

Preventing heart disease in women

► Cynthia A. Stuenkel, MD

To be complete, comprehensive care of midlife women must include an ongoing conversation about cardiovascular disease (CVD), the number one killer of women. One in 3 female adults has some form of CVD, and close to one half million women die annually from CVD (12-fold more deaths than from breast cancer).¹ Despite common perceptions, for the past 25 years, the number of CVD deaths for females has exceeded those of males! Perhaps most sobering is the frightening statistic that 2 out of 3 of women who die suddenly from coronary heart disease (CHD) never reported previous symptoms.

Presentation

Symptoms of CHD in women do not necessarily mimic the classic male

presentation of crushing substernal chest pain and diaphoresis. In one study, 515 women, mean age of 66 years, were interviewed 4 to 6 months after experiencing an acute myocardial infarction (MI). In this group, 43% reported no chest pain. Symptoms in approximately half of the women were more likely to include shortness of breath, weakness, and fatigue.² In other studies, common symptoms include back, neck, shoulder, and arm pain, or abdominal discomfort and nausea confused with indigestion. In the first study cited, 95% of the women reported prodromal symptoms at least 1 month prior to their MI. In 70% of those women, fatigue was the most common prodromal symptom; half reported a sleep disturbance or shortness of breath.² Given the nonspecific nature of these symptoms, in the past, women delayed seeking medical attention and providers dismissed women's complaints as anxiety or indigestion,

often with catastrophic outcomes. Increased awareness on both sides will hopefully lower the threshold for timely assessment and treatment.

Risk factors

How common are risk factors for heart attack and stroke in midlife women? In an interesting twist, the American Heart Association (AHA) now includes a section on their website presenting CVD statistics specific to Baby Boomers, those persons born from 1946 to 1964, that specifically includes data stratified by gender.³ The AHA applies US government data which delineate risks for the 45 to 54 and 55 to 64 year old age groups, roughly corresponding to the years surrounding the menopausal transition and the decade following, respectively. The results are alarming. Among women aged 45 to 54 years, more than 1/3 have hypertension and approximately 1/5 smoke. Total cholesterol exceeds 200 mg/dL in 60% of women and is more than 240 mg/dL in 20% of women. Fully 2/3 of women are overweight or obese (BMI ≥ 25 kg/m²) and 40% meet criteria for obesity (BMI ≥ 30 kg/m²). Diabetes, which confers the greatest risk for women, is present in 7.5% of women aged

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American Society for Reproductive Medicine
1209 Montgomery Hwy., Birmingham, AL 35216
(205) 978-5000 • asrm@asrm.org • www.asrm.org

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Managing Health Pro-Actively and Re-Actively

We have all heard and seen so much about the risk of heart disease in men that we tend to lose sight of its prevalence in women. Heart disease remains the #1 killer of women older than 45. Yet women are often taken unaware when the condition first strikes. The notion that they are inherently “immune” to this disorder delays diagnosis and fails to prompt a response among women with early warning signs. A lack of understanding of how the early presentation and risks for heart disease differ between men and woman also leads to a failure, on the part of many women, to appreciate the need for medical evaluation. Once diagnosed, women are again challenged by divergent and often worse treatment outcomes compared with men. What’s a woman to do? In this issue of Menopausal Medicine, Dr Cynthia Stuenkel provides a comprehensive assessment of risk factors and recommendations for early detection of heart disease—a model of preventive strategies to which every woman can and should attend. When it comes to heart disease, women cannot afford to watch and wait for symptoms to “declare themselves.” The benefits of prevention in terms of cholesterol reduction, blood pressure control, and treatment of underlying risk factors such as glucose intolerance and metabolic syndrome are just too great.

As opposed to heart disease, which is an immediate threat to life and limb, urinary problems are insidious, though similarly progressive. They should not merely be considered a nuisance. Urinary incontinence, urgency, and overactive bladder (OAB) all contribute to diminished quality of life, particularly in geriatric populations. In many instances, incontinence leads to institutionalization of otherwise sentient elderly women, as it reduces their ability to perform effective self-care. Drs Marsha Guess and Kathleen Connell provide an excellent review of the topic of OAB, with a particular emphasis on the elderly woman. The need to take a holistic approach in this clinical setting is apparent from the get-go, as Drs Guess and Connell describe the comorbidities and associations with OAB that the clinician must keep in mind, in order to appropriately treat his or her patients. OAB is a “re-active” condition in this context, because it is often the end result of a number of chronic processes. By addressing some of the underlying causes, physicians can temporize and provide relief, along with long-term support.

In our current health care reform climate, we cannot afford to overlook any opportunity to be pro-active. However, when such strategies are not available, we must be able to diagnose correctly and provide supportive care for our aging patients.

