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.[1–3]

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).[4]

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.[1]

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.[5,6] 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).[7]

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.[8] 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.[9,10]

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.[11,12] The prevalence of UI in nursing homes remains high, and the care of nursing-home residents with UI is the subject of clinical research.[13,14] In addition, UI is one of the measures used by the Centers for Medicare and Medicaid Services (CMS) to assess quality of care.[15–17]

Annual direct and indirect costs of managing UI in the U.S. is estimated at $25 billion for patients over 65 years of age.[18,19] The direct costs of UI include diagnostic procedures and the various treatment options, including pharmacotherapy.[20] Indirect costs include complications and disabilities, such as insomnia, falls, depression, caregiving, and nursing-home placement.[10,21] 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.[22–24]

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.[25,26] 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.[26–31]

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 urethra closure, atrophy of urethral areas, and prostatic hypertrophy) may contribute to UI.[32] 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.[33–37]

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

BPH	benign prostatic hyperplasia
LUTS	lower urinary tract symptoms
MUI	mixed urinary incontinence
OAB	overactive bladder
OFI	overflow incontinence
SUI	stress urinary incontinence
UI	urinary incontinence
UTI	urinary tract infection
UUI	urge urinary incontinence

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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.[47,48]

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.

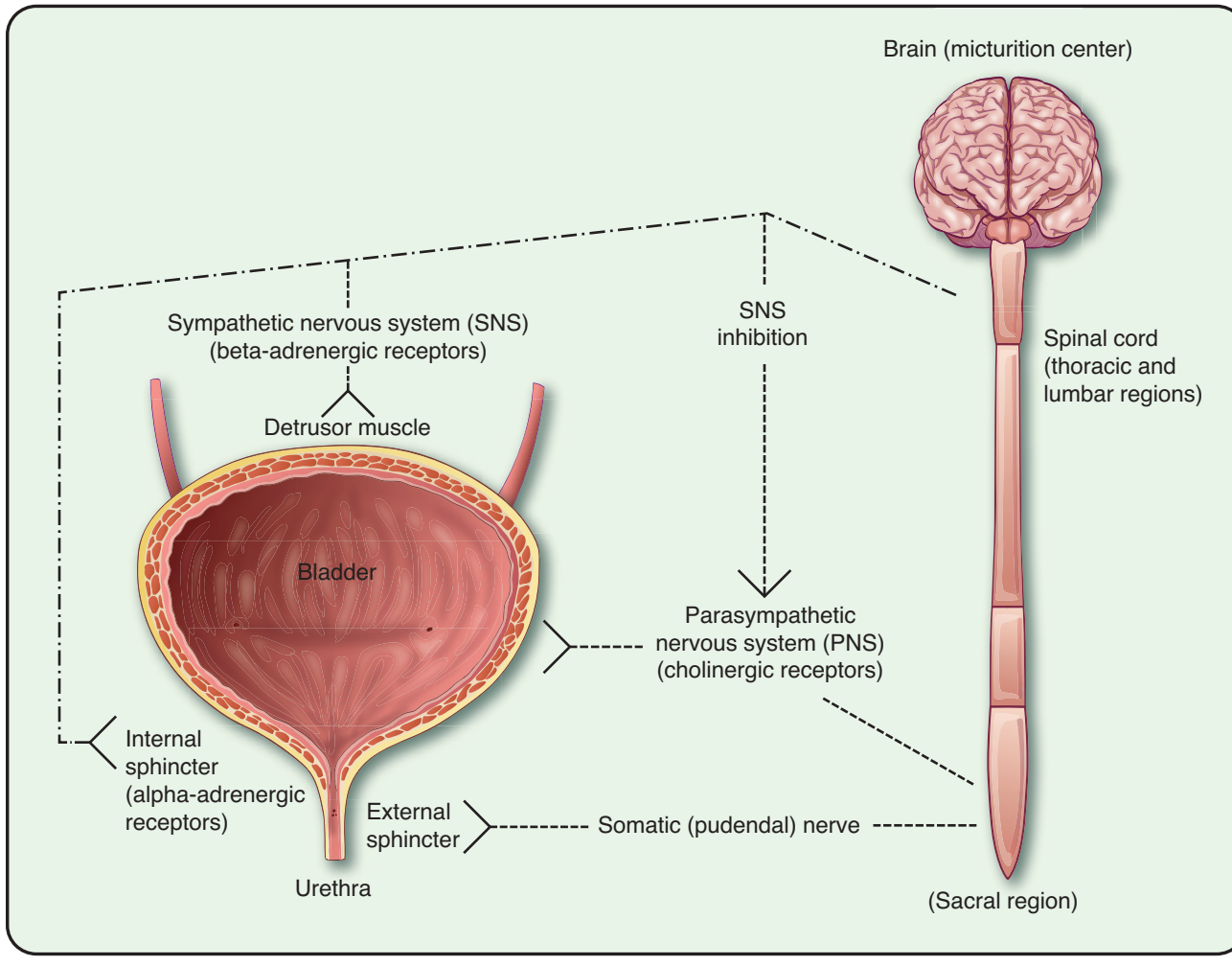

Figure 1 Bladder anatomy and physiology.

Illustration by Alison Schroeer

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.[7,41,51,52] 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.[53–61] A study of weight loss in overweight women reported a clinically relevant reduction in the frequency of both stress and urge incontinence episodes.[58] 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.

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.[62–68]

Table 1 Reversible Causes of Urinary Incontinence (DIAPPERS)

D	Delirium
I	Infection (urinary tract)
A	Atrophic
P	Pharmacological
P	Psychological
E	Endocrine/excess urine output
R	Restricted mobility
S	Stool impaction

Data adapted from references 38–46.

Pelvic floor (Kegel) muscle training and bladder training have been beneficial in resolving or improving UI.[69,70] 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.[69–71] 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.[53,54,56,72]

