Chapter 105: Urinary Incontinence

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 83, Urinary Incontinence.

KEY CONCEPTS

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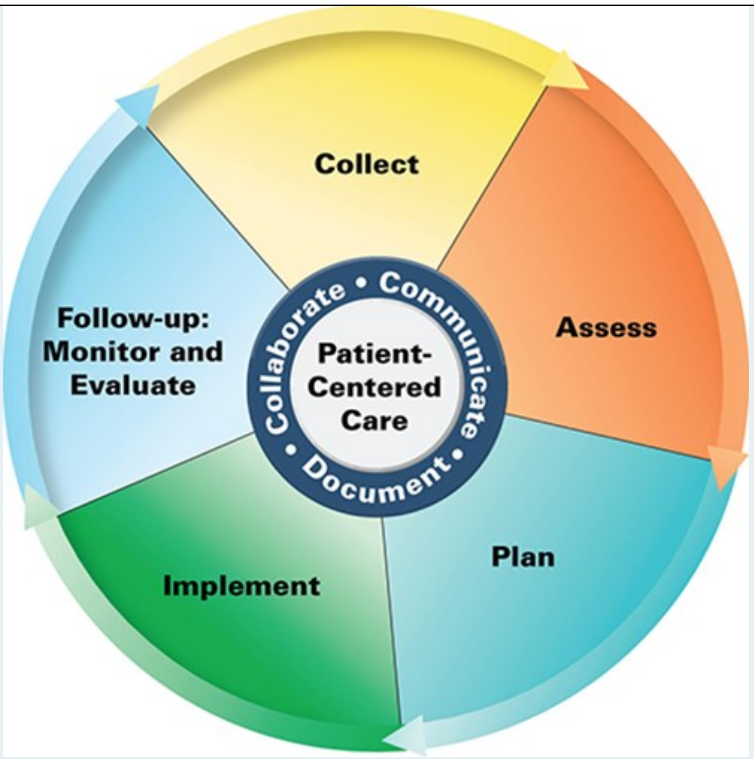
1. In evaluating urinary incontinence (UI), drug-induced or drug-aggravated etiologies must be ruled out.
2. Accurate diagnosis and classification of UI type are critical to the selection of appropriate pharmacotherapy.
3. Goals of treatment for UI are reduction of symptoms, minimization of adverse effects, and improvement in quality of life.
4. Nonpharmacologic, nonsurgical treatment is the first-line treatment for several types of UI, and should be continued even when drug therapy is initiated.
5. Antimuscarinic agents are second-line treatments for urgency incontinence. Choice of agent should be based on patient characteristics (eg, age, comorbidities, concurrent medications, and ability to adhere to the prescribed regimen).
6. β_3-Adrenergic agonists (mirabegron, vibegron) can be considered in patients who failed to achieve optimal efficacy or cannot tolerate adverse effects of antimuscarinic agents.
7. Duloxetine (approved in Europe only), α-adrenergic receptor agonists, and topical (vaginal) estrogens (alone or together) are the drugs of choice for urethral underactivity (stress urinary incontinence).
8. Assessment of patient outcomes should include efficacy, adverse effects, adherence, and quality of life.
9. Management of UI should target individualized goals and treatment preferences, which may change over time. If therapeutic goals are not achieved with a given agent at optimal dosage for an adequate duration of trial, consider switching to an alternative agent and/or surgery.

PATIENT CARE PROCESS

Patient Care Process for Urinary Incontinence



Collect

- Patient characteristics (eg, age, sex, pregnancy status, drug allergy profile)
- Patient medical and genitourinary surgical history including coexisting conditions that may influence UI
- Obstetric and menstrual history in women
- Past conservative, medical, and surgical treatment of UI
- Social history (tobacco/ethanol use; caffeine and fluid intake; environmental issues; exercise; availability of family caregiver, if relevant)
- Current medications (see Table 105-1) including over-the-counter (OTC), herbal products, and dietary supplements
- Objective data
  - Lab tests: urinalysis ± urine culture; if infected, treat and reassess if appropriate
  - Cough stress test to demonstrate stress UI (if appropriate)
  - Postvoid residual urine by bladder ultrasound or catheterization (if suspected urinary retention/overflow incontinence)

Assess

- Urinary symptoms including bladder diary (see Table 105-2)
- Presence of bowel symptoms or vaginal prolapse symptoms (in women); estrogen status in women
- Quality of life, treatment preferences, and goals
- Mental status, body mass index, physical dexterity, and mobility
- Abdominal, rectal, prostate (in men), neurological, and pelvic examination (in women)

Plan*

- Nonpharmacological interventions based on UI severity and subtype (see Table 105-3)
- Drug therapy regimen for urgency UI, if indicated (see Table 105-5)
- Monitoring parameters (see Tables 105-6 and 105-7); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug-specific information)
- Self-monitoring for resolution of UI symptoms and drug adverse events (if indicated)
- Referrals to other providers when appropriate (eg, urologist, urogynecologist, continence nurse practitioner, physical therapist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, adherence assessment, treatment response)

Follow-up: Monitor and Evaluate

- Monitor for patient response in 1 or 2 weeks after therapy initiation
- Assess efficacy after a minimum of 4 weeks to assess drug efficacy
- Resolution of UI symptoms
- Presence of adverse effects (eg, Table 105-7), or drug interactions
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate efficacy and necessary duration of therapy every 3 to 6 months

Collaborate with patient, caregivers, and other healthcare professionals.

BEYOND THE BOOK

BEYOND THE BOOK

Watch one of the two videos titled “Taking Control of Overactive Bladder (OAB)” by the Urology Care Foundation. Reflect on the impact of OAB from the patient’s perspective. Available at: https://www.urologyhealth.org/urology-a-z/o/overactive-bladder-(oab)

Next, develop a table with two columns, one titled antimuscarinic agents and one titled β_3-adrenergic agonists. In each column, identify one drug that represents the drug class. Compare the advantages and disadvantages of these two agents when used for the treatment of OAB (efficacy, dosage form, dosing, side effects, drug interactions, drug cost, etc.).

INTRODUCTION

Urinary incontinence (UI) is defined as involuntary loss of urine.[1] It is frequently accompanied by other bothersome lower urinary tract symptoms, such

as urgency, increased daytime frequency, and nocturia. It is one of the most common health conditions occurring in adults, and yet it is an underdetected and under-reported problem that can significantly affect quality of life. Patients with UI may have depression as a result of the perceived lack of self-control, loss of independence, and lack of self-esteem, and they often curtail their activities for fear of an "accident." UI may also have serious medical and economic ramifications for untreated or undertreated patients, including perineal dermatitis, worsening of pressure ulcers, urinary tract infections, and falls.

This chapter highlights the epidemiology, etiology, pathophysiology, treatment of stress, urgency, mixed, and overflow UI in men and women.

Editors' note: In this and other chapters in Pharmacotherapy, references to biologic gender (as assigned at birth) are used based on prior literature being discussed or anatomical or physiologic differences. We recognize that not all individuals identify with their gender at birth, and to the degree possible when discussing therapeutics, we avoid use of references to gender. In this chapter on Urinary Incontinence, "men" and "women" are used in discussing prior studies, published guidelines, and other recommendations for diagnosis and treatment based on biological gender and do not necessarily reflect an individual's gender identity.

EPIDEMIOLOGY

UI is highly prevalent, and the impact of this condition is substantial, crossing all racial, ethnic, and geographic boundaries. In addition, lower urinary tract symptoms (eg, urgency, urinary frequency, and nocturia) associated with OAB are also quite debilitating. Evidence from several studies indicates that UI is associated with reduced levels of social and personal activities, increased psychological distress, and overall decreased quality of life.[2] The condition can affect people of all age groups, but the peak incidence of UI, at least in women, occurs around the age of menopause, with a slight decrease in the age group 55 to 60 years, and then a steadily increasing prevalence after the age of 65 years.

Globally, the prevalence of UI ranges between 25% and 45%.[3] Determining the true prevalence of UI is difficult because of problems with definition, reporting bias, and other methodological issues. The condition is stigmatizing as it is associated with considerable embarrassment, as well as real or perceived loss of self-control. Such perceptions may lead to a decrease in reporting, especially self-reporting. Prevalence estimates vary by age, gender, and racial/ethnic group, setting (noninstitutionalized vs institutionalized), and incontinence subtype (stress, urgency, mixed, and overflow UI). Prevalence tends to be highest in women, those of advanced age, and living in long-term care settings.[2] Globally, women have three times the prevalence of urinary incontinence than men. The prevalence of incontinence increases as women age. Ten percent of adult women have incontinence, but this prevalence increases to 40% for women aged 70 years and older.[3] The National Health and Nutrition Examination Survey (NHANES) reported a prevalence rate of 43.8% in noninstitutionalized adults aged 65 years and over, with more than half of women and one-quarter of men reporting urine leakage.[2] Twelve percent of older women had severe or very severe scores on a validated incontinence severity index representing daily urine leakage with more than drops or small splashes, whereas older men had slight or moderate incontinence scores representing less-frequent urine leakage.[2]

Relatively little is known about differences in clinical and epidemiologic characteristics of incontinence across racial or ethnic groups, especially in men. Almost all population-based studies comparing UI prevalence across racial and ethnic groups are from the United States which limits generalizability. The majority of studies report that White women have a higher prevalence of UI overall and stress UI.[4] There is less consistency regarding prevalence of UI subtypes in Black women. In the BACH study, Black women had higher rates of mixed UI,[5] and in the EPI study, Black women had higher rates of urgency UI.[6] Using data from the NHANES program, no racial or ethnic differences were found in UI prevalence in men.[7] However, differences in access to healthcare as well as cultural attitudes and more may contribute to these differences.[8,9] Importantly, there are considerable differences in the causes and treatments of UI between genders.

UI prevalence is highest in nursing home residents, with 36.7% of short-stay residents and 70.3% of long-term residents having bladder control problems.[2] Residents who were aged 85 years and more compared to those aged 65 to 74 years had rates 1.5 times higher for short-term residents and 1.2 higher for long-term residents. UI is associated with several other medical conditions, such as falls,[10] urinary tract infection, skin breakdown, sexual function, and depression.

ETIOLOGY AND PATHOPHYSIOLOGY

Anatomy

The lower urinary tract consists of the bladder, urethra, urinary or urethral sphincter, and surrounding musculofascial structures, including connective tissue, nerves, and blood vessels. The urinary bladder is a hollow organ composed of smooth muscle and connective tissue located deep in the bony pelvis in men and women. The urethra is a hollow tube that acts as a conduit for urine flow out of the bladder. An epithelial cell layer termed the *urothelium*, which is in constant contact with urine, lines the interior surface of both the bladder and the urethra. Previously considered inert and inactive, the urothelium may play an active role in the pathophysiology of many lower urinary tract disorders, including interstitial cystitis/bladder pain syndrome and UI[11] and may be a targeted location for future pharmacologic therapeutic interventions for some types of lower urinary tract dysfunction.[12] The urinary or urethral sphincter is a combination of smooth and striated muscle within and surrounding the proximal portion of the urethra adjacent to the bladder. In the male, the prostate gland lies just beyond the bladder outlet and is intimately associated with the urethral sphincter. Its location accounts for both the favorable effects of pharmacological manipulation on male lower symptoms as well as the risk of UI in males following some types of prostate surgery.

To understand the principles of pharmacotherapy for UI, an understanding of the neuroanatomy and neurophysiology of the bladder and urethra is needed. The primary motor (efferent) input to the detrusor muscle of the bladder is parasympathetic and travels along the pelvic nerves emanating from spinal cord segments S2 to S4. Pharmacologic as well as nonpharmacologic stimulation, modulation, or blockade of afferent and efferent neural pathways between the spinal cord and the lower urinary tract by various mechanisms are important options for treatment for some types of urinary incontinence. Acetylcholine is the primary neurotransmitter at the neuromuscular junction in the human lower urinary tract. Both volitional and involuntary detrusor contractions are mediated by activation of postsynaptic muscarinic receptors by acetylcholine. Of the five known subtypes of muscarinic receptors, the majority of bladder smooth muscle cholinergic receptors are of the M_2 variety. In humans, the ratio of M_2/M_3 receptor numbers is approximately 3:1. However, M_3 receptors are the subtypes responsible for both emptying contractions of normal micturition as well as involuntary bladder contractions that may result in UI.[11] Thus, most pharmacologic antimuscarinic therapy is primarily anti-M_3 based. Administration of such agents results in detrusor smooth muscle relaxation and a reduction of bladder overactivity.