Nanette F. Santoro, MD

45 to 54 years; prediabetes occurs in 27.6%. For every risk category, the rates in women aged 55 to 64 years exceed those of the younger decade. What can be done to curb this tide?

Establishing a priority

Efforts to identify and reduce CVD risk are necessary on both sides of the consultation table. In a national study of physician awareness and adherence to CVD prevention guidelines, *perception of risk* by the provider was the primary factor associated with CVD preventive recommendations.⁴ Gender disparities in recommendations for preventive therapy were explained largely by the lower perceived risk despite similar calculated risk for women versus men. In a national study of women's awareness, preventive action, and barriers to cardiovascular (CV) health, fewer than half of women were aware of healthy levels of risk factors. When they became aware that their personal level was not healthy, women took action to improve risk.⁵ It seems clear from these surveys, that if you talk, your patients will listen.

What is a good age to initiate such conversations? According to the National Cholesterol Education Program (NCEP) Guidelines, an initial cholesterol determination should be obtained at age 20.⁶ That seems like a good time to start the dialogue about CV health and prevention. Certainly by midlife, women should be more concerned about risks of CV events. By the time your patient is in her 50s, however, the game may have already changed beyond prevention of risks to risk management.

Risk assessment

If women already have experienced a CV event (MI or stroke), if they have evidence of other vascular disease (peripheral vascular disease or abdominal aortic aneurysm), if they have a history of diabetes or chronic kidney disease,

or if their 10-year Framingham global risk is >20%, they are considered to be at "high risk."⁷ Aggressive comprehensive risk factor management improves survival, reduces recurrent events and the need for interventional procedures, and improves quality of life for these patients.⁸

For other women, the presence of even one traditional risk factor places them "at risk."⁷ Risk factors include cigarette smoking, poor diet, physical inactivity, obesity (especially central obesity), family history of premature CVD (defined as <55 years of age in male relative and <65 years of age in female relative), hypertension, dyslipidemia, evidence of subclinical vascular disease, metabolic syndrome, or poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise. Women at optimal risk have a healthy lifestyle and no risk factors.

The term "metabolic syndrome" refers to a cluster of risk factors for CVD and type 2 diabetes.¹ Metabolic syndrome is diagnosed in women when ≥ 3 of the following 5 risk factors are present: fasting plasma glucose ≥ 100 mg/dL, HDL cholesterol <50 mg/dL, triglycerides ≥ 150 mg/dL, waist circumference ≥ 88 cm, blood pressure ≥ 130 mm Hg systolic or 85 mm Hg diastolic.

Women with symptoms suggestive of angina (typical or atypical chest pain at ≥ 50 years of age and those <50 years of age with typical angina), or diabetes, or multiple risk factors are at increased CHD risk and should be considered for treadmill exercise testing.⁹ Stress echocardiography provides higher specificity and accuracy than the standard treadmill test in symptomatic women with intermediate to high probability of CHD.

Support is growing for the use of CVD risk screening (including imaging of subclinical atherosclerotic disease) in asymptomatic women with an intermediate Framingham Risk Score, although formal recommendations are

still pending. Current evidence does not support the use of screening in asymptomatic, low-risk women.⁹

Noninvasive imaging studies such as carotid intima-media thickness (IMT) and coronary artery calcium (CAC) determinations evaluate subclinical vascular disease. If a woman has a strong family history for premature CHD in the absence of usual risk factors, a noninvasive imaging study can help establish her risk. When you (or your patient) are undecided about instituting a preventive therapy, a positive imaging study adds impetus to treat. Revised guidelines with updated recommendations as to how to incorporate these important imaging techniques into clinical practice are anticipated soon. Considerations such as cost and availability of technical resources will factor into this equation.

Mood and psychological makeup both contribute to CV health and disease although their effects are less well quantified and not included in current risk paradigms. Depression increases CVD risk and portends poor outcome in women after a cardiac event.¹⁰ Perceived stress, style of managing anger, and lack of control contribute to individual risk.¹¹

Your patient's reproductive history reveals other clues. Menstrual irregularity might suggest bouts of hypoestrogenic amenorrhea¹² or polycystic ovary syndrome¹³—both associated with an increased risk of CHD. A history of eventful pregnancies (gestational diabetes, preeclampsia, or an abruptio placentae) portend later CVD risk.¹⁴ While premature menopause or oophorectomy can double CV risk, conditions that predispose to a hysterectomy (fibroids, endometrial hyperplasia/cancer) might also reflect underlying CVD risks (lower income and education levels, more obesity and diabetes, and more adverse CVD risk factors).¹⁵

In a combined analysis of both arms of the Women's Health Initiative

(WHI) trial, women aged 50 to 59 or within 10 years of the menopause had no increase in CHD events with hormone therapy.¹⁶ In the estrogen-alone arm, however, composite outcomes, including MI, CHD death, and coronary revascularization, were reduced by 34% in women aged 50 to 59.¹⁷ Stroke risk, while very low in younger women, did not significantly differ by age or years since menopause. Observational studies suggest that lower doses¹⁸ and transdermal preparations¹⁹ might reduce CVD risks, but trials with clinical endpoints are lacking.

