Overactive bladder is a highly prevalent condition, affecting approximately 33 million adults in the United States, which is approximately 16.5% of the population. The condition affects an equal number of men and women, though the severity and nature of the condition’s symptoms may be determined by gender (e.g., overactive bladder without urge incontinence is more common in men than in women).2

The International Continence Society (ICS) defines overactive bladder as urgency (with or without urge incontinence), usually with frequency and nocturia, in the absence of other pathologic or metabolic conditions that might explain the symptoms.3 Urgency is defined as a sudden and compelling desire to pass urine that is difficult to defer. Nocturia is defined as waking one or more times per night to void urine. The ICS definition of overactive bladder describes the condition using patient symptoms rather than urodynamic findings. This is an important distinction, as urodynamically detectable detrusor overactivity may not be present in up to 25% of patients with overactive bladder.4

Patient quality of life (QOL) is substantially impacted by this disorder as social, psychological, occupational, domestic, physical, and sexual functioning are all affected.5 As a consequence, severe bladder symptoms can have a tremendous negative impact on patient social interaction, sexual intimacy, and even willingness to leave home. In addition, while most people recognize that incontinence, frequency, and nocturia affect patients’ QOL, a 2004 survey6 suggests that urinary urgency alone also has a significant impact on QOL.

In fact, the impact of this disorder extends beyond basic QOL issues and into financial implications and patient comorbidities. In 2000, for example, the total costs associated with overactive bladder in the United States were estimated at $12 billion.7 These expenses comprise indirect costs (e.g., lost productivity) and direct costs, including diagnosis, treatment, and routine care. Comorbidities associated with this condition include skin infections, urinary tract infections, depression, and, in older adults, injuries associated with falls that occur as a result of hurrying to the toilet.

The past 10 years have seen many developments related to overactive bladder, both in terms of physicians’ greater understanding of the implications of this condition and the treatment options available. In 2003 and 2004, the US Food and Drug Administration (FDA) approved three new agents—darifenacin, solifenacin succinate, and trospium chloride—for the treatment of patients with overactive bladder. Some of these agents differ substantially from earlier compounds and may allow for optimization of therapy, particularly among older patients. The present article provides an overview of the pathophysiology of overactive bladder and reviews the current diagnostic approaches as well as treatment strategies.

Pathophysiology

The two functions of the bladder are to store and void urine. The process of micturition involves neural circuits (afferent and efferent neural pathways and central and peripheral neurotransmitters) in the brain and spinal cord that coordinate the anatomic components of the lower urinary tract. However, the direct connection and contribution of these elements are not completely understood.

As bladder volume increases, involuntary contractions of the detrusor muscle are often associated with overactive

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Recognition and Diagnosis

Overactive bladder has sometimes been referred to as the “hidden condition” because, despite the impact on their lives, patients are often embarrassed by the condition and do not want to discuss it with their physicians. Many patients also consider overactive bladder to be a normal part of aging and may assume nothing can be done to alleviate their symptoms.

To manage overactive bladder effectively, physicians must first encourage patients to speak openly with them. Given the prevalence of this condition, annual physical examinations or medical check-ups may be a good opportunity to discuss urinary problems with patients. A simple question such as “Are you bothered or worried by your urine control?” may be sufficient to initiate discussion. If a patient is concerned about his or her urine control, the physician should ask the patient to fill out a diary detailing the time, estimated volume of urine voided, and experience of each urination (ie, whether or not the urination was associated with urgency). Such a diary can be useful at the diagnosis stage to establish the extent and severity of any urinary problems.

Achieving a differential diagnosis is a relatively straightforward process that can be performed in the physician’s office using a simple diagnostic algorithm for overactive bladder (Figure 1). For patients presenting with one or more symptoms of this condition (frequency, urgency, urge incontinence, or nocturia), a patient history should be obtained— including information about past genitourinary disorders—to exclude symptoms resulting from comorbid conditions or concomitant medications.

A physical examination of the abdomen, rectum, pelvis, and genitalia should be performed to exclude obvious pathologies such as inflammation, prolapse, or masses. Urinalysis should be performed to exclude conditions that are sometimes associated with overactive bladder (eg, bacteria in the urine would suggest an infection, excess glucose in the urine could be a result of diabetes, and blood or protein in the urine may indicate kidney disease). In instances where urinalysis results suggest an associated condition, it may be necessary to refer the patient for additional diagnostic testing. For example, if a patient has unexplained hematuria, a urology referral for cystoscopy is recommended. In the absence of infection or other pathologies, including bladder cancers, a diagnosis of overactive bladder can be made.