β_3-Adrenergic receptors are found in the lower urinary tract at the level of the detrusor muscle and the urothelium.[11] Although found elsewhere, stimulation of these receptors in the detrusor results in smooth muscle relaxation. Clinically, administration of β_3-agonists is associated with attenuation of bladder contractility and, similar to antimuscarinics, it is used clinically to treat overactive bladder (OAB) and related urgency incontinence. β-Receptors are also located on the urethra but their clinical significance is considered to be negligible.

Clinically relevant α-adrenergic receptors are located at the level of the bladder outlet on the smooth and striated muscle of the urethra.[11] Stimulation of these receptors with α-adrenergic agonists results in increased urethral closure pressure. Such effects are usually not pronounced enough to treat stress urinary incontinence (SUI); however, the use of these agents may result in unwanted adverse effects such as aggravation of bladder outlet obstruction and result in poor bladder emptying (urinary retention), especially in men.

Other potentially relevant motor and sensory pathways, neurotransmitters, and receptors have been identified in the lower urinary tract (eg, transient receptor potential channels, E-series prostaglandin receptors). However, the exact role of such targets, as well as ways of modulating their activity pharmacologically in humans, has yet to be elucidated and further discussion is beyond the scope of this chapter.

Urinary Continence

To prevent incontinence during the bladder filling and storage phase of the micturition cycle, the urethra, or more accurately the urethral sphincter, must maintain adequate closure in order to resist the flow of urine from the bladder at all times until voluntary voiding is initiated. Urethral closure or resistance to flow is maintained to a large degree by the proximal (under involuntary control) and distal (under both voluntary and involuntary control) urinary sphincters. Variable contributions to urethral closure may also come from the urethral mucosa, submucosal spongy tissue, and the overall length of the urethra. During bladder filling and urinary storage, the bladder accommodates increasing volumes of urine flowing in from the upper urinary tract without a significant increase in bladder (intravesical) pressure. The maintenance of a low intravesical pressure despite increasing volumes of urine is a unique property of the bladder and is termed *compliance*. In addition, bladder or detrusor smooth muscle activity is normally suppressed during the filling phase by centrally mediated neural reflexes. Normal bladder emptying occurs with opening of the urethral sphincters concomitant with a volitional bladder contraction. Bladder contraction occurs in a coordinated fashion, resulting in a rise in intravesical pressure. The

rise in intravesical pressure is ideally of adequate magnitude and duration to empty the bladder to completion. Opening and funneling of the bladder outlet results in urine flow into the urethra until the bladder is emptied to near completion.

The bladder and urethra normally operate in unison during the bladder filling and storage phase, as well as the bladder emptying phase of the micturition cycle. The smooth and striated muscles of the bladder and urethra are organized during the micturition cycle by a number of reflexes coordinated at the pontine micturition center in the midbrain. Disturbances in the neural regulation of micturition at any level (brain, spinal cord, or pelvic nerves) often lead to characteristic changes in lower urinary tract function that may result in UI.[13,14]

Mechanisms of Urinary Incontinence

Simply stated, UI may occur as a result of abnormalities of only the urethra (including the bladder outlet and urinary sphincter) or only the bladder or as a combination of abnormalities in both. Abnormalities may result in either overactivity or underactivity of the bladder and/or urethra, with resulting development of UI. Although this simple classification scheme excludes extremely rare causes of UI such as congenital ectopic ureters and urinary fistulas, it is useful for gaining a working understanding of the condition and understanding the basis for therapeutic intervention including pharmacotherapy of various lower urinary tract disorders.

Urethral Underactivity (SUI)

Stress urinary incontinence is defined as the involuntary loss of urine on effort or physical exertion (including sporting activities) or on sneezing or coughing.[1] The pathophysiology of SUI is related to decreased or inadequate urethral closure forces. In individuals with SUI, the muscular tissues surrounding the urethra that form the urethral sphincter are compromised and thus not able to resist the expulsive forces resulting from transient increases in intra-abdominal pressure during physical activity. Such forces are transmitted to the bladder (an intra-abdominal organ), compressing it to such an extent as to cause the egress of urine through the urethra. SUI is characterized by episodic, usually low-volume urinary leakage but is clearly proportional to the amount of physical exertion or other increases in abdominal pressure such as that related to coughing and sneezing as well as the ambient urethral closure forces.

Risk factors for SUI in woman include pregnancy, childbirth, menopause, cognitive impairment, obesity, and aging.[15] In men, SUI is most commonly the result of prior lower urinary tract surgery and injury to the sphincter mechanism within and external to the urethra. Radical prostatectomy for treatment of adenocarcinoma of the prostate and transurethral resection of the prostate (TURP) is probably the most common proximate causes of SUI in the male. Notably, compared with its prevalence in women, SUI in men is actually quite rare.

SUI may be caused or aggravated by some pharmacologic agents such as α-antagonists and angiotensin-converting enzyme (ACE) inhibitors.[16] α-Antagonists may relax the smooth muscle at the level of the urethral sphincter, resulting in a weakened closure mechanism and the onset of SUI. Alternatively, some α-agonists, such as those used clinically for nasal congestion or weight loss, may improve SUI in some individuals, and may even potentially aggravate some types of voiding problems such as those related to bladder outlet obstruction from an enlarged prostate. An adverse effect of some ACE inhibitors is chronic cough, which can also aggravate existing SUI.

Bladder Overactivity (Urgency Urinary Incontinence [UUI])

Urgency UI is defined as the involuntary loss of urine associated with urgency.[1] This is most often related to detrusor (bladder) overactivity due to involuntary bladder contractions. Bladder overactivity describes the condition in which the detrusor muscle contracts inappropriately during urinary storage that, in the neurologically normal individual, results in a sense of urinary urgency. Overactive bladder is a symptom syndrome characterized by urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence (OAB-wet) or without (OAB-dry), in the absence of urinary tract infection or other detectable diseases.[1] The terms *overactive bladder* and *detrusor (bladder) overactivity* are distinct and should not be used interchangeably.

Increased *frequency* is defined as the complaint that micturition occurs more frequently during waking hours than previously deemed normal; numerically, it is often quantified as more than eight times per day. *Urgency* is described as a sudden compelling desire to urinate that is difficult to defer.[1] People with OAB typically have to empty their bladder frequently, and, when they experience a sensation of urgency, they may leak urine if they are unable to reach the toilet quickly. Many patients have associated nocturia (>1 micturition per night) and/or nocturnal incontinence (enuresis). Patients with urgency urinary incontinence (UUI) often, but invariably, experience high-volume urine leakage when it occurs. Although detrusor

overactivity may be related to OAB, the former diagnosis requires urodynamic testing while the latter is symptomatically defined.

Most patients with OAB and UUI have no identifiable underlying etiology and thus are classified as "idiopathic." Patients with a combination of a relevant neurologic condition and UI related to involuntary bladder contractions demonstrated on urodynamic testing are classified as having neurogenic detrusor overactivity. Clearly identifiable risk factors for UUI include normal aging, neurologic disease (including stroke, Parkinson's disease, multiple sclerosis, and spinal cord injury), and bladder outlet obstruction resulting in pathological changes to the detrusor muscle (eg, due to benign prostatic hyperplasia [BPH] or prostate cancer).[4]

The pathophysiology of OAB and UUI is not well understood but is likely related to either neurogenic or myogenic factors or a combination of both.[1] A full discussion of these differences is complex and beyond the scope of this chapter. However, in practice, although the cause of UUI is difficult to define, the treatment is identical regardless of etiology and pathophysiology.

Some pharmacologic agents may cause or aggravate UUI. Diuretics will cause the rapid accumulation of urine in the bladder with resulting urinary urgency and frequency that can result in UUI. Alcohol will have similar effects. Anticholinesterase inhibitors may also produce urgency and frequency.

Urethral Overactivity and/or Bladder Underactivity (Overflow Incontinence)

Overflow incontinence is urinary leakage resulting from an overfilled and distended bladder that is unable to empty. This type of UI occurs when the bladder is filled to capacity at all times but is unable to empty, causing urine to leak from a distended bladder past a normal or even overactive sphincter. Another term related to overflow incontinence is *chronic urinary retention*.[1]

Overflow incontinence is the result of urethral overactivity, bladder underactivity, or a variable combination of both. Clinically and practically, the most common causes of urethral overactivity in men are anatomic urethral obstruction, including that due to BPH and prostate cancer. In women, urethral overactivity is rare but may result from cystocele formation (with resultant kinking or obstruction of the urethra) or surgical overcorrection following surgery for the repair of SUI (iatrogenic obstruction). In both men and women, overflow UI may be associated with systemic neurologic dysfunction or diseases, such as spinal cord injury or multiple sclerosis.

Bladder underactivity occurs as a result of the detrusor muscle of the bladder becoming suddenly or progressively weakened and eventually losing the ability to voluntarily contract and expel urine during voiding. In the absence of adequate contractility, the bladder is unable to empty completely, and large volumes of residual urine are left after voiding. Both myogenic and neurogenic factors have been implicated in producing the impaired contractility seen in this condition. Clinically, overflow incontinence is most commonly seen in the setting of long-term chronic bladder outlet obstruction in men, such as that due to BPH or prostate cancer, diabetes mellitus, or denervation due to radical pelvic surgery, such as abdominopelvic resection or radical hysterectomy.

1 Many commonly used medications may precipitate or aggravate existing voiding dysfunction and UI (Table 105-1).[17] Agents that increase urethral resistance or closure pressure include α-agonists and tricyclic antidepressants. Over-the-counter cold and cough remedies as well as diet pills may contain agents with α-adrenergic properties and/or antihistaminic properties that can result in voiding dysfunction and urinary retention. Agents that can decrease bladder contractility include anticholinergics, tricyclic antidepressants, calcium channel blockers, narcotic analgesics, and antipsychotics.

TABLE 105-1

Medications That Influence Lower Urinary Tract Function

Medication	Effect
Diuretics, acetylcholinesterase inhibitors	Polyuria resulting in urinary frequency, urgency
α-Receptor antagonists	Urethral muscle relaxation and stress urinary incontinence
α-Receptor agonists	Urethral muscle contraction (increased urethral closure forces) resulting in urinary retention (more common in men)
Calcium channel blockers	Urinary retention due to reduced bladder contractility
Narcotic analgesics	Urinary retention due to reduced bladder contractility
Sedative hypnotics	Functional incontinence caused by delirium, immobility
Antipsychotic agents	Anticholinergic effects resulting in reduced bladder contractility and urinary retention
Anticholinergics	Urinary retention due to reduced bladder contractility
Antidepressants, tricyclic	Anticholinergic effects resulting in reduced bladder contractility (urinary retention), and α-antagonist effects resulting in reduced urethral smooth muscle contraction (stress incontinence)
Alcohol	Polyuria resulting in urinary frequency, urgency
ACEIs	Cough as a result of ACEIs may aggravate stress urinary incontinence

ACEIs, angiotensin-converting enzyme inhibitors.

Mixed Incontinence and Other Types of Urinary Incontinence

Various types of UI may coexist in the same patient. The combination of bladder overactivity resulting in urinary incontinence (urgency UI) and urethral underactivity resulting in urinary incontinence (SUI or stress UI) is termed *mixed incontinence*. The diagnosis is often difficult because of the confusing array of presenting symptoms. Bladder overactivity may also coexist with impaired bladder contractility. This occurs most commonly in the elderly and is termed *detrusor hyperactivity with impaired contractility*.[1]

Functional incontinence (also known as disability-associated urinary incontinence) is not caused by bladder- or urethra-specific factors. It occurs in the presence of a functional inability to reach a toilet or urinal in time because of a physical or mental impairment, such as cognitive or mobility deficits. It is linked to the primary disease process more than any extrinsic or intrinsic deficit of the lower urinary tract. An example of functional incontinence occurs in patients after orthopedic surgery. Following extensive orthopedic reconstructions such as total hip arthroplasty, patients are often immobile secondary to pain or traction. Therefore, patients may be unable to access toileting facilities in a reasonable amount of time and may become incontinent as a result. Treatment of this type of UI may involve simple interventions such as placing a urinal or commode at the bedside that allows for uncomplicated access to toileting. Pharmacologically, functional incontinence can be induced by sedative-hypnotics, narcotic analgesics, and other medications with cognitive adverse effects.