In the WHI women more distant from menopause, higher hormone therapy (HT)-associated CHD risks appeared to be concentrated in the subset of women with persistent moderate or severe vasomotor symptoms.¹⁶ The authors suggested that women in their 70s with persistent hot flashes should be carefully scrutinized for CHD risk. In a subset of women aged 45 to 58 years participating in the Study of Women's Health Across the Nation (SWAN), hot flashes were associated with significantly lower flow-mediated dilation and increased aortic calcification.²⁰ While these 2 studies suggest that the presence of hot flashes might be associated with CHD risk, a prospective population-based analysis of the Rancho Bernardo Study reported that women with hot flashes and night sweats (at the time of menopause) had a lower all-cause mortality during an average of 11.5 years of follow-up.²¹ The intriguing relationship between vasomotor symptoms and CVD merits further study.

Subgroup analyses from the Heart and Estrogen-progestin Replacement Study (HERS)²² and the WHI²³⁻²⁵ suggest that women with high LDL or low HDL have more adverse response to hormone therapy, possibly as a consequence of more subclinical coronary artery disease. It seems prudent, then, to measure the LDL/HDL ratio prior to initiating HT. Depending on the

anticipated risks and benefits for an individual woman, proceed with caution if her LDL/HDL ratio exceeds 2.5²⁴ or her LDL is more than 155 mg/dL.^{22,23,25}

In an effort to select symptomatic women with minimal CVD risk for HT, Martin and Manson propose a decision-making paradigm.²⁶ They consider HT only in women with no history of CHD, stroke, or transient ischemic attack and a Framingham Stroke Score of <10%. They then stratify women by years since menopause and the Framingham 10-year CHD Risk Score. They advise withholding HT for women at high risk (>20%), moderate risk (10%-20%) if they are also more than 6 years past menopause, and for women >10 years past menopause (all groups likely to be associated with more advanced atherosclerosis). They suggest transdermal therapy for groups with moderate (10%-20%) risk if within 5 years of menopause and for women at low (5%-10%) risk if between 6 and 10 years past menopause.

In the Raloxifene Use for the Heart (RUTH) Study, women with a history of CHD or at high risk for CHD experienced neither an increase nor a decrease in CHD events overall.²⁷ In a post hoc subgroup analysis using age groups defined in the WHI, the incidence of coronary events in women younger than 60 years was 41% less in women assigned to raloxifene.²⁸ An increase in cases of fatal stroke was reported,²⁷ however, current smokers²⁹ and women with Framingham Stroke Risk Score ≥ 13 ³⁰ appeared to be most vulnerable.

The physical examination reveals other clues to CVD risk. The blood pressure (optimal <120/80 mm Hg), resting pulse, and BMI (target <25 kg/m²) truly are vital signs. Waist circumference (targeted to be ≤ 35 inches) has been proposed as the single most important marker for cardiometabolic and global Framingham risk.³¹ Clinicians can auscultate for evidence of bruits and examine peripheral pulses for evidence of vascular disease.

From a laboratory assessment, glucose, lipid profile (LDL and HDL), and renal function should be measured. The American Diabetes Association (ADA) suggests repeating glucose screening every 3 years.³² If normal, NCEP guidelines suggest repeating lipids at least every 5 years.³³ If a nonfasting sample is all that is available, the total and HDL cholesterol can be measured and non-HDL-cholesterol can be calculated. If the triglyceride level is >200 mg/dL or HDL is <40 mg/dL, a fasting profile is required to measure the LDL-cholesterol. Fasting triglyceride levels are useful in identifying women with the metabolic syndrome. In the absence of chronic inflammatory conditions, given the findings of the widely reported JUPITER trial, consider measuring highly sensitive C-reactive protein (hs-CRP).³⁴ (The Reynolds Risk calculator incorporates CRP values.³⁵) Lipid fractionation and assessment of particle size might be indicated if family history is positive for premature CHD, but identifiable risk factors are absent.

