ABSTRACT

Nocturia, which is commonly thought to be the most bothersome of lower urinary tract symptoms, has a consistently high impact on well-being and quality of life. The reported prevalence of nocturia in patients older than 50 years has been as high as 90%; the prevalence and inconvenience associated with nocturia increase with age. There are several causes of nocturia, which can be related to bladder storage problems (e.g., infection or detrusor overactivity), nocturnal polyuria (e.g., renal insufficiency or autonomic dysfunction), or polyuria (e.g., diabetes mellitus or diabetes insipidus). Nocturia can be mimicked by other urinary and neurologic medical conditions that must be ruled out when evaluating the patient's condition. Treatment of nocturia is generally started with conservative measures (e.g., restriction of fluids, leg elevation, or changes in medication schedules). Behavior modification therapy and pharmacotherapy are considered first-line treatment options; surgery is a second-line treatment option. This article will review the definition, causes, diagnosis, evaluation, and treatment of nocturia using information from randomized controlled trials and unstructured reviews.

individual has to wake at night 1 or more times to void.6,7 Within this definition, night is the period between going to bed with the intention of sleeping and waking with the intention of rising.6 Before this definition was adopted by the International Continence Society (ICS) in 2002, nocturia was commonly defined as 2 or more nocturnal voids. With the standardization of the new definition, nocturia is no longer restricted to a specific number of nocturnal voids.2

Nocturia is equally present in men and women,3 and although it can occur at any age, it is particularly common among the elderly.7 The reported prevalence of nocturia has been as high as 90% in patients older than 50 years; the prevalence increases with age.8 Most men and women aged 80 years or older will rise at least once at night to empty their bladder. Over the seventh decade of life, the prevalence of nocturia increases in a linear fashion in association with increasing age; the inconvenience associated with nocturia also increases.1

The ICS notes the importance of a frequency-volume chart (voiding diary) spanning over 24 to 72 hours for evaluating this symptom. Each urinary void should include a voiding time, amount voided (ie, mL), and degree of urgency. This information can help determine whether nocturia is caused by 24-hour polyuria, nocturnal polyuria, or bladder storage problems.8,9

**CAUSES OF NOCTURIA**

Following the completion of a voiding diary, the patient’s condition can be classified into several types: low nocturnal bladder capacity, nocturnal polyuria, and mixed (combination of nocturnal polyuria and low nocturnal bladder capacity). Nocturnal polyuria is the production of an abnormally large volume of urine during sleep. The ICS defines nocturnal polyuria as a nocturnal urine volume of greater than 20% (young adults) to 33% (older than 65 years) of total 24-hour urine volume; this percentage is age-dependent.8 Nocturnal polyuria also has been defined as nighttime urine production that is greater than 35% of total 24-hour urine volume or greater than 0.9 mL per minute. A patient who has nocturia but does not have nocturnal polyuria would be classified with a bladder storage problem (Table 1).6,7,9,10

Advanced age, childbirth, and menopause also may contribute to the occurrence of nocturia in women.10 In men and women, other causes of nocturia that were not listed earlier in this article include stroke, peripheral edema, myeloneuropathy, and sleep disorders.10,11

Some patients that appear to have bladder storage problems following an analysis of their 24-hour voiding may be experiencing a sleep disturbance. Sleep disorders that may be related to nocturia include the following: insomnia, obstructive and central apnea syndrome, periodic leg syndrome, restless leg syndrome, and sleep-related breathing disorders.10,11

The ICS notes the importance of a frequency-volume chart (voiding diary) spanning over 24 to 72 hours for evaluating this symptom. Each urinary void should include a voiding time, amount voided (ie, mL), and degree of urgency. This information can help determine whether nocturia is caused by 24-hour polyuria, nocturnal polyuria, or bladder storage problems.8,9

### Table 1. Causes of Nocturia

<table>
<thead>
<tr>
<th>Bladder Storage Problems</th>
<th>Nocturnal Polyuria</th>
<th>Polyuria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced functional bladder capacity</td>
<td>Abnormal diurnal secretion of arginine vasopressin or reverse in nocturnal or diurnal urine production</td>
<td>Diabetes mellitus (type 1 or type 2)</td>
</tr>
<tr>
<td>Reduced nocturnal bladder capacity</td>
<td>Primary water diuresis (idiopathic)</td>
<td>Diabetes insipidus (pituitary, renal, gestational, or primary polydipsia)</td>
</tr>
<tr>
<td>Detrusor overactivity • Neurogenic (eg, multiple sclerosis) • Non-neurogenic</td>
<td>Secondary water diuresis (excessive evening intake of fluid, caffeine, or alcohol)</td>
<td></td>
</tr>
<tr>
<td>Bladder hypersensitivity</td>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Bladder outlet obstruction with postvoid residual urine</td>
<td>Sleep apnea syndrome</td>
<td></td>
</tr>
<tr>
<td>Urogenital aging</td>
<td>Autonomic dysfunction</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Renal insufficiency</td>
<td></td>
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<tr>
<td>Interstitial cystitis</td>
<td>Estrogen deficiency</td>
<td></td>
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<tr>
<td>Infection</td>
<td></td>
<td></td>
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<tr>
<td>Inflammation</td>
<td></td>
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</tbody>
</table>