Many localized or systemic illnesses may result in UI because of their effects on the lower urinary tract or the surrounding structures:

1. Dementia/delirium
2. Depression
3. Urinary tract infection (cystitis)
4. Postmenopausal atrophic urethritis or vaginitis
5. Diabetes mellitus
6. Neurologic disease (eg, stroke, Parkinson's disease, multiple sclerosis, spinal cord injury)
7. Pelvic malignancy
8. Constipation
9. Congenital malformations of the urinary tract

Generally, stress UI is considered the most common type of UI and probably accounts for at least a portion of UI in more than half of all incontinent women. Some studies have found that mixed UI (stress UI and urgency UI) is the most common type of UI. However, the proportions of SUI, UUI, and mixed UI vary considerably with age group and gender of patients studied, study methodology, and a variety of other factors.

CLINICAL PRESENTATION

UI may present in a number of ways, depending on the underlying pathophysiology. A complete medical and medication history, including an assessment of symptoms and a physical examination, is essential for correctly classifying the type of incontinence and thereby assuring appropriate therapy.

Urine Leakage

UI represents a spectrum of severity in terms of both volume of leakage and degree of bother to the patient. Carefully consider the level of patient discomfort and bother when discussing urine leakage as each individual may or may not desire therapy. A careful and complete history during the patient interview is essential to accurately determine the precise nature of the problem. The onset, nature, timing, and volume of incontinence are recorded as is the use of pads. Use of absorbent products, such as panty liners, pads, or briefs, is an important point of discussion, but the clinician must keep in mind that the use of these products varies among patients. The number and type of pads may not relate to the amount or type of incontinence, as their use is a function of personal preference and hygiene. A high number of absorbent pads may be used everyday by a patient with severe, high-volume UI or, alternatively, by a fastidiously hygienic patient with low-volume leakage who simply changes pads often to prevent wetness or odor. Nevertheless, a large number of pads that are described by the patient as "soaked" is indicative of high-volume urine loss.

Regardless of the volume of urine loss, the desire to seek evaluation for UI in the majority of patients is most commonly elective and therapy is often contingent on the degree of bother to the individual patient. As with the use of absorbent products, patients differ with regard to the amount of urine loss they will tolerate before considering the condition bothersome enough to seek assistance. However, it is critically important that in some individuals new-onset UI may be the first manifestation of an undiagnosed illness (eg, diabetes, multiple sclerosis), or may occur as a result of treatment or drug therapy of an unrelated condition. It is these individuals who mandate a full evaluation and treatment.

Symptoms

Under the best of circumstances, UI is difficult to categorize based on symptoms alone (Table 105-2). In a study of patients who have SUI based on symptoms and patient history, urodynamics showed that only 72% of patients had SUI as the sole cause of incontinence.[18]

CLINICAL PRESENTATION: Stress Urinary Incontinence

General

- The patient usually notes UI during activities such as exercise, running, lifting, coughing, and sneezing. Occurs much more commonly in women (generally seen only in men with prior lower urinary tract surgery, neurologic disease, or other injury compromising the sphincter).

Symptoms

- Urine leakage with physical activity (volume is proportional to activity level). No UI with physical inactivity, especially when supine (minimal or no nocturia). May develop urgency and frequency as a compensatory mechanism (or as a separate component of bladder overactivity).

Diagnostic Tests

- Observation of urethral meatus while patient coughs or strains (cough stress test).

TABLE 105-2

Differentiating Bladder Overactivity–Related UI (Urgency Urinary Incontinence) from Urethral Underactivity–Related UI (Stress Urinary Incontinence)

Symptoms	Bladder Overactivity (UUI)	Urethral Underactivity (SUI)
Urgency (strong, sudden desire to void)	Yes	Not common
Frequency with urgency	Yes	Rarely
Leaking during physical activity (eg, coughing, sneezing, lifting)	No	Yes
Amount of urinary leakage with each episode of incontinence	Large if present	Usually small
Ability to reach the toilet in time following an urge to void	No or just barely	Yes
Nocturnal incontinence (presence of wet pads or undergarments in bed)	Yes	Rare
Nocturia (waking to pass urine at night)	Usually	Seldom

SUI, stress urinary incontinence; UUI, urgency urinary incontinence.

Patients with SUI characteristically complain of urinary leakage with physical activity. Volume of leakage is proportional to the level of activity. They will often leak urine during periods of exercise, coughing, sneezing, lifting, or even when rising from a seated to a standing position. Patients with pure SUI will not have leakage when physically inactive, especially when they are supine. Often they will have little or no UI at night, will not awaken to void during the night (nocturia), will not wet the bed, and often do not even wear absorbent products during the night. Urinary urgency and frequency may be associated with SUI, either as a separate component caused by bladder overactivity (mixed incontinence) or as a compensatory mechanism wherein the patient with SUI learns to toilet frequently to prevent large-volume urine loss during physical activity.

Typical symptoms of UUI and bladder overactivity include frequency, urgency, and high-volume incontinence. Nocturia and nocturnal incontinence are often present. Urine leakage is unpredictable, and the volume loss may be quite large. Patients often wear protection both day and night. Urinary frequency can be affected by a number of factors unrelated to bladder overactivity, including excessive fluid intake (polydipsia) and bladder hypersensitivity states such as interstitial cystitis and urinary tract infection. In some patients, bladder overactivity manifests as UI without awareness in the absence of a sense of urinary urgency or frequency. *Urinary urgency*, a sensation of impending micturition, requires intact sensory input from

the lower urinary tract. In patients with spinal cord injury, sensory neuropathies, and other neurologic diseases, a diminished ability to perceive or process sensory input from the lower urinary tract may result in bladder overactivity and UI without urgency or urinary frequency. When bladder contraction occurs without warning and sensation is absent, the condition is referred to as *reflex incontinence*.

Patients with overflow incontinence may present with lower abdominal fullness as well as considerable obstructive urinary symptoms, including hesitancy, straining to void, decreased force of urinary stream, interrupted stream, and a vague sense of incomplete bladder emptying. These patients may also have a significant component of urinary frequency and urgency. In patients with acute urinary retention and overflow incontinence, lower abdominal pain may be present. Although these symptoms are not specific for overflow incontinence, they may warrant further investigation, including an assessment of postvoid residual urine volume.

Signs

A presenting complaint of UI mandates a directed physical examination and a brief neurologic assessment. The workup ideally includes an abdominal examination to exclude a distended bladder, neurologic assessment of the perineum and lower extremities, pelvic examination in women (looking especially for evidence of prolapse or hormonal deficiency), and genital and prostate examination in men. Perineal skin maceration, erythema, breakdown, and ulceration may be indicative of chronic, severe UI. Patients with chronic incontinence, especially those who are obese, may also manifest fungal infections of the skin of the perineum and upper thighs.

SUI can usually be objectively demonstrated by having the patient cough or strain during the examination and observing the urethral meatus for a sudden spurt of urine (cough stress test). In women, SUI may be associated with varying degrees of vaginal prolapse, including cystourethrocele (bladder and urethral prolapse).

In both men and women, digital rectal examination provides an opportunity to assess neurological integrity by checking ambient rectal tone, perianal sensation, and the integrity of the sacral reflex arc (eg, anal wink) as well as assess the patient's ability to perform a voluntary pelvic floor muscle contraction (ie, Kegel exercise), which may be an important factor in deciding on appropriate therapy. In men, a digital examination of the prostate assesses for the presence of prostate cancer, inflammation, and BPH.

A targeted neurologic examination includes assessment of reflexes, rectal tone, and sensory or motor deficits in the lower extremities, which might be indicative of systemic or localized neurologic disease. Neurologic diseases have the potential to affect bladder and sphincter function and thus may have significant implications in the incontinent patient.

CLINICAL PRESENTATION: Urgency Urinary Incontinence

General

- Can have bladder overactivity and UI without urgency if sensory input from the lower urinary tract is absent.

Symptoms

- Urinary frequency (>8 micturitions per day), urgency with or without UI; nocturia (≥1 micturition per night) and enuresis may be present.

Diagnostic Tests

- Urodynamic studies are the gold standard for diagnosis for the diagnosis of detrusor overactivity when the finding of involuntary bladder contractions on the study reproduces the patient's symptoms. Urinalysis and urine culture should be negative (rule out urinary tract infection as the cause of frequency).

CLINICAL PRESENTATION: Overflow Incontinence (Chronic Urinary Retention)

General

- Important but uncommon type of UI in both men and women. Urethral overactivity is usually due to prostatic enlargement (men) or cystocele formation or surgical overcorrection following stress incontinence surgery in women. Bladder underactivity resulting in overflow incontinence can result from many causes including neurogenic disease, diabetes, and postoperatively from pelvic surgery (eg, radical hysterectomy).

Symptoms

- Lower abdominal fullness, hesitancy, straining to void, decreased force of stream, interrupted stream, sense of incomplete bladder emptying. May have urinary frequency and urgency. Abdominal pain if acute urinary retention is present.

Signs

- Increased postvoid residual urine volume.

Diagnostic Tests

- Assessment of postvoid residual urine either by imaging (ultrasound, etc.) or by catheterization. Renal function tests to rule out renal failure due to chronic urinary retention.

Prior Medical or Surgical Illness

UI may present in the setting of concurrent, seemingly unrelated illnesses. New-onset UI may be the initial manifestation of systemic illnesses such as diabetes mellitus, metastatic malignancies, and neurologic diseases such as Parkinson's disease, brain tumors, and multiple sclerosis. Central nervous system (CNS) disease, or injury above the level of the pons, generally results in symptoms of bladder overactivity and UUI. Spinal cord injury or disease may manifest as bladder overactivity and UUI or as overflow incontinence, depending on the spinal level and completeness of the injury or disease.

Medications may have wide-ranging effects on lower urinary tract function (see Table 105-1). A thorough inquiry into the use of new medications in the setting of recent-onset UI may show a relationship. Acute UI manifesting in the immediate postoperative setting may be secondary to a number of factors, including surgical manipulation and immobility, and to a number of medications, especially opioid analgesics and sedative-hypnotics.

Prior surgery may have effects on lower urinary tract function. UI following prostate surgery in men is highly suggestive of injury to the sphincter and resultant SUI. Pelvic surgery for benign and malignant conditions may result in denervation or injury to the lower urinary tract. This includes bowel surgery and gynecologic procedures. For example, new-onset total UI following gynecologic surgery suggests intraoperative urinary tract injury and subsequent development of a postoperative genitourinary fistula. Radiation therapy to the pelvis for malignant disease (eg, prostate cancer or cervical cancer) may result in injury to the bladder or urethra and subsequent UI.

In women, UI may be related to several gynecologic factors including childbirth, hormonal status, and prior gynecologic surgery, although the relationship of some of these factors to UI has come under debate.[19] Pregnancy and childbirth, particularly vaginal delivery, are associated with SUI and pelvic prolapse. Significant SUI in the nulliparous woman is uncommon. UI that becomes progressive at or around menopause suggests a hormonal component that may be responsive to estrogen or hormone replacement therapy.

UI may present in the setting of other significant pelvic floor disorders, signs, and symptoms. Constipation, diarrhea, fecal incontinence, dyspareunia, sexual dysfunction, and pelvic pain may be related to UI. A history of gross hematuria in the setting of UI mandates further urologic investigation, including radiologic imaging of the upper urinary tract and cystoscopy. Acute dysuria with or without hematuria in the setting of UI suggests cystitis. Urinalysis and urine culture should be performed in these patients.

TREATMENT

Desired Outcomes

3 The efficacy goals for the management of UI include restoration of continence, reduction of the number of UI episodes, and prevention of complications (perineal dermatitis, pressure ulcers, falls, etc.). Other desired outcomes are minimization of adverse treatment consequences and cost, improvement in the patient's quality of life, lesser care burden, and reduced risk of nursing home placement.

General Approach to Treatment

Nonsurgical, nonpharmacologic intervention is the first-line treatment for UI. Drug therapy may be considered in patients whose UI is not adequately controlled by nonpharmacologic therapies and in those who have no major contraindications to drug treatment. In general, pharmacotherapy provides a better response when combined with behavioral interventions.[20] Selection of agent should be based on the type of UI, and patient characteristics (eg, age, comorbidities, concurrent drug therapies, ability to maintain medication adherence). Surgery can be considered when the degree of bother or lifestyle compromise is sufficient and other nonsurgical interventions are undesired or ineffective.

