Management of Urinary Incontinence

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DISEASE OVERVIEW

Urinary incontinence (UI) may be defined as any involuntary or abnormal urine loss. UI is characterized by lower urinary tract symptoms (LUTS), which include both storage and voiding problems. UI can be further defined by the patient’s presentations and symptoms. Urge urinary incontinence (UUI) is defined as involuntary urine leakage associated with urgency. Stress urinary incontinence (SUI) is defined as involuntary urine leakage associated with specific activities (e.g., sneezing and coughing). Mixed urinary incontinence (MUI) includes features of both UUI and SUI.

Overflow incontinence (OFI) is caused by a hypotonic bladder, bladder outlet obstruction, or other forms of urinary retention. OFI may result in LUTS and in the loss of small amounts of urine; it most often occurs in men with benign prostatic hyperplasia (BPH).

The term overactive bladder (OAB) is often used to describe UI. OAB comprises a constellation of symptoms typically characterized by urgency, with or without UUI, accompanied by frequency and nocturia.

Epidemiology

Approximately 10 million patients in the U.S. have UI, which is associated with significant morbidity and decreased quality of life. In 2007, it was estimated that more than 25 million people in the U.S. experienced episodes of UI. The prevalence of UI is higher in women than in men 80 years of age or younger, but both men and women are affected almost equally after age 80. UI may be associated with certain comorbidities, including hypertension and depression, although these associations are not fully understood. Among women, the incidence of UI is highest in Caucasians (7.3/100 person-years), followed by Asians (5.7/100 person-years) and African-Americans (4.8/100 person-years).

As a result of the social stigma associated with UI or the assumption that UI is a normal part of aging, the prevalence of this disorder may be underestimated because of unreported cases. UI is also often undocumented upon hospital discharge; it is a neglected syndrome in nursing facilities; and it is underreported by health care professionals, who may view the condition as a symptom rather than as a medical problem.

UI is primarily associated with aging, affecting up to 30% of elderly people. It occurs in 85% of long-term-care patients and is often the reason for admission to these facilities. The prevalence of UI in nursing homes remains high, and the care of nursing-home residents with UI is the subject of clinical research. In addition, UI is one of the measures used by the Centers for Medicare and Medicaid Services (CMS) to assess quality of care.

Annual direct and indirect costs of managing UI in the U.S. is estimated at $25 billion for patients over 65 years of age. The direct costs of UI include diagnostic procedures and the various treatment options, including pharmacotherapy. Indirect costs include complications and disabilities, such as insomnia, falls, depression, caregiving, and nursing-home placement. The indirect costs of UI are associated with a significant decrease in health-related quality of life, especially in women. Other “costs” of UI are difficult to measure but are significant. These include the consequences of social withdrawal or isolation resulting from the perceived stigma of UI or from the fear of leakage or odor.

Bladder Anatomy and Physiology

The anatomy and physiology of the bladder are complex, but a basic understanding of these topics is essential in order to appreciate the various types of UI and their management. Figure 1 illustrates the basic anatomic structures and nervous system “wiring” involved in bladder function, including the detrusor muscle, the internal and external sphincters (bladder neck and proximal urethra, respectively), and their neurological components.

Reduced activation of the sympathetic nervous system (SNS) results in relaxation of the detrusor muscle, closure of the sphincter, and bladder filling. When the volume of urine in the bladder reaches 200 to 400 mL, the sensation of urge to void is relayed via the spinal cord to the brain centers. Voluntary voiding (micturition) involves the parasympathetic nervous system and the voluntary somatic nervous system. Influences from these systems cause contractions of the detrusor muscle and corresponding somatic nervous activity, leading to sphincter relaxation.

Etiology and Risk Factors

Multiple factors, including age-related physiological changes, may result in or contribute to the various syndromes of UI. Both genitourinary and non-genitourinary factors may contribute to incontinence in aging patients. Age-related functional changes in the urinary tract (detrusor overactivity, impaired bladder contractility, decreased pressure in urethral closure, atrophy of urethral areas, and prostatic hypertrophy) may contribute to UI. In women, risk factors for these genitourinary changes include multiple or complex vaginal deliveries, high infant birth weight, a history of hysterectomy, and physiological changes related to the transition to postmenopause. Smoking, a high body mass index, and constipation are also associated with an increased risk of UI.

Pathophysiological causes of UI include lesions in higher micturition centers, in the sacral spinal cord, and in other neurological areas as well. UI may also be associated with numerous comorbidities, such as Parkinson’s disease, Alzheimer’s disease,

Key Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BPH</td>
<td>benign prostatic hyperplasia</td>
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<tr>
<td>LUTS</td>
<td>lower urinary tract symptoms</td>
</tr>
<tr>
<td>MUI</td>
<td>mixed urinary incontinence</td>
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<tr>
<td>OAB</td>
<td>overactive bladder</td>
</tr>
<tr>
<td>OFI</td>
<td>overflow incontinence</td>
</tr>
<tr>
<td>SUI</td>
<td>stress urinary incontinence</td>
</tr>
<tr>
<td>UI</td>
<td>urinary incontinence</td>
</tr>
<tr>
<td>UUI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>UTI</td>
<td>urge urinary incontinence</td>
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Disclosure: The authors report that they have no financial, commercial, or industrial relationships in regard to this article.

Accepted for publication January 23, 2012.
cerebrovascular disease, diabetes, hypertension, obstructive sleep apnea, and normal-pressure hydrocephalus. Functional factors, including mobility and dexterity, along with reaction time and lack of access to a bathroom facility, may also contribute to UI.33–37

Reversible causes of UI, often described by the mnemonic DIAPPERS, include urinary-tract infections (UTIs), stool impaction, and drugs (Table 1).35–44 Incontinence in older adults may or may not be associated with the genitourinary system. Pharmacological causes and contributors should be considered in patients with UI, especially if they are taking multiple medications (Table 2).32,38–44 Primary care providers and specialists should work as a team to manage patients with UI and to evaluate the broad spectrum of factors that may contribute to incontinence in older adults.32,38,40

**Diagnosis and Evaluation**

Patients with signs and symptoms of UI should undergo a complete medical evaluation to rule out reversible causes of the disorder. Formulating an accurate diagnosis may require the participation of clinicians with specialized training in urology. Clinically, patients with UI present with a variety of symptoms, depending on the type and severity of the condition. Patients with UUI usually experience urgency episodes that result in loss of urine. Women with SUI usually experience small amounts of leakage related to external stimuli, such as coughing or sneezing. Men with OFI secondary to BPH usually experience LUTS, including difficulty initiating a urine stream, the presence of a weak stream, a sense of incomplete emptying, nocturia, and dribbling.1,4,25,38 The importance of a correct diagnosis cannot be overemphasized. A complete review of the patient’s history, including comorbidities, is necessary for the development of an appropriate treatment plan.57,46

Urodynamic studies assist clinicians in determining the precise cause of UI and are an important part of the diagnostic process. Urodynamic assessments include a variety of measures that evaluate urine flow, including flow rate, post-void residual urine, filling cystometry, bladder pressure, and urethral pressure. These assessments provide an extensive description of lower urinary tract function and are helpful in determining the appropriate management strategy or in evaluating treatment failures.1,49–51

Because UI in older adults is associated with a high risk of institutionalization and comorbidities, including depression and UTIs, appropriate assessment of transient UI is essential. Transient UI may have an abrupt onset and may last less than 6 months. Because caregivers and health care professionals may erroneously consider UI an inevitable consequence of aging, failure to identify transient forms of the disorder may result in a permanent diagnosis and poor patient outcomes. Various tools, including bladder diaries and the mnemonic described in Table 1, should be helpful in identifying and treating underlying causes of transient UI.
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Initial questions for patients suspected of having UI may include “Have you ever leaked urine?” or “Have you lost bladder control?” Bladder diaries may be used to assess patterns of voiding, frequency, and volume. Questionnaires may also be helpful, although they depend on the patient’s or the caregiver’s memory.45–49

Because only approximately 20% of women with UI seek medical attention, and because there is the misconception that urinary leakage is a normal part of aging, health care practitioners should aim discussions at identifying women who are experiencing UI and need further evaluation.24,41,53 Pharmacists should have a thorough understanding of UI and its pharmacotherapeutic management. A comprehensive understanding of UI is necessary to optimize pharmacotherapy and to allow the pharmacist to review the patient’s medical profile for medications that might be causing or exacerbating the disorder.33,34,25,42 Because many patients with UI are older, it is often necessary to make dosage adjustments in their medications. Because of changes in both pharmacokinetics and pharmacodynamics in elderly populations, additional monitoring to avoid drug-related adverse events is required.52

Nonpharmacological Management: Conservative Measures and Exercises

The management of UI should include an evaluation of potential reversible contributors and trials of nonpharmacological interventions, which depend on the type of UI identified. Clinical studies support proper nutrition, the avoidance of constipation, weight loss, and physical activity as beneficial in improving symptoms.33–61 A study of weight loss in overweight women reported a clinically relevant reduction in the frequency of both stress and urge incontinence episodes.36 Women who are able to engage in regular daily exercise of moderate intensity are reported to have a lower incidence of UI than sedentary women, although the ability to exercise may be limited by physical disabilities in elderly women.62

Other non-drug interventions for UI include prompted or timed voiding, habit retraining, and praises for appropriate toileting. Success with these interventions requires the patient’s awareness of the need to void and the ability to delay voiding if necessary. These interventions, along with exercise, are associated with modest and short-term improvements in daytime UI. Absorbent products or pads may also be helpful to some patients; the use of these products should be based on the needs of the patient rather than on the convenience of the caregiver or facility staff. The drugs listed in Table 2 are often problematic in these patients and may contribute to or exacerbate UI; thus, evaluation may be necessary.52–68

Pelvic floor (Kegel) muscle training and bladder training have been beneficial in resolving or improving UI.60,70 Kegel exercises involve strengthening and retraining the detrusor bladder muscle to regain some control of urinary function. Evidence supports the use of this behavioral intervention in the treatment of UUI, SUI, and MUI. Choi et al. suggested that these exercises might be most effective in younger women with predominantly stress-related incontinence.71

The training process involved in learning these exercises may be complex for some patients, especially older adults with memory disorders.50–71 Comparisons of various conservative techniques, using a device that monitors compliance and the performance of exercises, showed that pelvic floor exercises, alone or in combination with biofeedback or electrical stimulation, may be beneficial for patients with SUI or MUI.33,34,13,72

The treatment of UI in older adults living in the community is

Table 1 Reversible Causes of Urinary Incontinence

<table>
<thead>
<tr>
<th>Classification</th>
<th>Medication</th>
<th>Activity</th>
</tr>
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<tbody>
<tr>
<td>D</td>
<td>Delirium</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Infection (urinary tract)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Atrophic</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>Pharmacological</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>Psychological</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Endocrine/excess urine output</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>Restricted mobility</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>Stool impaction</td>
<td></td>
</tr>
</tbody>
</table>

Data adapted from references 38–46.