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

Table 2 Medications That Can Cause or Exacerbate Urinary Incontinence

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

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

often overlooked, but if the disorder is identified in these individuals, it can be successfully managed with conservative measures. The use of nonpharmacological interventions, including Kegel exercises and bladder retraining, can be effective even in frail older adults, especially with caregiver assistance. Medications may be necessary in some patients, however, and treatment outcomes may be less successful in patients with advanced age and severe UI.[73]

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.[74–77] 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 (SUI).[74–77,85–92]

Some clinical trials, however, have not supported the use of oral HT for managing UI.[84,93] 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 progestin 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 progestin 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 progestin 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/Progestin Replacement Study (HERS), a randomized, placebo-controlled, double-blinded trial, evaluated conjugated estrogen plus progestin for the secondary prevention of heart disease in 1,200 women. Estrogen plus progestin 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 progestin 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.[74,106] Topical estrogen formulations may include creams or estradiol-impregnated 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.[107–109]

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.[3,4,30,31,110–112] 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 UI.[1,31]

UUI occurs primarily as a result of detrusor muscle overactivity, resulting in uninhibited or involuntary muscle contractions.[26–28] 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.[31,114] The primary causes of UUI (see Table 3) include idiopathic detrusor overactivity (resulting from UTIs) and neurogenic detrusor overactivity (resulting from stroke, trauma, neurological diseases, or medications).[25–28,43–46,112] 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.[115,116]

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 urge-suppression techniques, was found to be ineffective in improving outcomes in women with UUI.[53,54,119]

Pharmacotherapy

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

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. Table 5 lists the available antimuscarinic (anticholinergic) agents used to treat UUI. Each of these agents is discussed on the following pages.[123–126]

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.[25,120,127,128]

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.[129–134]

Table 3 Causes, Symptoms, and Treatment of Urinary Incontinence

Type of Incontinence	Common Causes	Common Symptoms	Treatment Options
Urge urinary incontinence (UUI)			