Antimuscarinic agents have been the mainstay of pharmacotherapy for OAB and UUI. According to the American Urological Association (AUA) guideline,[21] clinicians should avoid antimuscarinic agents in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist. Antimuscarinic agents should be cautiously used in patients with frailty, impaired gastric emptying, or a history of urinary retention, or in those who are taking other drugs with anticholinergic properties. When one agent offers inadequate symptom control and/or unacceptable adverse drug events, consider a dose modification or switching to another agent. Before initiating antimuscarinic therapy, patients should be informed of adverse effects and strategies to minimize them. Before abandoning effective antimuscarinic therapy, clinicians should manage constipation and dry mouth (bowel regimen, fluid management, dose modification, or alternative antimuscarinics).[21] β_3-Agonists are newer drug alternatives for UUI.

Nonpharmacologic Nonsurgical Treatment

4 Nonpharmacologic, nonsurgical treatment of UI is recommended as the first-line treatment at a primary care level. It is the only option for patients in whom pharmacologic and/or surgical management is inappropriate or undesired. Examples of patients who fulfill these criteria for nonpharmacologic treatment include those with mild-to-moderate symptoms and who do not want to take medication; those with comorbid conditions that place them at high risk for adverse effects from drug therapy; those who are not medically fit for surgery; those who plan future pregnancies (which may adversely affect long-term surgical outcomes); those with overflow incontinence whose condition is not amenable to surgery or drug therapy; and those who are delaying surgery or do not want to undergo surgery.[22]

Nondrug interventions for UI include behavioral interventions, external neuromodulation, anti-incontinence devices, and supportive interventions (Table 105-3).[21] Behavioral interventions are generally the first-line treatment for SUI, UUI, and mixed UI. Interventions include lifestyle modifications, voiding schedule regimens, and pelvic floor muscle rehabilitation based on the patient's treatment preferences. Notably, both stress and urgency urinary incontinence are associated with obesity. Several studies have demonstrated that weight loss benefits patients with UI.[23] Because the key to success with any type of behavioral intervention is motivation of patients or caregivers, these individuals must be active participants in developing a treatment plan. Regular follow-up is needed to help motivate patients and caregivers, provide reassurance and support, and monitor treatment outcomes. Patients should be informed that it takes 8 to 12 weeks for behavioral interventions to be effective.

TABLE 105-3

Nonpharmacologic Management of Urinary Incontinence

Intervention	Description	Patient Characteristics
Lifestyle Modifications		
Behavioral changes (eg, fluid and caffeine modifications,	Self-management strategies targeted toward reducing or eliminating risk factors that cause or exacerbate UI	Used as first-line therapies or in combination with pharmacological treatment in patients with stress, urgency, and mixed incontinence

smoking cessation, weight loss, constipation prevention)		
Scheduling Regimens		
Timed voiding	Toileting on a fixed schedule where interval does not change, typically every 2 hours during waking hours	Used for patients with cognitive or physical impairments causing disability-associated incontinence
Habit training	Scheduled toiletings with adjustments of voiding intervals (longer or shorter) based on patient's voiding pattern	Used for institutionalized or homebound patients with cognitive or physical impairments
Prompted voiding	Scheduled toiletings that require prompts to void from a caregiver, typically every 2 hours; patient assisted in toileting only if response is positive; used in conjunction with operant conditioning techniques for rewarding patients for maintaining continence and appropriate toileting	Used for patients who are functionally able to use toilet or toilet substitute, able to feel urge sensation, and able to request toileting assistance appropriately; primarily used in institutional settings or in homebound patients with an available caregiver
Bladder training	Scheduled toiletings with progressive voiding intervals; includes teaching urgency suppression strategies using relaxation and distraction techniques, self-monitoring, and use of reinforcement techniques; sometimes combined with drug therapy	Used for stress, urgency, and mixed incontinence in patients who are cognitively intact, able to toilet, and motivated to comply with training program
Pelvic Floor Muscle Rehabilitation		
Pelvic floor muscle exercises (eg, Kegel exercises)	Regular practice of pelvic floor muscle contractions; may involve use of pelvic floor muscle contraction for prevention of stress leakage and urge inhibition	Used for stress, urgency, and mixed incontinence in patients who can isolate and correctly contract pelvic floor muscles; requires cognitively intact and highly motivated patient
Biofeedback	Use of electronic or mechanical instruments to display visual or auditory information about neuromuscular or bladder activity; used to teach correct pelvic floor muscle contraction or urge inhibition; home trainers available	Used for stress, urgency, and mixed incontinence in patients who have the capability to learn voluntary control through observation and are motivated; used in conjunction with pelvic floor muscle exercises
Vaginal weight training	Active retention of increasing vaginal weights; typically used in combination with pelvic floor muscle exercises at least twice per day	Women with stress incontinence who are cognitively intact, can correctly contract pelvic floor muscles, able to stand, and have sufficient vaginal vault and introitus to retain cone, and are highly motivated; contraindicated in patients with moderate-to-severe pelvic organ prolapse
External Neuromodulation		
Nonimplantable electrical stimulation	Application of electrical current through vaginal, anal, surface, or fine needle electrodes; used to inhibit bladder overactivity and improve awareness, contractility, and efficacy of pelvic floor muscle	Used for stress, urgency, and mixed incontinence in patients who are highly motivated; contraindicated in patients with diminished sensory perception; urinary retention, history of cardiac arrhythmia, cardiac pacemakers, implantable defibrillators, pregnant or attempting

	contraction; handheld stimulators for home use are available	pregnancy; vaginal or anal electrodes are contraindicated in moderate or severe pelvic organ prolapse
Percutaneous tibial nerve stimulation	Application of a pulsed electrical current through a fine needle electrode placed externally near the tibial nerve	Used for treatment of overactive bladder with urinary urgency, frequency, and urgency incontinence; contraindicated in patients with pacemakers or implantable defibrillators, prone to excessive bleeding, or women who are pregnant
Extracorporeal magnetic electrical stimulation	Pulsed magnetic stimulation to pelvic floor musculature causing depolarization of motor neurons, thus inducing pelvic floor muscle contraction; stimulation is provided through a specially designed chair that contains a device for producing a pulsing magnetic field	Used for treatment of stress, urgency, and mixed incontinence; contraindicated in patients with demand cardiac pacemakers or metallic joint replacements; may be useful treatment option when other approaches fail or are not feasible
Alternative Medicine Therapies		
Acupuncture	Involves insertion of disposable sterile fine stainless steel needles into points on the skin that are thought to suppress or stimulate spinal and/or supraspinal reflexes to the bladder and/or urethra	Used for stress, urgency, and mixed incontinence and UI due to spinal cord injury
Anti-Incontinence Devices		
Bed or pant alarms	Sensor devices that respond to wetness; used to awaken or alert individuals via noise or vibrating mechanism	Primarily used for nocturnal enuresis in children; system available for monitoring incontinence in home care and institutional environments
Pessaries	Intravaginal devices designed to support the bladder neck, relieve minor-to-moderate pelvic organ prolapse, and change pressure transmission to the urethra	Used for female stress incontinence and mild-to-moderate pelvic organ prolapse; in postmenopausal women, topical estrogen therapy is typically prescribed to prevent ulceration and breakdown of vaginal tissue; requires good manual dexterity to manipulate device
Urethral insert (women only)	Intraurethral device	Used in female stress incontinence with stress incontinence who are cognitively intact and have good manual dexterity
Urethral compression device (men only)	Penile clamp	Used in men patients with stress incontinence who are cognitively intact and have good manual dexterity
External collection devices (men only)	Condom catheter with leg bag	Used in men with urgency, stress, and overflow incontinence and in those with functional impairments
External urine collection devices for women	Female external catheter with suction wicking system that pulls urine through collector tubing into collection canister	Used in women with incontinence related to functional impairments in rehabilitation and hospital settings
Catheters	Disposable, intermittent urethral catheters and indwelling urethral and suprapubic catheters	Used for overflow incontinence; used in patients who are bed-bound or with significant mobility impairments and severe incontinence; those with terminal illness; those with sacral pressure ulcers until healing

		occurs
Supportive Interventions		
Toileting substitutes and other environmental modifications	Female and male urinals, bedside commodes, elevated toilet seats, grab bars, and frames	Used for patients with mobility impairments that make reaching toilet in timely fashion difficult
Absorbent products	Variety of reusable and disposable liners, pads, male drip collectors, male guard, collector undergarment, fitted brief, and pant systems; some products contain a polymer that absorb and wick urine away from the body	Used for all types of incontinence
Physical therapy	Gait and/or strength training	Used for older patients with mobility impairments that make reaching a toilet in timely fashion difficult

External neuromodulation may include nonimplantable electrical stimulation (EStim), percutaneous tibial nerve stimulation (PTNS), or extracorporeal magnetic stimulation (MStim). Electrical stimulation is typically prescribed when traditional pelvic floor muscle rehabilitation has failed. Anti-incontinence devices such as bed alarms, catheters, pessaries, penile clamps, and external collection devices are reserved for special situations depending on patients' UI symptoms, cognitive and mobility status, and overall health status. Supportive interventions such as physical therapy may be beneficial for patients with muscle weakness and slow gait to reach the toilet in a timelier manner, and absorbent products will provide greater confidence in dealing with unpredictable urine loss. Penile clamps and external collection devices are available for men and women with significant functional impairment.

Surgical Treatment

Only rarely does surgery play a role in the initial management of UI. In the absence of secondary complications from UI (eg, skin breakdown or infection), the decision to surgically treat symptomatic UI should be based on the premise that the degree of bother or lifestyle compromise to the patient is great enough to warrant an elective operation, and that nonsurgical therapy either is undesired or has been ineffective.

Successful application of surgery depends mostly on defining the underlying abnormalities responsible for UI (bladder vs urethra, underactivity vs overactivity). Once the underlying factors are determined, other considerations include renal function, sexual function, severity of leakage, history of abdominal or pelvic surgery, presence of concurrent abdominal or pelvic pathology requiring surgical correction, and finally the patient's suitability for the procedure and willingness to accept the risks of surgery.

If patients with uncomplicated SUI become dissatisfied with the initial management approaches of pelvic floor exercises, medications, and/or behavioral modification, surgical treatment assumes the primary role. Surgical correction of female SUI (urethral underactivity) is directed toward either (a) repositioning the urethra and/or creating a backboard of support, or otherwise stabilizing the urethra and bladder neck in a well-supported retropubic (intra-abdominal) position that is receptive to changes in intra-abdominal pressure; or (b) improving the sealing mechanism and/or creating compression or otherwise augmenting the urethral resistance provided by the intrinsic sphincteric unit, with (ie, sling) or without (ie, periurethral injectable bulking agents) urethral and bladder neck support.

Bulking agents are injected into the urethra at the level of the urinary sphincter as an office-based procedure and are generally considered quite safe. However, their durability and efficacy are likely inferior to other options.[24]

Midurethral synthetic slings have become the most common approach to the treatment of SUI in women in the United States. These can be inserted as outpatient procedures that have shorter convalescence periods and allow faster return to usual activities compared with many of the older

procedures. These procedures are generally felt to be highly durable and efficacious. However, safety concerns have been expressed regarding the implantation of surgical mesh in some patients, the implications of which are yet to be fully clarified.[25]

SUI in men is rare in the absence of prior pelvic surgery, injury, or neurologic disease. When it occurs, SUI in men can be treated in a number of ways.[26] Bulking agents can be injected periurethrally and submucosally into the region of the external urinary sphincter but have fallen out of favor due to poor short- and long-term outcomes. This approach is less effective and far less durable than alternative surgical procedures, although it can be performed in the office setting without the need for general anesthesia. The artificial urinary sphincter is generally considered to be the gold standard for treatment of male SUI.[27] Placement of this manually operated silicone device has been associated with high long-term success and satisfaction rates.[27] Male slings and external urethral compression devices placed through a perineal incision are alternatives to the artificial urinary sphincter in some individuals with mild-to-moderate SUI.[28] However, long-term efficacy and safety data on large numbers of patients is lacking.[29]

Most patients with UUI are managed nonsurgically with a combination of behavioral modification, pelvic floor exercises, and pharmacologic therapy. However, for patients refractory to such measures, invasive therapy can be beneficial. Posterior tibial nerve stimulation is an office-based percutaneous treatment for UUI or OAB. Therapy consists of weekly 30-minute treatments with a needle placed posteriorly to the medial malleolus of the ankle for 3 months.[30] Efficacy is similar to or slightly better than oral pharmacotherapy. However, long-term efficacy and safety data are lacking.