Table 2 Medications That Can Cause or Exacerbate Urinary Incontinence

<table>
<thead>
<tr>
<th>Classification</th>
<th>Medication</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-adrenergic agonists</td>
<td>Nasal decongestants</td>
<td>Urinary retention in men with overflow incontinence related to BPH</td>
</tr>
<tr>
<td>Alpha-adrenergic antagonists</td>
<td>Prazosin, terazosin, doxazosin, silodosin, alfuzosin</td>
<td>Urethral relaxation; may cause or exacerbate stress incontinence in women</td>
</tr>
<tr>
<td>Anticholinergic drugs</td>
<td>Antihistamines, tricyclic antidepressants, some antipsychotics</td>
<td>Anticholinergic actions; urinary retention in overflow incontinence or impaction</td>
</tr>
<tr>
<td>Antineoplastic drugs</td>
<td>Vincristine</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>Dihydropyridines (e.g., nifedipine)</td>
<td>Urinary retention; nocturnal diuresis resulting from fluid retention</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Furosemide, bumetanide</td>
<td>Polyuria; frequency; urgency</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>Opiates</td>
<td>Urinary retention; sedation</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Long-acting benzodiazepines (e.g., diazepam, flurazepam)</td>
<td>Sedation; delirium; immobility</td>
</tr>
</tbody>
</table>

BPH = benign prostatic hyperplasia.
Data adapted from references 25, 33, 34, and 42–46.
Pharmacotherapy: Estrogen Replacement

The loss of estrogen during menopause has multiple effects on postmenopausal women, including atrophic tissue changes in the urogenital tract. These physiological changes may result in dryness, burning, itching, dyspareunia, and infections along with additional LUTS, including frequency and urgency.76–77 Hormone therapy (HT) has always been considered a therapeutic option for the management of postmenopausal symptoms. HT offers significant benefits in the management non-urogenital features, such as hot flashes, and may relieve the vaginal dryness associated with menopause. In addition, HT has been used to improve LUTS because of its effect on estrogen receptors in the urogenital area.78,79

During the past decade, the use of exogenous estrogen in postmenopausal women has become controversial because of concerns about increased rates of breast cancer and the risk of vascular disease–related morbidity (e.g., clotting and stroke).80 The role of estrogen in the management of UI is also controversial because data have suggested that HT provides only minimal benefit in UI and may even exacerbate the disorder.81–85 The basis for the assumption that estrogen would be beneficial in UI is the presence of estrogen and progesterone receptors throughout the genital tract, bladder, and vaginal epithelium. The presence of these receptors led investigators to theorize that HT could be a useful treatment for UI, especially stress urinary incontinence (SUD).74–77,86–88

Some clinical trials, however, have not supported the use of oral HT for managing UI.88,89 In a meta-analysis of 28 clinical studies of approximately 3,000 women with UI and in controlled trials of estrogen in more than 700 women with features of UUI and SUI, greater improvement of symptoms was reported for estrogen-treated patients with UUI than for the control groups; however, no beneficial effects were observed among patients with SUI.94

Other controlled studies showed that the use of estrogen alone or in combination with progesterin may contribute to or increase the incidence of UI, especially SUI, in postmenopausal women.95–102 The Nurse Health Study reported an increased risk of UI associated with the use of estrogen, with or without progesterin therapy, in younger postmenopausal women (37–54 years of age).95 Additional retrospective data from this study suggested an association between the use of oral contraceptives and UI in premenopausal women.96

The Women's Health Initiative (WHI), a randomized controlled trial involving more than 23,000 postmenopausal women 50 to 79 years of age, reported that HT increased the incidence of UI at 1 year; the highest incidence was in women with SUI. Estrogen alone or taken with progesterin increased the risk of UI among continent women and worsened the features of UI among symptomatic women after 1 year.97–100 The Heart Estrogen/Progesterone Replacement Study (HERS), a randomized, placebo-controlled, double-blinded trial, evaluated conjugated estrogen plus progesterin for the secondary prevention of heart disease in 1,200 women. Estrogen plus progesterin increased the risk of UUI and SUI within 4 months after initiation of treatment.101,102

These trials showed that conjugated estrogen alone and in combination with progesterin increased the risk of UI and exacerbated existing UI in postmenopausal women. HT, therefore, should not be used for the prevention or treatment of UI. Additional associations between HT and cerebrovascular disease and breast cancer in postmenopausal women should further increase the reluctance to use HT in postmenopausal women with UI.103,104

The role of topical estrogens in the management of UI is unclear; more study is needed to investigate these formulations in UI.78,105 Evidence supports the use of topical or localized estrogen in treating UUI caused by postmenopausal atrophic changes, which result in the loss of urethral support and in symptoms of UI.78,106 Topical estrogen formulations may include creams or estradiol-imregnated vaginal rings. The mechanisms of topical estrogen in this setting may include an increased blood supply and increased mucosal thickness, resulting in improved function of the lower urogenital system. Although these benefits have been reported in elderly women with atrophic changes and concurrent OAB, they have not been reported in women with SUI.105–108

Classification and Treatment

Urinary incontinence is usually classified in the format described in Table 3, although many patients may experience symptoms that suggest a mixed disorder. An overview of the various types of UI is presented in Table 3.4,13,31,106–110 The next sections discuss urge UI, stress UI, overflow incontinence, and mixed UI.

URGE URINARY INCONTINENCE

Urge (urgency) urinary incontinence (UUI) is a common cause of incontinence in elderly people. It is characterized by urgency, followed by involuntary loss of urine. UUI is sometimes referred to as OAB. However, the terms are not interchangeable, because about two-thirds of patients with OAB do not have UUI.121

UUI occurs primarily as a result of detrusor muscle overactivity, resulting in uninhibited or involuntary muscle contractions.25–28 Patients with UUI describe a sudden desire to urinate that is difficult to defer, resulting in leakage of urine. These episodes may occur at various times during the day or night.25,114 The primary causes of UUI (see Table 3) include idiopathic detrusor overactivity (resulting from UIs) and neurogenic detrusor overactivity (resulting from stroke, trauma, neurological diseases, or medications).25,26,45,46,117 The severity of age-related volumetric changes in the brain’s white matter may be associated with urinary urgency, and this process may have implications for future UI therapies.113,116

Nonpharmacological Management

The nonpharmacological management of UUI includes bladder training, behavioral treatments; pelvic floor exercises; the avoidance of caffeine; the use of pads for temporary bladder support; and, in some cases, surgery.117,118 Behavioral therapy in combination with drug therapy has produced variable results. Behavioral interventions, including educational brochures with verbal reinforcement, were beneficial in UUI patients who were dissatisfied with anticholinergic drug therapy.118 Behavioral training, including Kegel exercises and urine-suppression techniques, was found to be ineffective in improving outcomes in women with UUI.94,119,120

Pharmaco therapy

Anticholinergic (Antimuscarinic) Agents

The current focus of pharmacotherapy for UUI is control of detrusor muscle overactivity through the inhibition of M2 and M3 muscarinic (acetylcholine) receptors on the bladder.120–122 Numerous drugs that act as acetylcholine antagonists (anticholinergic agents) are available for the treatment of UUI and can reduce
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Symptoms of urgency and improve bladder control. Because muscarinic receptors are located in other organ systems throughout the body, their inhibition can have a variety of physiological and adverse effects.

The five most commonly used types of muscarinic receptors, their anatomic locations, and the adverse effects that can result from their inhibition are presented in Table 4. Each of these agents is discussed on the following pages. Antimuscarinic side effects are associated with both central and peripheral adverse reactions (see Table 4). Central adverse effects include delirium, confusion, and exacerbation of existing memory loss; these effects are especially concerning in elderly patients. Peripheral adverse effects include constipation, dry eye, and urinary retention.

Contraindications to the use of anticholinergic agents include uncontrolled narrow-angle glaucoma, a risk of urinary or gastric retention, the presence of underlying delirium or dementia, and a hypersensitivity to these drugs. Cautious use of anticholinergic drugs is recommended in patients with myasthenia gravis and with some gastrointestinal (GI) disorders, such as ulcerative colitis, intestinal atony, and gastroesophageal reflux disease.

Antimuscarinic side effects are associated with both central and peripheral adverse reactions (see Table 4). Each of these agents is discussed on the following pages.

Table 3 Causes, Symptoms, and Treatment of Urinary Incontinence

<table>
<thead>
<tr>
<th>Type of Incontinence</th>
<th>Common Causes</th>
<th>Common Symptoms</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urge urinary incontinence (UUI)</strong></td>
<td>Urinary tract infections</td>
<td>Urgency and frequency, day or night</td>
<td>Anticholinergic drugs</td>
</tr>
<tr>
<td>Idiopathic detrusor overactivity</td>
<td></td>
<td></td>
<td>• Oxybutynin</td>
</tr>
<tr>
<td></td>
<td>Neurological disorders</td>
<td></td>
<td>• Tolterodine</td>
</tr>
<tr>
<td></td>
<td>• Parkinson’s disease</td>
<td></td>
<td>• Surgery</td>
</tr>
<tr>
<td></td>
<td>• Alzheimer’s disease</td>
<td></td>
<td>• Intravesical Botox</td>
</tr>
<tr>
<td></td>
<td>• Cerebrovascular accidents (e.g., stroke)</td>
<td></td>
<td>• Sacral nerve stimulation</td>
</tr>
<tr>
<td></td>
<td>• Trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stress urinary incontinence (SUI)</strong></td>
<td>Pelvic surgery</td>
<td>Small volumes of urine loss with coughing or sneezing</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Stress incontinence (outlet incompetence)</td>
<td>Parity (childbirth)</td>
<td></td>
<td>• Kegel (pelvic floor) exercises with or without biofeedback</td>
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<tr>
<td></td>
<td>Constipation</td>
<td></td>
<td>• Sling procedures</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Transurethral collagen denaturation (Renessa procedure)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Transurethral bulking agents</td>
</tr>
<tr>
<td><strong>Mixed urinary incontinence (MUI)</strong></td>
<td>Pelvic surgery</td>
<td>Symptoms may include urge and stress features</td>
<td>Treatment depends on predominant symptoms</td>
</tr>
<tr>
<td>Mixed UUI and SUI</td>
<td>Parity (childbirth)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overflow incontinence (OFI)</strong></td>
<td>Benign prostatic hyperplasia (BPH)</td>
<td>Poor stream, incomplete emptying, and dribbling</td>
<td>Alpha-adrenergic blockers</td>
</tr>
<tr>
<td>Overflow incontinence</td>
<td>Bladder outlet obstruction</td>
<td></td>
<td>• 5-alpha-reductase inhibitors</td>
</tr>
<tr>
<td></td>
<td>Fecal impaction</td>
<td></td>
<td>• Intermittent catheterization</td>
</tr>
<tr>
<td></td>
<td>Hypotonic/neurogenic bladder</td>
<td></td>
<td>• Surgical options</td>
</tr>
<tr>
<td></td>
<td>Urethral stricture disease</td>
<td></td>
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</tr>
<tr>
<td><strong>Other types of incontinence</strong></td>
<td>Disruption or denervation of pelvic floor muscle fibers</td>
<td>Stress incontinence and dribbling</td>
<td>Kegel pelvic floor exercises</td>
</tr>
<tr>
<td>Post-prostatectomy incontinence</td>
<td>Stress incontinence and dribbling</td>
<td></td>
<td>Male urethral sling</td>
</tr>
<tr>
<td>Fistula (e.g., colovesical or vesicovaginal)</td>
<td>Postsurgical complications</td>
<td>Continuous, steady incontinence</td>
<td>Artificial urinary sphincter</td>
</tr>
<tr>
<td></td>
<td>Crohn’s disease</td>
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<tr>
<td></td>
<td>Diverticulitis</td>
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<tr>
<td></td>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional incontinence</td>
<td>Limited mobility</td>
<td>Symptoms vary</td>
<td>Eliminate causes</td>
</tr>
<tr>
<td></td>
<td>Change in mental status</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data compiled from references 1–4, 30, and 110–112.
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Gopal et al. reported high discontinuation rates for anticholinergic drugs that were used to treat LUTS in women. The study authors estimated overall and drug-specific discontinuation rates for nine agents in approximately 30,000 women over a 6-month period. Discontinuation rates were high for all anticholinergic drugs regardless of class. The overall discontinuation rate was 60%; oxybutynin (Ditropan, Janssen) and extended-release (ER) tolterodine (Detrol LA, Pfizer) were discontinued at rates of 71% and 54%, respectively. Some limitations of the study included diagnoses based on electronic medical data and a lack of data about why patients stopped therapy. The results suggest a need for more effective and tolerable therapies for UI, including more vigilant use of nonpharmacological interventions, such as fluid modification, pelvic floor rehabilitation, and bladder training.

