BY MICKEY KARRAM, MD, and STEVE KLEEMAN, MD

OBG MANAGEMENT

Office evaluation of overactive bladder: 4 easy steps

Urgency, frequency, and urge incontinence can usually be diagnosed and managed without sophisticated urodynamic testing.

A 66-year-old woman complains of urinary urgency, frequency, and incontinence, and estimates that she voids 15 or more times within a typical 24-hour period. So far, she has lost only small amounts of urine—because she hurries to void at the first sense of urgency—but she is distressed and worried that she will have a major accident.

Sound familiar? Overactive bladder affects 17 to 33 million US women.[1] Thanks to greater awareness and openness, more women today are seeking medical help for their troubling symptoms, although only a fraction have done so up to now.[2] Ob/Gyns who are prepared to quickly evaluate the problem and initiate effective management can help restore the quality of life these patients enjoyed before onset of symptoms. This article:

- reviews the pathophysiology of "overactive bladder";
- describes a 4-step evaluation and management routine that should be feasible for any gynecology office setting;
- discusses the action and the efficacy of available and forthcoming drugs;
- uses newly revised terminology that reflects greater sensitivity to the patient.

▪ *Dr. Karram is director of urogynecology at Good Samaritan Hospital in Cincinnati, Ohio, and professor of obstetrics and gynecology at the University of Cincinnati. Dr. Kleeman is assistant director of the division of urogynecology and reconstructive surgery at Good Samaritan Hospital in Cincinnati.*

Revised terminology

One of the most notable changes in the terms used to describe lower urinary tract dysfunction, proposed by the International Continence Society,[3] is organization of the terminology into 3 categories: symptoms, signs, and urodynamic observations.

Symptoms are now defined to more closely reflect the way the patient perceives her problem, and are set forth without specifying the volume of urine required for a diagnosis of "abnormal" sensation or urgency.

Signs can be observed by the physician, such as leakage of urine when the patient coughs.

Urodynamic observations are made during urodynamic studies.

Overall, the new and revised terms are relatively vague to allow for patient-to-patient variability. Here are a few examples:

- **Overactive bladder** is a syndrome of symptoms that suggest dysfunction of the lower urinary tract. It is characterized by

4-STEP EVALUATION AND MANAGEMENT

1. Ask the right questions, get voiding diary, assess quality of life.
2. Perform 'eyeball' cystometry.
3. Conduct a thorough physical assessment.
4. Begin bladder retraining, pelvic floor muscle rehabilitation, and appropriate medical therapy.

urgency with or without urge incontinence, usually involving frequency and nocturia.

- **Urinary incontinence** is any involuntary leakage of urine.
- **Daytime frequency.** The patient feels she voids more frequently than she should during the day.
- **Nocturia.** The patient wakes 1 or more times at night to void.
- **Urgency**. The patient feels a sudden, compelling desire to pass urine.
- **Urge urinary incontinence** is involuntary leakage accompanied by or immediately preceded by urgency.
- **Bladder sensation** is identified during history taking: normal, increased, reduced, absent, and nonspecific.
- **Detrusor overactivity** replaces the term "detrusor instability" or "hyperreflexia." It is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase, and may be spontaneous or provoked. It may be further qualified as neurogenic (if a neurologic condition underlies the problem) or as idiopathic.

What is abnormal bladder function?

Any actual incontinence should be considered abnormal, whether diurnal or nocturnal.

Frequency: More than 8 voids in 24 hours. Although an ordinary voiding pattern is not fully defined, most experts agree that a frequency of 8 or fewer voids in 24 hours is "normal."

Urgency: Patient's opinion determines. The sensation of urgency is more difficult to objectively define; hence, the need to rely on the patient's perceptions. If a patient is voiding more frequently than normal because she has an uncomfortable, sudden desire to pass urine, she is considered to have urgency. In contrast, a woman who voids frequently because she has stress incontinence and wants to keep her bladder as empty as possible to avoid leakage has frequency without urgency. Urgency is best classified as being sensory or motor in nature.

- **Sensory urgency** is a strong, uncomfortable need to void without fear of impending leakage; for whatever reason, the bladder has become hypersensitive. Delaying voiding may result in pain but rarely leads to incontinence.
- Patients with **motor urgency** urinate frequently because they are afraid of experiencing a complete or partial involuntary void as a result of an involuntary bladder contraction.

