Management of Overactive Bladder

Joseph G. Ouslander, M.D.

OVERACTIVE BLADDER IS A SYMPTOM COMPLEX THAT INCLUDES URINARY URGENCY WITH OR WITHOUT URGE INCONTINENCE, URINARY FREQUENCY (VOIDING EIGHT OR MORE TIMES IN A 24-HOUR PERIOD), AND NOCTURIA (AWAKENING TWO OR MORE TIMES AT NIGHT TO VOID). The International Continence Society classifies overactive bladder as a syndrome for which no precise cause has been identified, with local abnormalities ruled out by diagnostic evaluation. This review extends beyond the International Continence Society's current definition of overactive bladder, since a broader approach to this syndrome is essential for optimal management.

Because overactive bladder is a recently defined syndrome, its prevalence and natural history have not been well studied. In a telephone survey of 16,776 adults who were 40 years of age or older in Europe, 16 percent of men and 17 percent of women reported syndromes suggestive of overactive bladder. The prevalence was 3 percent among men 40 to 44 years of age, 9 percent among women 40 to 44 years of age, 42 percent among men 75 years of age or older, and 31 percent among women 75 years of age or older.

Similar data on the prevalence of overactive bladder have been reported in the United States.

Patients with symptoms of overactive bladder tend to curtail their participation in social activities and to isolate themselves and are predisposed to depression. Nocturia is associated with sleep disruption, which decreases the quality of life. Postmenopausal women with urge incontinence have a substantially higher risk of falling and sustaining a fracture than women without urge incontinence. The costs of overactive bladder are probably high but have not been studied systematically. The total costs of urinary incontinence in the United States in 1995 were estimated to be approximately $26 billion. A substantial proportion of this cost is attributable to urge incontinence, one of the cardinal symptoms of overactive bladder.

PATHOPHYSIOLOGY

The symptoms of overactive bladder have many potential causes and contributing factors (Table 1). Urination involves the higher cortex of the brain; the pons; the spinal cord; the peripheral autonomic, somatic, and sensory afferent innervation of the lower urinary tract; and the anatomical components of the lower urinary tract itself. Disorders of any of these structures may contribute to the symptoms of overactive bladder. The normal bladder functions like a compliant balloon as it fills, with pressure remaining lower than urethral resistance. With the initiation of normal urination, urethral resistance decreases and a phasic contraction of the detrusor muscle empties the bladder (Fig. 1A). The symptoms of overactive bladder are usually associated with involuntary contractions of the detrusor muscle (Fig. 1B). Overactivity of the detrusor muscle, whether neurogenic or idiopathic, can result in urgency or urge incontinence, depending on the re-
Increasing attention has been paid to the role of sensory afferent nerves in normal voiding and detrusor overactivity. During bladder filling, afferent activity from the bladder and urethra reaches the spinal cord predominantly by means of the pelvic nerve. Sensory input during bladder filling results in an increase in sympathetic tone, which inhibits bladder parasympathetic motor nerves, causing contractions of the bladder base and urethra. Adrenergic activity may also cause relaxation of the detrusor muscle through the stimulation of $\beta_3$-adrenergic receptors (Fig. 2). Myelinated A delta sensory fibers respond to passive distention and active contraction of the detrusor muscle. Unmyelinated C sensory fibers have a higher mechanical threshold and respond to a variety of neurotransmitters (Fig. 3). C fibers are relatively inactive during normal voiding, but they may have a critical role in symptoms of overactive bladder in patients with neurologic and other disorders. Several types of receptors have been identified on afferent nerves, including vanillyloid receptors, which are activated by capsaicin and possibly by endogenous anandamide; purinergic receptors (P2X), which are activated by ATP; neurokinin receptors, which respond to substance P and neurokinin A; and receptors for nerve growth factor (trk-A receptors). Other substances, including nitric oxide, calcitonin gene–related protein, and brain-derived neurotropic factor, may also have an important role in modulating the sensory afferents in the human detrusor. A better understanding of the complex interplay among these various neurotransmitters and other substances derived from uroepithelium, detrusor-muscle cells, and afferent fibers themselves should yield new and more specific targets for drug treatment of overactive bladder.