Surgery for the treatment of UUI generally consists of implantation of a sacral nerve stimulator (neuromodulation) or endoscopic office-based injection of botulinum toxin directly into the detrusor muscle.[31,32] Neuromodulation is a staged surgical procedure in which a neurostimulator lead is placed transforaminally at the level of sacral spinal cord root S3. Its exact mechanism is unknown, but the device may exert its favorable effects on urination and UUI by rebalancing the afferent and efferent nerve impulses to the lower urinary tract and pelvic floor. The injection of botulinum toxin is performed in the office generally with local anesthesia. Following transurethral injection directly into the detrusor muscle using a small needle in a template fashion, the toxin is taken up by the local neurons. The intracellular toxin cleaves SNAP-25, a cystoplasmic protein critical for the attachment of neurotransmitter containing vesicles to the cell membrane at the nerve terminal. As the vesicles containing neurotransmitter are unable to fuse to the cell membrane and release its contents into the synaptic cleft, neural transmission to the postsynaptic muscle fascicle is interrupted. This results in a graded, initially irreversible but transient weakness and paralysis of the affected muscle. The duration of effect of the toxin is about 4 to 8 months, after which repeat injection is necessary to maintain effect. The therapeutic algorithm involving these two choices for treatment of refractory UUI is evolving, and is determined largely by patient preference.[33]

Few surgical treatments for bladder underactivity are effective. After an appropriate evaluation for reversible causes, the most effective management of this condition is intermittent self-catheterization performed by the patient or a caregiver three or four times per day. Sacral nerve stimulation (neuromodulation) has shown some efficacy in this patient population, but success rates for detrusor underactivity (nonobstructive urinary retention) are inferior to that seen for the indication of urgency UI with urinary frequency and urgency.[34] Proper patient selection for this therapy remains poorly defined. Alternative methods of management that are less satisfactory or more invasive include indwelling urethral or suprapubic catheters and urinary diversion.

Urethral overactivity is most commonly caused by anatomic obstruction. Anatomic obstruction in men is most often caused by benign prostatic enlargement. Treatments may include transurethral surgical resection of the prostate (see Chapter 104, “Benign Prostatic Hyperplasia”). Rarely, bladder outlet obstruction is caused by a functional obstruction at the level of the bladder neck or external sphincter. Hypertrophy of the smooth muscle fibers at the level of the bladder neck in men and women may result in obstruction to the flow of urine. In patients who do not respond to pharmacologic therapy with α-adrenergic receptor antagonists, endoscopic incision using the cystoscope (resectoscope) is highly effective in treating this uncommon condition.

Pharmacologic Therapy

Urgency Urinary Incontinence

5 Antimuscarinic agents and β_3-adrenergic agonists are the second-line drug treatments for urgency UI. Table 105-4 summarizes AUA recommendations for treating OAB in adults.[21] Table 105-5 lists the usual dosage for approved agents for OAB or UUI. Table 105-6 suggests common monitoring parameters for these agents.

TABLE 105-4

AUA Guideline for Treatment of Overactive Bladder in Adults

Recommendation	Evidence Strength Grade[a]
First-Line Treatments	
Behavioral therapies (eg, bladder training, bladder control strategies, pelvic floor muscle training, fluid management)	B
Behavioral therapies may be combined with pharmacologic therapies	C
Second-Line Treatments	
Oral antimuscarinics or β_3-adrenergic agonist as second-line therapy	B
If an IR and an ER formulation are available, prefer ER formulations because of lower rates of dry mouth	B
Transdermal oxybutynin (patch or gel) may be offered	C
Combination therapy with an oral antimuscarinic and a β_3-adrenergic agonist is acceptable for patients refractory to monotherapy with either class of drug	C
Third-Line Treatments	
Intradetrusor onabotulinum toxin A (100 units) in carefully selected patients who have been refractory to first- and second-line OAB treatments[b]	B
Peripheral tibial nerve stimulation in a carefully selected patient population	C
Sacral neuromodulation in carefully selected patients with severe refractory OAB symptoms or in those who are not candidates for second-line therapy and are willing to undergo a surgical procedure	C

AUA, American Urological Association; ER, extended-release; IR, immediate-release; OAB, overactive bladder.

[a]When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate), or C (low). Both B and C indicate that benefits outweigh risks/burdens.

[b]The patient must be able and willing to return for frequent postvoid residual evaluation and able and willing to perform self-catheterization if necessary.

TABLE 105-5

Dosing of Medications Approved for OAB or UUI

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Anticholinergics/Antimuscarinics					
Oxybutynin	Ditropan	2.5 mg	2.5-5 mg		Titrate in increments of 2.5

IR		twice daily	two to four times daily		mg/day every 1-2 months; available in oral solution
Oxybutynin XL	Ditropan XL	5-10 mg once daily	5-30 mg once daily		Adjust dose in 5-mg increments at weekly interval; swallow whole
Oxybutynin TDS	Oxytrol Oxytrol for Women (OTC)		3.9 mg/day apply one patch twice weekly		Apply every 3-4 days; rotate application site
Oxybutynin gel 10%	Gelnique		One sachet (100 mg) topically daily		Apply to clean and dry, intact skin on abdomen, thighs or upper arms/shoulders; contains alcohol
Oxybutynin gel 3%	Gelnique 3%		Three pumps (84 mg) topically daily		Same as above
Tolterodine IR	Detrol		1-2 mg twice daily	1 mg twice daily if patient is taking CYP3A4 inhibitors, or with renal/hepatic impairment	Avoid in patients with creatinine clearance less than 10 mL/min (0.17 mL/s) or severe hepatic impairment
Tolterodine LA	Detrol LA		2-4 mg once daily	2 mg once daily in those who are taking CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, or ritonavir), with hepatic impairment (Child-Pugh class A or B), or severe renal impairment [creatinine clearance 10 to 30 mL/min (0.17-0.50 mL/s)]	Swallow whole; avoid in patients with creatinine clearance ≤10 mL/min (0.17 mL/s) or severe hepatic impairment
Trospium chloride IR	Sanctura		20 mg twice daily	20 mg once daily in patient age ≥75 years or creatinine clearance ≤30 mL/min (0.5 mL/s)	Take 1 hour before meals or on empty stomach; patient age ≥75 years should take at bedtime
Trospium chloride ER	Sanctura XR		60 mg once daily	Avoid in patient age ≥75 years or creatinine clearance ≤30 mL/min (0.5 mL/s)	Take 1 hour before meals or on empty stomach; swallow whole
Solifenacin	VESIcare	5 mg daily	5-10 mg once daily	5 mg daily if patient is taking CYP3A4 inhibitors or with creatinine clearance ≤30 mL/min (0.5 mL/s) or moderate hepatic impairment;	Swallow whole

			Pediatric: use suspension dosed based on body weight	avoid in severe hepatic impairment	
Darifenacin ER	Enablex	7.5 mg once daily	7.5-15 mg once daily	7.5 mg daily if patient is taking potent CYP3A4 inhibitors or with moderate hepatic impairment; avoid in severe hepatic impairment	Titrate dose after at least 2 weeks; swallow whole
Fesoterodine ER	Toviaz	4 mg once daily	4-8 mg once daily	4 mg daily if patient is taking potent CYP3A4 inhibitors or with creatinine clearance ≤30 mL/min (0.5 mL/s); avoid in severe hepatic impairment	Prodrug (metabolized to 5-hydroxymethyl tolterodine); swallow whole
β_3-Adrenergic Agonist					
Mirabegron ER	Myrbetriq	25 mg once daily	25-50 mg once daily	25 mg once daily if creatinine clearance 15-29 mL/min (0.25-0.49 mL/s) or moderate hepatic impairment; avoid in patients with ESRD or severe hepatic impairment	Swallow whole
Vibegron	Gemtase	75 mg once daily		Avoid in patients with end-stage kidney disease with or without hemodialysis, or severe hepatic impairment	Swallow whole. Tablets may be crushed and mixed with applesauce

CYP, cytochrome P450 enzyme; ER, extended-release; ESRD, end-stage renal disease; IR, immediate release; LA, long acting; OAB, overactive bladder; OTC, over-the-counter; TDS, transdermal system; UUI, urge urinary incontinence; XL, extended release.

TABLE 105-6

Monitoring of Medications Approved for OAB or UUI

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Antimuscarinic			
Oxybutynin IR Oxybutynin XL Oxybutynin TDS Oxybutynin gel 10% Oxybutynin gel 3% Tolterodine IR Tolterodine LA Trospium chloride IR Trospium chloride ER Solifenacin Darifenacin ER Fesoterodine ER	Anticholinergic adverse effects: dry mouth, constipation, headache, dyspepsia, dry eyes, blurred vision, cognitive impairment, tachycardia, sedation, orthostatic hypotension Application site reactions (topical agents): pruritus, erythema	Contraindications and precautions: urinary retention, gastric retention, severely decreased GI motility, angioedema, myasthenia gravis, uncontrolled narrow-angle glaucoma Worsening of renal/hepatic condition or concomitant drug therapy, which may necessitate dosage reduction or drug cessation Mental status change or risk for falls in elderly or frail patients	In general, ER, LA, XL, and topical products are associated with fewer anticholinergic adverse effects, particularly dry mouth Possible transference of drug from topical application Avoid open fire or smoke until alcohol-based gel has dried
β_3-Adrenergic Agonist			
Mirabegron ER	Hypertension, nasopharyngitis, urinary tract infection, headache	Precautions: urinary retention, severe uncontrolled hypertension Worsening of renal/hepatic condition, which may necessitate dosage reduction or drug cessation Increased effect of narrow therapeutic index drugs that are CYP2D6 substrates QT prolongation	Mirabegron is a CYP2D6 inhibitor; may increase digoxin level
Vibegron	Headache, nasopharyngitis, hot flashes, gastrointestinal symptoms, upper respiratory tract infection	Precautions: bladder flow obstruction, hepatic/renal impairment	Minor substrate of CYP3A4, P-glycoprotein/ABCB1; may increase digoxin level

CYP, cytochrome P450 enzyme; ER, extended-release; IR, immediate release; LA, long acting; OAB, overactive bladder; TDS, transdermal system; UUI, urge urinary incontinence; XL, extended release.

Antimuscarinic agents (see Table 105-5) antagonize muscarinic receptors and suppress premature detrusor contractions, thereby enhance bladder storage. They have similar contraindications, precautions, and side-effect profiles, with incidence/severity varies with each individual agent.[35] These agents improve quality of life, and are considered equally effective based on clinical efficacy in reducing UI episodes, decreasing micturitions per day, and increasing urine volume voided per micturition.[36] Antimuscarinic agents may worsen cognitive function, especially in older adults. Also, they may antagonize the therapeutic effects of acetylcholine esterase inhibitors indicated for dementia.

Oxybutynin

Oxybutynin immediate release (IR) is the oldest and least expensive treatment for UUI. It gives substantial nonurinary antimuscarinic effects, including orthostatic hypotension, sedation, and weight gain (see Table 105-6).[37] These adverse effects may jeopardize medication adherence and prevent dose escalation. Its multiple daily dosing may be too complicated for patients with cognitive impairment or those who are taking multiple medications. Consider dose reduction if side effects become bothersome. Use sugarless gum, hard candy, or a saliva substitute for dry mouth and increase fluid/fiber intake, physical activity, and/or laxative therapy for constipation.