Anticholinergics have the potential to interact with other medications that have the same side-effect profile and with other centrally acting drugs. The concomitant use of acetylcholinesterase inhibitors for dementia and anticholinergic drugs may exacerbate cognitive decline and should be avoided if possible.

As shown in Table 5, all of the anticholinergic agents used to treat UI, except trospium chloride (Sanctura, Allergan/Espirit/Indevus), are metabolized by hepatic cytochrome P450 (CYP) enzymes; inhibitors of these enzymes, therefore, may potentiate the adverse effect of anticholinergic drugs. Clinicians should monitor patients with UI, especially older adults and those taking multiple medications, for adverse effects, drug interactions, and potential contraindications during treatment with anticholinergics.

Older drugs, such as propantheline (Pro-Banthine, Shire), dicyclomine (Bentyl, Axcan Pharma), and flavoxate (Urispas, Ortho-McNeil), are still available, but they are rarely used because of their questionable efficacy and side-effect profiles. The tricyclic antidepressant imipramine (Tofranil, Mallinckrodt) has been used to treat patients with UI and may have a role in MUI because of its dual anticholinergic and alpha-adrenergic properties.

Currently, the anticholinergic drugs most commonly used in clinical practice for the treatment of UI include transdermal oxybutynin (Oxytrol, Watson Pharma), oxybutynin gel (Gelnique, Watson Pharma), tolterodine (Detrol and Detrol LA, Pfizer), trospium chloride, darifenacin (Enablex, Novartis), solifenacin (vesicare, Astellas/GlaxoSmithKline), and ER fesoterodine (Toviaz, Pfizer) (see Table 5).

As mentioned, several anticholinergic agents are available in various doses, formulations, and routes of administration, providing clinicians with several treatment options for UI. These drugs are usually used to treat UI and OAB in patients who have not achieved symptom relief and improved quality of life with conservative nonpharmacological interventions.

Clinical Efficacy

Efficacy data for anticholinergic drugs in patients with UI have been obtained from a number of meta-analyses and head-to-head trials. Two large meta-analyses reported similar clinical efficacy among the available anticholinergic agents, as measured by reductions in episodes of urgency and incontinence, frequency, daily micturition, nocturnal awakenings, increased volume per void, patient satisfaction, and quality of life.

Another meta-analysis included data from 50 randomized controlled trials and three pooled analyses that included various formulations and doses of anticholinergic agents. This study reported advantages with ER formulations in terms of efficacy and safety. Dose escalations with immediate-release (IR) formulations provided some improvement in efficacy but with an increased risk of adverse events.

Head-to-head trials with anticholinergic agents have reported similar efficacy or insignificant differences among the various drugs. Tolerability differences were evident in some studies, especially when other drugs were compared with IR oxybutynin. One report described the available anticholinergic agents as equivalent first choices, except for oral oxybutynin administered at dosages of more than 10 mg/day, which were associated with a higher rate of adverse effects. The study data showed a smaller treatment effect with anticholinergics compared with placebo than what might be expected in clinical practice. This difference might have been due to the use of concurrent bladder training in some patients who were prescribed these drugs in the clinical setting, compared with the absence of this intervention in clinical trials. The literature is devoid of direct comparisons between anticholinergic drugs and bladder-training interventions.

Oxybutynin (Ditropan, Oxytrol). Oxybutynin is the oldest of the agents currently used to treat UI. It is available in IR and ER oral formulations (Ditropan and Ditropan XL, Janssen), along with a dermal patch and topical gel formulations (see Table 5). Oxybutynin is considered the gold standard with which other agents in the class are compared. Trial data indicate that the efficacy of oxybutynin is similar to that of other anticholinergic drugs. The significance of its proposed muscle-relaxant properties is unclear. The ER tablet, dermal patch, and topical gel may offer improved tolerability because of reduced levels of the active metabolite, N-desethyloxybutynin.

### Table 4 Muscarinic Receptor Subtypes and Adverse Effects of Receptor Inhibition

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Receptor Subtype</th>
<th>Adverse Effects of Inhibition (Anticholinergic Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder (detrusor muscle)</td>
<td>M2, M3</td>
<td>Decreased contractions; urinary retention</td>
</tr>
<tr>
<td>Cardiac tissue</td>
<td>M2</td>
<td>Tachycardia; palpitations</td>
</tr>
<tr>
<td>Central nervous system and brain (cortex and hippocampus)</td>
<td>M1, M2, M3, M4, M5</td>
<td>Effects on memory, cognition, and psychomotor speed; confusion; delirium; sedation; hallucinations; sleep disruption</td>
</tr>
<tr>
<td>Eyes (ciliary muscle and iris)</td>
<td>M3, M5</td>
<td>Dry eyes; blurred vision; mydriasis (dilation of the pupil)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>M1, M2, M3</td>
<td>Slowed transit time; constipation; effects on sphincter tone and gastric acid secretion</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>M1, M3, M4</td>
<td>Xerostomia (dry mouth)</td>
</tr>
</tbody>
</table>

M = muscarinic receptor.

Data adapted from references 122–126.
### Table 5 Anticholinergic Agents Used for Urinary Incontinence

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Adult Dose</th>
<th>Pharmacokinetic Properties</th>
</tr>
</thead>
</table>
| Darifenacin (Enablex ER, Novartis) | 7.5–15 mg q.d.; swallowed whole with liquid; should not be chewed, divided, or crushed | • Bioavailability, 17%; peak levels, 7 hours post-dose; protein binding, 98% (alpha, - acid-glycoprotein)  
  • Extensively metabolized by CYP2D6/3A4⁴; half-life, 13–19 hours; elimination: 60% in urine, 40% in feces  
  • Dose adjustment for moderate hepatic impairment; poor CYP2D6 metabolizers may have higher drug levels |
| Fesoterodine (Toviaz ER, Pfizer) | 4–8 mg q.d.; swallowed whole with liquid; should not be chewed, divided, or crushed | • Bioavailability, 52% peak levels, 5 hours post-dose; protein binding, 50%; metabolized by CYP2D6/3A4⁴; active metabolite, 5-hydroxymethyl-tolterodine (5-HMT)  
  • Higher parent drug levels may occur in poor CYP2D6 metabolizers  
  • Elimination: 70% renal as 5-HMT; half-life, 7 hours  
  • Dose adjustments for moderate hepatic impairment and severe renal impairment (CrCl < 30 mL/minute); not recommended in severe hepatic impairment |
| Oxybutynin IR (Ditropan, Janssen) | 2.5–5 mg b.i.d. or t.i.d.; maximum dosage, 5 mg q.i.d. | • Rapidly absorbed; peak levels, 1 hour post-dose; dose-dependent, linear pharmacokinetics; bioavailability, approximately 6%; extensively metabolized by CYP3A4⁴; active metabolite, desethyloxybutynin; half-life, 2–5 hours  
  • May have direct smooth muscle-relaxant properties and local anesthetic effects  
  • Caution recommended in renal impairment |
| Oxybutynin gel 10% (Gelnique, Watson) | 1 g (sachet) applied daily to dry, intact skin; rotate application sites (abdomen, thigh, shoulder, upper arm) | • Enters systemic circulation by passive diffusion across stratum corneum  
  • Bypasses first-pass GI and hepatic metabolism, reducing formation of N-desethyl-oxybutynin metabolite  
  • Steady state: achieved within 3–7 days of continuous dosing  
  • Metabolized primarily by CYP3A4⁴; half-life: ~30 hours (3%); ~70 hours (10%)  
  • Kinetic profiles similar to that of transdermal formulation (Oxytrol)  
  • After application, wait 1 hour before showering; may apply sunscreen 30 minutes before or after application |
| Oxybutynin gel 3% (Anturol, Antares) | Three pumps (84 mg); applied as above; may rotate site if necessary | • Enters systemic circulation by passive diffusion across stratum corneum  
  • Bypasses first-pass GI and hepatic metabolism, reducing formation of N-desethyl-oxybutynin metabolite; half-life, approximately 7–8 hours  
  • Kinetic profile similar to that of gel formulations |
| Oxybutynin transdermal patch (Oxytrol, Watson) | 36-mg patch applied twice weekly (every 3–4 days); delivers 3.9 mg daily; rotate administration sites (abdomen, hip, buttock) | • Enters systemic circulation by passive diffusion across stratum corneum  
  • Bypasses first-pass GI and hepatic metabolism, reducing formation of N-desethyl-oxybutynin metabolite; half-life, approximately 7–8 hours  
  • Kinetic profile similar to that of gel formulations |
| Oxybutynin XR (Ditropan XL, Janssen) | 5–10 mg q.d.; may be increased to a maximum of 30 mg/day; swallowed whole; should not be chewed, divided, or crushed | • Peak levels, 4–6 hours post-dose; consistent plasma concentrations  
  • Osmotically active bilayer; released over 24 hours  
  • Metabolized by CYP3A4⁴; half-life, 12–13 hours |
| Solifenacin (VESIcare, Astellas Pharma US) | 5–10 mg q.d.; swallowed whole with water | • Bioavailability, 90%; protein binding, 98%; metabolized by CYP3A4⁴  
  • Elimination: 70% renal (<15% unchanged), 22% feces; half-life, 55 hours  
  • Dose adjustments for moderate hepatic impairment and severe renal impairment (CrCl < 30 mL/minute); not recommended for use in severe hepatic impairment |
| Tolterodine IR (Detrol, Pfizer) | 1–2 mg b.i.d. | • Rapidly absorbed; bioavailability, at least 77%; peak levels, 1–2 hours post-dose; protein binding, 96% (mainly to alpha₁-acid glycoprotein)  
  • Extensively metabolized by CYP2D6 to active metabolite (5-HMT); metabolized by CYP3A4⁴ in patients devoid of CYP2D6  
  • Half-life in extensive/poor metabolizers, 3 hours/9.6 hours  
  • Elimination: approximately 77% of dose in urine, 17% in feces (metabolites)  
  • Dose adjustments for substantially reduced hepatic or renal function |
| Tolterodine (Detrol LA, Pfizer) | 2–4 mg q.d.; swallowed whole with liquid | • Rapidly absorbed; bioavailability, at least 77%; peak levels, 2–6 hours post-dose; protein binding, 96% (mainly to alpha₁-acid glycoprotein)  
  • Extensively metabolized by CYP2D6 to active metabolite (5-HMT); 7% of Caucasians are poor metabolizers of CYP2D6  
  • Half life in extensive/poor metabolizers, 7 hours/18 hours  
  • Elimination: approximately 77% of dose in urine, 17% in feces (metabolites)  
  • Dose adjustments for substantially reduced hepatic or renal function |