*Urine output >40 mL/kg body weight per 24 hours.
Data from Van Kerrebroeck et al; Marinkovic et al; Weiss et al.
drome, parasomnias, sleep disorders related to medical diseases (eg, chronic obstructive lung disease or cardiac diseases), and sleep disorders related to neurologic diseases (eg, Alzheimer’s disease, Parkinson’s disease, or nocturnal epileptic seizures). In addition, the consequences of sleep deprivation in patients with nocturia can be detrimental. It is estimated that up to 10% of hip fractures in the elderly are secondary to waking and rising at night to void. Mortality rates as a result of cardiac disease, stroke, cancer, and suicide have been shown to be at least 1.5 times higher in elderly patients with disrupted sleep. Sleep deprivation also can affect life expectancy, general well-being, daytime fatigue levels, dysphoric mood occurrence, and immune function, which can affect productivity, vitality, and overall quality of life.6,7,12

Results from a recent study showed that there was no significant association between nocturia and the following factors: hypertension, heart failure, angina pectoris, diabetes mellitus, snoring, use of diuretics or hypnotics, or treatment for these conditions. In this study, a significant association was observed among the number of nocturnal voids and incontinence, daytime urge, and nocturnal thirst, which suggests a close association between nocturia and the occurrence of OAB or the frequency-urgency syndrome.1,3

The symptoms of OAB, including nocturia, can be mimicked by several other medical conditions, such as urinary tract infections, bladder cancer, and neurologic conditions. These medical conditions must be ruled out as part of the routine evaluation of a patient’s condition.13

OAB = overactive bladder.


Overactive bladder is defined by the ICS as urinary urgency, with or without urge incontinence, and is usually accompanied by urinary frequency (voiding ≥8 times in a 24-hour period). OAB also is frequently associated with nocturia (awakening ≥1 times at night to void). All other pathologies should be excluded to confirm a diagnosis of OAB.5,14 The prevalence of OAB was estimated to be approximately 33 million among US residents aged 18 years or older in 2003.15 The worldwide prevalence of OAB was estimated to be between 50 and 100 million in 2001.16

Overactive bladder can be further classified as “with incontinence” or “without incontinence.” The “with incontinence” form includes those individuals with urge incontinence, whereas the “without incontinence” form includes those with irritative symptoms without involuntary leakage. The National Overactive Bladder Evaluation Program reported the incidence of OAB “without incontinence” to be 13.6% in men and 7.6% in women, whereas OAB “with incontinence” had an incidence of 2.6% and 9.3% in men and women, respectively.4,17

Normal urination involves several structures within the body: 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. A disruption in the normal function of any of these structures may contribute to OAB symptoms. Figure 1 compares normal bladder function with the involuntary contractions of the detrusor muscle that are present in OAB.19 In patients with nor-
normal bladder function, the bladder acts like a balloon, expanding with filling to maintain a pressure (<10 cm of water) that is lower than the urethral resistance pressure. Urethral sphincter muscle activity increases as the bladder volume increases. At a urinary volume of 300 to 400 mL, normal voluntary voiding occurs. Bladder emptying occurs following a cessation of muscle activity in the urethral sphincter, a decrease in urethral resistance, and a contraction of the phasic detrusor. Involuntary bladder contractions occur in patients with OAB, which may cause symptoms of urgency and urine loss. Although these contractions can occur at any bladder volume, they most commonly occur at a volume of less than 200 mL. Acetylcholine is the predominant peripheral neurotransmitter involved in bladder contraction in the normal human bladder, and it interacts with M₃ muscarinic receptors (Figure 2). Through a series of steps depicted in Figure 2, acetylcholine causes the release of calcium from the sarcoplasmic reticulum, which results in contraction of the smooth muscle of the bladder. Acetylcholine also can mediate bladder contraction through an interaction with M₂ muscarinic receptors, which inhibits adenylate cyclase activity and decreases intracellular cyclic adenosine monophosphate levels. The sensitivity to muscarinic stimulation can be altered in pathologic states. A small amount of muscle contraction is resistant to atropine in the normal bladder, which is a result of the interaction of adenosine triphosphate with purinergic receptors; however, adenosine triphosphate may play a more important role in OAB. Bladder muscle relaxation can be caused by β₃ adrenergic stimulation.