How the normal bladder functions

The process of bladder storage and evacuation can be visualized as a complex of neurocircuits in the brain and spinal cord that coordinate the activity of smooth muscle in the bladder and urethra (FIGURE). These circuits act as "on/off" switches in the lower urinary tract, alternating between the 2 modes of operation: storage and elimination.

As the bladder gradually fills with urine, a woman initially perceives a first sensation of filling between 75 and 125 cc of urine, feels the first need to void at approximately 300 cc, and reaches maximum capacity and a strong urge to void at 400 to 700 cc.

Since the bladder is a low-pressure reservoir, intravesical bladder pressure typically rises very little despite increasing amounts of urine and distention of the smooth muscle or detrusor muscle of the bladder. Pressure ranges from 2 to 6 cm of water in an empty state and rarely exceeds 10 cm of water at maximum capacity.

At maximum capacity, a woman should be able to get to the toilet easily, initiate voluntary bladder contraction with complete relaxation of her pelvic floor, and void to completion.

Urge incontinence is more detrimental to quality of life

Of women who complain of urinary incontinence, more than 90% have either loss of detrusor muscle control (urge incontinence) or urethral sphincteric incompetence (stress incontinence).[4] In addition, 30% to 50% of women with stress inconti-

FIGURE

Bladder relaxation and contraction: An interplay of nerve impulses

1 Signals in the parasympathetic system originate at spinal cord levels S2-S4, traveling to the bladder via the pelvic nerve and binding to muscarinic receptors—specifically M2 and M3 subtypes. When M3 subtypes are set in motion, they trigger a chain of events that leads to muscle contraction. M2 receptor activation ultimately inhibits the relaxation caused by the sympathetic system.

2 The striated muscle of the external urethral sphincter is innervated by motor neurons that originate in Onuf's nucleus (located within the sacral spinal cord) and travel via the pudendal nerve.

3 In the sympathetic nervous system, signals exit at spinal cord levels T1 through L2 and travel to the bladder via the hypogastric nerve, where noradrenaline is released. Noradrenaline binds to the beta receptors, causing a chain reaction that ultimately causes relaxation of the bladder.

