small quadrapolar leads are inserted into the S3 foramen via a percutaneous technique under fluoroscopic guidance. The leads are connected to an external neurostimulator and patient response is tested over a two-week period. Preprocedure and postprocedure voiding diaries are used to objectively assess response. If the patient responds, defined as a 50% reduction in symptoms, the patient proceeds to the second stage. The second-stage procedure

Table 2. Drugs Available to Treat OAB[14,15,17,20-23]

Generic Name	Trade Name(s)	Daily Dosage	Special Considerations	Available Data
Oxybutynin	Oxybutynin Ditropan XL Oxytrol	5 mg qid 5 mg, 10 mg, 15 mg qd 3.9 mg twice a week	Generic available at low cost; high incidence of dose-related SE Convenient dosage able to titrate; high incidence of SE Transdermal formulation avoids first-pass effect; decreased SE; skin irritation; increase of efficacy of oxybutynin	+++ +++ ++
Tolterodine	Detrol LA	4 mg qd	Longest experience/Large amount of data; no titration dose	+++
Solifenacin	Vesicare	5 mg, 10 mg qd	Long half-life; high compliance rate	++
Darifenacin	Enablex	7.5 mg, 15 mg qd	M3 selective; decrease in cardiac/cognitive SE	++
Trospium chloride	Sanctura	20 mg bid	Renal metabolism with decreased drug interaction; local bladder effect; bid dosing	+++

SE=side effects

involves removal of the nondominant lead and attachment of the pacemaker to the dominant lead with subdermal placement. For those patients who do not respond, the leads are removed. The patient can then control and adjust the neuromodulation using a remote that controls the pacemaker through transdermal communication. Success rates have been reported to be as high as 70% in refractory patients. The device is US Food and Drug Administration (FDA) approved for urgency-frequency symptoms, urge incontinence, and nonobstructive incomplete bladder emptying. Trials are under way for fecal incontinence, interstitial cystitis, and pelvic pain. Benefits include constant neuromodulation, while disadvantages include risks with foreign body placement and need for anesthesia. The battery life of the pacemaker is four to six years, and it does have to be changed periodically to maintain effect.[25]

New Treatment Modalities

Recently, botulinum toxin (Botox) has been described for treatment of refractory OAB. One hundred to 300 units of Botox are injected into multiple sites in the detrusor muscle via cystoscopy. The procedure is well tolerated and does not carry a significant risk. Success rates can be as high as 60%, but patients often take three to four weeks to respond. The effects can last up to 6 months, at which time additional injections may be required. The procedure can be performed in the operating room or in the office setting for appropriately selected patients.[26] Benefits include no need for patient compliance and good effect, while disadvantages include a low incidence of incomplete bladder emptying and poor insurance coverage. Although not FDA approved, botulinum toxin is being offered to refractory patients in many areas. A company-sponsored study is in progress.

Conclusion

OAB is a significant health care problem for many patients. It is expected that the impact and prevalence of the condition will only increase with the aging of the population and improved awareness of the condition. The obstetrician-gynecologist is in a unique position to address the needs of women with significant OAB symptoms. The evaluation in the office is easy to perform and multiregimen treatment programs can be implemented with good results in most patients. Treatment should be individualized and should begin with education and counseling, followed by behavioral modification, pelvic floor exercises, and, when appropriate, anticholinergic medication. A variety of anticholinergic medications with similar efficacy is available, but the current data may prompt clinicians to use one medication over another, depending on potential for cardiac and cognitive side effects. Patients with a complicated clinical picture or refractory symptoms may be best referred for subspecialty evaluation. Even these patients may have significant improvement in their symptoms using alternative treatment options such as sacral neuromodulation. Further research is under way to provide even safer and more effective treatment options in the near future.

Answers for Case Studies
1. c, 2. b, 1. c, 2. e

Case Studies

DM is a 37-year-old woman with a one-year history of progressively worsening OAB, with complaints of daytime frequency and sensory urgency. She voids 12 to 15 times per day and once at night. She denies any associated prolapse or stress incontinence. She does admit to increased caffeine and fluid intake. Physical exam is normal. Pelvic muscle tone is weak. The patient was asked to come to the office with a full bladder and voided 200 cc and was noted to have a PVR of 25 cc when catheter was inserted to obtain a urine specimen for culture. Urinalysis was negative.