Assessment of patients with OAB should begin by obtaining detailed information on their current complaints and an evaluation of past genitourinary disorders or other conditions that may cause or contribute to the symptoms of OAB. Questionnaires and patient diaries may be helpful in determining urinary frequency, volume, pattern of voiding, and any contributing factors or potential causes of OAB. Each patient should have a physical examination that includes a genitourinary, pelvic, and rectal examination. Hematuria and infection should be ruled out by evaluating a clean urine specimen. Patients with risk factors for urinary retention (eg, diabetes, spinal cord disease, or benign prostatic hypertrophy) should be evaluated to determine if residual urine after voiding is present. Cystoscopy is indicated in patients with sterile hematuria, risk factors for bladder cancer, or a history of recurrent urinary tract infection.

**EVALUATION**

Treatment of nocturia and the constellation of other symptoms associated with OAB are driven by symptom etiology. Consequently, a proper diagnostic assessment before starting treatment is crucial to achieving treatment success. The evaluation of a patient experiencing nocturia should begin with a complete history, physical examination, and laboratory tests, considering the following important aspects: presence of sleep disorders, urinary problems, fluid intake, medications, and cardiac problems. A 24-hour voiding diary is a very important tool to classify the type of nocturia. These tests can help exclude polyuria and nocturia resulting from different diseases associated with edema (ie, congestive heart fail-

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

- **AMP** = adenosine monophosphate; **ATP** = adenosine triphosphate.
ure or renal disease), reduced renal concentrating capacity (ie, diabetes insipidus or renal insufficiency), and irritative bladder symptoms associated with bacterial cystitis, chronic interstitial cystitis, bladder calculi, or bladder cancer. Endoscopic and urodynamic techniques may be useful when evaluating bladder capacity. Referral to a sleep laboratory may be necessary in patients with underlying sleep disorders.6,7,10,12

**TREATMENT**

When and if warranted, treatment is started with conservative measures that may be escalated as needed. Behavior modification therapy and pharmacotherapy are first-line treatment measures. Symptoms that are refractory to these methods may be treated with surgical options.18

In addition to direct treatment modalities, such as pharmacotherapy or surgery, there are several supportive measures and lifestyle modifications that may resolve or ameliorate nocturia. A detailed medication history should be taken to evaluate the use of medication (diuretics) or timing of medication (eg, administration of diuretic close to bedtime) that may predispose the patient to nocturnal voiding; changes to medication/medication schedule should be made if possible (eg, administration of diuretic 6–8 hours before bedtime or use of time-release diuretics). Restriction of fluids, particularly caffeine and alcohol, may reduce episodes of nocturia.1-3,10 Additional supportive treatment measures include elevation of legs or use of compression stockings to reduce fluid accumulation,1,10 treatment with antidiuretic hormone, or napping in the afternoon.10

**EMPIRIC/BEHAVIORAL TREATMENT**

Behavior modification therapy is a simple, yet fundamental, treatment for nocturia and other symptoms of OAB. Behavior modification therapy addresses physical habits and responses, in addition to self-monitoring practices, to improve control of the voiding process.19 Bladder retraining is a standard method of behavior modification therapy focused on physical habit and is particularly effective in patients with OAB of non-neurologic origin or patients with voiding frequency or urgency without incontinence. The goal of bladder retraining is to restore cortical control of voiding. Patients are instructed to resist the urge to void for a set interval of time that is based on the patient’s bladder diary. As the patient’s ability to suppress voiding urges improves, the interval is gradually extended until the patient can resist the urge to void for 2.5 to 3 hours.16 As compliance may be a challenge for some patients, providing support and encouragement to patients is instrumental to realizing the full benefit of this treatment method.19

Multicomponent behavioral training, which includes pelvic floor muscle training and exercise (sometimes referred to as Kegel exercise), is a method of behavior modification therapy that focuses less on a patient’s voiding habits and more on changing the physiologic responses of the pelvic floor and bladder muscles.13,19 Using training methods, such as biofeedback, patients contract their pelvic floor muscles to inhibit bladder contraction; mean reductions of incontinence with biofeedback-assisted behavior training range from 76% to 86%.19

Behavior modification therapy can be used effectively as stand-alone treatment; however, use of behavior modification therapy in conjunction with another treatment modality is more successful than the use of either treatment alone. Given its utility and safety, behavior modification therapy should be included in every treatment strategy, and all patients should at least be counseled on the basic methods of behavior modification therapy.16,18,19

**PHARMACOTHERAPY**

*Desmopressin acetate*

Desmopressin acetate is a long-acting synthetic analogue of vasopressin. It has an antidiuretic effect and is useful for the treatment of nocturia and nocturnal enuresis.20

Recent randomized, double-blind, placebo-controlled trials demonstrate that desmopressin acetate can reduce nocturia in men and women. During a 3-week oral exposure, desmopressin acetate was shown to reduce the number of nighttime voiding episodes by at least 50% in 33% of the patients compared to 3% of patients in the placebo group. In addition, desmopressin acetate caused a significant increase in the duration of sleep before the first nighttime voiding versus that observed in placebo-treated patients.16