*table continues*
In December 2011, the FDA approved oxybutynin topical gel 3% (Anturol, Watson/Antares) for the treatment of OAB in patients with symptoms of UUI, urgency, and frequency.\(^{144}\)

Adverse events associated with oral oxybutynin include the dose-related anticholinergic effects described previously, along with erythema and pruritus resulting from the transdermal and gel formulations. The incidence of dry mouth is reported to be as high as 50% to 70% with the IR formulation, secondary to the creation of N-desethyl-oxybutynin during the drug’s extensive first-pass metabolism. In addition, oxybutynin may have a higher affinity for muscarinic receptors in the parotid (salivary) glands.\(^{148–153}\)

The IR formulation of oxybutynin is also associated with orthostatic hypotension as a result of the drug’s alpha-adrenergic-blocking properties, as well as sedation resulting from its histamine-blocking effects. The IR and ER formulations have similar efficacy, but the ER formulation allows the release of a controlled amount of drug in the GI tract over 24 hours. In addition, reduced first-pass metabolism results in greater parent-to-metabolite ratios, lower peaks, and fewer concentration-dependent side effects.

The oxybutynin transdermal patch was reported to be effective in treating UUI, with a more tolerable side-effect profile than that of the other formulations, although application-site reactions, including pruritus and erythema, were more common. A large multicenter trial with the transdermal formulation reported improved quality of life and a low incidence of adverse events in 2,878 patients 65 years of age and older; 131 patients older than 85 years of age were treated with this formulation.\(^{155–158}\)

Drug interactions include the expected additive side effects when oxybutynin is used with other anticholinergic agents. In addition, concomitant use with CYP2D6 and CYP3A4 pathway inhibitors (e.g., fluconazole or erythromycin) may potentiate oxybutynin-related adverse effects.\(^{148}\) The patient’s medications should be reviewed when oxybutynin is prescribed with other agents because of potential CYP450 drug interactions and additive anticholinergic effects.\(^{120,146,153}\)

The 10% gel formulation of oxybutynin was approved in 2009. The gel’s clinical efficacy was reported to be similar to that of the other formulations, but it showed excellent patient tolerability. Significant side effects, when compared with placebo, included dry mouth and application-site reactions. Practical tips for using the oxybutynin gel include showering 1 hour after application and using sunscreen 30 minutes before or after application. The transfer of gel between individuals may occur if vigorous skin contact is made at the application site. Patients should avoid an open fire or exposure to smoking after application until the gel has dried.\(^{139–141}\)

The use of oxybutynin in older adults should be limited to short-term treatment with the extended-release formulation, the dermal patch, or the topical gel.\(^{148}\)

**Tolterodine (Detrol).** Like oxybutynin, tolterodine is available in both IR and ER oral formulations (Detrol and Detrol LA, Pfizer) (see Table 5). Tolterodine offers improved tolerability compared with that of IR oxybutynin chloride, and it provides efficacy and tolerability similar to that of the other available agents.\(^{151,152}\) The bioavailability, time to peak serum levels, and elimination of tolterodine depend on the CYP2D6 metabolism phenotype. In individuals who are extensive CYP2D6 metabolizers, the active metabolite 5-hydroxymethyltolterodine is formed, resulting in a faster onset of peak concentrations. In poor metabolizers (7% of Caucasians), who are devoid of the CYP2D6 enzyme, tolterodine is metabolized to N-dealkylated tolterodine via CYP3A4, resulting in higher serum concentrations of parent tolterodine. Poor metabolizers also experience a slower onset to peak concentrations (2 and 4 hours for the IR and ER formulations, respectively).

The elimination half-life of tolterodine also depends on the metabolism phenotype and on the drug’s formulation. The IR capsules have half-lives of 3 and 9 hours in extensive and poor metabolizers, respectively. The corresponding half-lives of the ER capsules are 7 and 18 hours. Drug interactions with tolterodine are similar to those reported with oxybutynin chloride.\(^{153–156}\)

For patients who cannot tolerate IR tolterodine, the ER product is an effective alternative and may offer improved tolerability. In one study, diary entries showed that ER tolterodine resulted in a high degree of satisfaction and improved bladder variables among patients who were previously dissatisfied with the IR formulation or other anticholinergic agents.\(^{157–170}\)

### Table 5 Anticholinergic Agents Used for Urinary Incontinence, continued

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Adult Dose</th>
<th>Pharmacokinetic Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trospium IR (Sanctura, Allergan)</td>
<td>20 mg b.i.d., at least 1 hour before meals or on empty stomach</td>
<td>• Bioavailability: &lt;10%; peak levels, 5–6 hours post-dose&lt;br&gt;• Metabolism: ester hydrolysis with subsequent conjugation (minimal CYP450 involvement)&lt;br&gt;• Elimination: 85% in feces, 6% in urine (60% unchanged); half-life, approximately 20 hours&lt;br&gt;• Dose adjustments or avoid in severe renal impairment; should be used with caution in moderate/severe hepatic impairment</td>
</tr>
<tr>
<td>Trospium (Sanctura XR, Allergan)</td>
<td>60 mg q.d. in morning, at least 1 hour before breakfast, with water or on empty stomach</td>
<td>• Peak levels, 5 hours post-dose; protein binding, 50–85%&lt;br&gt;• Metabolism: ester hydrolysis with subsequent conjugation (minimal CYP450 involvement)&lt;br&gt;• Elimination: 85% in feces, 6% in urine (60% unchanged); half-life, approximately 35 hours&lt;br&gt;• Not recommended in severe renal impairment; no information on effect of severe hepatic impairment</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily;  q.Cr = creatinine clearance;  CYP = cytochrome P450;  GI = gastrointestinal;  IR = immediate release;  IV = intravenous;  q.d. = once daily;  q.i.d. = four times daily;  t.i.d. = three times daily;  XR = extended release.

* CYP3A4 metabolism: use lower dose if patient is taking concurrent CYP3A4 inhibitor (e.g., clarithromycin, ketoconazole).

Data adapted from references 120, 122, and 138.
Second-Generation Anticholinergic Agents

The search for UI drugs with improved tolerability led to the approval of three new anticholinergic agents in 2004 and one in 2009. Although these drugs appear to offer no significant advantages over oxybutynin chloride and tolterodine in terms of efficacy, they may have some individual advantages in terms of pharmacokinetic profile, delivery, and tolerability.171–180

Trospium chloride (Sanctura). One second-generation anticholinergic drug approved in 2004 was trospium chloride (see Table 5). This quaternary, amine-structured molecule has a limited ability to penetrate the blood–brain barrier because of its hydrophilic nature.181–183 Its structure suggests a reduced potential for anticholinergic CNS side effects, but the tradeoff is poor bioavailability, especially when the drug is administered with food.

The metabolism of trospium chloride is minimal. Renal elimination is via tubular secretion, for which dose adjustments are required in patients with a creatinine clearance (CrCl) below 30 mL/minute. The drug’s efficacy is similar to that of other drugs in its class, but it may be better tolerated in some patients.173,176,184–187 Potential drug interactions are limited to agents that compete for tubular secretion (metformin and digoxin) and to drugs with additive anticholinergic side-effect profiles. Contraindications are similar to those of the anticholinergics discussed earlier.173,188,189

An ER formulation of trospium chloride allows once-daily dosing (see Table 5). This ER product was reported to be convenient, effective, and well tolerated, and it may be an excellent alternative for elderly patients.193–195

Solifenacin (vesicare). Solifenacin, taken once daily, is a second-generation anticholinergic that was approved in 2004 (see Table 5). Its bioavailability is better than that of trospium chloride. Solifenacin is metabolized primarily by CYP3A4; it is Renelly eliminated; therefore, dosage adjustments are required in patients with a CrCl of less than 30 mL/minute.172,194,195 Solifenacin has been reported to be effective and well tolerated, with efficacy similar to that of others in the class. In clinical trials, solifenacin reduced urgency episodes, incontinence, frequency of micturition, and nocturia. The drug’s benefits were observed within 3 days after administration.196–198 In one study, fewer micturitions were reported with solifenacin than with tolterodine during a 24-hour period.274 Solifenacin may offer improved tolerability compared with IR oxybutynin, especially a lower incidence of severe dry mouth. Clinical data suggest that the overall efficacy of solifenacin is similar to that of other anticholinergics, but one trial reported improved urgency and diary-documented symptoms in patients previously treated with tolterodine.206–208

Adverse effects of solifenacin and contraindications to its use are similar to those of the other anticholinergic drugs, although prolonged corrected QT intervals have been reported with high-dose solifenacin, suggesting that this agent should be used with caution in at-risk patients. As with oxybutynin chloride and other agents in this class (see Table 5), the metabolism of solifenacin involves the hepatic CYP450 enzyme system; patients therefore require appropriate monitoring to avoid drug interactions.172,208,211

Darifenacin (Enablex). Darifenacin (Enablex, Novartis) was approved in 2004, providing another daily option for treating UUI (see Table 5). The drug’s pharmacokinetic properties include poor bioavailability and CYP2D6-dependent metabolism. Approximately 7% of Caucasian patients and 2% of African-American patients are poor CYP2D6 metabolizers and are dependent on the CYP3A4 isoenzyme for metabolism. Dosage adjustments are recommended in patients with hepatic impairment, and caution is suggested in patients with renal disease.211,212 Darifenacin has a greater affinity for bladder M3 receptors, suggesting increased selectivity and tolerability, although clinical evidence of this advantage is lacking.212–214 The adverse effects and contraindications associated with darifenacin are similar to those of the other anticholinergic drugs.211

Clinical trials with darifenacin reported efficacy similar to that of other agents in the class, but tolerability was better than that of oxybutynin chloride. Darifenacin provided improvements in micturition variables that were similar to those of other anticholinergics, including nocturnal voids, incontinence episodes, and improved quality of life.177,214–216 A community-based survey found that patients with OAB experienced benefits with darifenacin and were generally satisfied with the drug.211