**DIAGNOSTIC EVALUATION**

Effective treatment of patients with symptoms of overactive bladder necessitates a targeted diagnostic evaluation. Guidelines for the management of urinary incontinence and benign prostatic hyperplasia are relevant to the evaluation of symptoms of overactive bladder. A focused history that includes information about past genitourinary disorders and other conditions outlined in Table 1 should be elicited from all patients. A symptom index for benign prostatic hypertrophy (recommended by the American Urological Association) or a similar symptom index is helpful to include as part of the evaluation in older men. A variety of questionnaires regarding lower urinary tract symptoms have also...
Table 1. Conditions That Can Cause or Contribute to Symptoms of Overactive Bladder.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Mechanisms or Effect</th>
<th>Implications for Management</th>
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<tbody>
<tr>
<td>Lower urinary tract conditions</td>
<td></td>
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<tr>
<td>Both sexes</td>
<td></td>
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<tr>
<td>Urinary tract infection</td>
<td>Inflammation with activation of sensory afferent innervation can result.</td>
<td>Treat infection before other interventions are considered.</td>
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<tr>
<td>Obstruction</td>
<td>Obstruction can contribute to detrusor overactivity and urinary retention.</td>
<td>Consider surgical intervention.</td>
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<tr>
<td>Impaired bladder contractility</td>
<td>Urinary retention and reduced functional bladder capacity can result.</td>
<td>Avoid drugs that decrease bladder contractility. Teach patients to enhance voiding (e.g., Credé's method). Intermittent catheterization is helpful in selected patients.</td>
</tr>
<tr>
<td>Bladder abnormalities or inflammation (e.g., tumors, calculi, interstitial cystitis)</td>
<td>Intravesical abnormalities can precipitate detrusor overactivity.</td>
<td>Sterile hematuria and risk factors for bladder cancer should prompt further evaluation.</td>
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<tr>
<td>Women</td>
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<tr>
<td>Estrogen deficiency</td>
<td>Inflammation from atrophic vaginitis and urethritis can contribute to symptoms.</td>
<td>Topical estrogen may ameliorate symptoms.</td>
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<tr>
<td>Sphincter weakness</td>
<td>Leakage of urine into proximal urethra may precipitate urgency. Ability to inhibit detrusor by sphincter contraction may be diminished.</td>
<td>Topical estrogen and pelvic-muscle exercises may help strengthen the sphincter. Periurethral injections or surgical procedures may be helpful in selected patients.</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate enlargement</td>
<td>Benign or malignant prostate enlargement can contribute to detrusor overactivity.</td>
<td>Evaluation and treatment for prostate cancer should be considered. Alpha-adrenergic blockers may improve symptoms. 5a-Reductase inhibitors may reduce prostate size. Surgical removal of obstructing prostate may be indicated.</td>
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<tr>
<td>Neurologic conditions</td>
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<td></td>
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<tr>
<td>Brain</td>
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<tr>
<td>Stroke, Alzheimer's disease, multi-infant dementia, other dementias, Parkinson's disease, multiple sclerosis</td>
<td>Higher cortical inhibition of the bladder is impaired, causing neurogenic detrusor overactivity.</td>
<td>Management must include a means of compensation for impaired cognition, improved mobility, or both.</td>
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<tr>
<td>Spinal cord</td>
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<tr>
<td>Multiple sclerosis, cervical or lumbar stenosis or disk herniation, spinal cord injury</td>
<td>Neurogenic detrusor overactivity or urinary retention can result.</td>
<td>Presence of neurologic symptoms or signs may require further evaluation. Urodynamic testing is often indicated for diagnostic purposes.</td>
</tr>
<tr>
<td>Peripheral innervation</td>
<td>Urinary retention and low functional bladder capacity can result.</td>
<td>History suggestive of nerve injury or neurologic signs require further evaluation.</td>
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</tbody>
</table>

been developed for women. In addition, diaries can be helpful in determining the frequency, volume, and pattern of voiding, as well as providing clues to underlying causes and contributing factors. All patients should undergo a focused physical examination that includes genitourinary, pelvic, and rectal examinations; a clean urine specimen should be obtained to rule out hematuria and infection.

Further evaluation should be considered in selected patients. The presence of residual urine after voiding should be determined in patients with risk factors for urinary retention (diabetes, spinal cord disease, and benign prostatic hypertrophy). This can be accomplished by sterile in-and-out catheterization. A portable ultrasonographic device is available that permits noninvasive identification of clinically significant residual urine (>100 ml), with an accuracy rate of more than 90 percent; it costs approximately $8,000. Patients with sterile hematuria or
risk factors for bladder cancer should undergo cystoscopy, and their urine should be sent for cytologic analysis. Cystoscopy is also indicated in patients with a history of recurrent urinary tract infection. Although some urologists and gynecologists suggest that all patients in whom symptoms of overactive bladder develop should undergo cystoscopy to rule out carcinoma in situ and other intravesical abnormalities, the cost effectiveness of this approach is uncertain. Because early prostate cancer can cause symptoms of overactive bladder, the possibility of prostate cancer should be assessed.