Risk management

Healthy lifestyle choices remain the cornerstone of CVD prevention. In the Nurses' Health Study, women who exercised 30 minutes per day, consumed a healthy diet, did not smoke, consumed alcohol modestly, and maintained a BMI <25, had an 83% reduction in CHD events³⁶ and a 79% reduction in stroke.³⁷ In the 3-year Diabetes Prevention Program, high-risk participants (68% women) who lost 5% of body weight and exercised 150 minutes per week, reduced their risk of developing diabetes by 58%.³⁸

Cardiovascular risk rises proportionately as blood pressure increases, starting at levels previously considered normal. Pharmacotherapy is indicated for blood pressure >140/90 mm Hg, unless women have diabetes or chronic kidney disease, when treatment of blood pressure >130/80 is appropriate.⁷

The US Preventive Services Task Force (USPSTF) now recommends that any adult with sustained blood pressure (treated or untreated) >135/80 mm Hg be screened for diabetes.³⁹

According to the ADA, criteria for the diagnosis of diabetes include a fasting plasma glucose ≥ 126 mg/dL (no caloric intake for at least 8 hours).³² In women with symptoms of hyperglycemia, a casual (anytime without regard to time since last meal) plasma glucose of ≥ 200 mg/dL is diagnostic. A 2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test, using a 75-g glucose load, is the third criteria. Women with established diabetes should be treated to achieve an HbA1c <7%, if this can be accomplished without

substantial hypoglycemia.⁷

Lipid-lowering therapy should be instituted according to NCEP guidelines.⁶ Per these guidelines, clinicians should treat LDL >130 mg/dL in patients with multiple risk factors and 10-year risk 10% to 20%; and treat LDL >160 mg/dL in patients with multiple risk factors even if 10-year absolute risk is <10%; treat LDL >190 mg/dL regardless of presence or absence of other risks. Lipid level goals include LDL <100 mg/dL, HDL >50 mg/dL, and triglycerides <150 mg/dL. The JUPITER trial provided evidence that hs-CRP >2.0 mg/dL should also be considered as a target for statin therapy, even in the presence of desirable LDL levels.³⁴

The USPSTF recommends the use

of aspirin for women aged 55 to 79 years when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage.⁴⁰ Benefits for stroke prevention exceed gastrointestinal harm for women aged 55 to 59 years who have a 10-year stroke risk of 3%. The USPSTF recommends against the use of aspirin for stroke prevention in women younger than 55 years. The optimum dose of aspirin is not known, but a dosage of approximately 75 mg/d seems as effective as higher doses.⁴⁰ ■

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Diagnosing and treating overactive bladder: Special considerations for an aging population

► Marsha K. Guess, MD, MS, and Kathleen A. Connell, MD

Overactive bladder (OAB) is a chronic, debilitating disorder that greatly impairs a woman's quality of life. The prevalence of OAB is estimated to range from 10% to 17% in the United States, and age, body mass index, childbearing, previous hysterectomy, and thyroid problems have all been implicated as risk factors for developing OAB.¹⁻³ The National Overactive Bladder Evaluation (NOBLE) Program, a US, population-based study that included over 2700 women, found a significant association between the prevalence of OAB with and without urge incontinence with increasing age, with the most dramatic changes seen in perimenopausal and menopausal women. The prevalence of OAB with urge incontinence in women ages 45 to 55 years was more than 3 times that of women younger than 35 years, and continued to increase with advancing age.² Moreover, women with OAB with urge incontinence have significantly poorer health-related quality of life, mental health, and sleep quality when compared with age-matched controls.² This article will review our current understanding of OAB, giving special consideration to factors that are particularly relevant to aging women.

Marsha K. Guess, MD, MS
Kathleen A. Connell, MD
Yale University School of Medicine
Section of Urogynecology & Reconstructive
Pelvic Surgery
Department of Obstetrics, Gynecology, &
Reproductive Sciences
New Haven, Connecticut

Assessment

Signs and symptoms

The term *overactive bladder* was defined by The International Continence Society (ICS) as urinary urgency, with or without urge incontinence, the involuntary loss of urine that is immediately preceded by or accompanied by a sudden urge to urinate.⁴ It is frequently associated with a constellation of symptoms, including daytime frequency and nocturia, an implacable urge to void that wakes an individual from sleep. While previous literature assigned a specific number of voids to the definitions of daytime frequency and nocturia, the most updated report from The ICS Standardization Subcommittee has removed these arbitrary values and defines daytime frequency simply as the patient complaining that he or she urinates too often and nocturia as the need to wake up at least 1 time during the night to void.⁴