Urodynamic assessment can also be used in the diagnosis of overactive bladder, though the value of such assessments for this purpose is controversial. A recent report suggests that a positive urodynamic assessment for incontinence does not influence treatment success, indicating that these expensive, invasive, and complex tests should be reserved for patients with unusual symptoms or when initial therapy is unsuccessful.

Treatment Strategies

Treatment of overactive bladder can include nonpharmacologic interventions, pharmacologic interventions, or a combination of both. Approaching these options in consideration of the whole patient allows physicians to determine the best therapy.

Nonpharmacologic Treatment

Nonpharmacologic interventions in the treatment of patients with overactive bladder usually involve “bladder retraining,” which generally consists of patient education, scheduled voiding, and urge-suppression techniques. Educating patients about bladder function is important in deterring patients from using harmful coping behaviors, such as restricting fluid intake. Patients should also be alerted that consuming certain products (eg, alcohol, caffeine, spicy foods, and tomato-based products) may exacerbate their condition. In addition, scheduled voiding can help patients correct the habit of frequent urination and increase bladder capacity. Finally, urge suppression

Figure 1. Algorithm to assist physicians in diagnosing patients with overactive bladder.
techniques such as pelvic floor muscle exercises (Kegel exercises), which involve tightening and relaxing the muscle around the rectum, and biofeedback-assisted training can strengthen and improve voluntary control of muscles.

Within the primary care setting, bladder retraining can be labor-intensive and time-consuming for both the patient and the physician, and successful implementation requires considerable motivation and commitment on the part of the patient. Despite these obstacles, bladder retraining should always be considered in the management of overactive bladder, as it is a safe treatment option from which many patients can benefit. Moreover, behavioral modifications that occur as a result of bladder retraining may enhance the outcomes obtained with pharmacologic interventions.

Pharmacologic Treatment

While a range of drugs have been used in the past for the management of overactive bladder—from smooth muscle relaxants to tricyclic antidepressants—antimuscarinic agents now form the mainstay in the armamentarium used to control the symptoms associated with this condition. Conventional wisdom holds that antimuscarinic agents act by blocking the muscarinic receptors on the detrusor muscle (which are normally stimulated by acetylcholine released from parasympathetic nerves) thereby diminishing the intensity of involuntary detrusor muscle contractions. Emerging research, however, suggests that anti-muscarinic agents mainly act during the storage phase, decreasing urge and increasing bladder capacity, during which time there is normally no activity in the parasympathetic nerves. Studies are now focusing on the ability of antimuscarinics to modulate afferent fibers as a means of effectiveness.

Antimuscarinic agents differ at the structural and molecular level, resulting in different metabolism, absorption, potency, and selectivity profiles, as follows:

- Tertiary vs quaternary amines—Antimuscarinic agents are either tertiary or quaternary amines, the latter of which are lipophilic, resulting in a limited ability to cross the blood-brain barrier. (Tertiary amines, on the other hand, are hydrophilic.) Consequently, quaternary amines minimize central nervous system side effects, such as confusion and blurred vision. This feature may be particularly important in elderly patients with overactive bladder. Such patients may be more sensitive to the cholinergic effects of antimuscarinic therapy as a result of reductions in metabolism and elimination—in addition to increased risk of pharmacokinetic drug interactions. Elderly patients are also more likely to be taking prescription and over-the-counter medications with anticholinergic properties, which, combined with antimuscarinics for the treatment of overactive bladder, may result in a substantial anticholinergic load, putting them at risk for cognitive side effects.

The hydrophilicity of quaternary amines also affects the rate of absorption across the gastrointestinal tract, which in turn may require physicians to adjust doses individually to each patient.

- Muscarinic receptor subtypes and selectivity—The five known muscarinic receptor subtypes (M1 through M5) play key physiologic roles in the brain as well as in the peripheral organs. The predominant muscarinic receptors (M1 receptors) are present in the bladder wall and urothelium and may be involved with detrusor contraction. The smaller population of M3 receptors mediates direct contraction of the detrusor muscle. Although the presence of the M4 and M5 receptors are minimal, the M1 receptor is thought to play an important role in the central nervous system. Therefore, cognitive changes may be seen with drugs that bind to the M1 receptor.