An extended-release (XL) formulation of oxybutynin is an alternative therapy in patients who cannot tolerate IR formulation. It delivers a controlled amount of oxybutynin over a 24-hour period, and has a reduced first-pass metabolism. It gives a lower concentration of active metabolite, *N*-desethyloxybutynin, which is associated with dry mouth as a side effect.[38] In short-term studies, oxybutynin XL was better tolerated than oxybutynin IR, and at least as effective as tolterodine IR or long acting (LA) in managing urinary symptoms.[38] Drug interactions may occur when oxybutynin is used with other anticholinergic drugs, potent CYP3A4 inhibitors (eg, itraconazole, miconazole, erythromycin, and clarithromycin), and acetylcholinesterase inhibitors.[38]

Nonoral formulations of oxybutynin are available for better tolerability. The oxybutynin transdermal system (TDS) is the first OTC treatment for OAB in women aged 18 years or older. It has a similar efficacy as oxybutynin IR or tolterodine LA.[39,40] It bypasses first-pass hepatic and gut metabolism and is more tolerable (anticholinergic side effects <10%).[39] It has been associated with improved quality of life and work productivity. Patients should apply oxybutynin TDS to dry, intact skin on the abdomen, hip, or buttocks every 3 to 4 days (twice weekly). Rotating application site at least weekly helps to minimize local reactions: pruritus (14%-17%) and erythema (6%-9%).[39]

Oxybutynin topical gel causes less dry mouth than oral oxybutynin (6.1% vs 73.1%).[41-43] In older patients with frailty, long-term use warrants proper monitoring for cognitive impairment and anticholinergic effects.[44] Patients should not apply sunscreen within 30 minutes before or after application or shower within 1 hour after application. They should also avoid the transfer of gel to others via vigorous skin contact at the application site; avoid open fires or exposure to smoking until the alcohol-based gel has dried.[41,42]

Tolterodine

Tolterodine is a competitive muscarinic receptor antagonist that is as effective as oxybutynin IR, but gives better tolerability and thus medication adherence.[45] Tolterodine is predominantly eliminated by hepatic metabolism, which is partially under the control of genetic polymorphism.[46] The principal metabolic pathway in extensive metabolizers involves oxidation of the parent drug by CYP isoenzyme 2D6 to the active 5-hydroxymethyl metabolite (DD01). In CYP2D6 poor metabolizers (approximately 7% of the US population), the principal metabolic pathway involves CYP3A4. Because tolterodine is principally metabolized by CYP3A4 in this case, monitor for impaired drug limitation when given concomitantly with CYP3A4 inhibitors (eg, fluoxetine, sertraline, fluvoxamine, macrolide antibiotics, azole antifungals, and grapefruit juice). Concurrent use of fluoxetine, a dual inhibitor of CYP2D6 and 3A4 can significantly increase tolterodine level.[46] Caution is also advised with individuals who carry nonfunctional CYP2D6*13 allele.[46,47] The maximum benefit from tolterodine may take up to 8 weeks after therapy initiation or dose escalation.[46] The most common adverse effects of tolterodine are dry mouth, dyspepsia, headache, constipation, and dry eyes. Of note, patients who have known hypersensitivity to fesoterodine fumarate should not receive tolterodine because both agents are metabolized to DD01. Monitor for QT prolongation with concomitant use of Class IA (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol) antiarrhythmic medications.[47]

Tolterodine long acting (LA) offers a convenient once-daily dosing and causes less dry mouth than IR formulation.[48] It also improves OAB symptoms in men who were taking α-adrenergic blockers.[49] It may take up to 8 weeks to see maximum benefit after starting therapy or dose escalation.[48]

Fesoterodine Fumarate

Fesoterodine fumarate is also indicated for symptoms of urinary frequency, urgency, or urgency incontinence. It is a prodrug that is metabolized to its active metabolite, 5-hydroxymethyl tolterodine (also a metabolite of tolterodine), by nonspecific plasma esterases.[50] In a short-term study, fesoterodine was better than tolterodine ER 4 mg and placebo on reducing UUI episodes, micturitions, urgency, and improving health-related quality of life. However, fesoterodine caused more dry mouth (28% vs 13%) and constipation (4% vs 3%).

More patients discontinued fesoterodine therapy due to adverse events (5% vs 3%).[51] The most common adverse effects of fesoterodine are dose-related dry mouth (27%), constipation (5.1%), dyspepsia (2%), and dry eyes (1.6%).[50] The most common adverse effects of fesoterodine are dose-related dry mouth (27%), constipation (5.1%), dyspepsia (2%), and dry eyes (1.6%).

Trospium Chloride

Trospium chloride, a quaternary ammonium anticholinergic, is a second-generation antimuscarinic agent for urgency UI. Trospium chloride is poorly absorbed after oral administration (<10%), and food reduces bioavailability by 70% to 80%. It is principally cleared by the renal route (60%). Metabolites account for approximately 40% of the excreted dose following oral administration. The major metabolic pathway is hypothesized as ester hydrolysis with subsequent conjugation. CYP is not expected to contribute significantly to the elimination of trospium. The plasma half-life is approximately 20 hours; with renal clearance about 30 L/hr. Active tubular secretion is a major route of elimination for trospium. When creatinine clearance is less than 30 mL/min (0.50 mL/s), drug exposure and drug concentration are significantly increased.[45]

Trospium chloride IR was noninferior to oxybutynin IR, but was associated with less dry mouth.[52] Anticholinergic side effects occur more often in patients aged 75 years and older due to pharmacodynamics changes (ie, increased sensitivity). Trospium may interact with other drugs that are eliminated by active tubular secretion via competition (eg, procainamide, pancuronium, morphine, vancomycin, and tenofovir).[45] Trospium chloride extended-release offers once-daily dosing with established efficacy and safety in patients with OAB.[53] Trospium is eliminated primarily unchanged in the urine; thus it is not recommended in patients with severe renal impairment. It interacts with alcohol (increased drowsiness), antacid (increase or decrease trospium exposure), and metformin (reduced trospium level by 34%).[54] It must be taken on an empty stomach (1 hour before or 2 hours after meals) as food decreases the bioavailability by up to 60%.[53] Common adverse effects with trospium chloride ER are dry mouth (11%), constipation (9%), dizziness (2%), dry eyes (1.6%), flatulence (1.6%), nausea (1.4%), and abdominal pain (1.4%).[54]

Solifenacin Succinate

Solifenacin succinate is a second-generation antimuscarinic agent indicated for the treatment of OAB with urgency incontinence, urgency, and urinary frequency.[55] It is also indicated for neurogenic detrusor overactivity in children 2 years or older and adolescents.[56] Solifenacin is associated with less dry mouth than oxybutynin IR (35% vs 83%). It is well absorbed (bioavailability 88%) and taken without regard to food. It is principally eliminated via metabolism (CYP3A4) and renal excretion of metabolites. It has a terminal disposition half-life of 50 to 60 hours.[55]

The recommended dose of solifenacin is 5 mg once daily with or without food. If the drug is well tolerated, the dose can be increased to 10 mg once daily. See Table 105-6 for dose adjustment based on renal/hepatic impairment and drug interactions. The most common adverse reactions of solifenacin are dry mouth (11%-28%), constipation (5%-13%), urinary tract infection (4%-5%), and blurred vision (3%-5%). It interacts with CYP3A4 inhibitors and inducers; close patient monitoring is required. Prolonged corrected QT intervals have been reported with high-dose solifenacin.[55]

Darifenacin

Darifenacin is another second-generation antimuscarinic for the management of OAB or UUI. It improves urinary symptoms, and quality of life.[57,58] The bioavailability of extended-release (ER) formulation is low (25%), and is affected by CYP2D6 genotype and treatment dose. Darifenacin is extensively metabolized, with cumulative urinary excretion of the parent compound less than 10%. The 2D6 and 3A4 isoenzymes of CYP are responsible for darifenacin metabolism. Thus, pharmacogenomic profile may impact the clinical response to darifenacin.[59] With a mean terminal disposition half-life of 3 to 5 hours (depending on CYP2D6 metabolizer status), an ER formulation is needed to allow once-daily dosing.[60] Darifenacin ER should be initiated at 7.5 mg once daily, and may be increased to 15 mg once daily after 2 weeks to target clinical response. See Table 105-6 for dose adjustment based on

renal/hepatic impairment and drug interactions. It must be swallowed whole without chewing, dividing, or crushing. Common adverse reactions are constipation (21%), dry mouth (19%), headache (7%), dyspepsia (5%), and nausea (4%). Darifenacin may interact with substrates of CYP2D6 (flecainide, thioridazine, and tricyclic antidepressants).[60]

Mirabegron

Mirabegron is approved by FDA for the treatment of OAB with symptoms of UUI, urgency, and urinary frequency.

Mirabegron is another first-line drug treatment for managing UUI. It increases bladder capacity by relaxing the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle through the activation of β_3-adrenergic receptors. Similar to antimuscarinic agents, it is modestly effective and reduces urinary frequency and incontinence episodes by less than one per day. It is associated with nonsignificant improvements in UUI, urgency episodes, and quality-of-life measures. It has been shown to have similar efficacy as with tolterodine ER.[21,61] It reduces mean number of incontinence episodes per 24 hours, mean number of micturitions per 24 hours, and increased mean volume voided per micturition. The efficacy is usually seen during 4 to 8 weeks of therapy.[62]

Mirabegron reaches its peak plasma concentrations at approximately 3.5 hours and has an oral bioavailability of 29% to 35%. It achieves steady state within 7 days of therapy. It can be taken with or without food. Mirabegron is extensively distributed in the body, with a volume of distribution of approximately 1,670 L. It has protein binding of approximately 71% to both albumin and α_1-acid glycoprotein. Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, glucuronidation, and amide hydrolysis. It has two inactive metabolites (16% and 11% of total exposure), respectively. Isoenzymes CYP2D6 and 3A4 play a limited role in its elimination. Poor metabolizers of CYP2D6 had an increased mean peak concentration and drug exposure compared to extensive metabolizers of CYP2D6 (16% and 17%, respectively). Other enzymes that are involved in mirabegron metabolism include butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), and possibly alcohol dehydrogenase.

Total body clearance of mirabegron is about 57 L/hr, with a terminal elimination half-life of 50 hours. Renal clearance equals approximately 13 L/hr, primarily through active tubular secretion along with glomerular filtration. The urinary elimination of unchanged mirabegron is dose dependent and ranges from 6% to 12% after a daily dose of 25 to 100 mg.[61]

Mirabegron should be initiated at 25 mg once daily, and may titrate upward to 50 mg once daily after 8 weeks, based on individual efficacy and tolerability; limit dose to 25 mg once daily in patients with severe renal impairment or moderate hepatic disease. Mirabegron is available in ER tablets, and should be swallowed whole with water without chewing, dividing, or crushing. It should be avoided in patients with end-stage renal disease, severe hepatic impairment, or severe uncontrolled hypertension (≥180/110 mm Hg). Most commonly reported adverse reactions were hypertension (7%-11%), nasopharyngitis (4%), urinary tract infection (3%-6%), and headache (3%-4%). Patient should be monitored for increased blood pressure and urinary retention, particularly in patients with bladder outlet obstruction or those who are taking anticholinergic drugs.[62] Mirabegron has similar adverse effects (except less dry mouth) when compared with tolterodine ER. Blood pressure and heart rate changes were minimal (<1 mm Hg and <2 beats/min, respectively).[21] Mirabegron is a moderate inhibitor of CYP2D6, and may affect the dosage requirement for some 2D6 substrates (eg, metoprolol and desipramine). Thus, drug-level monitoring for certain medications with a narrow therapeutic range, such as thioridazine, flecainide, and propafenone, is advised.[61] The efficacy and safety of combination therapy with mirabegron (25 or 50 mg) and solifenacin (5 mg) have been evaluated in clinical trials.[63-65] Combination therapy demonstrated improved efficacy without significant increase in side effects as seen in monotherapy.[21]

Vibegron

Vibegron is approved by FDA for the treatment of OAB with symptoms of UUI, urgency, and urinary frequency in adults.

Like mirabegron, vibegron is a β_3-adrenergic receptor agonist. It activates β_3-adrenergic receptors in the bladder, resulting in relaxation of the detrusor smooth muscle during the urine storage phase, thus increasing bladder capacity. Vibegron reaches its peak plasma concentrations within 1 to 3.5 hours of administration and has a protein binding of 50%. The usual dose is 75 mg once daily with or without food.

Vibegron is extensively distributed in the body, with a volume of distribution of approximately 6,000 L. It is metabolized via minor metabolism

hepatically via CYP3A4. It has a terminal elimination half-life of 30 hours and is excreted unchanged in feces (54%) and urine (19%).[66] Other β_3-adrenergic agonists in development include solabegron, ritobegron, and vibegron.[67-69]

Table 105-7 lists the frequencies for the most common adverse events for all approved treatment oral agents based on manufacturers' product information.