Fesoterodine (Toviaz). Pfizer’s extended-release fesoterodine entered the market in 2009 for the treatment of UUI and OAB (see Table 5). Fesoterodine is well absorbed, is not affected by food, and is metabolized by both the CYP2D6 and CYP3A4 enzyme systems. It is a prodrug, with no activity itself, but it is rapidly and completely metabolized to its active metabolite, 5-hydroxy methyl-tolterodine (5-HMT), which is responsible for all of fesoterodine’s anticholinergic effects. 5-HMT is also the active metabolite of tolterodine. With festerodine, however, the metabolite is the single active moiety; thus, fesoterodine delivers more 5-HMT via esterase metabolism compared with tolterodine.222–226

Excretion is primarily via the kidneys, with approximately 70% excreted as active and inactive metabolites.173,222 As with other agents in this class, dose-related increases in anticholinergic adverse events, including dry mouth and constipation, were reported in clinical trials of fesoterodine. However, discontinuation rates associated with these side effects were minimal.224–226

Fesoterodine has the potential to interact with inhibitors of the CYP2D6 and CYP3A4 enzyme systems. When fesoterodine is used concurrently with inhibitors of these enzymes, the dosage of fesoterodine should not exceed 4 mg daily. However, coadministration of fesoterodine with CYP3A4 inducers may result in subtherapeutic levels. Dosage adjustments may be necessary in patients with severe hepatic impairment (Child–Pugh class C) and in those with severe renal impairment (CrCl below 30 mL/minute). The recommended dosage in these patients is 4 mg daily.213,223,226

The clinical efficacy of fesoterodine in managing UUI is similar to that of other agents in the class. Clinical trials with doses of 4 mg and 8 mg reported significant reductions in daytime frequency, nocturia, urgency, and quality of life in addition to excellent tolerability.227–229 In a comparison study with extended-release tolterodine (4 mg) and placebo, fesoterodine (8 mg) provided greater decreases in incontinent episodes, volume per void, severity of urgency, and continent days per week. The drug also had a greater effect on quality-of-life measures while offering options of dosing flexibility and titration.235,236 In one trial, patients who had been dissatisfied with previous tolterodine treatment reported excellent tolerability and satisfaction with fesoterodine.217

Role of Anticholinergic Therapy

Anticholinergic drugs have a role in the management of UUI, but nonpharmacological interventions should generally be considered first. Although none of the six currently available anticholinergic agents appears to have a clear advantage in terms of efficacy, dosing convenience and drug tolerability may influence the choice of therapy. ER formulations offer daily dosing, improved compliance, and improved tolerability profiles, especially when compared with dose escalation of IR products. Trospium chloride, with its quaternary amine structure and reduced penetration of the
Management of Urinary Incontinence

blood–brain barrier, may be an option for patients who experience excessive CNS side effects from other drugs in the class.

Topical formulations, such as the oxybutynin transdermal patch and topical gels, may offer more tolerable and convenient dosing for some patients with UUI. Pharmacokinetic differences among the various agents may be relevant in patients with renal or hepatic impairment or when drug interactions are a concern. Pharmacogenomic metabolic profiles may also play a role in drug selection in some patients, based on their CYP450 metabolism genotype.

Finally, financial considerations may influence the selection of an anticholinergic agent because of the significant cost differences among these drugs (i.e., generic vs. brand). A cost analysis reported greater clinical benefits and improved quality of life with the newer agents, such as solifenacin, but these drugs were not cost-effective compared with IR oxybutynin for measures of frequency and incontinence.230

The initial dosage of anticholinergics should be low, especially in older adults. The dose may be titrated, if necessary, with careful monitoring for adverse effects and drug interactions. An adequate trial of 1 to 2 months is recommended before clinicians consider alternative agents or therapies.

Patient education should focus on adequate water and fiber consumption and regular exercise to minimize constipation. Dry mouth can be reduced with the use of sugar-free candies or saliva substitutes. Excessive alcohol consumption should be avoided because of the potential for additive sedative effects.141–143,146,147

Other Therapies for Urge Urinary Incontinence

Botulinum toxin. Botulinum toxin A (BTX-A), a powerful neurotoxin produced by the bacterium Clostridium botulinum, has been studied as therapy for idiopathic detrusor overactivity in a variety of patients, including those who did not respond to anticholinergic drugs. BTX-A prevents the release of acetylcholine at the neuromuscular junction. This effect, in turn, inhibits depolarization of the detrusor muscle, resulting in chemical denervation and includes prevention strategies, the use of temporary absorbent interventions, and Kegel (pelvic floor) exercises.108,256–263 A retrospective analysis of women discharged from a large academic medical center reported that SUI inpatient procedures in this population have increased significantly over the last 25 years, with the number of inpatient procedures rising from approximately 50,000 in 1979 to 100,000 in 2004. Most of the women were older than 52 years of age. There was also a decrease in the use of some types of procedures, such as retropubic urethral suspensions, and an increase in the use of others (pubovaginal and transobturator sling procedures).284

Nonpharmacological Management

The treatment of SUI is primarily nonpharmacological in nature and includes prevention strategies, the use of temporary absorbent bladder-protection pads for social situations, behavioral interventions, and Kegel (pelvic floor) exercises.208,209–211 A retrospective analysis of women discharged from a large academic medical center reported that SUI inpatient procedures in this population have increased significantly over the last 25 years, with the number of inpatient procedures rising from approximately 50,000 in 1979 to 100,000 in 2004. Most of the women were older than 52 years of age. There was also a decrease in the use of some types of procedures, such as retropubic urethral suspensions, and an increase in the use of others (pubovaginal and transobturator sling procedures).284

Numerous procedures are available for men and women with SUI and are necessary in a high percentage of patients. Surgery is typically used to improve urethral resistance, thereby reducing urine leakage and preserving normal bladder function.204 Surgery is usually recommended when conservative measures have failed in postmenopausal women; however, an operation may increase the risk of postoperative voiding complications. A comprehensive evaluation is necessary in patients with apparent SUI to clarify the specific type of UI being treated and to consider comorbidities, age, childbearing preferences, and urodynamics.205–207

Women with SUI are often treated with sling procedures, which are designed to correct sphincter deficiencies and urethral hypermobility. Tissue or various materials are placed below the urethra to elevate it and to increase urethral compression. A commonly used, minimally invasive procedure, the mid-urethral sling, uses tension-free vaginal tape to provide urethral support and to decrease urethral hypermobility by compressing the urethra when
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intra-abdominal pressure increases.268

Other urethral suspension techniques include suprapubic arc, transobturator, and colposuspension (Burch) procedures. These approaches are reported to be effective for the treatment of SUI, with similar complication rates.268,269,270

Surgery is also associated with improved quality of life and is an excellent option for some patients.275,276

Conservative (Nonsurgical) Management

Conservative management should be considered as a first-line option in patients with SUI, especially younger women of childbearing age. Clinical evidence suggests that postpartum SUI may be self-limiting and may resolve on its own. Treatment should be reserved for women whose symptoms continue for 6 months or longer.

The risk of SUI increases with multiple pregnancies, and the benefits of surgical continence procedures may be negated by future pregnancies and childbirth. Although tampons and absorbent bladder-protection pads are usually inadequate or inappropriate for most situations, many women with SUI use these items as a temporary first-line treatment to decrease leakage in situations when abdominal pressure may increase (during exercise or physical activity). Nonsurgical methods include the use of postpartum pelvic floor exercises, weight loss, biofeedback, weighted vaginal cones, electrical stimulation units, and pessaries.273–277

Kegel exercises help to rehabilitate the muscles of the pelvic floor: These muscles consist of slow-twitch (70%) and fast-twitch (30%) fibers. During urination, these muscles, especially the fast-twitch type, are used to close the urethra.268,269 The exercises involve the conscious contraction and relaxation of the pubococcygeus muscle, with the goal of increasing the resting tension of the sphincter components in this region.277–279 Motivated patients who follow a rigid exercise regimen for up to 3 months typically experience beneficial effects.278 The best results are achieved with the use of verbal instructions, along with supervision by trained clinical professionals.279,280

Lifestyle changes include smoking cessation, fluid restriction (1.5 to 2.0 L daily), and reduced daily caffeine and alcohol intake. Patients’ awareness of their continence status should always be taken into consideration in the evaluation process.273,274,276

To achieve the maximum benefits from conservative management of SUI, proper education is necessary along with an emphasis on the importance of the patient’s role in therapy. Support and encouragement are vital because some interventions may take time to produce results. Patients need to understand the importance of working with their practitioners and of having an active role to achieve positive outcomes.279,274

Biofeedback

Biofeedback, in combination with pelvic floor exercises, offers a cost-effective method of reducing SUI. Vaginal or rectal sensors are used to obtain a visual indication of contraction activity and muscle strength. The purpose of biofeedback is to guide women regarding which muscles to contract to maximize the benefits of pelvic floor exercises.281–284

Intravaginal Devices

Weighted cone devices attached to vaginal muscles may also help women with SUI. These devices are designed to help patients improve pelvic-floor tone through active, continuous muscle contractions. The weight of the cone retained by the patient is in direct proportion to the improvement in muscle tone and to subsequent improvement in SUI.271

A similar device, the Colpexin Sphere, is placed in the vaginal canal to provide support for pelvic floor muscles. This device improves prolapse defects and the utility of pelvic floor exercises. Proper counseling and training are necessary, and small trials have reported success in motivated patients.275

Pessaries

Vaginal continence pessaries are used for the treatment of various pelvic floor disorders, including UI and prolapse.285,286 Although these devices may be considered first-line options for the treatment of SUI, they are not used extensively in this setting because of their perceived inconvenience. Specific types of pessaries have effectively treated SUI by providing support for the bladder neck at the urogenital angle. One short-term trial reported greater patient satisfaction and less bothersome incontinence symptoms with behavioral therapy compared with the use of pessaries at 3 months, but these differences were not sustained at 12 months; further, combination therapy was not superior to behavioral therapy alone or the use of pessaries alone.287 Pessaries may have a role as a temporary management strategy before surgery or when surgery is contraindicated, or they may be useful in women with SUI who are planning to become pregnant.286

To obtain the maximum benefit from pessaries, patients must be instructed in their appropriate use by trained practitioners. Complications associated with the use of pessaries include vaginal discharge, odor, pelvic pain, and bleeding. Other problems may include the failure to retain the pessary or vaginal prolapse, which may be more common in women who have undergone a hysterectomy. Pessaries are a conservative, safe, and effective method for managing SUI in women and may be considered an alternative to surgery in some patients.288

Electrical Stimulation Units

A rectal or vaginal probe is used to apply electrical stimulation to the pelvic floor, with the aim of inhibiting the micturition reflex and improving contraction of the pelvic floor musculature.273,274,278 These units may provide a less invasive alternative to surgery in patients with SUI. However, the devices are time-consuming to use. Kegel exercises may be equally effective and less expensive.273,284

Other Conservative Approaches

Other minimally invasive options for managing women with less severe symptoms of SUI include the injection of transurethral bulking agents, such as collagen, and transurethral collagen denaturation (the Renessa procedure). Transurethral collagen denaturation uses nonablative radiofrequency to reduce tissue compliance. Both transurethral bulking and transurethral collagen denaturation can be performed in the office, and both provide an option for high-risk surgical candidates and for patients with less severe symptoms of SUI.288