Idiopathic detrusor overactivity	Urinary tract infections	Urgency and frequency, day or night	• Anticholinergic drugs
			  • Oxybutynin
			  • Tolterodine
			• Surgery
			  • Intravesical Botox
			  • Sacral nerve stimulation

Neurogenic detrusor overactivity	• Neurological disorders
	  • Parkinson's disease
	  • Alzheimer's disease
	• Cerebrovascular accidents (e.g., stroke)
	  • Trauma
	  • Medications		

Stress urinary incontinence (SUI)			
Stress incontinence (outlet incompetence)	• Pelvic surgery • Parity (childbirth) • Constipation	Small volumes of urine loss with coughing or sneezing	• Weight loss • Kegel (pelvic floor) exercises with or without biofeedback • Sling procedures • Transurethral collagen denaturation (Renessa procedure) • Transurethral bulking agents
Mixed urinary incontinence (MUI)			
Mixed UUI and SUI	• Pelvic surgery • Parity (childbirth) • Constipation	Symptoms may include urge and stress features	Treatment depends on predominant symptoms
Overflow incontinence (OFI)			
Overflow incontinence	• Benign prostatic hyperplasia (BPH) • Bladder outlet obstruction • Fecal impaction • Hypotonic/neurogenic bladder • Urethral stricture disease	Poor stream, incomplete emptying, and dribbling	• Alpha-adrenergic blockers • 5-alpha-reductase inhibitors • Intermittent catheterization • Surgical options
Other types of incontinence			
Post-prostatectomy incontinence	Disruption or denervation of pelvic floor muscle fibers	Stress incontinence and dribbling	• Kegel pelvic floor exercises • Male urethral sling • Artificial urinary sphincter
Fistula (e.g., colovesical or vesicovaginal)	• Postsurgical complications • Crohn's disease • Diverticulitis • Cancer	Continuous, steady incontinence	Surgical repair
Functional incontinence	• Limited mobility • Change in mental status	Symptoms vary	Eliminate causes

Data compiled from references 1–4, 30, and 110–112.

Gopal et al. reported high discontinuation rates for anticholinergic drugs that were used to treat LUTS in women.[135] 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 UUI, including more vigilant use of nonpharmacological interventions, such as fluid modification, pelvic floor rehabilitation, and bladder training.[135]

Anticholinergics have the potential to interact with other medications that have the same side-effect profile and with other centrally acting drugs.[120] The concomitant use of acetylcholinesterase inhibitors for dementia and anticholinergic drugs may exacerbate cognitive decline and should be avoided if possible.[136]

As shown in Table 5, all of the anticholinergic agents used to treat UI, except trospium chloride (Sanctura, Allergan/Esprit/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 UUI, especially older adults and those taking multiple medications, for adverse effects, drug interactions, and potential contraindications during treatment with anticholinergics.[25,120,137]

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 UUI and may have a role in MUI because of its dual anticholinergic and alpha-adrenergic properties.[120, 128,138–141]

Currently, the anticholinergic drugs most commonly used in clinical practice for the treatment of UUI 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).[138–141]

As mentioned, several anticholinergic agents are available in various doses, formulations, and routes of administration, providing clinicians with several treatment options for with UUI.[128,132,137,138,141] These drugs are usually used to treat UUI 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 UUI 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.[141,142] 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.[143]

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.[144] 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.[53,54,142–147]

Oxybutynin (Ditropan, Oxytrol). Oxybutynin is the oldest of the agents currently used to treat UUI. 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.[148] The ER tablet, dermal patch, and topical gel may offer improved tolerability because of reduced levels of the active metabolite, *N*-desethyloxybutynin.[149–153]

Table 4 Muscarinic Receptor Subtypes and Adverse Effects of Receptor Inhibition

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

M = muscarinic receptor.
Data adapted from references 122–126.