The role of urodynamic testing in the evaluation of patients with symptoms of overactive bladder is controversial. A noninvasive determination of the urinary flow rate, combined with a measurement of residual urine after voiding, appears to be a sensitive method of ruling out obstruction in older men. More complex urodynamic testing may be necessary in patients with nonspecific symptoms and may be a more accurate approach to the diagnosis of obstruction than less invasive testing. Because this test is relatively expensive and invasive, it is recommended only to evaluate symptoms of overactive bladder in cases in which the findings will clearly influence treatment, such as after the failure of initial therapy.\cite{1,3,7}

**THERAPY**

Optimal therapy for overactive bladder depends on a thorough evaluation, followed by treatment of all the likely causes and contributing factors (Table 1). The genesis of symptoms of overactive bladder is
mixed urge-stress incontinence. Educating patients about bladder function, appropriate fluid intake (avoidance of caffeine, maintenance of adequate hydration, and the timing of fluid intake), and managing constipation is important for all patients with overactive bladder. Education may, in fact, underlie the prominent placebo effects (approximately 30 percent improvement in symptoms) demonstrated repeatedly in drug trials for incontinence and overactive bladder. Several randomized, controlled trials, largely involving middle-aged women and women under 75 years of age who had urge or mixed urge-stress incontinence, suggest that cognitively intact, motivated patients have a positive response to pelvic-muscle exercises and "bladder training." Approximately 70 percent of patients have a reduction in the number of episodes of incontinence within two to three months. The long-term effectiveness of these interventions requires further study.

Many patients can be taught pelvic-muscle exercises during a pelvic or rectal examination or can learn them with the use of simple educational tools such as an audiotape or a booklet. A substantial proportion of older patients benefit from biofeedback-assisted training. "Bladder training" generally refers to a combination of patient education, scheduled voiding and urge-suppression techniques, and pelvic-muscle exercises. For some patients with cognitive impairment, limited mobility, or both, the use of toileting-assistance protocols such as prompted voiding can be very helpful in the management of overactive bladder. All these behavioral interventions can also be effective adjuncts to drug therapy.

Some patients with severe symptoms of overactive bladder that are refractory to proven behavioral treatment may benefit from other nonpharmacologic interventions. A wide variety of highly absorbent pads and undergarments are available that can be effective and acceptable in selected patients with refractory symptoms in order to maintain "social continence" and good perineal hygiene. Only limited evidence of efficacy is available regarding more invasive interventions. Electrical stimulation delivered by vaginal or rectal probes can be helpful in teaching some patients the proper use of pelvic muscles (an approach similar to biofeedback), and lower-frequency stimulation can inhibit bladder contraction. Sacral neuromodulation by means of implantable stimulators is used in selected patients with severe neurogenic detrusor overactivity. Magnetic stimulation has also been approved for the

Figure 1. Normal Voiding Physiology (Panel A) and Involuntary Detrusor Contraction Commonly Associated with Symptoms of Overactive Bladder (Panel B). Normally, as bladder volume increases, the detrusor muscle functions like a compliant balloon and maintains a low intravesical pressure (less than 10 cm of water) — substantially lower than urethral resistance pressure (Panel A). As bladder volume continues to increase, the activity of the striated muscles of the urethral sphincter increases. At the time of normal voluntary voiding, which generally occurs at a urinary volume of 300 to 400 ml, muscle activity in the sphincter ceases, urethral resistance decreases, and a phasic detrusor contraction empties the bladder. In patients with symptomatic overactive bladder, involuntary bladder contractions can cause urgency and may precipitate urine loss, depending on the response of the sphincter (Panel B). Involuntary contractions may occur at any bladder volume, but they commonly occur at volumes of less than 200 ml. The sphincter-muscle activity depicted in Panel B is a response to the involuntary contraction of the detrusor muscle (as opposed to detrusor-sphincter dyssnergy). Detrusor overactivity can be neurogenic or idiopathic and can be accompanied by urgency or be without sensation.