1. What is/are the next step(s) for evaluation and treatment of this patient (select one)?
a) Voiding diary
b) Anticholinergic medication
c) Caffeine/Fluid modification
d) Pelvic floor exercises
e) All the above

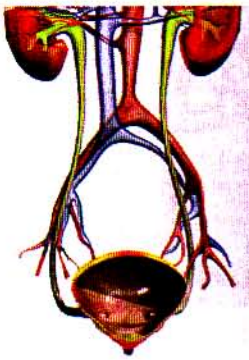
2. If she is not improved on follow-up at eight weeks, all of the following would be reasonable treatment options EXCEPT (select one):
a) Increase medication dose if no side effects or change to second-line anticholinergic
b) Recommend Interstim neuromodulation
c) Refer to pelvic floor physical therapy
d) Schedule further testing (multichannel urodynamics and/or cystoscopy)
e) Refer to subspecialist

AF is a 75-year-old woman with a long history of OAB and diabetes, including daytime frequency, nocturia, and urge incontinence. She has previously tried anticholinergic medication without significant improvement in her symptoms. She reports an altered urine stream. On exam, she has significant grade 3 cystocele; the uterus and posterior vaginal wall are well supported. The patient was asked to come to the office with a full bladder and voided 50 cc and was noted to have a PVR of 150 cc when catheter was inserted to obtain a urine specimen for culture. Urinalysis was equivocal.

1. Possible next steps for evaluation and treatment of this patient include all of the following EXCEPT (select one):
a) Multichannel urodynamics
b) Subspecialty referral
c) Alternative anticholinergic medicine
d) Pessary insertion
e) Urine culture

2. In her case, OAB could be related to (select one):
a) Increased fluid intake/urine production
b) Bladder outlet obstruction
c) Nerve dysfunction related to diabetes
d) Urinary tract infection
e) All the above

References
1. 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. *Am J Obstet Gynecol.* 2002;187(1):116-126. 2. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol.* 2003;20(6):327-336. 3. de Groat WC. A neurologic basis for the overactive bladder. *Urology.* 1997;50(6A suppl):36-52. 4. Brading AF. A myogenic basis for the overactive bladder. *Urology.* 1997;50(6A suppl):57-67. 5. Abrams P, Andersson KE. Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. *Br J Pharmacol.* 2006;148(5):565-578. 6. Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fantl JA. Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group. *Neurourol Urodyn.* 1995;14(2):131-139. 7. Brown JS, Bradley CS, Subak LL, et al; Diagnostic Aspects of Incontinence Study (DAISy) Research Group. The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. *Ann Intern Med.* 2006;144(10):715-723. 8. Coyne KS, Zyczynski T, Margolis MK, Eliroff V, Roberts RG. Validation of an overactive bladder awareness tool for use in primary care settings. *Adv Ther.* 2005;22(4):381-394. 9. Fitzgerald MP, Mulligan M, Parthasarathy S. Nocturic frequency is related to severity of obstructive sleep apnea, improves with continuous positive airways treatment. *Am J Obstet Gynecol.* 2006;194(5):1399-1403. 10. Gray M, David DJ. Does biofeedback improve the efficacy of pelvic floor muscle rehabilitation for urinary incontinence or overactive bladder dysfunction in women? *J Wound Ostomy Continence Nurs.* 2005;32(4):222-225. 11. Burgio KL. Behavioral treatment options for urinary incontinence. *Gastroenterology.* 2004;126 (1 suppl 1):S82-S89. 12. Diokno AC, Appell RA, Sand PK, et al; OPERA Study Group. 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(6):687-695. 13. Shaw GL, Patel HR. Transdermal oxybutynin: a review. *Expert Opin Drug Metab Toxicol.* 2007;3(3):435-439. 14. Detrol LA (package insert). New York, NY: Pfizer Inc; 2006. 15. Vesicare (package insert). Deerfield, IL: Astellas Pharma US, Inc.; 2005. 16. Chapple CR, Martinez-Garcia R, Selvaggi L, et al, for the STAR study group. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol.* 2005;48(3):464-470. 17. Enablex (package insert). East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2006. 18. Kay G, Crook T, Rekeda L, et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. *Eur Urol.* 2006;50(2):317-326. 19. 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(6):392-399. 20. Oxybutynin chloride (package insert). Weston, FL: Apotex Corporation; 2005. 21. Ditropan XL (package insert). Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; 2004. 22. Oxytrol (package insert). Corona, CA: Watson Pharmaceuticals, Inc; 2003. 23. Sanctura (package insert). East Brunswick, NJ: Esprit Pharmaceuticals; 2006. 24. Nuhoglu B, Fidan V, Ayyildiz A, Ersoy E, Germiyanoglu C. Stoller afferent nerve stimulation in woman with therapy resistant over active bladder; a 1-year follow up. *Int Urogynecol J Pelvic Floor Dysfunct.* 2006;17(3):204-207. 25. Kohli N, Rosenblatt PL. Neuromodulation techniques for the treatment of the overactive bladder. *Clin Obstet Gynecol.* 2002;45(1):218-232. 26. Mallina R, Sahai A, Khan MS, Dasgupta P. Botulinum toxin a in the overactive bladder: current status and future directions. *BJU Int.* 2007;99(6):1549-1550.