In other studies of specialized patient populations with diabetes insipidus, autonomic dysfunction, and Parkinson’s disease, desmopressin acetate has been shown to be effective in reducing or eliminating nocturia.16
Desmopressin acetate has proven long-term safety and is associated with mild side effects.\textsuperscript{14,20} The main adverse event associated with desmopressin acetate is hyponatremia.\textsuperscript{3,14} In a recent meta-analysis, the incidence of hyponatremia in older adults using desmopressin acetate for nocturia was 7.6%.\textsuperscript{3} Desmopressin acetate should be used with caution in older adult patients, particularly those with coronary heart disease, hypertension, cardiac insufficiency, or epilepsy.\textsuperscript{3,20}

**Imipramine**

The tricyclic antidepressant, imipramine, has been shown to be useful for the treatment of nocturnal enuresis and nocturia.\textsuperscript{20} Imipramine relaxes the bladder and increases urethral resistance to flow. The effects of imipramine are mediated by its ability to increase synaptic levels of norepinephrine and serotonin through inhibition of their reuptake by presynaptic membranes. In addition, imipramine exerts anticholinergic and \( \alpha \)-adrenergic properties and acts as a local anesthetic. This agent must be used with caution because it can cause postural hypotension and cardiac conduction abnormalities.\textsuperscript{14,20}

**Muscarinic receptor antagonists**

Nocturia caused by detrusor overactivity can be treated with an antimuscarinic agent.\textsuperscript{14} Muscarinic receptor antagonists can abolish or reduce detrusor overactivity and the symptoms of OAB. The reduction in detrusor overactivity by muscarinic receptor antagonists is mediated by the M\textsubscript{3} receptor subtype and probably also by the M\textsubscript{2} receptor. Antagonism of the M\textsubscript{3} receptor subtype by antimuscarinic agents prevents activation of phospholipase C and subsequent generation of inositol triphosphate. Inositol triphosphate is the second messenger responsible for the release of Ca\textsuperscript{2+} from the sarcoplasmic reticulum that activates the contractile machinery responsible for bladder contraction.\textsuperscript{21}

Blockade of these and other muscarinic subtypes present in nonbladder tissues is responsible for some of the common adverse events associated with antimuscarinic drugs. Dry mouth with antimuscarinic agents may occur as a consequence of antagonism of the M\textsubscript{1} and M\textsubscript{3} receptors that mediate salivary gland secretion. Constipation may be present because of blockade of the M\textsubscript{3} receptor involved in gastrointestinal (GI) motility. Blurred vision associated with the use of antimuscarinic agents also is mediated by M\textsubscript{3} receptors that mediate contraction of the ciliary muscle. Problems with cognitive function that are mediated through blockade of the M\textsubscript{1} receptor may occur with the use of antimuscarinic agents; however, this is usually not reported because several of the commonly used drugs to treat OAB, such as tolterodine and trospium, do not readily cross a normal blood-brain barrier. This may be more of a concern with oxybutynin, a tertiary amine that is able to pass into the central nervous system (CNS) through a normal blood-brain barrier.\textsuperscript{21}

**Oxybutynin.** Oxybutynin is a nonselective muscarinic receptor antagonist that also has direct muscle-relaxant effects and local anesthetic actions. It exhibits high affinity for muscarinic receptors in human bladder tissue and shows a slightly higher affinity for M\textsubscript{1} and M\textsubscript{3} receptors than for M\textsubscript{2} receptors. Its active metabolite, N-desethyl oxybutynin, has similar pharmacologic properties to its parent compound and occurs at much higher concentrations. Thus, it is assumed that the metabolite is the predominant biologically active compound.\textsuperscript{21} To date, no studies have been performed to evaluate the effect of oxybutynin on nocturia as a primary endpoint.

Oxybutynin is available in immediate- and extended-release formulations. The extended-release formulation allows once-daily dosing and shows advantages over the immediate-release formulation.\textsuperscript{21}

**Tolterodine.** Tolterodine also is a nonselective muscarinic receptor antagonist, but it is thought to display functional selectivity of the bladder over the salivary glands. Tolterodine also has an active metabolite with pharmacologic properties similar to the parent compound that is thought to contribute significantly to its biological action.\textsuperscript{15,21} Tolterodine is available in immediate- and extended-release formulations. The extended-release formulation allows once-daily dosing and shows advantages over the immediate-release formulation through a decrease in side effects.\textsuperscript{21}

**Placebo-controlled tolterodine extended-release study.** A randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study was completed to evaluate the effect of tolterodine extended release versus placebo on nocturia in patients with symptoms of OAB. This study included the largest percentage of patients with OAB, with and without incontinence to date.\textsuperscript{22}
After a 1-week screening period, patients entered a 2-week, single-blind placebo run-in period. At the completion of the run-in period, patients with 25% or less placebo response were eligible for the randomized portion of the trial. Eligible patients were randomized to receive tolterodine extended release 4 mg (n = 429) or placebo (n = 421) once daily (≤4 hours before bedtime) for 12 weeks.