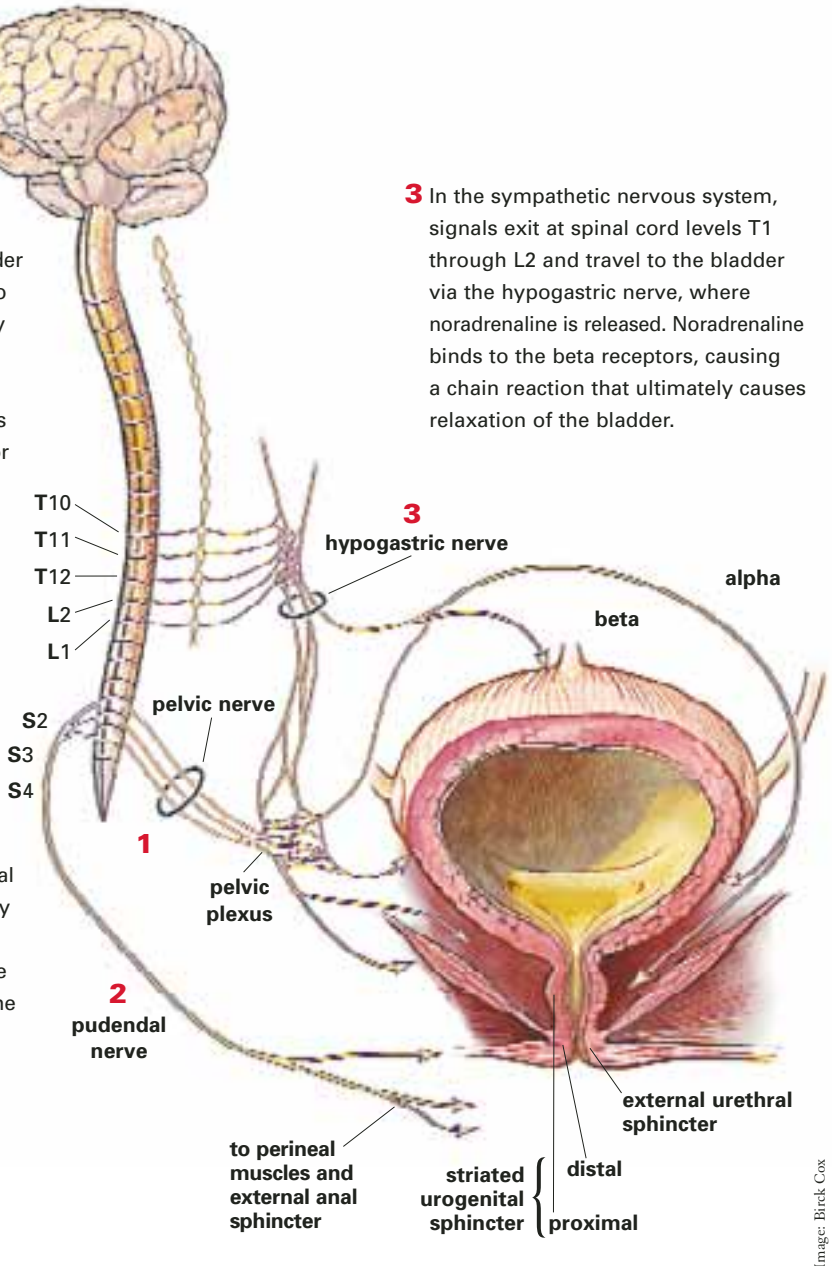

Image: Birck Cox

nence have coexistent urge incontinence.[1]

Urge incontinence has a much more dramatic impact on a woman's quality of life than stress incontinence, because stress incontinence is predictable and controllable. The patient understands she will leak urine only with increases in intraabdominal pressure associated with exercise, coughing, etc. These leakages tend to occur in small spurts that are easily absorbed by protective wear. In contrast, urge incontinence manifests as an unpredictable, involuntary void in which

urine is released in a gushing stream, often in quantities large enough to soak through heavy absorbent pads.

Although one might assume that subjective complaints would readily distinguish the 2 conditions, the bladder is a very poor "witness." What the patient perceives often fails to correlate with the true mechanism of incontinence. Since therapies for these 2 conditions are completely different, the evaluation of incontinence is very important.

In aging women, the prevalence of frequency, urgency, and urge incontinence is much higher than that of stress incontinence. Among women 60 to 80 years of age—growth-wise, the largest segment of our population—as many as 50% experience frequency, urgency, and urge incontinence.

High economic cost. The tremendous expense of urinary incontinence is increasingly recognized. In 1995, for example, the economic cost in the United States was $26.3 billion, or $3,565 per person 65 years or older with the condition.[5,6] Of these resources, 48%, or $12.53 billion, were drawn directly from the economy to diagnose, treat, care for, and rehabilitate patients with incontinence.

Contributing factors and causes of overactive bladder

Overactive bladder is thought to be multifactorial. Symptoms often occur in the absence of any obvious pathology, which makes it difficult to pinpoint a cause. Coexisting conditions may also contribute to symptoms or may even be the sole cause.

Examples include infection or inflammation of the lower urinary tract, such as a simple case of cystitis, or a foreign body in the bladder.

Injury or diseases of the nervous system can disrupt voluntary control of voiding in adults, triggering the reemergence of reflex voiding, which leads to bladder hyperactivity and urge incontinence. At a local level, urge incontinence can develop secondary to intrinsic detrusor myogenic abnormalities.

Outlet obstruction can result in urge incontinence such as the well recognized symptoms of urethral obstruction in men with benign prostatic hyperplasia.

Detrusor sphincter dysnergia, most commonly secondary to spinal cord injury or multiple sclerosis, may affect younger men and women.

A deficient urethral sphincter in women with stress incontinence may induce urge incontinence, as urine leaking into the urethra secondary to the stress incontinence stimulates urethral afferents that induce involuntary voiding reflexes.[7]

Women with stress incontinence may unwittingly contribute to overactive bladder by voiding more and more often, hoping to prevent any involuntary urine loss. As a result of the frequent voiding, they develop frequency and urgency symptoms. That is, over time, this frequent, voluntary voiding leads to decreased bladder compliance. Thus begins a vicious cycle that ultimately leads to more frequency and urgency.

Urogenital atrophy. Irritative symptoms of the lower urinary tract in the form of frequency, urgency, and dysuria can result from lack of estrogen, leading to urogenital atrophy.

Pelvic organ prolapse is another common coexisting condition. Although the correlation between anatomic descent of pelvic organs and lower urinary tract symptoms is poorly understood, frequency and urgency—with or without urge incontinence—coexist with symptomatic pelvic organ prolapse in approximately 30% to 50% of cases.