Vital information from the patient's medical history

A detailed history is essential when evaluating a patient with OAB. Specific questions about the number of voids and incontinence episodes per day, whether or not the patient uses pads or liners, and factors that exacerbate or alleviate the severity should be included in the history of present illness. It is also imperative to inquire about the amount of fluid intake, including the quantity of caffeine and alcohol. The medical history should include comorbidities that may contribute to the patient's symptoms, including diabetes mellitus, neurological disorders,

and prior pelvic radiation, as well as disorders in which there is a relative or absolute contraindication to initiating anticholinergic therapy, such as renal failure, cardiac failure, narrow-angle glaucoma, and myasthenia gravis. Patients with nocturia should be assessed for peripheral vascular disease, obstructive sleep apnea, and diabetes. Medications that are known to increase urinary frequency, such as diuretics, should also be documented. It is also important to note prior pelvic and reconstructive surgeries and whether or not the patient's symptoms predated the procedures. Previous incontinence procedures may cause denervation to the bladder and/or urinary retention and may alter the course of therapy for affected individuals. Radical hysterectomy is also associated with OAB symptoms, which are thought to result from a disruption in the autonomic nerve fibers as they course through the pelvic plexus.⁵ Lastly, the patient should be queried about the ingestion of known bladder irritants, including acidic or spicy foods and chocolate. Although information about the patient's obstetrical history may be collected while obtaining the patient's history, several population-based studies have failed to find an association between parity and OAB with or without urge incontinence.^{6,7}

Pertinent positives on the physical examination

The physical examination should include a comprehensive evaluation of all organs while focusing on several key

factors. The height and weight of all patients should be measured and the body mass index calculated, because increasing body mass index is a known, modifiable risk factor for developing urge incontinence.¹⁻³ The patient's abdomen should be thoroughly explored for suprapubic or lower abdominal scars that may help to determine the type of pelvic or reconstructive surgeries the patient may have undergone.

A basic neurological assessment including gait and cognition, as well as lower extremity motor, strength, sensation, and deep tendon reflexes, should be performed. When abnormalities are present, patients should be referred to a neurologist to assess for central or peripheral nervous system pathologies, which can adversely affect bladder function. The strength and tone of the pelvic floor muscles should be determined by asking the patient to clench her muscles around a vaginally or rectally placed index finger. This maneuver allows physicians to quantify the degree of laxity of the pelvic floor, and when abnormal it can supplement the neurological exam in determining the presence of nerve damage.

When examining the pelvis, observing the external genitalia for atrophy and irritation or skin breakdown can give the practitioner information about the estrogen status of the patient and the severity of incontinence. The urethra should be inspected to confirm normal anatomy and assessed for hypermobility, which is especially important when the patient has coexisting symptoms of stress incontinence. Patients should be asked to cough or perform the Valsalva maneuver (forcibly exhaling against a closed airway), to help determine if pelvic organ prolapse, particularly anterior wall descent (cystocele), is present. Notes should also document the presence or absence of a uterus or cervix. When OAB symptoms are accompanied by bladder pain, it is prudent to palpate

the anterior vaginal wall overlying the bladder to determine if the pain is reproducible, as this could suggest other etiologies for the OAB symptoms, such as a urinary tract infection or interstitial cystitis (TABLE 1).

The essential laboratory tests

The post-void residual volume should be determined in all patients who present with a complaint of an OAB. This helps distinguish patients in whom urinary retention contributes to their OAB symptoms, as well as individuals who are not candidates for anticholinergic therapy. Urinalysis is performed routinely to evaluate for the presence of leukocytes and nitrites, hematuria, or glucosuria. Leukocytes, nitrites, and hematuria are typical findings in urinary tract infections. Isolated hematuria, while often an inconsequential finding, may indicate the presence of nephrolithiasis, interstitial cystitis, or a renal mass, and glucosuria may be found in patients with poorly controlled diabetes mellitus. The presence of proteinuria should prompt coordination with the patient's primary care physician to rule out nephropathies. Urine specific gravity may also be useful to distinguish patients with diabetes insipidus who have increased urine production and polyuria rather than OAB.

A urine culture is essential in evaluating women with OAB, because urinary tract infections typically present with urinary urgency and frequency with or without dysuria or incontinence. Sending the urine for cytologic evaluation is reserved for smokers and women with hematuria or previous gynecological malignancies; primary bladder cancer is relatively uncommon but highest among these populations of women.^{8,9} Patients with newly discovered glucosuria should undergo further testing with a random blood glucose, a fasting blood glucose, or an oral glucose tolerance test and referred to their internist or an endocrinologist. Newly diagnosed

TABLE 1 Differential diagnosis of overactive bladder

Behavioral	Interstitial cystitis
Infections	Urethral diverticulum
Medications	Urethral syndrome
Uncontrolled DM	Bladder foreign body
Neurogenic bladder	Bladder tumor

patients, as well as those with a positive history of diabetes, should have HbA1c performed routinely to ensure good glucose control in an effort to avoid diabetes-related urinary frequency and polyuria, which may exacerbate OAB symptoms.

Ancillary laboratory and physiological tests

A simple, noninvasive tool used in the assessment of a patient with OAB is the voiding diary. Patients are instructed to measure and document their total oral liquid intake and urinary output for a 24-hour period. Review of these diaries give a general picture of drinking and voiding patterns and an estimate of the bladder capacity on a typical day. They can also be used to objectively determine the efficacy of a treatment modality if the diary is readministered after a given time period and compared to the patient's baseline status.