The study population consisted of patients (≥18 years of age; approximately 50% were female) with OAB symptoms of urgency (with or without urge incontinence), frequency (≥8 micturitions per 24 hours), and nocturia (mean of ≥2.5 nocturia episodes per night), and a mean volume voided of 200 mL or less per micturition and mean nighttime volume voided of 40% or less of the 24-hour volume.

Patients completed 7-day micturition diaries before the baseline, randomization, week 4, and week 12 visits. Patients also recorded their sleep cycles (the time the patient intended to fall asleep until the time the patient intended to awaken or actually awakened [whichever came earlier]). For each micturition, patients recorded the level of urgency associated with it on a 5-point urgency rating scale: 1 = no urgency; 2 = mild urgency; 3 = moderate urgency; 4 = severe urgency; and 5 = urge incontinence. For the purposes of this study, all micturitions during the sleep cycle were considered nocturia; nocturia episodes included any micturitions at any urgency level (ratings 1–5).

The primary efficacy endpoint was the change in the mean number of nocturia episodes per night from baseline to week 12. There were many secondary efficacy variables, including changes in nocturia or other OAB symptoms, patient assessment of treatment benefits/satisfaction, and quality of life.

Although there was no statistical evidence of the superiority of tolterodine extended release over placebo with respect to its effects on the mean number of nocturia episodes per night (primary efficacy endpoint), results of nocturia-related secondary efficacy variables showed a statistically significant difference (P <.05) on several measures at week 12, favoring tolterodine extended release over placebo. These differences included:

- Mean numerical decrease and median percentage decrease in nocturia episodes from baseline in patients whose nocturia episodes had urgency ratings of 3 to 5.

Tolterodine extended release also was associated with statistically significant improvements on several quality-of-life measures and in patient perception of treatment benefit/willingness to continue treatment at week 12 compared to placebo. Tolterodine extended release did not affect normal micturitions (urgency ratings of 1–2) that may lead to the development of urinary retention. This finding further defines the safety and use of this therapy to address pathologic voiding associated with day and nighttime OAB. Dry mouth and constipation were the most common adverse events in the tolterodine extended-release group; the incidence of dry mouth was 8.9% for tolterodine extended release versus 1.9% for placebo, and the incidence of constipation was 3.0% for tolterodine extended release versus 1.9% for placebo. Other adverse events were infrequent (incidence of <3% in each treatment group); the incidences of other adverse events were similar between treatment groups or slightly higher in the placebo group. The incidences of treatment-related adverse events in this study were substantially lower than in previous studies; this may be partly explained by the nighttime dosing used in this study versus the morning dosing used in previous studies.

Trospium. Trospium is a nonselective antimuscarinic agent that binds to M1, M2, and M3 muscarinic receptors. It is a quaternary ammonium compound that is poorly absorbed from the GI tract with low bioavailability that also does not readily cross the blood-brain barrier and theoretically would have reduced cognitive effects in people with a normal blood-brain barrier system.

In a randomized, double-blind, placebo-controlled phase III study, the efficacy and tolerability of trospium were examined in 523 patients (74.4% female) with OAB and urge incontinence. Eligible patients had urinary urgency, a minimum voiding frequency of 70 voids per week, and 7 or more urge incontinence episodes per week. Patients were randomized to receive trospium 20 mg twice a day (n = 262) or placebo (n = 261) for 12 weeks.

Overall, patients administered trospium showed less frequency, less urgency, and fewer incontinence episodes than those patients administered placebo.
The mean number of urgent voids per day and nocturnal voids per night were significantly reduced from baseline to 12 weeks in the trospium group compared to the placebo group ($P \leq 0.05$). In addition, the average volume per void over 24 hours significantly increased from baseline to 12 weeks in the trospium group compared to the placebo group ($P <.001$). There also was a significant improvement in quality of life in the trospium-treated patients versus those in the placebo group, as measured by parameters, such as the impact of urge incontinence on travel, social relationships, and emotional health.25

The most commonly reported adverse events in the trospium-treated group versus the placebo group were dry mouth (21.8% vs 6.5%, respectively), constipation (9.5% vs 3.8%, respectively), and headache (6.5% vs 4.6%, respectively). Adverse event-related withdrawal from the study was observed in 8.8% of the trospium-treated patients compared to 5.7% of the placebo group. The frequency of CNS-related adverse events was comparable between groups.26 In 2 randomized studies, trospium caused a mean increase in heart rate of 3 and 4 beats per minute compared to placebo.26 This unique finding is attributed to its selective effect on the $M_3$ receptor in cardiac tissue.