Selectivity for muscarinic receptor subtypes has been proposed as a mechanism by which antimuscarinic agents can provide efficacy for overactive bladder while minimizing adverse effects. The clinical impact of subtype selectivity on adverse-effect profiles, however, remains to be proven.

- Metabolism and excretion—The metabolism of antimuscarinic agents by cytochrome P-450 enzymes in the liver may result in interactions with concomitant medications metabolized by the same pathways. Antimuscarinic agents not metabolized in the liver may therefore be a better treatment option, particularly for elderly patients with overactive bladder in whom polypharmacy is common. Agents excreted in an active form may provide additional and prolonged clinical efficacy, as they may deliver local effects in the bladder (eg, to the urothelium). An understanding of these differences—particularly in how they impact the efficacy and safety of the agents—is important and allows physicians to make informed decisions about the most suitable treatment option for their patients’ needs.

There are currently five antimuscarinic agents available in the United States for the treatment of overactive bladder: oxybutynin, tolterodine tartrate, darifenacin, solifenacin (all tertiary amines), and trospium (a quaternary amine). The tertiary amines are predominantly metabolized by the cytochrome P-450 enzymes in the liver with little active compound being excreted in the urine. Of administered doses, <0.1%, <1%, and <15% of unchanged oxybutynin, tolterodine, and solifenacin, respectively, is excreted in the urine. For darifenacin, 3% of the dose excreted in urine is unchanged. By contrast, trospium (quaternary amine) is minimally metabolized in the liver, with the majority (60%) of the absorbed compound being excreted in its active form. The different pharmacologic profiles of these antimuscarinic agents may contribute to the differences in safety and efficacy seen in clinical practice studies.
release oral tablets (oxybutynin chloride) and as a transdermal patch.30,35 The most commonly reported adverse event for extended-release oral oxybutynin is dry mouth, experienced by up to 68% of patients and causing some patients to discontinue therapy.36 Transdermal oxybutynin results in a far lower incidence of dry mouth (<10%) but is associated with local skin reactions such as pruritis.30 This lower incidence of dry mouth is believed to result from the lack of presystemic metabolism to form an active metabolite with similar properties to the parent compound (N-desethyl-oxybutynin).

Certain attributes of oral oxybutynin, such as its relatively small size, highly lipophilic nature, and its neutral charge, make it more likely to cross the blood-brain barrier than other antimuscarinic agents available for the treatment of overactive bladder. Therefore, central anticholinergic effects, which could result in cognitive impairment, are a concern in patients (particularly elderly patients) taking oxybutynin.37

Tolterodine, which is orally administered, has been available in the United States since 1998. Originally launched as an immediate-release formulation, tolterodine is now available as an extended-release formulation. Initiated and maintained at a dose of 4 mg once daily, tolterodine extended-release for-

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### Table: Differentiating features of antimuscarinic agents and their potential impact on safety, efficacy, and tolerability

<table>
<thead>
<tr>
<th>Feature</th>
<th>Physiologic Effect</th>
<th>Clinical Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Tertiary amines</td>
<td>Allows transfer across the blood-brain barrier into CNS</td>
<td>May result in adverse cognitive effects, particularly among elderly patients</td>
</tr>
<tr>
<td></td>
<td>Allows good absorption across GI tract</td>
<td>Does not necessitate dose adjustment</td>
</tr>
<tr>
<td>□ Quaternary amines</td>
<td>Limits transfer across the blood-brain barrier into CNS</td>
<td>Reduces the potential for cognitive adverse effects</td>
</tr>
<tr>
<td></td>
<td>Limits absorption across GI tract</td>
<td>Necessitates dose adjustment</td>
</tr>
</tbody>
</table>