An enlarged uterus or adnexal mass may cause external compression of the bladder and lead to lower urinary tract symptoms.

Previous surgery of the anterior vaginal wall or bladder neck may sometimes trigger de novo symptoms of frequency, urgency, and urge incontinence. In women who have undergone a previous antiincontinence procedure, these symptoms may be related to some form of outlet obstruction. In some cases these patients have no increase in the

postvoid residual, and only subtle urodynamic testing elicits evidence of obstruction.

Step 1

Ask the right questions, get voiding diary, assess quality of life

Most women can be thoroughly evaluated within the clinical practice setting of any gynecologist. The first and most important aspect of this assessment is understanding and appreciating the severity of a patient's lower urinary tract symptoms. This can be done by asking pointed questions, in the following approximate sequence:

1. Do you have problems with accidental loss of urine?
2. How many months or years have you had leakage?
3. Do you have to wear pads or protective clothing to prevent or help with urinary loss? If so, how many pads do you wear a day?
4. How many trips do you make to the bathroom during the day? At night?
5. Do you ever wet the bed while sleeping?
6. Are you bothered by a strong sense of urgency to void? Can you overcome it?
7. Do you sometimes fail to reach the bathroom in time?
8. Does the sound, sight, or feel of running water cause you to lose urine?
9. Do you lose urine when you cough, sneeze, run, or lift heavy objects?
10. Do you lose urine with posture changes, standing, or walking?
11. Do you feel as though you are constantly wet?
12. Do you feel as though your bladder is completely empty after passing urine?
13. Do you have difficulty starting a stream of urine?

Also ask about pelvic organ prolapse, defecatory dysfunction, and sexual dysfunction.

Take a thorough medical history, as well as a surgical history with emphasis on previous bladder or gynecologic procedures.

Also review all prescription medications.

48-hour voiding diary. Give the patient a voiding diary to fill out 48 hours prior to her office visit. The reason: The diary often reveals more information than can be elicited from the patient's history. For example, it may highlight daily activities associated with voiding, such as excessive consumption of liquids, high caffeine intake, high-impact exercise, and so on.

Quality-of-life assessment. An objective means of quantifying the effects of incontinence on the woman's quality of life is recommended. We use the short form of the Incontinence Impact Questionnaire and the Urinary Distress Inventory.

Step 2

Perform 'eyeball' cystometry, a simple and revealing office test

Ask the patient to go to the restroom and comfortably empty her bladder into a urine-collection device to determine the amount voided. Have a nurse measure the postvoid residual using a soft red rubber catheter. A sample can be taken for urinalysis and, if necessary, sent for culture.

Next, perform a simple filling or "eyeball" cystometry. Connect a Toomey syringe to the end of the red rubber catheter and pour sterile water into it. Ask the patient to tell you when she feels the first sensation of filling, first desire to void, strong urge to void, and maximum capacity, recording the levels at which each occurs. During filling, any evidence of bladder contraction will be revealed by a rise in the column of water. Record any significant discomfort or other observations during the filling portion of the study. When maximum capacity is reached, remove the catheter.

Step 3

Conduct a thorough physical assessment

With the patient in the supine position, separate the labia and ask her to cough forcefully and perform the Valsalva maneuver 3 times, recording any evidence of water or urine loss through the urethral meatus. (If the patient has advanced pelvic organ prolapse, try

Treating overactive bladder: An expanding 'pharmacopeia'

Antimuscarinic medications have been the mainstay of pharmacologic therapy for overactive bladder. In fact, the 2 most commonly prescribed drugs for overactive bladder are antimuscarinics: oxybutynin and tolterodine. Other medications also are available that affect different aspects of the neurophysiology of micturition.

Oxybutynin. The bladder contains 5 subtypes of muscarinic receptors, with a predominance of M2 and M3 subtypes. Oxybutynin has some selectivity for M3 receptors. It has been shown to inhibit bladder contractions, but because of muscarinic blockade in other parts of the body, it can have bothersome side effects. For example, oxybutynin has shown a higher affinity for muscarinic receptors in the parotid gland than the bladder, leading to dry mouth. In addition, the active metabolite of oxybutynin, N-Desethyl-oxybutynin, can reach concentrations that are 6 times the parent compound after oral administration.[9] Other side effects include constipation, gastrointestinal upset, and blurry vision.