**Selective $M_3$-receptor antagonists**

Darifenacin and solifenacin are selective antimuscarinic $M_3$-receptor antagonists. These agents block activation of the $M_3$ receptor that is primarily responsible for normal micturition contraction in the human detrusor muscle. Although $M_3$-receptor–mediated activity in nonbladder tissues includes salivation, GI motility, and contraction of ciliary muscles, $M_3$-receptor antagonists theoretically have fewer systemic side effects than nonselective antimuscarinic agents. However, the clinical efficacy and adverse events of a drug are not only based on its receptor affinity, but also on its pharmacokinetics and the importance of muscarinic receptors for a given organ function.14,21,27

**Darifenacin.** The efficacy and safety of darifenacin has been evaluated in a pooled analysis of 3 phase III studies that involved 1059 patients (aged 19–88 years; 85% female) with at least a 6-month history of OAB symptoms, yet nocturia has not been evaluated as a primary or secondary endpoint to date. After a 2-week washout and a 2-week placebo run-in period, patients were randomized to receive controlled-release darifenacin 7.5 mg ($n = 335$) or matched placebo ($n = 271$) or controlled-release darifenacin 15 mg ($n = 330$) or matched placebo ($n = 384$) for a 12-week period.27

Both doses of darifenacin were significantly superior to placebo in improving OAB symptoms, as shown by decreases in the median number of incontinence episodes per week, decreases in the median micturition frequency per day, increases in bladder capacity, and decreases in the frequency and severity of urgency ($P <.01$ for all).27

In a safety analysis of the described pooled phase III studies in 1049 patients, controlled-release darifenacin was found to be safe and well tolerated. Side effects were dose-related and of mild-to-moderate severity. Dry mouth and constipation were the most commonly reported adverse events. Dry mouth was observed in 20%, 35%, and 8% of patients receiving controlled-release darifenacin 7.5 mg, controlled-release darifenacin 15 mg, and placebo, respectively. Constipation was reported in 15%, 21%, and 6% of patients receiving controlled-release darifenacin 7.5 mg, controlled-release darifenacin 15 mg, and placebo, respectively. Low rates of withdrawal were observed: controlled-release darifenacin 7.5 mg, 0.6%; controlled-release darifenacin 15 mg, 2.1%; and placebo, 0.3%.27

**Solifenacin.** Solifenacin was studied in 2 large, multinational, randomized, double-blind, placebo-controlled phase III trials with more than 1800 patients. Following a 2-week placebo run-in period, patients were treated with solifenacin 5 mg or solifenacin 10 mg versus placebo (or versus an active control tolterodine in 1 study) in a double-blind manner. Described in this section are the data pooled from these 2 studies that focus on solifenacin 5 mg as the recommended dose.28

The mean age of patients in these pooled studies was 56.9 years in the placebo group and 56.7 years in the solifenacin 5-mg group. Patients were 78.7% and 78.1% female in the placebo- and solifenacin-treated groups, respectively. Eligible patients had the following inclusion criteria: 8 or more micturitions per 24 hours and 1 or more episodes of incontinence per 24 hours and/or 1 or more episodes of urgency per 24 hours at baseline. The primary efficacy variable was change from baseline in micturition frequency per 24 hours.28

Solifenacin was associated with statistically significant improvements based on median percentage change from baseline to endpoint on the following parameters: number of micturitions, urgency episodes,
and incontinence episodes per 24 hours, and volume voided per micturition (P < .05 for all); there were no statistically significant improvements in the placebo group. A post hoc analysis was performed in patients treated with the 5-mg dose of solifenacin to evaluate changes in the number of nocturnal voids (defined as those voids occurring after bedtime and before the time of awaking as listed by the study patient in the voiding diary). A 33% reduction in nocturnal voids was observed in solifenacin-treated patients compared to a 25% reduction with placebo (P = .008).28

The most common adverse events described in these pooled phase III studies were dry mouth, constipation, and blurred vision of mild-to-moderate severity. Dry mouth was reported in 10.9% of patients treated with solifenacin 5 mg compared to 3.5% of patients in the placebo group. Constipation was observed in 5.4% of patients receiving solifenacin 5 mg versus 1.9% of placebo-treated patients. Blurred vision was reported in 3.8% of the solifenacin group compared to 2.5% in the placebo group. In these pooled phase III studies, fewer than 3% of the patients receiving solifenacin 5 mg withdrew because of adverse events versus 3.5% of patients in the placebo group.28

Table 2 summarizes the receptor activity, dose, and cost of commonly used muscarinic receptor antagonists used for the treatment of nocturia and OAB.29-34