In a randomized controlled study, acupuncture of the hand had positive effects on vaginal contraction pressure, sexual life, and social activity. Kim et al. established 11 acupuncture points on the hand as a basic treatment formula.289

Pharmacotherapy

No medications have been approved for the treatment of SUI in the U.S. Alpha-adrenergic agonists, such as pseudoephedrine and phenylephrine, are used off-label for this indication based on the urethral smooth-muscle response to alpha stimulation and on improvements in intrinsic sphincter deficiency. However, the clinical utility of these drugs in SUI is limited by the lack of proven effi-
cacy and by concerns regarding adverse side effects, including in-
omnia, anxiety, hypertension, arrhythmias, and stroke.\textsuperscript{4,114,290–292}

**Imipramine.** The tricyclic antidepressant imipramine (Tof-
rainil) has been used off-label to treat patients with SUI. The alpha-
adrenergic and anticholinergic properties of this agent may pro-
vide the dual benefit needed in these patients. However, the use of
imipramine in patients with SUI, especially elderly patients, is
limited by its anticholinergic side-effect profile.\textsuperscript{25,120,293}

**Duloxetine.** The lack of approved drugs for SUI has led to stud-
ies of alternative agents, including duloxetine (Cymbalta, Eli Lilly).
Although duloxetine, a dual serotonin–norepinephrine reuptake
inhibitor (SNRI), is approved for the treatment of SUI in Europe,
it is indicated only for the treatment of depression and neuro-
pathic pain in the U.S. Duloxetine is believed to influence neuro-
transmitters on the pudendal nerve. As a result, urethral sphinc-
ter contraction is strengthened, and the increased urethral
 closure forces prevent urine leakage.\textsuperscript{274,293,294}

In clinical trials, duloxetine has reduced incontinence episodes
and has increased the quality of life in women with SUI. Side
effects leading to discontinuation included dry mouth, fatigue,
nausea, constipation, and hyperhidrosis. In one study, treatment-
related nausea was noted in 40% of patients; in most of these
patients, the nausea occurred early in treatment, was transient, and
was mild to moderate in severity.\textsuperscript{295–298}

Duloxetine has also been evaluated as a potential treatment op-
tion for men with SUI after radical prostatectomy. The drug
reduced incontinence episodes and improved quality of life.\textsuperscript{299}

**Venlafaxine.** Venlafaxine (Effexor, Pfizer), another dual SNRI,
has been evaluated for the management of SUI. It was reported to be
effective in a double-blind, randomized, placebo-controlled study
of women with SUI. Nausea occurred in 40% of the venlafaxine
group compared with 15% of the placebo group ($P < 0.05$).\textsuperscript{300}

The use of antidepressants with dual neurotransmitter mecha-
nisms for the treatment of SUI requires further study, but these
drugs may have future utility in some patients.

**OVERFLOW INCONTINENCE**

**Etiology and Diagnosis**

Overflow incontinence (OFI) is described with variable nomen-
clature in the literature. It is a condition of paradoxical incontinence
cau sed by chronic urinary retention. In this situation, the intra-
vesical pressure eventually equals the urethral resistance, result-
ing in periodic leakage or dribbling. OFI may be caused by obstruc-
tive processes anywhere in the lower urinary tract or by
impaired disorders of bladder outlet.\textsuperscript{4}

The most common cause of this type of UI is bladder outlet
obstruction secondary to BPH in men. Other bladder-outlet
obstructive disorders include urethral stricture disease, post-
prostatectomy bladder neck contracture, and pelvic organ pro-
lapse. Another common cause of OFI is impaired emptying of the
bladder owing to decreased bladder contractility. Common causes
of impaired contractility include hypotonic or neurogenic bladder
states, often resulting from diabetes, spinal cord injuries, pro-
longed urinary obstruction, and adverse drug effects.\textsuperscript{4}

Although OFI is less common in women than in men, bladder
prolapse or alignment problems can contribute to OFI in women.
Extrinsic factors include multiple medications with anticholinergic
side effects that can lead to UI and OFI symptoms (see Table 2).\textsuperscript{3}

OFI most commonly occurs in men with benign prostatic hyper-
rophy (BPH). BPH is defined as the proliferation of epithelial and
stromal cells in the prostate gland, characterized by discrete nod-
ules in the periurethral area, which can cause various degrees of

**Nonpharmacological Management**

**General Considerations**

The nonpharmacological treatment of OFI associated with BPH
includes the elimination of potential triggers, such as alcohol,
cafeine, and medications, along with various invasive and non-
invasive procedures, including transurethral resection of the
prostate (TURP).\textsuperscript{301,307–309} The American Urological Association
Symptom Index provides an objective, validated tool to determine
symptom severity and to provide guidance for management. An ini-
tial digital rectal examination and, in some cases, a urinalysis are
recommended to rule out other urological disorders or problems.

Watchful waiting with yearly follow-up is usually recommended
for men with mild BPH symptoms when other conditions have
been excluded. Failure to respond to nonpharmacological inter-
ventions or the presence of hematuria, renal insufficiency, bladder
stones, hydroureteritis, or recurrent infections requires further evaluation.\textsuperscript{398,304}

**Surgical Options**

The surgical management of BPH continues to evolve. Although
TURP has long been the standard of care, it is not without com-
lications. In one cohort study that looked at the complications of
TURP, the cumulative incidence of repeated interventions was
approximately 15% among 23,000 cases.\textsuperscript{310,311}

Alternative procedures have emerged over the last 15 years, but
few have shown significant advantages over TURP. Transurethral
incision of the prostate (TUIP) was developed for men with a
smaller prostate gland (less than 40 g). Although TUIP offers a shorter procedure time, less bleeding, and fewer complications, it might not be as effective as TURP in reducing urinary symptoms.

Resection techniques using electrical currents have included monopolar TURP, bipolar transurethral vaporization of the prostate, bipolar transurethral resection of the prostate, and bipolar enucleation of the prostate. These procedures have both advantages and disadvantages, and none has replaced TURP as the gold standard.

Several laser procedures have also been evaluated, including interstitial laser coagulation of the prostate, holmium laser ablation of the prostate (HoLaP), holmium laser enucleation of the prostate (HoLEP), photoselective vaporization of the prostate (PVP), and thulium laser resection of the prostate (TmLRP).

Other minimally invasive treatments include transurethral microwave thermotherapy (TUMT), water-induced thermotherapy, high-intensity focused ultrasonography (HIFU), and transurethral needle ablation (TUNA).

Clinical studies have compared various minimally invasive procedures with TURP and other surgical interventions, such as open simple prostatectomy. Although these noninvasive techniques may have advantages over simple prostatectomy, no clear superiority over TURP has been shown. Some laser procedures (e.g., HoLaP) may be benefit certain patients, including critically ill patients or those with a high risk of bleeding.

More invasive procedures include conventional open laparoscopic prostatectomy and, more recently, robotic-assisted laparoscopic prostatectomy.

Open prostatectomy procedures are being replaced by less invasive surgery in the management of BPH. The early, nonselective AABs include peripheral alpha-adrenergic blockade. These treatments may include watchful waiting rather than initial pharmacotherapy. Because many men do not undergo TURP or other procedures until they reach their 60s or 70s, patients in this age group may have a larger prostate gland and additional comorbidities. The aging status of many patients in this category has triggered research to develop less invasive therapies in patients who do not respond to initial treatment.

Most patients with BPH are treated based on symptom severity. These treatments may include watchful waiting rather than initial pharmacotherapy. Because many men do not undergo TURP or other procedures until they reach their 60s or 70s, patients in this age group may have a larger prostate gland and additional comorbidities. The aging status of many patients in this category has triggered research to develop less invasive therapies in patients who do not respond to initial treatment. For initial pharmacotherapy, the choice between TURP and other procedures over TURP are not entirely clear. Most patients with BPH are treated based on symptom severity. These treatments may include watchful waiting rather than initial pharmacotherapy. Because many men do not undergo TURP or other procedures until they reach their 60s or 70s, patients in this age group may have a larger prostate gland and additional comorbidities. The aging status of many patients in this category has triggered research to develop less invasive therapies in patients who do not respond to initial treatment.

Management of Urinary Incontinence

Pharmacotherapy

Pharmacotherapeutic options for OFI secondary to BPH include peripheral alpha-adrenergic blockers (AABs), 5-alpha-reductase inhibitors (ARIs), or a combination of the two (Table 6, page 359). For initial pharmacotherapy, the choice between the two classes is usually based on symptoms and prostate size. Patients with moderate-to-severe symptoms of BPH usually begin with an AAB to provide a more rapid onset of action and symptom relief. Men with larger baseline prostate volumes (greater than 40 mL) may start with an ARI or an ARI/AAB combination. ARIs are more effective than AABs at reducing the progression of BPH.

Alpha-adrenergic blockers. The early, nonselective AABs were developed to treat hypertension, although they are rarely used for that indication today (see Table 6). The most available drugs in this class were phenoxycbenzamine (Dibenzyline, GlaxoSmithKline), approved for the treatment of pheochromocytoma, and prazosin (Minipress, Pfizer), approved for the treatment of hypertension. AABs have evolved over the last 30 years, and more prostate-selective agents are now used for the management of BPH. As their class designation indicates, the mechanism of action of the nonselective AABs is peripheral alpha-adrenergic blockade.

Alpha_1_ receptors, the most common receptor subtype in the prostate gland, play a key role in mediating the contraction of smooth muscle. Blocking these receptors at the prostate level results in muscle relaxation and improved urine outflow. Alpha_1B_ receptors are found in arterial vessels, and their blockage is associated with blood pressure (BP) reduction along with certain BP-related adverse effects, such as orthostatic hypotension. Research has focused on developing agents with minimal alpha_1B_ effects to minimize BP lowering, especially in patients at risk of orthostatic hypotension, such as the elderly.

Nonselective AABs may have a greater effect on resting BP compared with uroselective AABs and may be associated with a greater risk of orthostatic hypotension. The labeling for all of the nonselective AABs includes a warning regarding the potential for hypotension. The AABs have differing pharmacokinetic profiles, including half-life and elimination properties, and bioavailability varies among formulations (see Table 6). AABs are metabolized by the hepatic CYP450 enzyme system, predominantly the CYP2D6 and CYP3A4 pathways. Awareness of potential drug interactions should be part of the monitoring plan when AABs are used with other medications.

Adverse effects of AABs include the potential for orthostatic hypotension, in addition to dizziness, peripheral edema, sedation, ejaculatory dysfunction, flu-like symptoms, headache, and GI effects. Because the nonselective AABs terazosin (Hytrin, Abbott) and doxazosin (Cardura, Pfizer) lack prostate selectivity and have increased vasodilatory properties, side effects (hypotension, dizziness, fatigue) are more common with these drugs. The uroselective AABs alfuzosin (Uroxatral, Sanofi) and tamsulosin (Flomax, Boehringer Ingelheim) are associated with a greater incidence of hypotension and ejaculatory dysfunction, respectively. The newest AAB, silodosin (Rapaflo, Watson), was reported to be effective in managing the symptoms of BPH, but the clinical and tolerability advantages of this agent have not been determined.