Table 5 Anticholinergic Agents Used for Urinary Incontinence

Drug	Recommended Adult Dose	Pharmacokinetic Properties
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$_1$-acid-glycoprotein) • Extensively metabolized by CYP2D6/3A4*; 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 CYP2D6/3A4*; 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 CYP3A4*; 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) Oxybutynin gel 3% (Anturol, Antares)	1 g (sachet) applied daily to dry, intact skin; rotate application sites (abdomen, thigh, shoulder, upper arm) 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 • Steady state: achieved within 3–7 days of continuous dosing • Metabolized primarily by CYP3A4*; 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 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 CYP3A4*; 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 CYP3A4* • 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 alpha$_1$-acid glycoprotein) • Extensively metabolized by CYP2D6 to active metabolite (5-HMT); metabolized by CYP3A4* 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 alpha$_1$-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

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

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

b.i.d. = twice daily; CrCl = 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.

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.[154]

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.[120,148,153]

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.[159–161]

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.[153,162] 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.[163–166]

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.[167–170]

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.[190–193]

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 renally 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.[196–205] In one study, fewer micturitions were reported with solifenacin than with tolterodine during a 24-hour period.[174]

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.[206–209]

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.[17,210,211]

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 ae 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.[171,212]

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.[171]

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.[177,214–220] A community-based survey found that patients with OAB experienced benefits with darifenacin and were generally satisfied with the drug.[221]

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-hydroxymethyl-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.[173,223,226]

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.[227–234] 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.[237]

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

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.[238]

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 of the bladder. BTX-A is administered via a cystoscopic technique that is reported to be safe and well tolerated. The toxin is injected directly into the detrusor muscle. In clinical trials, the duration of response was typically 3 to 6 months. Intravesical injections of BTX-A in patients with OAB resulted in increased bladder capacity, increased bladder compliance, and improved quality of life.[239,240]

A study of onabotulinumtoxinA (Botox, Allergan, Inc.) in patients with idiopathic UUI or OAB indicated that doses ranging from 100 U to 150 U were effective in managing the disorder. Adverse effects included UTIs and urinary retention.[240]

Although clinical trials with BTX-A have not been robust, they suggest that this agent may offer potential benefits for patients with UUI. Further research is necessary to substantiate the usefulness of BTX-A in this population.

Sacral nerve stimulation. Sacral nerve stimulation has been used as a second-line therapy for incontinence secondary to OAB since the 1980s. Several reports have demonstrated the efficacy of this treatment in UUI. The underlying principle of neuromodulation for detrusor overactivity is the induction of somatic afferent inhibition of sensory processing in the spinal cord.[241]

Investigational agents. Agents being evaluated for the management of UUI include imidafenacin (Ono/Kyorin), an antimuscarinic agent from Japan, and neurokinin-1 receptor antagonists.[242,243] The latter agents have been useful in treating OAB but offer no advantages in efficacy compared with tolterodine.

Mirabegron (Astellas), a once-daily, oral selective beta$_3$-adrenoceptor agonist, has been shown to reduce episodes of UI and micturition frequency in patients with OAB.[244] Astellas submitted a New Drug Application for mirabegron to the FDA in August 2011. In July 2011, mirabegron was granted marketing approval in Japan. Researchers continue to develop agents that are effective and better tolerated for the treatment of UUI, especially in more sensitive older adults.[242–244]

STRESS URINARY INCONTINENCE

Stress urinary incontinence (SUI), the most common type of UI in elderly women, is most prevalent in Caucasians. SUI is primarily a disorder of urethral hypermobility or intrinsic sphincter deficiency. Risk factors for SUI include anatomic changes related to aging, pelvic and gynecological surgery, multiple births, medications, obesity, and neurological disorders.[43,59,93,245–247] In addition to the high economic costs of treatment, the social costs and the detrimental effects of SUI on elderly women are also significant.[20,248,249] Patients with SUI describe involuntary loss of urine triggered by coughing, sneezing, or rising quickly. Patients with "pure" SUI may lack urgency and nocturia, although many of them may have mixed forms, with features of UUI.[246,247,250–252]