NONPHARMACOLOGIC INTERVENTIONS

Various clinical trials suggest that behavioral interventions are efficacious for managing urge and

commonly multifactorial, and multimodal therapy that includes nonpharmacologic as well as pharmacologic interventions may be indicated.
treatment of incontinence, but this requires multiple visits to a facility that has the stimulation equipment. Surgical procedures, including motor-nerve ablation and augmentation cystoplasty, are used only in patients with the most severe symptoms.49,50

**DRUG THERAPY**

Many classes of drugs have been studied or proposed for the treatment of symptoms of overactive bladder.1–3,20–22,11 The majority of clinical trials have targeted the symptoms of urinary incontinence, though more recent trials have specifically included subjects with overactive bladder. Several pitfalls limit the quality of many studies. Expert groups have proposed methodologic standards that should improve the science underlying drug therapy of overactive bladder.52–54

Table 2 lists drugs currently used to treat symptoms of overactive bladder and notes both evidence of efficacy and recommendations based on the International Consultation on Urological Diseases.7 A recent review summarizes the efficacy of anticholinergic drugs for the treatment of overactive bladder as reported in 32 placebo-controlled trials that included 6800 subjects, over 70 percent of whom were women.57

All anticholinergic drugs can have bothersome side effects. Although dry mouth is the most common, constipation, gastroesophageal reflux, blurry vision, urinary retention, and cognitive side effects can also occur. Both overactive bladder and dementia are common in older patients. Since various forms of dementia are routinely treated with cholinesterase inhibitors, the potential for adverse cognitive effects and delirium due to antimuscarinic drugs is a particular concern in this population.58,59 Although these drugs have not had major effects on cognition in clinical trials involving relatively healthy older adults, more subtle but functionally important changes could occur. Quantitative electroencephalographic data suggest that oxybutynin has more central nervous system effects than trospium or tolterodine.60 Long-acting anticholinergic agents and newer, more selective antimuscarinic agents should be tested for clinically important cognitive side effects, especially in older patients.

Among the anticholinergic agents, only oxybutynin, propiverine, tolterodine, and trospium (Table 2) have the highest level of clinical recommendation and evidence of efficacy; oxybutynin and tolterodine have been studied most extensively. Oxybutynin is a nonselective antimuscarinic agent that relaxes bladder muscles and has local anesthetic activity. It is available in immediate and extended-release forms, as well as in a transdermal patch. Immediate-release oxybutynin (usual adult dosage, 5 mg three times daily) appears to be efficacious for the treatment of neurogenic and non-neurogenic overactivity of the detrusor muscle with urge incontinence. Given in this formulation, oxybutynin has led to a clinically significant improvement, defined as a reduction in incontinence episodes by more than 50 percent,

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*Figure 2. Current Concepts of Autonomic Efferent Innervation Contributing to Bladder Contraction and Urine Storage.*

In the normal human bladder, acetylcholine is the predominant neurotransmitter that causes bladder contraction. Acetylcholine interacts with M3 muscarinic receptors and activates phospholipase C through coupling with G proteins, which generates inositol triphosphate, which in turn causes the release of calcium from the sarcoplasmic reticulum and the contraction of bladder smooth muscle. M2 receptors may contribute to bladder contraction by inhibiting adenylate cyclase activity and decreasing intracellular cyclic adenosine monophosphate (AMP) levels, which mediate bladder relaxation. In the normal human bladder, only a small proportion of muscle contraction is resistant to atropine. Resistance to atropine most likely results from the interaction of ATP with purinergic receptors, including P2X receptors. ATP and other non-cholinergically mediated processes may have a more important role in disorders that cause overactive bladder. Stimulation of β2 adrenergic receptors may also lead to relaxation of bladder smooth muscle. Plus signs indicate activation, and minus signs inhibition. Data are from Morrison et al.20 Yoshimura and Chincocello,21 and Andersson and Hedlund.22

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in approximately 60 to 80 percent of study subjects.\textsuperscript{31,32,51,61} The efficacy of immediate-release oxybutynin has been limited by antimuscarinic side effects of the parent drug and its active metabolite (N-desethyloxybutynin); dry mouth, for example, is reported in up to two thirds of subjects in some clinical trials. Generic immediate-release oxybutynin is relatively inexpensive and may be useful for patients whose symptoms are best managed by a short-acting drug (e.g., symptoms that are bothersome only when the patient is away from home or at night).