Alternate routes of administration have been developed to improve tolerability, including extended-release oral formulations, rectal administration, and a transdermal patch. Oxybutynin XL is the extended-release form, which incorporates a push-pull osmotic system. In parallel randomized, controlled clinical trials comparing immediate- and extended-release oxybutynin, oxybutynin XL was just as effective as the immediate-release formulation but had fewer side effects.[10-12] Absorption of oxybutynin XL may occur to a larger degree in the colon than in the stomach and proximal small intestine, thereby decreasing conversion to N-Desethyl-oxybutynin. Oxybutynin XL comes in 3 doses (5, 10, and 15 mg) and offers the advantage of dose titration, a very important aspect of management.

A transdermal version of oxybutynin was recently released. In theory, transdermal treatment offers potential advantages such as more stable plasma concentrations and lower presystemic metabolism, which may decrease the primary active metabolite of N-Desethyl-oxybutynin. In a randomized, placebo-controlled trial of 3 doses of transdermal oxybutynin (1.3, 2.6, and 3.9 mg daily), only the highest dose out-performed placebo for median changes in incontinence episodes, frequency, and normal void volume.[13] Quality of life also was significantly improved with the 3.9-mg dose. Anticholinergic side effects were comparable between active and placebo groups.

Tolterodine is a potent muscarinic-receptor antagonist without selectivity for particular subtypes. It is marketed in both immediate- and extended-release (tolterodine LA) formulations. A recent series compared both forms of the drug with placebo in 1,529 adults with overactive bladder.[14] The primary measure of efficacy was change in the mean number of incontinent episodes weekly. Both medications showed a significantly better response than placebo. Dry mouth was significantly lower with tolterodine LA. When the authors used median values instead of mean values (because of non-normal distributed data), tolterodine LA showed improved efficacy over the immediate-release formulation. This study was sponsored by the drug's manufacturer.

Comparisons of oxybutynin and tolterodine. In a prospective, double-blind, head-to-head study of the 2 drugs sponsored by the manufacturer of oxybutynin XL, 378 men and women were randomized to receive oxybutynin XL (10 mg daily) or tolterodine immediate-release (2 mg twice daily).[15] Inclusion criteria included 7 or more episodes of urge incontinence per week and at least 10

to reduce the prolapse to eliminate any anatomic distortion of the urethra.)

Then ask the patient to stand with a full bladder and to squat, again having her cough forcefully 3 times. Record any additional urinary loss. Finally, ask the patient to void and again record the amount voided.

After the patient has emptied her bladder, again ask her to cough forcefully 3 times in the supine position, noting any evidence of leakage from the urethra (empty supine stress test).

Perform an overall inspection of the per-

... continued

voids per 24 hours. The Overactive Bladder: Judging Effective Control and Treatment (OBJECT) trial demonstrated greater efficacy with extended-release oxybutynin than with tolterodine, although both medications decreased weekly episodes of urge incontinence. Oxybutynin XL also showed a small but significant advantage for mixed incontinence and urinary frequency. Dry mouth and central nervous system side effects were similar for the 2 drugs.

A second head-to-head study also was sponsored by the manufacturer of oxybutynin—this one a randomized, double-blind comparison of the extended-release versions of both drugs. The Overactive Bladder: Performance of Extended Release Agents (OPERA) trial randomized 790 women to oxybutynin XL (10 mg daily) or tolterodine LA (4 mg daily).[16] Inclusion criteria included at least 21 to 60 incontinent episodes per week and urgency and frequency exceeding 10 episodes per 24 hours. The drugs were similar in both measures, as well as in side effects, although dry mouth, usually mild, was more common among oxybutynin users. However, oxybutynin was significantly more effective in reducing micturition frequency, and 23% of women taking oxybutynin reported no episodes of incontinence, compared with 16.8% of women taking tolterodine. This finding was significant.

A third head-to-head study involved 2 separate trials conducted in parallel, with individual centers evaluating only 1 drug. In it, 1,289 patients were randomized to open-label treatment with either 2 mg or 4 mg of tolterodine LA in 1 trial and with 5 mg or 10 mg of oxybutynin XL in the other.[17] Inclusion criteria included 18 years of age or greater and symptoms of urinary urgency and frequency. After 8 weeks, tolterodine LA (4 mg) was found to be significantly more effective than either dose of oxybutynin XL, while tolterodine LA (2 mg) was similar to both doses of oxybutynin XL. This study was hampered by the fact that no data were supplied on the number of patients with isolated frequency and urgency versus those who had urge incontinence. Also, no objective parameters such as a voiding diary were utilized.