Although SUI is usually considered a female disorder, it can occur in men after prostate surgery. Post-prostatectomy SUI (PPSUI) occurs in over 90% of men during the postoperative period. PPSUI is usually self-limiting and improves within 12 months with proper education and a consistent Kegel exercise regimen.[253,254] Reassurance and encouragement are important parts of management. If symptoms of PPSUI last beyond 1 year postoperatively, surgical options should be considered. Surgical approaches include placing an implantable, artificial urinary sphincter (the gold standard) and urethral sling procedures. Only 5% to 10% of PPSUI patients require a continence procedure.[255]

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.[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).[264]

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.[108] 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.[265–267]

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

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.[266,269,270]

Surgery is also associated with improved quality of life and is an excellent option for some patients.[108,271,272]

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.[108] 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.[108,274]

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.[273]

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.[286]

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.[108,273,278] 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 denaturization 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 insomnia, anxiety, hypertension, arrhythmias, and stroke.[43,164,290–292]

Imipramine. The tricyclic antidepressant imipramine (Tofranil) has been used off-label to treat patients with SUI. The alpha-adrenergic and anticholinergic properties of this agent may provide 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.[25,120,293]

Duloxetine. The lack of approved drugs for SUI has led to studies 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 neuropathic pain in the U.S. Duloxetine is believed to influence neurotransmitters on the pudendal nerve. As a result, urethral sphincter contractions are strengthened, and the increased urethral closure forces prevent urine leakage.[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.[295–298]

Duloxetine has also been evaluated as a potential treatment option for men with SUI after radical prostatectomy. The drug reduced incontinence episodes and improved quality of life.[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 ($P < 0.05$).[300]

The use of antidepressants with dual neurotransmitter mechanisms 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 nomenclature in the literature. It is a condition of paradoxical incontinence caused by chronic urinary retention. In this situation, the intravesical pressure eventually equals the urethral resistance, resulting in periodic leakage or dribbling. OFI may be caused by obstructive processes anywhere in the lower urinary tract or by impaired disorders of bladder emptying.[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 prolapse. 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, prolonged urinary obstruction, and adverse drug effects.[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).[4]

OFI most commonly occurs in men with benign prostatic hypertrophy (BPH). BPH is defined as the proliferation of epithelial and stromal cells in the prostate gland, characterized by discrete nodules in the periurethral area, which can cause various degrees of bladder outlet obstruction secondary to compression of the prostate urethra. Studies suggest that BPH affects more than 30% of men 60 to 70 years of age and 90% of men in their 70s and 80s.[25,301]

In men with BPH, an enlarged prostate is noted on physical examination. In some cases, further evaluation may be necessary to rule out prostate cancer or other obstructive disorders.[301] The clinical presentation of OFI is characterized by lower urinary tract symptoms (LUTS). This spectrum of symptoms results from compression of the urethra, which in turn leads to an unstable detrusor muscle or to bladder distention and hypertrophy caused by the patient's chronic inability to completely empty the bladder. Symptoms of OFI include difficulty initiating a urine stream, a weak stream, a sense of incomplete emptying, nocturia, and dribbling. The severity of the symptoms might not be correlated with the degree of BPH, and a presentation of LUTS can be due to other causes.

Findings that suggest a further differential diagnosis in men with suspected OFI include fever or prostate tenderness, abnormal sphincter tone, hematuria, and prostate nodules or induration. These signs and symptoms may indicate prostatitis, neurogenic bladder, or malignancy of the bladder or prostate. A complicating clinical feature of LUTS associated with BPH is urgency symptoms, which may occur in up to two-thirds of patients.[301–305]