One adverse effect of AABs that may be significant in some patients is intraoperative floppy-iris syndrome (IFIS). IFIS was first described in 2005 as a clinical trial observed by ophthalmologists during cataract surgery. The triad is described as a billowing and fluttering of the iris stroma, resulting in susceptibility for prolapse of the iris and constriction of the pupil. This scenario imparts a greater risk of surgical complications, including trauma to and atrophy of the iris, posterior capsule rupture with vitreous loss, and postoperative macular edema. IFIS is irreversible and does not diminish or subside after the AAB is discontinued. Numerous reports have linked IFIS to the use of tamsulosin, possibly because of that drug’s propensity to selectively block alpha-1A receptors in the iris dilator muscle, thereby preventing mydriasis during cataract surgery. Although other AABs have been associated with IFIS, their relationship to that disorder is not as clearly defined.

In a study comparing men who received tamsulosin or alfuzosin, there was a significantly higher risk of IFIS and subsequent complications with tamsulosin during cataract surgery. A meta-analysis showed similar associations with IFIS among the various AABs, including tamsulosin, alfuzosin, terazosin, and doxazosin, along with a history of hypertension as an additional risk factor.

An awareness of a patient’s exposure to peripheral AABs should help ophthalmologists prepare for cataract surgery and alert them to the need for corrective measures to reduce the risk of complications. Various attempts to minimize IFIS and its complications during cataract surgery have included washout periods and ophthalmological interventions, including intracameral phenyle-
Management of Urinary Incontinence

Phrine, preoperative atropine, and iris expansion hooks. Pharmacists and other health care providers should be aware of the risk of IFIS, and patients should be advised about the importance of sharing information about their use of peripheral AABs. Pharmacists should ask all patients receiving AABs about their cataract history and should share this information with the patient’s ophthalmologist when necessary.343–345

Contraindications to the use of peripheral AABs include heart failure, hypotension, and the potential to exacerbate SUI in women. Because men usually present with symptomatic BPH later in life, the possibility of concurrent comorbidities exists. Sexual dysfunction, heart disease, hypertension, diabetes, and the metabolic syndrome may further complicate treatment decisions and may warrant the use of uroselective AABs.

The large Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) reported a higher risk of the combined endpoint of cardiovascular disease, stroke, and heart failure in hypertensive patients receiving the nonselective AAB doxazosin versus the diuretic chlorthalidone (e.g., Thalitone, Monarch). These data support the use of nonselective AABs as second-line or third-line options for hypertension, especially in patients with a history of cardiovascular disease.334–336,347–349

The uroselective AABs may offer a more tolerable side-effect profile than nonselective agents in patients with cardiovascular and sexual function disorders (see Table 6). Alfuzosin was well tolerated in men with multiple comorbidities, including those receiving phosphodiesterase type-5 (PDE5) inhibitors for erectile dysfunction. Tamsulosin was effective in men with BPH and LUTS without increasing the risk of cardiovascular disease.340,342,346 Peripheral AABs remain a mainstay of the pharmacological management of BPH-associated LUTS. These agents have demonstrated a class effect and provide benefits within 5 to 7 days, improving both symptoms and urinary flow rates. Although open-label and controlled trials have reported clinical benefits for up to 5 years, peripheral AABs have not reduced long-term complications or disease progression.344,345,347–349

When choosing among the five peripheral AABs that are available for the treatment of BPH, clinicians must consider several factors. Patients who can benefit from the antihypertensive properties of these drugs may be given a nonselective agent, such as terazosin. Patients who cannot tolerate the vasodilator properties of AABs, such as elderly patients with orthostatic hypotension, may benefit from one of the uroselective agents, such as alfuzosin.332 An important clinical consideration is that alfuzosin and tamsulosin can be initiated without dose titration. The cost of treatment should also be considered, especially since the older AABs are available in generic formulations.

Because comparable efficacy has been reported within the class, the focus of new drug development has been on improving convenience and tolerability. To choose the most appropriate AAB, clinicians need to identify patient-specific needs and should take into account several drug-related factors, including receptor selectivity, dosing frequency, the adverse-event profile, and concurrent comorbidities.335–338,341,342

When dispensing AABs, physicians and practitioners should review with patients the potential side effects, drug interactions, effects on BP, and the possibility of sedation and dizziness, as well as discuss future cataract surgery if relevant.333,334 When prescribing a nonselective AAB, the clinician should reiterate the importance of dose titration to reduce the risk of these complications.

5-alpha-reductase inhibitors. The ARIs finasteride (Proscar, Merck) and dutasteride (Avodart, GlaxoSmithKline) are also used to treat BPH, but usually in men with advanced disease or when AABs are contraindicated (see Table 6). ARIs are often combined with AABs because of their slow onset of action, which necessitates the use of AABs for more rapid symptom relief. The clinical use of ARI/AAB combinations has led to the development of a fixed-combination product containing the ARI dutasteride and the uroselective AAB tamsulosin (Jalyn, GlaxoSmithKline) (see Table 6).391,394 Dutasteride inhibits 5-alpha-reductase, the enzyme that converts intracellular testosterone to dihydrotestosterone (DHT). DHT is a more potent androgen than testosterone. Its production remains normal in aging men because of the increased activity of intra-prostatic 5-alpha-reductase. Inhibition of the 5-alpha-reductase enzyme leads to a reduction in androgenic prostate stimulation, which in turn decreases the size and volume of the prostate gland and improves restricted urine outflow and other symptoms of BPH.

The 5-alpha-reductase enzyme consists of two types. Type-1 is found in hair follicles, sebaceous glands, the liver, and skin, whereas type-2 occurs in prostate and genital tissues and in the scalp. Type-2 receptors appear to be involved in prostate gland enlargement and are overexpressed in prostate tissue in men with BPH and some prostate cancers.301,350

The pharmacokinetic characteristics of the ARIs include hepatic metabolism via the CYP3A4 pathway, with active metabolites. Clinicians should monitor patients for the use of concurrent inhibitors of this pathway during ARI therapy because of the potential for toxicity. Dutasteride is eliminated primarily in the feces and has limited renal clearance, with a half-life of 5 weeks. Finasteride has a substantially shorter half-life (6 to 8 hours), with elimination in the feces and urine. No dose adjustments are required for patients with renal impairment, but caution is recommended for patients with hepatic impairment.301,350,351

Although ARIs are effective in treating symptoms of BPH and are well tolerated, their side-effect profiles, especially the potential for sexual dysfunction, may be problematic in some men. ARIs may decrease ejaculate volume, affect libido and sexual function, and cause gynecomastia. Although these adverse effects may be self-limited, ARIs can create compliance issues for some patients.

ARIs are Pregnancy Category X drugs. Contact with these agents should be avoided by pregnant women or by women trying to conceive. Exposure of a pregnant woman to an ARI may result in a pseudohermaphroditic fetus with ambiguous genitalia. In addition, patients with a history of heart failure and those at risk of heart failure may require further evaluation before using ARIs because of an increased incidence of this event.301,305,334,350–354

As noted previously, ARIs are usually used as second-line drugs in the management of BPH and its associated symptoms because of their slow onset of action. Full clinical efficacy may take up to 3 to 6 months to be achieved. ARIs are approved for the treatment of moderate-to-severe symptomatic BPH to improve symptoms, to reduce the risk of acute urinary retention, and to reduce the need for BPH-related surgery. Similar efficacy was reported in clinical trials of dutasteride and finasteride. Their therapeutic benefits are due to a decrease in prostate volume, which results in the relief of LUTS, a reduced need for surgery, and a reduction in acute urinary retention, along with a delay in disease progression. Improvements in symptoms of BPH were maintained for up to 4 years in open-label extension trials.340,341,350,351,354

ARIs may be considered for first-line therapy in men with more severe symptoms of BPH, a prostate volume of 40 mL or more, and increased levels of prostate-specific antigen (PSA), such as 1.5 ng/mL or more, although an ARI/AAB combination might be warranted in these patients. Combination therapy appears to be
Table 6 Medications Used in the Treatment of Benign Prostatic Hyperplasia (BPH)

Nonselective Alpha-Adrenergic Blockers

<table>
<thead>
<tr>
<th>General comments</th>
<th>Nonselective Alpha-Adrenergic Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Used for both BPH and hypertension</td>
<td>• Dosage (immediate release): 1–8 mg q.d.</td>
</tr>
<tr>
<td>• Dosing based on patient response</td>
<td>• Dosage (extended release): 4–8 mg q.d. with breakfast; titrate dose every 3–4 weeks (maximum, 8 mg/day)</td>
</tr>
<tr>
<td>• Monitor for orthostatic hypotension (first dose)</td>
<td>• Elimination: fecal 60%, renal 9%</td>
</tr>
<tr>
<td>• Educate patients to rise slowly from supine position</td>
<td>• Half-life: 15–20 hours</td>
</tr>
<tr>
<td>• Bedtime dosing for immediate-release formulations</td>
<td>Prazosin (Minipress, Pfizer)</td>
</tr>
<tr>
<td>• Monitor efficacy, e.g., urine flow rates, symptoms</td>
<td>• FDA-approved for hypertension; not approved for BPH</td>
</tr>
<tr>
<td>• Potential for intraoperative floppy iris syndrome (cataract surgery)</td>
<td>• Dosage: 0.5–1.0 mg b.i.d.; titrate dose every 2–7 days (maximum, 2 mg/day)</td>
</tr>
<tr>
<td>• Use with caution with antihypertensive drugs and other drugs that lower blood pressure (e.g., vardenafil)</td>
<td>• Half-life: 2.5 hours</td>
</tr>
<tr>
<td>• Hepatic metabolism (primarily by CYP2D6/3A4*)</td>
<td>Terazosin (Hytrin, Abbott)</td>
</tr>
<tr>
<td>• Highly protein-bound</td>
<td>• Dosage: 1–5 mg q.d; titrate dose every 2–7 days (maximum, 20 mg/day)</td>
</tr>
<tr>
<td>• Mechanism: nonselective alpha₁-receptor blockade in bladder neck and prostate</td>
<td>• Elimination: fecal 60%, renal 40% (10% unchanged)</td>
</tr>
<tr>
<td></td>
<td>• Half-life: 12–14 hours</td>
</tr>
</tbody>
</table>

Uroselective Alpha-Adrenergic Blockers (Alpha₁A Receptors)