TABLE 105-7

Adverse Event Incidence Rates (%) with Approved Drugs for Bladder Overactivity[a]

Drug	Dry Mouth	Constipation	Dizziness	Vision Disturbance
Oxybutynin IR	71	15	17	10
Oxybutynin XL	61	13	6	14
Oxybutynin TDS	7	3	NR	3
Oxybutynin gel	10	1	3	3
Tolterodine	35	7	5	3
Tolterodine LA	23	6	2	4
Trospium chloride IR	20	10	NR	1
Trospium chloride XR	11	9	NR	2
Solifenacin	20	9	2	5
Darifenacin ER	24	18	2	2
Fesoterodine ER	27	5	NR	3
Mirabegron ER	3	3	3	NR
Vibegron	<1	2	<1	<1

IR, immediate release; LA, long acting; NR, not reported; TDS, transdermal system; XL, extended release; XR/ER, extended release.

[a]All values constitute mean data, predominantly using product information from the manufacturers.

Other Anticholinergics and Antimuscarinics

Tricyclic antidepressants are generally no more effective than oxybutynin IR, and give bothersome and potentially serious adverse effects (eg, orthostatic hypotension, cardiac conduction abnormalities, dizziness, and confusion). They are also potentially life-threatening in overdose. Therefore, their use should be limited to individuals who have one or more additional medical indications for these agents (eg, depression or neuropathic pain); patients with mixed UI (because of their effect of decreasing bladder contractility and increasing outlet resistance); and possibly those with nocturnal incontinence associated with altered sleep patterns. Desipramine and nortriptyline have lower incidences of adverse effects; they may be preferred over imipramine and doxepin. However, because of their lower anticholinergic activity, they may not be as effective. Propantheline,

flavoxate, dicyclomine, and hyoscyamine are not recommended for urgency UI.

Botulinum Toxin A

Enthusiasm is considerable for the application of botulinum toxin A for treatment of voiding dysfunction. Botulinum toxin is a naturally occurring powerful muscle relaxant produced by *Clostridium botulinum*. Injected into smooth or striated muscle, botulinum toxin acts as a neurotoxin by temporarily paralyzing the muscle. The mechanism of action of the paralytic effect is generally ascribed to prevention of the release of the neurotransmitter acetylcholine into the synapse at the neuromuscular junction, although other pathways in neurotransduction may also be affected.

This compound is commercially produced for medical use in a number of conditions such as muscle spasticity, hyperhidrosis, and cosmetic reduction of skin wrinkles. It is indicated for the treatment of detrusor overactivity associated with neurologic condition and OAB.[62,70,71] Intradetrusor onabotulinumtoxin A is recommended by AUA as the third-line treatment in adult patients with refractory OAB.[21] In the lower urinary tract, it has also been used to treat external urethral sphincter spasticity by direct injection into the external urethral sphincter.

Botulinum toxin is delivered into the detrusor muscle (intravesical injection) using a cystoscope equipped with a needle. The usual dosage is between 100 and 300 units/session. It is injected through the needle directly into the bladder muscle in 10 to 30 injections spaced over 5 to 10 minutes. The procedure is carried out as an outpatient procedure without general anesthesia. The duration of therapeutic effect varies, lasting usually from 4 to 8 months. Repeat injections are necessary to maintain the beneficial effects.[71]

The adverse effects of botulinum toxin A when used in the urinary tract most frequently include dysuria, hematuria, urinary tract infection, and urinary retention. Urinary retention occurs in up to 20% of treated individuals and persists until the paralytic effects have worn off (up to 6-8 months). Therapeutic and adverse effects may not become evident for 3 to 7 days, presumably because this period of time is required for uptake of the toxin following injection.[62,71]

Intravesical (ie, bladder) injection of botulinum toxin A in patients with refractory OAB resulted in increased bladder capacity, increased bladder compliance, and improved quality of life.[62,71] Adverse effects include urinary tract infection and urinary retention.[71] Comparative data with placebo and other interventions, long-term safety and efficacy outcomes, and data regarding the optimal dose of botulinum toxin for idiopathic OAB are needed.

An alternative mechanism of delivery other than intravesical injection would greatly improve the appeal of this agent as needle injection can be painful in some individuals. Results of an open-label trial of intravesical botulinum toxin A in dimethylsulfoxide in 21 women with refractory idiopathic detrusor overactivity demonstrated a significant reduction in the frequency of incontinence episodes without any effect on postvoid residual urine volumes.[72] Further studies are needed in this regard.

Catheterization Combined with Medications

Patients with UUI and an elevated postvoid residual urine volume due to retention may require intermittent self-catheterization along with frequent voiding between catheterizations. If intermittent catheterization is not possible, surgical placement of a suprapubic catheter may be necessary. Use of a chronic indwelling catheter should be avoided because of the increased occurrence of urinary tract infections and nephrolithiasis.

Regardless of catheterization status, patients may experience symptom relief with judicious use of oxybutynin (IR, XL, or TDS formulations), tolterodine (IR or LA formulations), trospium chloride, solifenacin, fesoterodine, darifenacin, or mirabegron, as these agents relax the detrusor muscle and enhance bladder storage. Patients with UUI and symptoms of urinary retention may also benefit from an α-adrenergic receptor antagonist that relaxes the internal bladder sphincter (eg, prazosin, terazosin, doxazosin, tamsulosin, silodosin, and alfuzosin). Although theoretically of benefit, bethanechol, a cholinergic agonist, has not been demonstrated effective in improving bladder emptying in well-done trials. In addition, it causes numerous bothersome (eg, muscle and abdominal cramping and diarrhea) and potentially life-threatening adverse effects and should not be used in patients with asthma or heart disease.[22]

Urethral Underactivity

Urethral underactivity, or SUI, may be aggravated by agents with α-adrenergic receptor blocking activity, including prazosin, terazosin, doxazosin,

tamsulosin, alfuzosin, silodosin, methyldopa, clonidine, guanfacine, and labetalol. The goal of therapy for SUI is to improve the urethral closure mechanism by stimulating α-adrenergic receptors in the smooth muscle of the bladder neck and proximal urethra, enhancing the supportive structures underlying the urethral epithelium, or enhancing the positive effects of serotonin and norepinephrine in the afferent and efferent pathways of the micturition reflex.[73]

Estrogens

Local and systemic estrogens have been used extensively for the pharmacologic management of SUI since the 1940s. Estrogens are believed to work via several mechanisms, including enhancement of the proliferation of urethral epithelium, local circulation, and numbers and/or sensitivity of urogenital α-adrenergic receptors. However, a trial has questioned whether estrogens exert a stimulatory effect on vaginal collagen production, at least over the short term.[74]

A meta-analysis of 34 trials evaluating the use of local or systemic estrogen therapy on UI in postmenopausal women found that systematic administration of estrogen alone or in combination with progesterone resulted in UI worsening.[75] In fact, observational studies have documented that oral or systemic estrogen use is associated with an increased risk of UI compared with that in nonusers.[76] There was some evidence that vaginal estrogen (vaginal cream or pessaries) may improve UI, and reduce urgency and frequency. The long-term effects of this therapy in older women are unknown. A recent meta-analysis of 17 trials of local estrogen compared to placebo or no treatment found beneficial effects on UI and OAB symptoms and some urodynamic parameters.[77] Different forms of vaginal estrogen (ring, pessary) have similar improvements in urinary symptoms (SUI, UUI, frequency, urgency). Studies comparing vaginal estrogen alone or in combination with antimuscarinic drugs (tolterodine or oxybutynin) or pelvic floor muscle exercises found greater improvement in subjective measures of UI in the combination approach. If estrogens are to be used for treatment of UI or OAB in postmenopausal women, only topical products should be administered, potentially combined with other treatment modalities such as pelvic floor muscle exercises or antimuscarinic drugs.

α-Adrenergic Receptor Agonists

Numerous open trials have supported the use of a variety of α-adrenergic receptor agonists in SUI, including ephedrine, norfenefrine, phenylpropanolamine, and midodrine. Phenylpropanolamine was withdrawn from the US market in 2000 because of a risk for stroke in women using the agent.[78] Patients may obtain the drug from international sources or via Internet. If so, individuals with the contraindications listed later in the chapter (especially coronary artery disease and/or cardiac arrhythmias) should be warned against self-treatment with this or other α-adrenergic receptor agonists.

Placebo-controlled comparative trials with phenylpropanolamine, norfenefrine, and norephedrine support the modest efficacy of these agents for treatment of mild or moderate SUI.[79] These agents have been found to variably affect maximum urethral closure pressure and functional urethral length. Adverse effects include hypertension, headache, dry mouth, nausea, insomnia, and restlessness. Contraindications to the use of these agents include the presence of hypertension, tachyarrhythmias, coronary artery disease, myocardial infarction, cor pulmonale, hyperthyroidism, renal failure, and narrow-angle glaucoma.

Several studies have evaluated whether the clinical and urodynamic effects of a combination of estrogen and an α-adrenergic receptor agonist exceed those of the individual therapies in SUI.[79] In general, combination therapy has resulted in somewhat superior clinical and urodynamic responses compared with monotherapy, including severity of complaints, amount of urine lost per episode, number of daily voluntary micturitions, number of leakage episodes per day, patient preference, pad use, maximum urethral closure pressure, functional urethral length, and pressure transmission ratio.

Duloxetine

Duloxetine, a dual inhibitor of serotonin and norepinephrine reuptake (SNRI), was approved in 2004 for treatment of depression and painful diabetic neuropathy in the United States.[80] It is approved for SUI in Europe only. It is believed to affect central serotoninergic and noradrenergic regions, which are involved in ascending and descending control of urethral smooth muscle and the external urethral sphincter. These mechanisms facilitate the bladder-to-sympathetic reflex pathway, increasing urethral and external urethral sphincter muscle tone during the storage phase.

Duloxetine is metabolized by CYP2D6 and 1A2 enzymes to form multiple metabolites and then eliminated in the urine. Duloxetine may increase the concentrations, drug exposure, and half-lives of CYP2D6 substrates (eg, desipramine). Meanwhile, the drug concentration of duloxetine can be increased by CYP2D6 inhibitors (eg, paroxetine) and CYP1A2 inhibitors (eg, fluvoxamine).[80] Moderate hepatic dysfunction (Child-Pugh class B) significantly increases mean AUC and terminal disposition half-life of duloxetine. Mild or moderate renal impairment (creatinine clearance 30-80 mL/min [0.50-1.33 mL/s]) does not affect drug disposition. In severe renal impairment (hemodialysis patients), mean peak plasma concentration and AUC are both increased 100%, whereas metabolite concentrations are increased up to 900%.[80]

In six large, double-blinded, randomized, placebo-controlled clinical trials that evaluated duloxetine for SUI, duloxetine therapy produced significant reductions in UI episode frequency and number of micturitions per day, improvement in incontinence quality-of-life questionnaire scores and patient self-assessment, and increase in mean micturition interval. Results were independent of baseline UI severity (severity based on incontinent episode frequency). Significant intergroup differences were seen by week 4. However, cure rates were generally not improved by duloxetine. When evaluating the absolute differences between treatments, the actual benefit of duloxetine was generally quite modest. Duloxetine also reduced incontinence episodes and improved quality of life in men with SUI after radical prostatectomy.[81]

A randomized, placebo-controlled clinical trial evaluated the effects of duloxetine (80 mg daily), pelvic floor muscle training (PFMT), and the combination of both modalities on incontinent episode frequency, incontinence-related quality of life, pad use, and patient global impression of change. Sham PFMT was used in the placebo group. Results indicated that duloxetine plus PFMT were probably additive in effect and that combination therapy afforded greater improvement than either monotherapy.[82]

The adverse events associated with duloxetine may make adherence problematic. In the SUI trials, treatment-emergent adverse events occurred in 68% to 93% of duloxetine and 50% to 72% of placebo recipients. Premature study withdrawal rates (due to adverse events) were as high as up to 33%. The most common adverse events reported with duloxetine were nausea (≤46%), headache (≤27%), constipation (≤27%), dry mouth (≤22%), and insomnia (≤14%). Of interest, the drug may be associated with small increases in blood pressure (such as venlafaxine, another SNRI) and withdrawal symptoms (sleep disturbances). Unfortunately, adherence to long-term therapy is quite poor due to a combination of adverse events and lack of efficacy.[83]

Despite these negatives, duloxetine is the first drug approved by a regulatory agency for treating SUI in Europe. Based on studies conducted to date, a dosage regimen of 40 to 80 mg/day (in one or two doses) is reasonable. Gradual dose titration (40 mg daily for 2 weeks, then 80 mg daily) helps reduce the risks of nausea, dizziness, and premature drug discontinuation. If cessation of duloxetine is desired, consider tapering the dosage by 50% for 2 weeks before discontinuation to avoid withdrawal symptoms.