A once-daily controlled-release formulation of oxybutynin appears to have the same beneficial effects as immediate-release oxybutynin, with fewer side effects — a benefit ascribed to the more constant levels of the parent drug and, possibly, a lower rate of conversion to the active metabolite in the stomach and small intestine.\textsuperscript{62} Most studies of controlled-release oxybutynin have reported a reduction in episodes of urge incontinence by approximately 70 percent.\textsuperscript{63,64} A transdermal oxybutynin patch is also available that is as efficacious as immediate-release oxybutynin but with half the incidence of dry mouth.\textsuperscript{67,68} In one placebo-controlled trial, the patch caused local skin erythema in more than half the subjects (3 percent of cases were severe) and was associated with pruritus in up to 17 percent.\textsuperscript{68}

Tolterodine is a muscarinic antagonist that is available in short-acting (twice-daily) and long-acting (once-daily) preparations. Both forms have had statistically and clinically significant effects on symptoms of overactive bladder in multiple, randomized, controlled clinical trials.\textsuperscript{69-77} Side effects are similar to those of short-acting oxybutynin, with dry mouth in 20 to 25 percent of patients, and the rates of discontinuation due to side effects are similar to those for placebo (5 to 6 percent). Tolterodine appears to be equally efficacious in old and young...
## Table 2. Drugs Used to Treat Symptoms of Overactive Bladder.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dose</th>
<th>Level of Evidence/Grade of Recommendation‡</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td><strong>Drugs with predominantly anticholinergic or antimuscarinic effects</strong></td>
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<tr>
<td>Hyoscymine</td>
<td>0.375 mg twice daily orally</td>
<td>2/D</td>
<td>The drug is also available in sublingual and elixir forms; it has prominent anticholinergic side effects.</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>2.5–5.0 mg thrice daily orally (short-acting) 3.9 mg over a 96-hr period (transdermal)</td>
<td>1/A</td>
<td>Long-acting and transdermal preparations have fewer side effects than short-acting preparations. The transdermal patch can cause local skin irritation in some patients.</td>
</tr>
<tr>
<td>Propantheline</td>
<td>15–30 mg 4 times daily orally</td>
<td>2/B</td>
<td>The drug has prominent anticholinergic side effects.</td>
</tr>
<tr>
<td>Propiverine</td>
<td>15 mg thrice daily orally</td>
<td>1/A</td>
<td>The drug has complex pharmacokinetics with several active metabolites; it is not currently available in the United States.</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1–2 mg twice daily orally (short-acting) 4 mg daily orally (long-acting)</td>
<td>1/A</td>
<td>The long-acting and short-acting preparations have similar efficacy.</td>
</tr>
<tr>
<td>Trospium</td>
<td>20 mg twice daily orally</td>
<td>1/A</td>
<td>The agent is a quaternary ammonium compound, which does not cross the blood-brain barrier and may have fewer cognitive side effects than other anticholinergic agents; it is not currently available in the United States.</td>
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<tr>
<td><strong>Estrogen (for women)</strong></td>
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<tr>
<td>Vaginal estrogen preparations</td>
<td>Approximately 0.5 g cream applied topically nightly for 2 wk, then twice per week Estradiol ring, replaced every 90 days Estradiol, 1 tablet daily for 2 wk, then 1 tablet twice a week</td>
<td>4/D</td>
<td>Local vaginal preparations are probably more effective than oral estrogen, but definitive data on effectiveness are lacking.</td>
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<tr>
<td><strong>Alpha-adrenergic antagonists (for men)</strong></td>
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<tr>
<td>Alfuzosin</td>
<td>2.5 mg thrice daily orally</td>
<td>4/D‡</td>
<td>These agents are useful in men with benign prostatic enlargement.</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>1–16 mg daily orally</td>
<td></td>
<td>Postural hypotension can be a serious side effect.</td>
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<tr>
<td>Prazosin</td>
<td>1–10 mg twice daily orally</td>
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<td>Doses must be increased gradually to facilitate tolerance.</td>
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<tr>
<td>Tamulosin</td>
<td>0.4–0.8 mg daily orally</td>
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<tr>
<td>Terazosin</td>
<td>1–10 mg orally each day at bedtime</td>
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<tr>
<td><strong>Other drugs</strong></td>
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<tr>
<td>Imipramine</td>
<td>10–25 mg thrice daily orally</td>
<td>2/C</td>
<td>This agent may be useful for mixed urge-stress incontinence; it can cause postural hypotension and bundle-branch block.</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>20–40 μg of intranasal spray daily at bedtime 0.1–0.4 mg orally 2 hr before bedtime</td>
<td>1/B</td>
<td>The intranasal spray is used for primary nocturnal enuresis in children; hyponatremia occurs commonly in older adults, and serum sodium levels must be monitored closely.</td>
</tr>
</tbody>
</table>

*Not all drugs listed in this table have proven efficacy specifically for symptoms of overactive bladder.