Three antimuscarinic drugs in the pipeline. Other antimuscarinic agents include trospium, a quaternary amine with some antimuscarinic activity. Because of its structure, it does not cross the brain barrier well and may thus have fewer central side effects.

Two new drugs awaiting approval from the US Food and Drug Administration are darifenacin, which has high selectivity for M3 receptors, and solifenacin, an M3 antagonist with greater selectivity for the bladder than the salivary glands in animal models.

All 3 drugs should be available in the United States some time in 2004.

Antiadrenergic medications. Because the bladder also contains alpha- and beta-adrenergic receptors, antiadrenergic medications have been developed. Currently available alpha-adrenergic agonists include ephedrine, phenylpropanolamine, and pseudoephedrine. Beta-adrenergic agonists include isoproterenol and terbutaline.

Serotonergic agents. Both sympathetic and parasympathetic autonomic nuclei—as well as urethral sphincter motor nuclei—receive serotonergic input from the Raphe nuclei in the caudal brain stem. Serotonergic pathways generally enhance urine storage by activating sympathetic pathways and inhibiting parasympathetic pathways. Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor that may be effective against both urge and stress incontinence. It is currently awaiting approval by the US Food and Drug Administration.

ineum and external genitalia and record a description in the patient's chart.

Attempt to elicit an anal wink, and perform a brief neurological examination to ensure that spinal cord segments S2, S3, and S4 are intact. Next, gently insert a finger into the vagina and ask the patient to forcefully squeeze around it. Record the forcefulness of the squeeze on a scale of 0 to 5, with 0 being no appreciable movement and 5 being the most forceful squeeze possible. During this portion of the exam, instruct the patient on how to perform a Kegel exercise

without recruiting the muscles of the buttocks and the abdominal wall.

Next, use a finger to gently massage the urethra, looking for any possible discharge from the urethral meatus that would be consistent with urethral diverticulum. Also note any tenderness or pain elicited during the exam.

Inserting a half-speculum into the vagina, displace the rectum away from the bladder. As the patient performs a Valsalva maneuver or coughs forcefully, evaluate the support of the anterior vaginal wall. Then turn the speculum 180 degrees and displace the bladder anteriorly, examining the posterior pelvic wall for any signs of prolapse. Also note any urogenital atrophy.

Finally, use a full speculum to evaluate the vaginal apex and cervix (if the patient has not had a hysterectomy). Bimanual and abdominal examinations also are important to rule out any abdominal or pelvic mass that could be irritating or causing pressure on the bladder.

Reexamine the patient for evidence of prolapse when she is standing. Some cases are difficult to detect when the patient is supine.

Step 4

Begin multipronged therapy

Bladder retraining. Review the patient's history, voiding diary, and findings from the physical exam to identify an appropriate treatment. After sharing all findings with the patient, instruct the patient on bladder retraining, which has 3 main components: education, scheduled voiding, and positive reinforcement. (Bladder retraining can be an extremely successful modality.)

Education consists of explaining the pathophysiology of overactive bladder and answering any questions the patient may have, so she understands why she is having the problem.

For scheduled voiding—also known as bladder retraining—examine the voiding diary to determine the approximate length of time between voids in a day. For instance, if the patient voids every hour, we generally ask her to continue doing so for the first week of retraining. The following week, we increase the interval to an hour and 15 minutes, the third week to 1.5 hours, and so on, with an ultimate goal of 3 hours between voids.

We also give instructions on pelvic floor rehabilitation or Kegel exercises. If the patient is able to voluntarily contract her pelvic floor muscles adequately, we recommend an exercise regimen that involves contracting her muscles numerous times a day for at least 10 seconds each time. If she is unable to contract her muscles or has a "dead" pelvic floor, she is referred to a physical therapist for biofeedback and possibly electrical stimulation.

We also instruct the patient to avoid racing to the bathroom when she feels an urge to void. Instead, have her stop, contract her pelvic floor muscles, and allow the urge to pass. She can then walk comfortably to the bathroom.

As mentioned earlier, the voiding diary may highlight problems such as excessive intake of fluids.

Local estrogen therapy can be added if there are signs of urogenital atrophy.