**Affinity for Muscarinic Receptor Subtypes**

□ M₁ | The M₁ receptor may play an important role in cognition | Reduced or absent affinity for M₁ is proposed as beneficial, as this may reduce the incidence of cognitive adverse effects |
□ M₂ | In the detrusor muscle, 80% of the muscarinic receptors are M₂. They may be indirectly involved in detrusor smooth muscle contraction via inhibition of muscle relaxation by β-adrenoceptors | Reduced or absent affinity for M₂ is proposed as a mechanism for reducing the incidence of cardiac adverse effects. If M₂ receptors are involved in contraction, reduced affinity may also impact efficacy |
□ M₃ | In the detrusor muscle, 20% of the muscarinic receptors are M₃ receptors. They are believed to be the main receptor subtype responsible for normal micturition contraction | Reduced affinity for the M₃ receptor subtype would lower the ability to inhibit unwanted detrusor contractions. Overly aggressive M₃ blockade could result in constipation |
□ M₄ | Not present in the bladder in significant numbers | Unknown |
□ M₅ | Not present in the bladder in significant numbers | Unknown |

**Metabolism and Excretion**

□ Metabolism by cytochrome P-450 enzymes | Antimuscarinics that are extensively metabolized via this route may be involved in drug-drug interactions | The effects of compounds metabolized via the same pathways may be altered |
□ Excretion in active form | Allows “local” inhibition of bladder muscarinic receptors | May result in prolonged and additional efficacy |

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**Figure 2.** Differentiating features of antimuscarinic agents and their potential impact on safety, efficacy, and tolerability.15-20 Tertiary amines are not readily soluble in water but are readily soluble in fats, while quaternary amines are readily soluble in water but not in fats. All muscarinic receptor subtypes are found in the central nervous system. In addition, M₁ receptors are found in autonomic ganglia and secretory glands; M₂ receptors are found in the heart; and M₃, M₄, and M₅ receptors are all found in smooth muscle. **Abbreviations:** CNS, central nervous system; GI, gastrointestinal.
### Table

**Efficacy and Tolerability of Antimuscarinic Agents Using Data From Key Clinical Studies**

<table>
<thead>
<tr>
<th>Antimuscarinic Agent</th>
<th>Dosage</th>
<th>Study Design</th>
<th>Subject Characteristics</th>
<th>Efficacy Outcomes</th>
<th>Adverse Event (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin chloride (oral extended-release)</td>
<td>5 mg to 30 mg every day</td>
<td>Three placebo-controlled and one open-label trial of varying duration</td>
<td>18-98</td>
<td>Urge or mixed incontinence</td>
<td>Dry mouth (60.8) Constipation (13.1) Somnolence (11.9) Headache (9.8) Diarrhea (9.1) Nausea (8.9) Asthenia (6.8) Pain (6.8) Dyspepsia (6.8) Dizziness (6.3) Blurred vision (7.7) Dry eyes (6.1) Rhinitis (5.6) Urinary tract infection (5.1)</td>
</tr>
<tr>
<td>Oxybutynin (transdermal patch)</td>
<td>3.9 mg/d over 96 hours</td>
<td>Two 12-week placebo-controlled phase 3 trials</td>
<td>18-89</td>
<td>Urge and mixed incontinence</td>
<td>Study 1: Pruritus† (16.8) Erythema† (5.6) Dry mouth (9.8) Study 2: Pruritus† (14.0) Erythema† (8.3) Dry mouth (4.1)</td>
</tr>
<tr>
<td>Tolterodine tartrate (oral, extended-release)</td>
<td>4 mg every day</td>
<td>One 12-week placebo-controlled phase 3 trial</td>
<td>20-93</td>
<td>Frequency and urge incontinence</td>
<td>Dry mouth (23) Headache (6) Constipation (6)</td>
</tr>
<tr>
<td>Darifenacin (oral)</td>
<td>7.5 mg/d or 15 mg/d</td>
<td>Pooled analysis of three 12-week placebo-controlled phase 3 trials</td>
<td>19-93</td>
<td>Frequency and urgency with urge incontinence</td>
<td>Significant improvements versus placebo in incontinence episodes per week, frequency and severity of incontinence, micturitions per day, and volume voided per micturition</td>
</tr>
<tr>
<td>Solifenacin succinate (oral)</td>
<td>5 mg/d or 10 mg/d</td>
<td>Four 12-week placebo-controlled trials</td>
<td>50-70</td>
<td>Urge or mixed incontinence</td>
<td>7.5 mg: Dry mouth (20.2) Constipation (14.8) 15 mg: Dry mouth (35.3) Constipation (21.3) Dyspepsia (8.4)</td>
</tr>
<tr>
<td>Trospium chloride (oral)</td>
<td>20 mg twice a day</td>
<td>Two 12-week placebo-controlled trials</td>
<td>19-94</td>
<td>Urge or mixed incontinence</td>
<td>5 mg: Dry mouth (10.9) Constipation (5.4) 10 mg: Dry mouth (27.6) Constipation (13.4)</td>
</tr>
</tbody>
</table>