Venlafaxine

Venlafaxine is another SNRI. A double-blind, randomized, placebo-controlled clinical trial has demonstrated the benefit of venlafaxine 75 mg once daily for 12 weeks over placebo in terms of incontinence episode frequency, voiding interval, quality of life, and patient global impression of improvement. Nausea occurred in 40% of the venlafaxine group compared with 15% of the placebo group.[84]

Overflow Incontinence

Overflow incontinence secondary to benign or malignant prostatic hyperplasia may be amenable to pharmacotherapy. For management of malignant prostatic disease, see Chapter 154, “Prostate Cancer.” The pharmacotherapy of BPH is discussed in Chapter 104.

EVALUATION OF THERAPEUTIC OUTCOMES

8 Assessment of patient outcomes should include efficacy, side effects, adherence, and quality of life. During long-term management of UI, patient-specific clinical signs and symptoms of most distress (“bother”) to the individual must be monitored. A daily diary may be useful in this regard. Some of the short-form instruments used in incontinence research for measuring symptom impact and condition-specific quality of life can be used in clinical monitoring. In addition, quantitating the use of ancillary supplies, such as pads, may be useful.

9 The main goal of therapy is to minimize the signs and symptoms most bothersome to the patient, as well as the use of pads and other ancillary

supplies or devices. Total elimination of UI signs and symptoms may not be possible, and patients and practitioners need to mutually establish realistic goals of therapy. Because the therapies for UI frequently have nuisance adverse effects (eg, anticholinergic effects such as dry mouth, constipation, and sedation) that may compromise regimen adherence, the presence and severity of adverse effects must be carefully elicited at each visit to the healthcare practitioner. Queries of the patient and caregiver regarding CNS effects are important in elderly or frail patient as these effects can be severe enough to cause loss of independent living skills. Emergence of adverse effects may necessitate drug dosage adjustment or use of alternative strategies (eg, chewing sugarless gum, sucking on hard sugarless candy, or use of saliva substitutes in xerostomia) or even drug discontinuation. Patient should be encouraged to persist with a particular treatment for 4 to 8 weeks before declaring treatment failure. Nonresponders to an antimuscarinic should be offered at least one other antimuscarinic and/or dose modification attempted to obtain a better balance between efficacy and side effects.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
AUA	American Urological Association
AUC	area under the plasma or serum concentration-versus-time curve
BPH	benign prostatic hyperplasia
CNS	central nervous system
CYP	cytochrome P450
DD01	5-hydroxymethyl metabolite
ER	extended-release
EStim	electrical stimulation
FDA	Food and Drug Administration
IR	immediate release
LA	long acting
MStim	magnetic stimulation
OAB	overactive bladder
PFMT	pelvic floor muscle training
PTNS	peripheral tibial nerve stimulation
SNRI	serotonin and norepinephrine reuptake
SUI	stress urinary incontinence
TDS	transdermal system
UI	urinary incontinence
UGT	uridine diphospho-glucuronosyltransferases
UUI	urgency urinary incontinence
XL	extended release

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SELF-ASSESSMENT QUESTIONS

1. Which of the following groups has the highest prevalence of urinary incontinence?

   A. Women of childbearing age

   B. Women age 70 years and older

   C. Men treated for prostate cancer

   D. Men aged 70 years and older

2. A 65-year-old woman reports leaking moderate amounts of urine several times during the day after feeling a sudden urge to urinate. She also reports leaking small amounts of urine after she coughs or sneezes. She is using 3 pads per day for incontinence. Urinalysis is unremarkable and her postvoid residual in 20 mL. What type of urinary incontinence does she most likely have?

A. Stress

B. Urgency

C. Overflow

D. Mixed

3. An 85-year-old man living in a nursing home has several episodes of incontinence daily. He has moderate dementia and uses a walker when ambulating. He needs prompting from caregivers to use the bathroom. What type of urinary incontinence should he be treated for?

A. Stress

B. Urgency

C. Disability associated

D. Overflow

4. A 32-year-old woman complains of losing small amounts of urine while she exercises and after she coughs or sneezes. She denies urinary frequency or having a compelling urge to urinate. She lost a small amount of urine during the cough test. She delivered three babies vaginally, the most recent being 1 year ago. What is the first-line treatment for her incontinence?

A. Pelvic floor muscle exercises

B. Bladder training

C. An antimuscarinic drug

D. Timed voiding

5. A 52-year-old postmenopausal woman reports losing small-to-moderate amounts of urine several times a day after having a strong urge to urinate. In an attempt to avoid these leaks, she is urinating every 2 hours. She is awakened at least two times each night with a strong urge to urinate and often leaks before she can get to the toilet. She is using 3 to 4 large absorbant pads a day to contain her leaks. Urinalysis is unremarkable and her post-void residual is 25 mL. Which is the best initial treatment for her?

A. Bladder training

B. Percutaneous tibial nerve stimulation

C. Timed voiding

D. Pelvic floor muscle exercises

6. A 60-year-old woman is diagnosed with overactive bladder with occasional urge urinary incontinence during daytime (once or twice weekly). Her past medical history includes congestive heart failure, chronic constipation, falls, glaucoma, hypothyroidism, spinal stenosis, and osteoarthritis. She is taking appropriate medications for her health conditions. She prefers an oral treatment that is least likely to cause constipation, dry mouth, or other anticholinergic side effects. She has a good prescription plan. You recommend:

A. Imipramine

B. Vibegron

C. Oxybutynin IR

D. Darifenacin

7. The most appropriate agent for managing atonic bladder or overflow incontinence is:

   A. Imipramine

   B. Topical estrogen

   C. Pseudoephedrine

   D. Bethanechol

8. A 75-year-old woman is diagnosed with overactive bladder with urge incontinence and nocturia. She has type 2 diabetes mellitus, hypertension, congestive heart failure, and insomnia due to home relocation one week ago. Her current medications include aspirin 81 mg daily, metoprolol extended release 100 mg daily, enalapril 5 mg daily, furosemide 40 mg daily, metformin 500 mg with breakfast, and melatonin 5 mg at bedtime. She reports nocturia one to two times per night since her doctor increased the dose of furosemide last month for lower extremity edema. Otherwise, she tolerates all of her medications. You recommend to:

   A. Switch furosemide to bumetanide

   B. Check glucose levels and HbA1c

   C. Start estradiol topical cream

   D. Switch melatonin to clonazepam

9. A 60-year-old patient is referred to the pharmacy clinic to initiate an appropriate drug therapy of overactive bladder. She has difficulty swallowing, and requires medications to be crushed. She is 5 ft 2 in. (157 cm) tall, and weighs 135 lb (61 kg). Her serum creatinine is 3 mg/dL (265 µmol/L). You recommend:

   A. Fesoterodine 8 mg daily

   B. Mirabegron 25 mg daily

   C. Solifenacin 10 mg at bedtime

   D. Trospium 20 mg at bedtime

10. A 55-year-old woman with potentially limited health literacy complains of “having water problem.” She complains of urinary urgency and frequency. She has no episode of urinary incontinence so far. She has not visited physicians for the past five years. She has self-initiated therapy with over-the-counter product oxybutynin 3.9 mg/day patch. She applies one patch every day for the past 3 days. She notices a little improvement in symptoms, but also reports dry mouth. Today her physician ruled out urinary tract infection, and diagnosed her to have overactive bladder. She has no prescription insurance, and wants “a medication that helps and does not cost too much.” Which of the following is most appropriate to initiate now?

    A. Counsel the patient on appropriate use of oxybutynin patch

    B. Add over-the-counter pseudoephedrine 15 mg three times daily

    C. Switch oxybutynin patch to mirabegron 25 mg daily

    D. Switch oxybutynin patch to cranberry extract daily

11. Following the initiation of behavioral therapy for urge urinary incontinence, a patient requests additional treatment. Appropriate pharmacologic therapy in this setting is:

    A. Phenylpropanolamine

B. Solifenacin

C. Bethanecol

D. Oral estrogen

E. Tamulosin

12. A 50-year-old premenopausal woman presents to her primary provider with bothersome symptoms of stress urinary incontinence. She reports losing a few drops of urine 2 to 4 times a week. Her physical examination is unremarkable. Appropriate initial therapy consists of behavioral modification and:

A. Absorbent pad

B. Pelvic floor muscle exercises

C. Diphenhydramine

D. Darifenacin

E. Vaginal estrogen

13. An 80-year-old man residing in a nursing home has urgency and urge incontinence that results in loss of urine several times a day as well as nocturnal enuresis. He voids every 5 to 6 hours during the day. This resident also has hypertension, heart failure, severe arthritis, diabetes, and mild dementia. The most appropriate choice of treatment is:

A. An antimuscaric agent

B. Suprapublic catheter

C. Timed toileting

D. Absorbent pads

E. Bed alarm

14. A 55-year-old postmenopausal, obese woman who smokes complains of small volume of urine leakage when she coughs or laughs. She reports no urinary frequency or incontinent episodes at night. She gave birth to two children in her 30s. Her risk factors for stress incontinence include:

A. Postmenopausal status

B. Childbirth

C. Obesity

D. Age

E. All of the above

15. Which of the following statements about mirabegron is correct?

A. It is a β_3-adrenergic antagonist.

B. It has been approved for stress incontinence in Europe only.

C. It should be swallowed whole.

D. Its use is associated with bradycardia.

E. It should not be administered concomitantly with oral estrogen replacement.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** The prevalence rate of incontinence is three times higher in women than in men. Women aged 70 years and older having the highest prevalence estimated at 40%.

2. **D.** Mixed urinary incontinence is defined as having symptoms of both stress and urgency urinary incontinence. Symptoms of urgency incontinence include leaking moderate amounts of urine after feeling a sudden urge to urinate. Symptoms of stress incontinence include losing small amounts of urine after coughing and sneezing.

3. **C.** Older people with cognitive and physical impairments have a high likelihood of experiencing disability associated urinary incontinence, which is defined as the complaint of urinary incontinence in the presence of a functional inability to reach a toilet or urinal in time because of a physical or mental impairment.

4. **A.** This patient is demonstrating symptoms of stress urinary incontinence, which is the most common type of incontinence in women of child-bearing age, particularly if they have had multiple vaginal deliveries. First line treatment for stress incontinence is pelvic floor muscle exercises. Bladder training and timned voiding are not appropriate, as she is not experiencing urinary frequency or urgency. Antimuscarinic drugs are also not appropriate as they are used to treat urgency incontinence.

5. **A.** This woman is experiencing urgency urinary incontinence as evidenced by urinary frequency, nocturia, and a sense of urgency prior to leaking. The best initial treatment to recommend is bladder training, which involves scheduled toiletings with progressive voiding intervals; the use of urgency suppression strategies using relaxation and distraction techniques, self-monitoring, and use of reinforcement techniques. She has developed a maladaptive behavior of urinating frequently that will be helped with bladder training.

6. **B.** Vibegron is a β_3-adrenergic agonist. It is least likely to cause anticholinergic side effects.

7. **D.** Bethanechol can be used for overflow urinary incontinence (atonic bladder) if no contraindication exists.

8. **B.** Hyperglycemia may exacerbate polyuria. Optimizing blood glucose control is an item to address during diagnostic evaluation of urinary incontinence.

9. **D.** The correct dose of trospium IR is 20 mg at bedtime in patients with creatinine clearance less than 30 mL/min (0.50 mL/s). Immediate-release products can be crushed.

10. **A.** Oxybutynin patch should be applied twice per week (every 3-4 days), not once daily. Proper patient education is important, taking in consideration of the level of health literacy in this patient. Over-the-counter oxybutynin patch is less expensive than prescription drugs, mirabegron, and darifeancin. The patch formulation produces less dry mouth.

11. **B.** Urgency incontinence calls for treatment with an antimuscarinic agent.

12. **B.** Pelvic floor muscle exercises can be helpful for stress incontinence.

13. **C.** Timed toileting can be helpful in older adults with frailty. Nonpharmacologic interventions should be considered as first-line treatment.

14. **E.** Decline in estrogen level in postmenopausal women, history of childbirth, obesity, and age (postmenopausal) are risk factors for stress incontinence.

15. **C.** Mirabegon should be swallowed whole. Do not chew, cut, or divide.