Urodynamic testing is recommended in patients with complex symptoms or extensive medical histories. Indications for these tests include an uncertain etiology of the incontinence, previous medical or surgical treatment failures for incontinence, prior radical pelvic surgery, and neurological disorders.¹⁰ When surgery is planned for incontinence or to correct pelvic organ prolapse, urodynamic testing should be performed on all patients, regardless of their medical or surgical history.

Cystoscopy is helpful in understanding the etiology of OAB in some patients. Indications for this office procedure

include frequent urinary tract infections, hematuria, atypical cells found on urine cytology, bladder pain, or suspected interstitial cystitis, and for closer evaluation of suspected or known bladder masses.

Radiographic imaging is rarely indicated in women with OAB. In women whose OAB is associated with recurrent urinary tract infections or hematuria, a renal ultrasound or computed tomography–intravenous pyelogram can help to identify stones that may be exacerbating the irritative bladder symptoms. Magnetic resonance imaging is useful in diagnosing urethral diverticuli and is typically reserved for women with OAB who also report post-void dribbling and/or those found to have a suburethral mass. When present, diverticuli can be well characterized using this modality. Women with OAB and significant neurological deficits should undergo brain and/or spinal cord imaging under the direction of a neurologist, to evaluate for disorders of the upper or lower neuron tract, such as multiple sclerosis, spinal stenosis, herniated discs, idiopathic intracranial hypertension (pseudo tumor cerebri), or intracranial plaques indicative of transient ischemic attacks or stroke.

Treatments for overactive bladder **Behavioral and lifestyle modification**

Behavioral modifications, focusing on modifiable risk factors, should be the first-line therapy for all women presenting with OAB. Patients should be encouraged to reduce their fluid intake by at least 25% while still ensuring a minimum intake of 1 liter/day.¹¹ Limiting caffeine and alcohol ingestion may be beneficial for some; however, there is conflicting evidence on the benefits of restricting these beverages to reduce OAB symptoms.¹²⁻¹⁵ In overweight and obese women, weight loss has proven effective in reducing the frequency of urge incontinence episodes.¹⁶ Patients

should be encouraged to consult with an internist and a dietitian prior to initiating dietary restrictions or an intense exercise program, particularly when rapid or drastic weight loss is anticipated. In elderly patients with limited mobility, placing a commode near the bedside may help avoid bedwetting and, potentially, dangerous falls.

Patients with OAB typically void frequently in response to a strong urge. To avoid accidents, many patients urinate before they develop a strong urge, thereby training themselves to void when the bladder has not reached its maximum capacity. Bladder drills are a mechanism whereby the patient consciously waits longer periods of time before urinating in an effort to “retrain” the bladder to accommodate larger volumes. They can be carried out as timed voids or timed delays. Timed voids require that the patient have regular access to a time piece or chronometer. Patients are instructed to void at designated intervals (eg, every hour), usually starting with a time interval in which, for them, leakage is uncommon. Timed delays assume that strong urges can present at anytime, prompting the patient to want to void. Once the patient feels the strong urge, she is instructed and encouraged to delay urination for a designated time frame, usually between 10 and 30 minutes. For both drills, patients should increase the time interval between voids by 10 to 30 minutes weekly, with changes dictated by the severity of the symptoms at baseline and the degree of improvement that is seen when changes are implemented. Lastly, in patients with dementia or Alzheimer’s disease, prompted voiding at regular intervals can help decrease the number of incontinent episodes.

Pelvic floor muscle rehabilitation

Pelvic floor muscle rehabilitation (PFMR) is another important, conservative treatment option for women with OAB. Kegel exercises are a free and simple technique designed to increase

the strength of the levator ani muscles, thereby enhancing the support of the pelvic floor, including the urethra. When performed consistently, Kegel exercises have proven success in increasing subjective cure and improvement rates for women with urge incontinence and reducing the number of daily incontinence episodes.¹⁷

When patients have difficulty isolating the pelvic floor muscles or problems generating sustained contractions, Kegel exercises should be supplemented with office-based therapy. These visits are typically covered by insurance companies, including Medicare and allow one-on-one interactions with care providers who can teach patients how to selectively contract and relax their pelvic floor muscles. Biofeedback that includes a vaginal probe with sensors and computer-generated visual cues, can inform patients when they have correctly isolated and contracted the pelvic floor muscles and is very helpful in these patients. When pelvic muscle floor rehabilitation with or without biofeedback is combined with behavioral therapy, patients can anticipate a 50% to 80% reduction in urinary frequency and incontinence.^{18,19}