† Levels of evidence are based on the Oxford System: a score of 1 indicates evidence from randomized, controlled trials; a score of 2 evidence from good-quality prospective cohort studies; a score of 3 evidence from good-quality retrospective case–control studies; and a score of 4 evidence from good-quality case series. The grade of recommendations is based on the definitions used by the International Consultation on Urological Diseases: A indicates consistent level 1 evidence; B consistent level 2 or 3 evidence or major evidence from randomized, controlled trials; C level 4 evidence or major evidence from level 2 or 3 studies or expert opinion based on the Delphi method; and D inconclusive, inconsistent, or nonexistent evidence or evidence based on expert opinion only.

‡ The rating is for symptoms of overactive bladder, not for overall symptoms of benign prostatic hyperplasia.
subjects and was well tolerated in one trial involving patients who were living in nursing homes.\textsuperscript{75,76,78} Two published studies, both industry-sponsored, have compared the long-acting forms of oxybutynin and tolterodine. In one study, participating medical practices were randomized,\textsuperscript{77} and in the other, women (mean age, 60 years) were randomly assigned to receive one or the other of these agents.\textsuperscript{79} The results of both trials suggest that the drugs have similar efficacy and effectiveness. In addition, both oxybutynin and tolterodine appear to be effective when combined with various types of behavioral interventions.\textsuperscript{78,80-82}

Randomized, controlled trials indicate that propiverine and trospium are effective for the treatment of urge incontinence and have fewer side effects than short-acting oxybutynin.\textsuperscript{83-86} Neither drug is currently available in the United States (trospium is being evaluated in clinical trials in the United States). Though hyoscyamine, like short-acting oxybutynin, may be useful for some patients with intermittent symptoms or under specific circumstances, it can be associated with prominent side effects. Propantheline has proven efficacy for the treatment of urge incontinence,\textsuperscript{81,87,88} but the need for multiple daily doses and the relatively high incidence of side effects are drawbacks. Imipramine, a tricyclic antidepressant with both anticholinergic and alpha-adrenergic effects and, possibly, a central effect on voiding reflexes, has been recommended for mixed urge–stress incontinence, which is common among older women with overactive bladder. Imipramine can cause postural hypotension and cardiac-conduction abnormalities and thus must be used carefully.

Postmenopausal women with symptoms of overactive bladder are commonly treated with oral or topical estrogen, but few data document the efficacy of these agents.\textsuperscript{89-92} Among men, symptoms of overactive bladder overlap with those of benign prostatic hyperplasty.\textsuperscript{93-99} In clinical practice, the approach to men with symptoms of overactive bladder depends on several factors, such as the degree to which specific symptoms bother the patient, the patient's preferences, evaluation of the risk–benefit ratio, and the physician's bias. Treatment decisions are further complicated by the fact that complex urodynamic studies are required to rule out bladder-outlet obstruction as a cause. Men with isolated symptoms of overactive bladder — in whom prostate cancer and obstruction have been ruled out — are often treated initially with alpha-adrenergic blockers (alpha-blockers). It is difficult to determine the efficacy of these drugs for overactive bladder, because the outcomes of most clinical trials have been based on composite scores that include symptoms of both overactive bladder and obstruction.\textsuperscript{100-107} Symptoms of overactive bladder tend to decrease with alpha-blocker therapy, but less so than do symptoms of obstruction.\textsuperscript{102,103} Because alpha-blockers can cause postural hypotension, they require a gradual titration of the dose and must be used carefully, especially in patients who are already taking antihypertensive agents.\textsuperscript{93,100-102}

Men who neither tolerate nor have a response to alpha-blockers and who are not candidates for surgical intervention may benefit from a trial of an anticholinergic agent, provided they are carefully monitored for the development of urinary retention. Further research is needed to determine the optimal use of alpha-blockers and anticholinergic drugs — alone, together, or combined with behavioral therapy — as a treatment for overactive bladder in men.