<table>
<thead>
<tr>
<th>General comments</th>
<th>Uroselective Alpha-Adrenergic Blockers (Alpha₁A Receptors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Used only for BPH</td>
<td>Alfuzosin (Uroxatral, Sanofi)</td>
</tr>
<tr>
<td>• Dosing based on patient response</td>
<td>• Dosage: 1 extended-release tablet (10 mg) q.d.</td>
</tr>
<tr>
<td>• Mechanism: selective alpha₁-receptor blockade in bladder neck and prostate; selectively reduce urinary tract alpha₁A-receptors</td>
<td>• Contraindication: moderate/severe liver disease</td>
</tr>
<tr>
<td></td>
<td>• Elimination: fecal 70%, renal 25% (10% unchanged)</td>
</tr>
<tr>
<td></td>
<td>• Half-life: 10 hours</td>
</tr>
<tr>
<td>Silodosin (Rapaflo, Watson)</td>
<td>Tamsulosin (Flomax, Boehringer Ingelheim)</td>
</tr>
<tr>
<td>• Dosage: 4–8 mg q.d. with food</td>
<td>• Dosage: 0.4–0.8 mg q.d.</td>
</tr>
<tr>
<td>• Elimination: fecal 55%, renal 33%</td>
<td>• Elimination: renal 75% (&lt;10% unchanged), fecal 20%</td>
</tr>
<tr>
<td>• Half-life: 14–24 hours; glucuronide conjugate</td>
<td>• Half-life: 15 hours</td>
</tr>
<tr>
<td>• Contraindication: hepatic Child–Pugh score &gt; 10</td>
<td>• Associated with intraoperative floppy iris syndrome (cataract surgery)</td>
</tr>
<tr>
<td></td>
<td>• Avoid use in patients with sulfa allergy</td>
</tr>
</tbody>
</table>

5-Alpha-Reductase Inhibitors

<table>
<thead>
<tr>
<th>General comments</th>
<th>5-Alpha-Reductase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Used only for BPH</td>
<td>Dutasteride (Avodart, Glaxo-Smith-Kline)</td>
</tr>
<tr>
<td>• Administered as monotherapy or with alpha-adrenergic blockers</td>
<td>• Dosage: 0.5 mg q.d.</td>
</tr>
<tr>
<td>• Contraindications: pregnancy, including pregnant blood transfusion recipient if donor had dose within 6 months; pediatric patients; cutaneous absorption (avoid capsule handling by pregnant or potentially pregnant women)</td>
<td>• Metabolized by CYP3A4*/3A5; active metabolites</td>
</tr>
<tr>
<td>• Monitor PSA and side effects: abnormal ejaculation, reduced libido, signs and symptoms of BPH (urine flow)</td>
<td>• Elimination: feces 45%, urine &lt; 1%</td>
</tr>
<tr>
<td></td>
<td>• Half-life: 5 weeks</td>
</tr>
<tr>
<td></td>
<td>• Mechanism: inhibits type-1 and type-2 5-alpha-reductase</td>
</tr>
<tr>
<td></td>
<td>• Possible risk of heart failure</td>
</tr>
</tbody>
</table>

*table continues*
Management of Urinary Incontinence

Table 6 Medications Used in the Treatment of Benign Prostatic Hyperplasia (BPH), continued

<table>
<thead>
<tr>
<th>5-Alpha-Reductase Inhibitors, continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutasteride/tamsulosin (Jalyn, GlaxoSmithKline)</td>
</tr>
<tr>
<td>• Dosage: 1 capsule (dutasteride 0.5 mg/tamsulosin 0.4 mg) q.d., taken 30 minutes after same meal each day</td>
</tr>
<tr>
<td>• See comments for dutasteride and tamsulosin on previous page</td>
</tr>
<tr>
<td>Finasteride (Proscar, Merck)</td>
</tr>
<tr>
<td>• Dosage: 5 mg q.d.</td>
</tr>
<tr>
<td>• Metabolized by CYP3A4*: active metabolites</td>
</tr>
<tr>
<td>• Elimination: feces 60%, urine 40%</td>
</tr>
<tr>
<td>• Half-life: 6–8 hours</td>
</tr>
<tr>
<td>• Mechanism: inhibits type-2 5-alpha-reductase</td>
</tr>
<tr>
<td>• Minimal drug interactions reported; monitor when used with CYP3A4 inhibitors; caution in patients with hepatic impairment</td>
</tr>
<tr>
<td>b.i.d. = twice daily; CYP = cytochrome P450; PSA = prostate-specific antigen; q.d. = once daily</td>
</tr>
<tr>
<td>* CYP3A4 metabolism: use lower dose or avoid if patient is taking a concurrent CYP3A4 inhibitor (e.g., clarithromycin, ketoconazole)</td>
</tr>
</tbody>
</table>
Adapted from references 301, 304, 333–338, and 342–349.

more effective than monotherapy for prostate volumes above 60 g.

Initial combination therapy with an ARI and an AAB may be changed to ARI monotherapy after several months when the benefits of the ARI become clinically evident. Studies have shown, however, that an ARI/AAB combination can be more effective than monotherapy in improving BPH-related symptoms and urine flow. Although adverse events were more frequent with combination treatment, they did not significantly affect compliance. In addition, studies reported that an ARI/AAB combination may reduce disease progression in some patients. Limited data suggest that combination therapy might be more effective in patients with underlying prostatic inflammation and that the use of long-term combination therapy may be warranted in some patients.301,304,333–338

In one trial, patients treated with an AAB had an increased risk of BPH-related surgery compared with patients treated with an ARI. This finding suggests the need for additional research to assess long-term outcomes and to identify optimal treatments for BPH patients based on their baseline characteristics.301,338–361

Another area of research is the role of ARIs in the prevention of prostate cancer.362 Two large controlled trials of ARIs in the prevention of prostate cancer reported an overall relative reduction in low-grade tumors of approximately 24%. However, it is debatable as to whether the use of this class of drugs is associated with higher grades of prostate cancer in patients who are ultimately found to have cancer.303,384 Some experts have suggested that ARIs may reduce the size of existing low-risk lesions rather than prevent the development of new cancers. ARIs continue to be studied as a means of reducing the risk of prostate cancer or slowing disease progression.365–367 Because ARIs can suppress PSA levels, monitoring of patients receiving ARI therapy should include the evaluation and adjustment of this antigen. It has been recommended that a multiple of 2 should be used to adjust PSA values in patients receiving chronic ARI therapy.301,334,354,366,377

Antimuscarinic (anticholinergic) drugs. Men with BPH who continue to experience significant lower urinary tract symptoms (LUTS, urgency, nocturia, hesitancy, and weak stream) or overactive bladder (OAB) while taking an AAB may benefit from the addition of an antimuscarinic agent. This combination may be useful for relieving symptoms of bladder outlet obstruction and detrusor overactivity. This treatment approach has been clinically effective, but clinicians experienced in the use of AAB/antimuscarinic combinations should carefully monitor treated patients to avoid acute urinary retention.305,359,368–374

Before antimuscarinic drugs are used in BPH patients with LUTS or OAB, a risk assessment is necessary. This assessment should include an evaluation of the patient’s post-void residual volume. Clinical trials have reported average post-void residual volumes of 25 to 50 mL in patients receiving antimuscarinic agents. These studies included a variety of antimuscarinic drugs in combination with AABs. Extended-release tolterodine, ER oxybutynin, and solifenacin were all studied in combination with the AAB tamsulosin (Flomax). These trials reported improvements in urinary frequency, urgency, nocturnal micturition, patient perceptions of bladder conditions, and the International Prostate Symptom Score (IPSS) compared with AAB monotherapy.305,359,368–374

A selected cohort of men were evaluated by clinicians with appropriate training in this area. In one trial, post-void residual volumes were higher with the combination, further emphasizing the importance of monitoring for potential urinary retention. It is noteworthy that antimuscarinic agents are not approved for the treatment of BPH. If they are used to treat LUTS in these patients, monitoring is essential, especially within the first 30 days after starting therapy, because of the potential for acute urinary retention.305,359,368–374

Other Therapies for Overflow Incontinence

PDE5 inhibitors. These drugs have shown promise in the treatment of BPH-associated LUTS and may have a role in men with concurrent erectile dysfunction.375 In October 2011, the FDA approved tadalafil (Cialis, Eli Lilly) for the treatment of BPH. Tadalafil had been approved for the management of erectile dysfunction in 2003, and this recent approval provides clinicians with an option for managing concurrent erectile dysfunction and BPH. Clinical trials have reported significant improvement in BPH symptoms with tadalafil 5 mg daily versus placebo, as indicated by reductions in the IPSS. Studies have also shown that tadalafil is safe and effective in reducing LUTS. Tadalafil should be avoided in men who are taking nitrates, and it should be used with caution when combined with AABs because of the potential for additive effects on BP.375,377

Although PDE5 inhibitors provide effective symptom relief in BPH, they appear to have limited effects on urinary flow rates. The precise mechanism of action of PDE5 inhibitors is unknown, but these agents may have multiple effects on pathways that contribute to LUTS, including smooth-muscle relaxation, smooth-muscle and endothelial-cell proliferation, nerve activity, and
tissue perfusion. 376–380

Botulinum toxin. A small trial of intraprostatic BTX-A in patients with BPH-associated LUTS reported clinical efficacy and improved quality of life. Some patients experienced sustained effects of treatment for up to 12 months. The mechanism of action of BTX-A in this setting may involve inhibitory effects on smooth-muscle tone rather than a change in prostate volume. 384

Herbal remedies and investigational agents. Other therapies that have been used in the management of OFI secondary to BPH include saw palmetto (which may have some ARI activity), rye-grass pollen extract, Pygeum africanum, and the Chinese herbal medicine gosha-jinki-gan. 301,304,382 Although some evidence supports the use of saw palmetto extract in BPH patients, a recent dose-escalation trial reported no beneficial effects on LUTS with this herbal preparation compared with placebo. 385

Various investigational agents, including long-acting AABs with improved tolerability profiles, are being studied for the treatment of BPH-associated LUTS. 384 A randomized, placebo-controlled study reported that transdermal DHT had no effect on prostate growth in healthy men. 385

MIXED URINARY INCONTINENCE

The International Continence Society defines mixed urinary incontinence (MUI) as “involuntary leakage associated with exertion and urgency.” MUI can be challenging to clinicians because successful treatment must address two components—urge incontinence (UI) and stress incontinence (SUI). 31,258 The failure to understand the role of both types of incontinence in patients with MUI may result in the persistence of UI after surgery for SUI, which patients may perceive as a treatment or surgical failure. 386

From 15% to 90% of patients with UI have MUI, but these estimates may depend on the questions that were asked during the assessment process. One study reported that when objective estimates may depend on the questions that were asked during the assessment process. One study reported that when objective methods (e.g., urodynamics) were used, as few as 8% of cases were identified as MUI. 387

Patients who experience symptoms suggestive of MUI require a comprehensive urological evaluation. Treatment may involve an array of procedures and pharmacotherapies (Table 7) (see UUI and SUI, pages 348 and 354). 35,43,47,110,388,389 Generally, in patients with MUI, the predominant condition should be treated first. 389

CONCLUSION

The pharmacological management of urinary incontinence requires appropriate evaluation by qualified clinicians. Pharmacists can offer educational support to patients by questioning them about their understanding of the disorder and by monitoring the effectiveness and tolerability of the agents prescribed. Taking time to get to know the patient in ambulatory and clinical settings allows the pharmacist and health care provider the opportunity to provide valuable instruction, intervention, and recommendations to improve patient outcomes in the management of UI.

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