Pharmacotherapy

Estrogen therapy. Estrogen receptors (ER) have been found in the epithelial tissues of the bladder, trigone, urethra, and levator ani muscles as well as the sensory neurons that innervate the bladder and trigone.^{20,21} This has prompted several investigators to evaluate the role of oral and topical estrogens on OAB symptoms and urinary incontinence. In 2 large multicenter, randomized controlled trials, the Women’s Health Initiative (WHI) and the Heart and Estrogen-Progestin Replacement Study (HERS) trials, the use of estrogen alone or in combination with progestin was associated with an increased likelihood of having or developing urinary incontinence compared with non-

users.^{22,23} Given the significant positive association between oral hormone use and incontinence in these large and diverse study populations, oral estrogen with or without progestin should not be prescribed for the treatment of OAB. Evidence on the use of vaginal estrogen for OAB is conflicting. Still, several small, randomized trials have reported a reduction in incontinence episodes, without coexisting changes in urinary urgency, frequency or nocturia.²⁴ Estrogen is also useful as an adjuvant therapy to treat vaginal atrophy and prevent unnecessary discomfort during PFMR.

Anticholinergic medications. Anticholinergic medications are the primary medical treatment for OAB in women of all ages (TABLE 2). They exert their biological effects by competitively binding to the muscarinic receptors on the detrusor muscle (M2 and M3 subtypes), thereby preventing acetylcholine's positive effects on contractility. They have been shown to reduce micturition frequency, urge incontinence episodes, and nocturia.²⁵

When initiating anticholinergic therapy for a patient, consideration should be given to the patient's prior experience with medications, including drugs they have tried and the efficacy of the therapy. It is important to make sure that the medication was consistently taken for at least 12 weeks because studies have shown that some medications take up to 3 months to show full effect.²⁶ Patients are encouraged to keep voiding diaries to objectively determine even mild improvements in their urinary habits. Patients with moderate to severe OAB may be refractory to treatment and may require longer courses of therapy and/or increased dosages to achieve optimal results. Additionally, the risks and the cost of the medication should be discussed candidly with the patient prior to initiating therapy. Compliance is important when medical therapy is selected and prescribed regimens may not be followed when the prices are prohibitive or intolerable side effects persist.

TABLE 2 Routinely prescribed anticholinergic medications

DRUG NAME	BRAND NAME	ROUTE	DOSE ^a	APPROXIMATE PRICE (\$) ^b
Tolterodine	Detrol LA	Oral	4 mg QD	148.00-156.00
Oxybutynin Chloride	Ditropan XL	Oral	5-15 mg QD	100.00-143.00
	Gelnique	Topical gel	1 sachet (100 mg)/day	150.00
Oxybutynin	Oxytrol	Topical patch	3.9 mg 2x/wk	179.00-192.00
Tropium chloride	Santura XR	Oral	60 mg QD	146.00-170.00
Solifenacin	VESIcare	Oral	5-10 mg QD	176.00-188.00
Darifenacin	Enablex	Oral	7.5-15 mg QD	164.00-173.00
Fesoterodine fumarate	Toviaz	Oral	4.8 mg QD	148.00

^aThe doses listed reflect those used for prescribing the extended release formulations

^bPrices reflect the average cost in US dollars for a 1-month supply for a non-insured patient based on quotes from 2 pharmacies in 2 different states.

erable side effects persist. Fortunately, most of these medications are partially or totally covered by insurance plans.

Anticholinergic medications are relatively safe, with side effects that result from muscarinic receptor blockade in other organs in the body. The most common side effects are dry mouth, pruritus, and constipation; however, blurred vision, tachycardia, constipation, and urinary retention have also been reported.²⁵ These drugs can also impair the central nervous system, causing mild (drowsiness, fatigue), moderate (restlessness, confusion), or severe effects (delirium, seizures, or cognitive impairment).²⁷ In individuals who have a higher risk for cognitive dysfunction or delirium, such as elderly patients or those with mild to moderate dementia, the use of the larger quaternary amine, trospium chloride, or the selective M3 receptor agonist darifenacin should be considered for first-line therapy, because studies suggest that these medications may be less likely to impair mental function.^{27,28}

If severe side effects are encountered by the patient, switching to a different anticholinergic medication is advised.

Absolute contraindications to using anticholinergic medications include narrow-angle glaucoma, intestinal obstruction, cardiac arrhythmia, and myasthenia gravis. Ultimately, establishing realistic and individualized treatment options is essential for all patients. When optimized, patients can expect a 43% to 70% reduction in their OAB and urge incontinence symptoms.²⁶

Desmopressin. Desmopressin is a less commonly used but effective treatment option for patients with nocturia. As a synthetic analogue of arginine vasopressin, it enhances reabsorption of water in the kidneys, thus reducing urine output and nightly voids with a measurable improvement in sleep quality.²⁹ Hyponatremia is the most serious side effect and can manifest as drowsiness, headache, confusion, anuria, or water intoxication. To avoid these symptoms, patients' serum sodium levels should be monitored closely when first starting this medication.