Treatment of nocturia, the most bothersome symptom of overactive bladder for many patients of both sexes, depends on the primary underlying cause or causes — detrusor overactivity, nocturnal polyuria, a primary sleep disorder, or some combination of these conditions.\textsuperscript{104,105} Nocturia that is primarily related to detrusor overactivity can be treated with an anticholinergic agent. Nocturnal polyuria related to volume overload (e.g., venous insufficiency or congestive heart failure with peripheral edema) may respond to a small dose of a rapid-acting diuretic taken in the late afternoon. Oral and intranasal preparations of desmopressin are approved for use in children with nocturnal enuresis.

Data supporting an association among nocturnal polyuria, nocturia, abnormal diurnal responsiveness to vasopressin, and levels of endogenous arginine vasopressin in adults are limited and conflicting.\textsuperscript{106-109} However, two randomized, controlled trials suggest that orally administered desmopressin can reduce nocturia in both women (mean age, approximately 57 years)\textsuperscript{110} and men (mean age, approximately 65 years).\textsuperscript{111} Both trials used a three-week run-in dose–titration design (0.1 to 0.4 mg), during which approximately one third of the patients were excluded. Among patients with some responsiveness and ability to tolerate desmopressin during the dose–titration phase, one third of the women and the men had at least a 50 percent reduction in the number of nighttime voiding episodes (as compared with 3 percent of patients in the placebo group) and a significant increase in the
duration of sleep before their first nighttime voiding during the three-week double-blind phase. Side effects were mild; hyponatraemia occurred in approximately 5 percent of patients but only during the three-week dose-levitation phase. On the basis of these data, oral desmopressin has been approved for the treatment of nocturia in several countries in Europe, but it is not yet approved for this indication in the United States.

Because of their mechanisms of action, several classes of drugs used for other conditions are of potential therapeutic value for patients with overactive bladder, but data from randomized, controlled clinical trials are lacking. Such drug classes include calcium-channel blockers, prostaglandin-synthesis inhibitors, dopamine D1-receptor agonists, beta-adrenergic (particularly β2) agonists, and γ-aminobutyric acid (GABA) agonists (Table 3).20-22 For example, pergolide, a D1-receptor agonist, may benefit patients with Parkinson's disease and lower urinary tract symptoms, and baclofen, a GABA agonist, has been used in patients with the detrusor hyperreflexia associated with spinal cord disorders. Direct injection of botulinum toxin into the detrusor muscle, which inhibits acetylcholine at the presynaptic cholinergic junction, appears to ameliorate detrusor hyperreflexia in patients with spinal cord injury112,113; it may have some therapeutic value in selected patients with severe refractory symptoms of overactive bladder. Although currently available beta-agonists have not been shown to be useful for overactive bladder, more selective β2-agonists may have therapeutic value.

There are several promising directions for the development of drugs to treat overactive bladder (Table 3). At least two antimuscarinic drugs (darifenacin and solifenacin) with selective M3-receptor-antagonist actions and, theoretically, fewer systemic anticholinergic side effects than currently available agents are being studied. Oxybutynin has been instilled intravesically through a catheter to treat severe overactivity of the detrusor muscle,114 and a