OVERACTIVE BLADDER (OAB) SYNDROME:

BRIDGING THE CLINICAL GAP

Self-Evaluation

Please complete the evaluation below.

1. **Overactive bladder (OAB) is (select one):**
   a) More common in women
   b) Related to aging
   c) Related to prostate conditions in men
   d) Associated with advanced pelvic prolapse
   e) All of the above

2. **First-line evaluation of OAB may include all of the following EXCEPT (select one):**
   a) History and physical exam
   b) Voiding diary
   c) Simple cystometrogram
   d) Uroflow
   e) Cystoscopy

3. **Indications for referral include all the following EXCEPT (select one):**
   a) Incomplete bladder emptying
   b) Excessive fluid/caffeine intake
   c) Hematuria
   d) Unsuccessful prior treatment
   e) Recurrent urinary tract infection

4. **First-line treatment of OAB includes (select one):**
   a) Interstim neuromodulation
   b) Suprapubic tube placement
   c) Augmentation cystoplasty
   d) Anticholinergic medication
   e) Referral to subspecialist

5. **Side effects of anticholinergic medications may include (select one):**
   a) Dry mouth
   b) Constipation
   c) Headache
   d) Blurry vision
   e) All of the above

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Activity Evaluation

After completing this monograph, record your answers to the self-assessment quiz and complete the activity evaluation. Your feedback is paramount to our providing quality educational activities. Thank you.

Answer each question using a scale of 1–5 (5 = strongly agree, 3 = agree, 1 = strongly disagree) (circle your response)

1. The activity improved my understanding of the current clinical information regarding OAB. 5 4 3 2 1
2. The activity discusses assessing, screening, and differentiating the types of incontinence for correct diagnosis and reviews various OAB treatment options. 5 4 3 2 1
3. As a result of this activity, I am more confident in identifying the symptomatic OAB candidate with a clearer understanding of the management and treatment provided in the algorithm. 5 4 3 2 1
4. The activity met its stated objectives. 5 4 3 2 1
5. Disclosure of faculty relationships with commercial organizations was made available to me before this activity. 5 4 3 2 1
6. The activity was balanced and free of commercial bias. ❑ Yes ❑ No
   If no, please explain. _____
7. Any off-label drug use and/or investigational drug use not yet approved by the FDA was disclosed in the activity. ❑ Yes ❑ No
   If no, please explain. _____
8. The content and amount of information was appropriate for my clinical responsibilities. 5 4 3 2 1
9. Based on this activity, what two new patient care strategies do you plan to use that you have not used before? _____
   _____
10. Identify areas that would be of most interest to you.
    a) Keeping current with clinical materials in my specialty
    b) Recent advances in diagnosis
    c) Recent advances in treatment
    d) Skills workshops
    e) Other: _____

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