## Table 2. Muscarinic Receptor Antagonists Used in the Treatment of Nocturia and OAB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor Activity</th>
<th>Dose</th>
<th>Cost (AWP)</th>
</tr>
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<tbody>
<tr>
<td><strong>Oxybutynin</strong></td>
<td>M&lt;sub&gt;1&lt;/sub&gt; &amp; M&lt;sub&gt;3&lt;/sub&gt; &gt; M&lt;sub&gt;2&lt;/sub&gt;</td>
<td>2.5–5.0 mg PO tid (short-acting)</td>
<td>Short-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–30 mg PO qd (long-acting)</td>
<td>5 mg = $1.15/tablet</td>
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<tr>
<td></td>
<td></td>
<td>3.9 mg over one 96-hour</td>
<td>Long-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>period (transdermal)</td>
<td>5 mg = $3.48/tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg = $3.49/tablet</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Nonselective</td>
<td>1–2 mg PO bid (short-acting)</td>
<td>Short-acting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 mg PO qd (long-acting)</td>
<td>1 mg = $1.95/tablet</td>
</tr>
<tr>
<td>Trospium</td>
<td>Nonselective</td>
<td>20 mg PO bid</td>
<td>20 mg = $1.64/tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg = $1.64/tablet</td>
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<tr>
<td>Darifenacin</td>
<td>M&lt;sub&gt;3&lt;/sub&gt;</td>
<td>7.5–15 mg PO qd</td>
<td>7.5 mg = $3.33/tablet</td>
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<td></td>
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<td>15 mg = $3.33/tablet</td>
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<tr>
<td>Solifenacin</td>
<td>M&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5–10 mg PO qd</td>
<td>5 mg = $3.51/tablet</td>
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<tr>
<td></td>
<td></td>
<td>10 mg = $3.51/tablet</td>
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AWP = average wholesale price; bid = twice a day; OAB = overactive bladder; PO = orally; qd = every day; td = 3 times daily.

Data from Ouslander; Andersson; Sanctura [package insert]; Ditropan XL [package insert]; Detrol LA [package insert]; Detrol [package insert]; Enablex [package insert]; VESIcare [package insert]; Medi-Span.
participated in this extension trial, 8 from the behavioral therapy group and 27 from the pharmacotherapy group. Although the original study showed that both therapies were effective as monotherapy, significant improvements were observed when combination therapy was instituted.36

The effectiveness of tolterodine can be augmented with the addition of a simplified behavioral therapy/bladder training regime. In a single-blind multicenter study, 505 patients (median age, 63 years) with symptoms of urinary frequency ($\geq 8$ micturitions per 24 hours) and urgency, with or without incontinence, were randomized to tolterodine 2 mg twice a day plus simplified behavioral therapy or tolterodine 2 mg twice a day as monotherapy. Changes in voiding diary variables (number of voids in 24 hours [primary efficacy variable], incontinence episodes in 24 hours, volume voided per void, and urgency episodes in 24 hours) were evaluated after 2, 12, and 24 weeks of treatment.37

There was a progressive and statistically significant decrease in voiding frequency in both treatment groups when compared to baseline. The addition of behavioral therapy significantly increased the efficacy of tolterodine in reducing voiding frequency ($P < .001$). At the study's end, the median percentage reduction in voiding frequency for those patients receiving combined therapy was 33%, whereas those patients receiving tolterodine alone had a 25% decrease ($P < .001$).37 A subanalysis of the effect on nocturia as a secondary endpoint has yet to be performed in this study.

**SURGERY**

Nocturia that does not resolve with pharmacotherapy, empiric treatment, or combination therapy may respond to surgical intervention. This summary includes information and data on transurethral incision of the prostate or transurethral resection of the prostate (TURP), surgery for pelvic organ prolapse, sacral nerve neuromodulation (SNN), detrusor myectomy, and augmentation cystoplasty, which also is known as clam cystoplasty.

**Transurethral incision of the prostate and TURP**

Nocturia has been shown to be a symptom of benign prostatic hyperplasia (BPH). In a study that evaluated the impact of TURP on nocturia in 138 patients with BPH, there were decreases in the percentage of patients with nocturia and in average nocturia scores after TURP.38

**Surgery for pelvic organ prolapse**

Women with pelvic organ prolapse often exhibit urinary symptoms, including stress incontinence, dysfunctional voiding, urinary hesitancy, and urinary frequency. These patients can be treated with surgical measures. Relief of lower urinary tract symptoms is among the primary goals of surgery. Prolapse surgery can be performed vaginally, abdominally, or laparoscopically. Surgical measures can be reconstructive (eg, sacral colpopexy) or obliterator (eg, colpocleisis).39

**Sacral nerve neuromodulation**

Initially approved in 1997 for intractable urge incontinence, SNN (also known as sacral nerve stimulation) is now a surgical option for patients with chronic symptoms of OAB who have failed conservative treatment methods and who suffer from diminished quality of life because of their symptoms. Possible candidates for SNN must not have neurologic impairment or structural bladder abnormality, such as scarring from radiation therapy or a diverticulum.40 The procedure is contraindicated in patients with benign prostatic hypertrophy, cancer, or urethral stricture.10 SNN also could potentially be contraindicated in patients who are incapable of operating the device or providing feedback on the comfort of stimulation and in patients who may require magnetic resonance imaging studies or other stimulation devices, such as a cardiac pacemaker, in the future.33 SNN is a minimally invasive, effective, and safe surgical treatment option for patients with refractory OAB; however, it is an expensive treatment option that should only be considered in patients with symptoms that are refractory to conservative treatment.16