The prevalence of OFI in men with BPH is unclear. One study indicated that incontinence occurs in approximately 2,700 of every 100,000 men, although the specific type of incontinence was not specified. In men who underwent BPH surgery or received alpha-blocker therapy, the risk of incontinence was increased, especially in the postsurgical group. The BPH-related incontinence in this study might have been a result of postsurgical complications, such as new-onset urgency or frequency, and other irritative symptoms. Additional diagnostic procedures, such as cystourethroscopy and urodynamic testing, might be necessary in men with BPH, especially post-BPH surgery patients, before therapy is initiated.[306]

Nonpharmacological Management

General Considerations

The nonpharmacological treatment of OFI associated with BPH includes the elimination of potential triggers, such as alcohol, caffeine, and medications, along with various invasive and non-invasive procedures, including transurethral resection of the prostate (TURP).[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 initial 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 interventions or the presence of hematuria, renal insufficiency, bladder stones, hydronephrosis, or recurrent infections requires further evaluation.[301,304]

Surgical Options

The surgical management of BPH continues to evolve. Although TURP has long been the standard of care, it is not without complications. In one cohort study that looked at the complications of TURP, the cumulative incidence of repeated interventions was approximately 15% among 23,000 cases.[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.[312]

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.[313–318]

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).[319–325]

Other minimally invasive treatments include transurethral microwave thermotherapy (TUMT), water-induced thermotherapy, high-intensity focused ultrasonography (HIFU), and transurethral needle ablation (TUNA).[326]

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.[318–325] More invasive procedures include conventional open laparoscopic prostatectomy and, more recently, robotic-assisted laparoscopic prostatectomy.[327–329]

Open prostatectomy procedures are being replaced by less invasive surgery in the management of BPH. Some of the new technological treatment options for BPH may also challenge TURP because of their potential for fewer complications, reduced hospital admission time, and cost effectiveness. The advantages of some of these procedures over TURP are not entirely clear.[330, 331]

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.[331,332]

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).[301,304] 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 first available drugs in this class were phenoxybenzamine (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.

$Alpha_{1A}$ 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.[332,333] The AABs have differing pharmacokinetic profiles, including half-life and elimination properties, and bioavailability varies among formulations (see Table 6).[333–338] 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.[336–339]

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.[333,338–342]

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 triad 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.[343–345]

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-

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.[334–338,341,346]

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 (PDE_5) 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.[334,335,347–349]

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).[301,334] 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 intraprostatic 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.[301,305,334,350–356]

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	

General comments	• Used for both BPH and hypertension
	• Dosing based on patient response
	• Monitor for orthostatic hypotension (first dose)
	  • Educate patients to rise slowly from supine position
	  • Bedtime dosing for immediate-release formulations
	• Monitor efficacy, e.g., urine flow rates, symptoms
	• Potential for intraoperative floppy iris syndrome (cataract surgery)
	• Use with caution with antihypertensive drugs and other drugs that lower blood pressure (e.g., vardenafil)
	• Hepatic metabolism (primarily by CYP2D6/3A4*)
	• Highly protein-bound
	• Mechanism: nonselective $alpha_1$-receptor blockade in bladder neck and prostate