Neuromodulation

Electrical stimulation. PFMR augmented with electrical stimulation offers a

relatively simple form of neuromodulation to treat OAB. A probe that emits electrical impulses is introduced into the vagina and stimulates the sacral plexus via the pudendal nerve, resulting in contractions of the levator ani muscles, bladder, and urethral muscles. The typical setting for OAB patients is 12.5 Hz with pulses of 5 seconds on and 5 seconds off. Patients participate in 8 to 10 weekly sessions in an office setting, with the duration of therapy dictated by the patient's subjective response. Patients who are effectively treated with this therapy are encouraged to perform home Kegel exercises during and after therapy, while those who require more intensive training may advance to using a handheld stimulator unit at home, which they administer themselves at more frequent intervals. Electrical stimulation serves as a supplement to office-based PFMR, requiring minimal additional time or out-of-pocket expense, as it is typically covered by insurance companies. Limited data suggest that PFMR with electrical stimulation may provide its greatest benefit as an adjuvant treatment in combination with anticholinergic medications.³⁰

Percutaneous tibial nerve stimulation. A slightly more invasive form of neuromodulation includes percutaneous tibial nerve stimulation (PTNS), commonly referred to as acupuncture. In this procedure, a fine needle electrode is inserted into the lower, inner aspect of the leg, slightly cephalad to the medial malleolus. This site allows stimulation of the sacral plexus via the tibial nerve. Among other functions, the sacral nerve plexus regulates bladder and pelvic floor function. On average, patients treated with PTNS reported a 25% reduction in daytime frequency, a 21% reduction in nighttime frequency, and a 35% reduction in urge incontinence symptoms.³¹ Intermittent follow-up sessions should be encouraged, as a decrease in the symptom-free interval has been reported in patients after a prolonged

discontinuation of therapy.³¹

As a relatively newer treatment option for OAB and urge incontinence, PTNS is inconsistently covered by insurance companies for this indication. Thus, as with all other therapies, risks, benefits, and potential out-of-pocket expenses should be discussed with patients prior to initiating therapy.

Sacral neuromodulation. An invasive form of sacral neuromodulation, known as InterStim[®], offers hope to women whose symptoms are refractory to behavioral and medical therapy. InterStim is a permanent device that provides mild electrical pulses to the sacral nerves through leads implanted near the sacrum. Studies suggest that 67% to 80% of individuals have achieved complete continence or more than 50% improvement with continued efficacy reported up to 5 years after placement of the device.³²

InterStim therapy should be reserved for patients who fail to respond to less invasive therapies. In this setting, InterStim is typically covered by insurance policies. Still, despite of the costs and seemingly low efficacy, patients with moderate to severe symptoms with a decreased quality of life should be offered this therapy since the remaining alternatives are severely limited and more invasive than InterStim. These patients must also be counseled about potential side effects, including pain at the implant or lead site and device-related problems such as lead migration, repositioning of the pulse generator, or infection, which have been reported in up to 50% of patients who receive the implant and treatment failure. Reoperation to remove the implant or reposition the leads can also occur in up to one-third of all treated patients.³²

Out with the old...in with the new Surgical treatment options

Due to the great advances in pharmacotherapy and biotechnology, invasive

surgical procedures are rarely used in treating OAB. For some patients, however, augmentation cystoplasty can provide a functional reservoir that allows for urinary continence and prevention of upper tract deterioration.

Neurotoxin therapy

Botulinum-A neurotoxin therapy (Botox) has been recently evaluated as an alternative treatment modality. Botox is a purified toxin made from *Clostridium botulinum*. It is injected into the bladder muscle to cause partial paralysis of the detrusor. Although Botox is a toxic product, its use has been standardized in a variety of disorders in medicine as well as in certain urological conditions. Rarely, patients may experience flu-like symptoms after the injection as well as headaches, light-headedness, fever, abdominal pain, and diarrhea. The efficacy for the use of Botox for OAB has been well established in clinical trials; however, its success in achieving FDA approval has been limited by the high incidence of posttherapy urinary retention, sometimes requiring prolonged intermittent straight catheterization.³³

Summary

OAB is a common, costly, and debilitating disease. The differential diagnoses involve numerous medical conditions, and a careful history and physical examination are essential to ensure maximal efficacy in treating patients with OAB. Numerous conservative and invasive treatment options are available and can be tailored to individual needs of the patient. With therapy optimized, successful treatment is certainly attainable and quality of life can be dramatically improved for many women. ■

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1209 Montgomery Hwy., Birmingham, AL 35216
(205) 978-5000 | asrm@asrm.org | www.asrm.org