* Adverse events occurred in more than 5% of the study population.
† Adverse effects appearing at application site.
mulation is efficacious in the treatment of overactive bladder. Tolterodine has comparable efficacy to oxybutynin, but with a reduced incidence of adverse events (eg, dry mouth). Although preliminary reports have drawn an association between tolterodine and impaired cognitive functioning, tolterodine is less lipophilic than oxybutynin and is therefore less likely to cross the blood-brain barrier.

Newer oral antimuscarinic agents darifenacin (7.5 mg and 15 mg) and solifenacin (5 mg and 10 mg) were approved for the treatment of overactive bladder and urge incontinence by the FDA in 2003 and 2004, respectively. Both agents are well-tolerated and substantially reduce urge incontinence episodes, frequency, and urgency, and increase the volume of urine voided. The most commonly reported adverse events for both darifenacin and solifenacin are dry mouth and constipation. Darifenacin has little affinity for the M1 muscarinic subtype receptor, a feature that is proposed to minimize cognitive effects that might arise if the compound were to cross the blood-brain barrier. Accordingly, adverse cognitive effects have not been reported for darifenacin. Solifenacin is a nonselective muscarinic antagonist that binds to the M1, M2, and M3 muscarinic receptors—though with slightly greater affinity for M1 and M3 receptors than M2 receptors. Animal studies suggest that solifenacin has the highest degree of bladder selectivity compared with oxybutynin, tolterodine, and darifenacin. In a recent head-to-head trial, a flexible dosing regimen with solifenacin was found to be superior to extended-release tolterodine for the majority of efficacy variables investigated. However, because this trial was designed to show non-inferiority, these results should be viewed with caution.

Trospium, an antimuscarinic agent approved by the FDA in 2004 for the treatment of overactive bladder, has been available in Europe for more than 20 years. The safety and efficacy of trospium have been demonstrated in clinical trials involving over 3000 patients in the United States and Europe and have been further demonstrated with postmarketing studies involving over 10,000 patients. Trospium is unique among the new antimuscarinic agents for several reasons: it has the least selectivity and the highest overall affinity for the muscarinic receptor subtypes; it is a positively charged quaternary amine, which prevents transfer across the blood-brain barrier; and it is minimally metabolized by cytochrome P-450 enzymes, with approximately 60% of the absorbed dose being excreted in the urine in active form. In addition, this agent demonstrates a rapid onset of effect, reducing frequency and urge incontinence within the first few days of treatment.

Trospium also has comparable efficacy to oral oxybutynin and tolterodine, but with fewer adverse events. The lack of cognitive adverse effects may result from the inability of trospium to transfer across the blood-brain barrier. The lack of adverse drug-drug interactions is a result of the lack of metabolism by cytochrome P-450 enzymes. Evidence supporting the possible additional benefits of a compound that is active in the urine was provided by a recent study in which urine from individuals who had ingested a variety of antimuscarinic agents was injected into the bladders of rats. The results of the study showed that, in accordance with its activity in urine, trospium has a local inhibitory effect on detrusor overactivity.

Conclusions

Overactive bladder is a widespread disorder that is distressing to patients and that is undiagnosed and undertreated by physicians. The detrimental impact of this condition on patients’ QOL makes it of paramount importance that physicians recognize and treat the symptoms associated with this troublesome condition. By recognizing the symptoms of overactive bladder, it is possible for physicians to diagnose and treat the condition within the primary care setting and without the need for complex urodynamic assessments.

Nonpharmacologic treatment options, alone or in combination with drug therapy, are effective in treating patients with overactive bladder. The development of new antimuscarinic agents and new formulations of more traditional agents widens the options available for the treatment of this disorder. The differences in efficacy and tolerability profiles among available agents provide the opportunity for physicians to choose the form of therapy that best suits the needs of the individual patient. When treating elderly patients, for example, consideration should be given to the use of agents with low potential to cause cognitive adverse events, and low potential for interaction with concomitant medications.

References