Candidates for SNN first undergo a 3- to 5-day trial of neuromodulation using a temporary device.16 If symptoms have improved by more than 50% at the conclusion of the neuromodulation trial, a permanent device is implanted in the patient. The magnitude of power transmitted by an implanted device can be adjusted by using an extracorporeal handheld device. Improvement in nocturia following SNN is apparent, with a reduction of more than 60% in episodes of nocturia. Up to 33% of patients who undergo SNN epe-
rience adverse events, such as implant site pain, lead migration, infection, and device-related issues.\textsuperscript{10} The complication rate associated with SNN is low,\textsuperscript{16} and the reversible procedure of SNN is generally recognized as an effective and safe treatment for symptoms of OAB, including nocturia.\textsuperscript{10}

**Detrusor myectomy**

Bladder augmentation is a surgical treatment of severe bladder dysfunction that is refractory to conservative treatment. Detrusor myectomy, also known as bladder autoaugmentation, is an effective method of bladder augmentation and has less associated morbidity than augmentation cystoplasty.\textsuperscript{41} In detrusor myectomy, a portion of detrusor muscle is removed from the dome and/or anterior wall of the bladder to expose the bladder mucosa, which is left intact to create a diverticulum that increases total bladder capacity. Removal of the detrusor muscle portion also reduces the magnitude and efficiency of residual bladder contractions. In general, subjective effects of detrusor myectomy are apparent almost immediately after surgery; however, patients who experience persistent detrusor contractions and/or poor compliance may be suitable candidates for alternate surgical treatment options, including augmentation cystoplasty.\textsuperscript{41,42}

**Augmentation cystoplasty**

Augmentation cystoplasty is the classic procedure of bladder augmentation; this procedure is associated with improvement in bladder capacity and compliance. In augmentation cystoplasty, the bladder is structurally enlarged by attaching a detubularized segment of ileum to a semilunar transverse cystotomy of the posterior bladder wall.\textsuperscript{42} Although this procedure effectively improves bladder storage capacity, patients without neurologic impairment who undergo augmentation cystoplasty must perform intermittent self-catheterization, which is a consideration when screening candidates for this procedure. Also, augmentation cystoplasty is associated with significant risk of complications (overall complication rate, ~20%).\textsuperscript{42} Complications can occur early (eg, wound cellulites, sepsis, small bowel obstruction and leak, vesicocutaneous fistula caused by long-term suprapubic tract, extraperitoneal urine extravasation, or prolonged ileus) or late (eg, bladder calculi, spontaneous bladder perforation caused by not performing self-catheterization, hyperchloremic metabolic acidosis, small bowel obstruction, or vitamin B\textsubscript{12} deficiency) relative to surgery.\textsuperscript{41,42}

**Scientific Evidence for Treatment of Nocturia**

Medication with or without behavioral therapy is the current standard of care for patients with nocturia. As normal and involuntary detrusor contractions are mediated by activation of muscarinic receptors, antimuscarinic agents are the treatment of choice when considering pharmacologic therapy for nocturia.\textsuperscript{13,16}

As outlined in this review, nocturia has seldom been evaluated as a primary or secondary outcome in studies of antimuscarinic treatment for OAB, despite its potential effect on the nocturnal part of the voiding cycle and its associated effect on quality of life. In a large randomized, double-blind, placebo-controlled, multicenter study in male and female patients with OAB with and without urge incontinence, the effect of tolterodine extended release on nocturnal voiding frequency was associated with significant improvements over placebo in several nocturia-related outcomes, such as severity of nighttime urgency and decrease in nocturia episodes in patients who had moderate-to-severe episodes or nighttime urge incontinence. In studies of patients with OAB with urge incontinence only (and mostly women), trospium and solifenacin were associated with significantly greater decreases in nocturnal voids than placebo, although nocturnal voids were not the primary outcome of the studies. Thus, reduction of nocturia can be attained through antimuscarinic pharmacotherapy, although additional data are warranted to further define the role of antimuscarinics for the treatment of nocturia in specific OAB patient populations.\textsuperscript{21,25,28}

Supplemental to pharmacotherapy are behavioral treatments, such as behavior modification, bladder retraining, and pelvic muscle exercises, which can be beneficial. Pelvic floor muscle rehabilitation through Kegel exercises can relieve OAB symptoms, but their effect on nocturia has not been rigorously evaluated. Bladder retraining can serve to re-establish cortical control over the neurologic axis and is particularly helpful in patients with a non-neurologic etiology and for patients complaining of frequency or urgency without incontinence, yet its isolated effect on nocturia remains to be studied.\textsuperscript{13,16}
REFERENCES