Medical therapy. In addition to education, timed voids, pelvic floor rehabilitation, and estrogen therapy, we usually start the extended-release form of tolterodine (4 mg) or oxybutynin (10 mg), which are antimuscarinic agents. *(See "Treating overactive bladder: An expanding 'pharmacopeia'" on page 24).*

We ask her to return for a follow-up visit in 4 to 6 weeks to inquire about her symptoms and any significant side effects. We ask the patient to prepare another voiding diary for that visit so we can objectively measure decreases in frequency, urgency, and urge incontinence.

Dose adjustment is very important in patients with overactive bladder. If the woman is experiencing minimal effect with no side effects, titrate the dosage upward. If she is having good effect with significant side effects, decrease the dosage or consider switching to the transdermal form of oxybutynin.

When all these conditions are met and the patient remains severely affected, we perform

multichannel urodynamic testing along with cystoscopy. If the testing supports the diagnosis of overactive bladder, and all other mechanisms for improvement have been exhausted, we counsel the patient about intravesical administration of botulism toxin, which relaxes skeletal and smooth muscle by preventing release of acetocholine from nerve terminal endings. Another option is sacroneuromodulation (InterStim therapy).

Implications of the placebo effect

We lack a complete understanding of how all the parts of this process interact and why. Most of the medications in use affect only 1 part of the complex process that governs urine storage and elimination.

In controlled trials, patients on placebo have experienced 30% improvement—or greater—in their symptoms. This would seem to suggest that education, behavioral retraining, and attention from physicians are responsible for some of the improvement. Indeed, in a recent systematic review of 32 trials involving 6,800 participants, Herbison et al[8] found significant but relatively small differences between anticholinergic medications and placebo for many of the outcomes studied. Obviously, we have more to learn about the intricacies of this condition before we can eliminate it completely. ■

REFERENCES

1. Stewart W, Herzog R, Wein A, et al. Prevalence of overactive bladder in the US: results from the Noble Program. Poster presented at the Second International Consultation on Incontinence, July 2001, Paris, France.
2. Voelker R. International group seeks to dispel incontinence 'taboo.' *JAMA*. 1998;280:951.
3. Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: report from the standardization sub-committee of the International Continence Society. *Neurol Urodynamics*. 2002;21:167-178.
4. Walters MD, Diaz K. Q-tip test: a study of continent and incontinent women. *Obstet Gynecol*. 1987;70:208-211.
5. Wagner TH, Hu TW. Economic costs of urinary incontinence in 1995. *Urology*. 1998;51:355.
6. Wagner TH, Hu TW. Economic costs of urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*. 1998;9:127.
7. Jung SY, Fraser MO, Ozawa H, et al. Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. *J Urol*. 1999;162:204.
8. Herbison P, Hay-Smith J, Ellis G, Moore K. Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. *BMJ*. 2003;326:841-844.
9. Gupta SK, Sathyan G. Pharmacokinetics of an oral once-a-day controlled-release oxybutynin formulation compared with immediate release oxybutynin. *J Clin Pharmacol*. 1999;39:289.
10. Anderson RU, Mobley D, Blank B, Saltzstein D, Susset J, Brown JS. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. *J Urol*. 1999;161:1809.
11. Birns J, Lukkari E, Malone-Lee JG. A randomized controlled trial comparing the efficacy of controlled-release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets (5 mg twice daily) in patients whose symptoms were stabilized on 5-mg twice daily of oxybutynin. *BJU Int*. 2000;85:793.
12. Versi E, Appell R, Mobley D, Patton W, Saltzstein D. Dry mouth with conventional and controlled-released oxybutynin in urinary incontinence. The Ditropan XL Study Group. *Obstet Gynecol*. 2000;95:718.
13. Dmochowski RR, Davila GW, Zinner NR, et al. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. *J Urol*. 2002;168:580-586.
14. Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology*. 2001;57:414.
15. Appell RA, Sand P, Dmochowski R, et al, for the OBJECT Study Group. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. *Mayo Clin Proc*. 2001;76:358-363.
16. Diokno AC, Appell RA, Sand PK, et al, for the 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;78:687-695.
17. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the Antimuscarinic Clinical Effectiveness Trial (ACET). *Curr Hosp Res Opin*. 2002;18:177-184.

Dr. Karram serves on the speakers bureau for Ortho-McNeil and the advisory boards of Ortho-McNeil and Watson. Dr. Kleeman serves on the speakers bureau for Pfizer.