Doxazosin (Cardura and Cardura XL, Pfizer)	• Dosage (immediate release): 1–8 mg q.d. • Dosage (extended release): 4–8 mg q.d. with breakfast; titrate dose every 3–4 weeks (maximum, 8 mg/day) • Elimination: fecal 60%, renal 9% • Half-life: 15–20 hours
Prazosin (Minipress, Pfizer)	• FDA-approved for hypertension; not approved for BPH • Dosage: 0.5–1.0 mg b.i.d.; titrate dose every 2–7 days (maximum, 2 mg/day) • Half-life: 2.5 hours
Terazosin (Hytrin, Abbott)	• Dosage: 1–5 mg q.d; titrate dose every 2–7 days (maximum, 20 mg/day) • Elimination: fecal 60%, renal 40% (10% unchanged) • Half-life: 12–14 hours
Uroselective Alpha-Adrenergic Blockers (Alpha$_{1A}$ Receptors)	
General comments	• Used only for BPH • Dosing based on patient response • Mechanism: selective $alpha_1$-receptor blockade in bladder neck and prostate; selectively reduce urinary tract $alpha_{1A}$-receptors
Alfuzosin (Uroxatral, Sanofi)	• Dosage: 1 extended-release tablet (10 mg) q.d. • Contraindication: moderate/severe liver disease • Elimination: fecal 70%, renal 25% (10% unchanged) • Half-life: 10 hours
Silodosin (Rapaflo, Watson)	• Dosage: 4–8 mg q.d. with food • Elimination: fecal 55%, renal 33% • Half-life: 14–24 hours; glucuronide conjugate • Contraindication: hepatic Child–Pugh score > 10
Tamsulosin (Flomax, Boehringer Ingelheim)	• Dosage: 0.4–0.8 mg q.d. • Elimination: renal 75% (<10% unchanged), fecal 20% • Half-life: 15 hours • Associated with intraoperative floppy iris syndrome (cataract surgery) • Avoid use in patients with sulfa allergy
5-Alpha-Reductase Inhibitors	
General comments	• Used only for BPH • Administered as monotherapy or with alpha-adrenergic blockers • 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) • Monitor PSA and side effects: abnormal ejaculation, reduced libido, signs and symptoms of BPH (urine flow)
Dutasteride (Avodart, Glaxo-SmithKline)	• Dosage: 0.5 mg q.d. • Metabolized by CYP3A4*/3A5; active metabolites • Elimination: feces 45%, urine < 1% • Half-life: 5 weeks • Mechanism: inhibits type-1 and type-2 5-alpha-reductase • Possible risk of heart failure

table continues

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

5-Alpha-Reductase Inhibitors, continued	
Dutasteride/ tamsulosin (Jalyn, GlaxoSmithKline)	• Dosage: 1 capsule (dutasteride 0.5 mg/tamsulosin 0.4 mg) q.d., taken 30 minutes after same meal each day • See comments for dutasteride and tamsulosin on previous page
Finasteride (Proscar, Merck)	• Dosage: 5 mg q.d. • Metabolized by CYP3A4*; active metabolites • Elimination: feces 60%, urine 40% • Half-life: 6–8 hours • Mechanism: inhibits type-2 5-alpha-reductase • Minimal drug interactions reported; monitor when used with CYP3A4 inhibitors; caution in patients with hepatic impairment

b.i.d. = twice daily; CYP = cytochrome P450; PSA = prostate-specific antigen; q.d. = once daily.
* CYP3A4 metabolism: use lower dose or avoid if patient is taking a concurrent CYP3A4 inhibitor (e.g., clarithromycin, ketoconazole)
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.[356–361]

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.[301,358–361]

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.[363,364] 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.[301,334,354,356,357]

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

PDE_5 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.[376,377]

Although PDE_5 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

Table 7 Management Options for Mixed Urinary Incontinence

	Men	Women
Initial management options (treat most bothersome symptom first)	• Pelvic floor muscle training with/without biofeedback for post-prostatectomy SUI • Scheduled voiding (bladder training) • Incontinence products • Antimuscarinic drugs for OAB with/without UUI • Alpha-adrenergic antagonists for bladder outlet obstruction	• Pelvic floor muscle training for SUI or OAB • Bladder training for UUI or OAB • Vaginal cones • Electrical stimulation • Duloxetine for SUI • Antimuscarinic drugs for OAB with/without UUI
Specialized management options (if initial therapy fails)	• Artificial urinary sphincter • Male sling • Neuromodulation	• Bulking agents • Tapes and slings • Colposuspension (Burch) procedure • Artificial urinary sphincter • Botulinum toxin • Neuromodulation • Bladder augmentation

OAB = overactive bladder; SUI = stress urinary incontinence; UUI = urge urinary incontinence.
Data from Thüroff JW, et al. *Eur Urol* 2011;59:387–400.[389]

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.[381]

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.[383]

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).[31,250] 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 evaluation 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).[25,43,47,110,388,389] 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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