<table>
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<tr>
<th>Drug Classes and Actions</th>
<th>Examples Studied in Humans</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Drugs used for other conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>Dilatexen</td>
<td>Agents inhibit bladder contraction by decreasing calcium available for smooth-muscle contraction; there is no evidence that these agents are effective for symptoms of overactive bladder.</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Inhibitors of prostaglandin synthesis</td>
<td>Flurbiprofen</td>
<td>Prostaglandins may increase the contraction of bladder smooth muscle; no currently available agents have proven efficacy.</td>
</tr>
<tr>
<td>γ-Aminobutyric acid–receptor agonists</td>
<td>Baclofen</td>
<td>Stimulation of γ-aminobutyric acid receptors inhibits the voiding reflex.</td>
</tr>
<tr>
<td>Neuraminoacidic-junction inhibition of acetylcholine release</td>
<td>Botulinum toxin</td>
<td>Botulinum toxin A injections have been used for refractory symptoms.</td>
</tr>
<tr>
<td>Drugs in development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimuscarinic agents more selective for M3 receptors than other antimuscarinic agents</td>
<td>Darifenacin</td>
<td>These agents decrease spontaneous detrusor–muscle contractions and can have clinically significant effects on blood pressure; potassium-channel gene therapy has also been studied.</td>
</tr>
<tr>
<td></td>
<td>Solifenacin</td>
<td></td>
</tr>
<tr>
<td>Potassium-channel openers</td>
<td>Cromakalim</td>
<td>The central serotonergic effects of these agents increase urethral striated sphincter–muscle tone.</td>
</tr>
<tr>
<td></td>
<td>Pinacidil</td>
<td></td>
</tr>
<tr>
<td>Serotonergic agonists</td>
<td>Duloxetine</td>
<td></td>
</tr>
<tr>
<td>Vanilloids and other afferent–nerve inhibitors</td>
<td>Capsaicin</td>
<td>These agents cause desensitization of unmyelinated C fibers; other afferent–nerve inhibitors may be useful.</td>
</tr>
<tr>
<td></td>
<td>Resiniferatoxin</td>
<td></td>
</tr>
<tr>
<td>Dopamine-D1–receptor agonists</td>
<td>Pergolide</td>
<td>D1-receptor stimulation inhibits the voiding reflex.</td>
</tr>
<tr>
<td>Nerve growth factor inhibitors</td>
<td>—</td>
<td>Nerve growth factor modulates sensory afferent function; antibody-based gene therapy to suppress nerve growth factor has also been studied.</td>
</tr>
<tr>
<td>Enkephalins</td>
<td>—</td>
<td>Opioid peptides, including enkephalins, suppress the voiding reflex; therapy with the herpes simplex virus proenkephalin gene has been studied.</td>
</tr>
</tbody>
</table>

* Drugs listed in this table do not have proven efficacy in the treatment of overactive bladder and should not be prescribed until data from clinical trials are published.
bladder pump is being developed that can deliver a constant dose of intravesicular oxybutynin for up to 30 days. Such a device may make this method of drug delivery more practical and acceptable and may result in fewer systemic anticholinergic side effects.

Drugs that act by means of potassium-channel transporters to hyperpolarize smooth muscle and decrease spontaneous bladder contractions may be useful for suppressing involuntary bladder contractions without interfering with normal voiding. However, first-generation agents in this class have had effects on vascular smooth muscle and can cause hypotension. Duloxetine is an inhibitor of serotonin and norepinephrine that appears to act centrally, increasing tone in the striated smooth muscle of the external urethral sphincter. Although it is being studied primarily for the treatment of stress incontinence, duloxetine may also have therapeutic benefits in patients with mixed stress–urge incontinence. Drugs that act on sensory afferent pathways are also being developed and hold promise when used either alone or in combination with other drugs. Capsaicin and resiniferatoxin desensitize C-fiber afferents and have been administered experimentally by the intravesicular route. Resiniferatoxin appears to be more potent and less irritating than capsaicin and may be more useful clinically. Other drugs that block receptors on sensory afferents, such as neurokinin-receptor antagonists (Fig. 3), might not cause urinary retention, which can occur with antimuscarinic agents.

SUMMARY

Symptoms of overactive bladder are common, can be distressing, and are associated with serious adverse consequences such as injurious falls. The symptoms may be caused by myriad factors, including disorders of the lower urinary tract, neurologic conditions, behavioral factors such as caffeine intake, and a variety of commonly prescribed drugs. The pathophysiologic process in an individual patient is often multifactorial. Diagnostic evaluation includes a focused history taking, targeted physical examination, and urinalysis. Selected patients should have a post-void residual determination, and some should undergo cystoscopy (such as those with hematuria) or complex urodynamic testing (such as those with urinary retention or neurologic disorders).

Patients with overactive bladder often benefit from supportive measures such as education, changes in fluid intake, and the use of bedside commodes or urinals, especially at night. Behavioral treatments such as pelvic-muscle exercises and bladder training are efficacious and can enhance the benefits of drug therapy. The mainstay of drug therapy is antimuscarinic agents. The two best-studied agents are oxybutynin and tolterodine; both have well-proven efficacy in short- and long-acting forms. The extended-release formulations and the oxybutynin skin patch are generally well tolerated, but all antimuscarinic drugs can have bothersome anticholinergic side effects. The effects of these agents on cognitive function are a particular concern in older adults. Men with symptoms of overactive bladder in association with benign prostatic hyperplasia may benefit from treatment with alpha-blockers. Promising future directions in drug therapy include the development of more specific antimuscarinic agents, new drug-delivery systems, and drugs that affect the sensory innervation of the lower urinary tract.

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