Chapter 82: Urinary Incontinence

INTRODUCTION

- *Urinary incontinence* (UI) is loss of bladder control, leading to involuntary leakage of urine.

PATHOPHYSIOLOGY

- The urethral sphincter, a combination of smooth and striated muscles within and external to the urethra, maintains adequate resistance to the flow of urine from the bladder until voluntary voiding is initiated.
- Volitional and involuntary bladder contractions are mediated by activation of postsynaptic muscarinic receptors by acetylcholine. Bladder smooth muscle cholinergic receptors are mainly of the M_2 variety; however, M_3 receptors are responsible for both emptying contraction of normal micturition and involuntary bladder contractions, which can result in UI. Therefore, most pharmacologic antimuscarinic therapy is anti-M_3 based.
- Stimulation of beta-3 adrenergic receptors in the detrusor results in smooth muscle relaxation. β_3-agonists attenuate bladder contractility, which is useful for treatment of overactive bladder (OAB) and urgency incontinence.
- UI occurs as a result of overactivity or underactivity of the urethra, bladder, or both.
- Urethral underactivity is known as *stress UI* (SUI) and occurs during activities such as exercise, running, lifting, coughing, and sneezing. The urethral sphincter no longer resists the flow of urine from the bladder during periods of physical activity.
- Bladder overactivity is known as *urgency UI* (UUI) and is associated with increased urinary frequency and urgency, with or without urge incontinence. The detrusor muscle is overactive and contracts inappropriately during the filling phase.
- Urethral overactivity and/or bladder underactivity is known as overflow incontinence. The bladder is filled to capacity but is unable to empty, causing urine to leak from a distended bladder past a normal outlet and sphincter. Common causes of urethral overactivity include benign prostatic hyperplasia (see Chapter 80); prostate cancer (see Chapter 64); and, in women, cystocele formation or surgical overcorrection after SUI surgery.
- Mixed incontinence includes the combination of bladder overactivity and urethral underactivity.
- Functional incontinence is not caused by bladder- or urethra-specific factors but rather occurs in patients with conditions such as dementia or cognitive or mobility deficits.
- Many medications may precipitate or aggravate voiding dysfunction and UI (**Table 82-1**).

TABLE 82-1

Medications That Influence Lower Urinary Tract Function

Medications	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
Opioid 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.

CINICAL PRESENTATION

- Signs and symptoms of UI depend on the underlying pathophysiology (**Table 82-2**). Patients with SUI generally complain of urine leakage with physical activity, whereas those with UUI complain of frequency, urgency, high-volume incontinence, and nocturia and nocturnal incontinence.
- Urethral overactivity and/or bladder underactivity is a rare but important cause of UI. Patients complain of lower abdominal fullness, hesitancy, straining to void, decreased force of stream, interrupted stream, and sense of incomplete bladder emptying. Patients can also have urinary frequency, urgency, and abdominal pain.

TABLE 82-2

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

DIAGNOSIS

- A complete medical history, physical examination (ie, abdominal examination to exclude distended bladder, pelvic examination in women looking for evidence of prolapse or hormonal deficiency, and genital and prostate examination in men), and brief neurologic assessment of the perineum and lower extremities are recommended.
- For SUI, the preferred diagnostic test is observation of urethral meatus while the patient coughs or strains.
- For UUI, the preferred diagnostic tests are urodynamic studies. Perform urinalysis and urine culture to rule out urinary tract infection.
- For urethral overactivity and/or bladder underactivity, perform digital rectal examination or transrectal ultrasound to rule out prostate enlargement. Perform renal function tests to rule out renal failure.

TREATMENT

- Goals of Treatment: Restoration of continence, reduction in the number of UI episodes, and prevention of complications while minimizing adverse treatment consequences and cost.

Nonpharmacologic Treatment

- Nonpharmacologic, nonsurgical treatment options include behavioral interventions, external neuromodulation, anti-incontinence devices, and supportive interventions. Behavioral interventions (eg, lifestyle modifications, voiding schedule regimens, and pelvic floor muscle rehabilitation) are generally first-line treatment for SUI, UUI, and mixed UI.
- Surgery rarely plays a role in initial management of UI but can be required for secondary complications (eg, skin breakdown or infection). The decision to surgically treat symptomatic UI requires that lifestyle compromise warrant an elective operation and that nonsurgical therapy be proven undesirable or ineffective.

Pharmacologic Treatment

Bladder Overactivity: Urgency Urinary Incontinence

- The pharmacotherapy of first choice for UUI includes antimuscarinic agents and β_3-adrenergic agonists drugs, which antagonize muscarinic cholinergic receptors (**Table 82-3**).

TABLE 82-3

Dosing of Medications Approved for OAB or UUI

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Anticholinergics/Antimuscarinics					
Oxybutynin IR	Ditropan	2.5 mg twice daily	2.5–5 mg two to four times daily		Titrate in increments of 2.5 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 intervals; swallow whole
Oxybutynin TDS	Oxytrol		3.9 mg/day apply one patch twice weekly		Apply every 3–4 days; rotate application site
	Oxytrol for Women (OTC)				
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	
Tolterodine LA	Detrol LA		2–4 mg once daily	2 mg once daily in patients taking CYP3A4 inhibitors or those with renal/hepatic impairment	Swallow whole; avoid in patients with creatinine clearance ≤10 mL/min (0.17 mL/sec)
Trospium chloride IR	Sanctura		20 mg twice daily	20 mg once daily in patients age ≥75 years or creatinine clearance ≤30 mL/min (0.5 mL/sec)	Take 1 hour before meals or on empty stomach; patients age ≥75 years should take at bedtime

Trospium chloride ER	Sanctura XR		60 mg once daily	Avoid in patients age ≥75 years or creatinine clearance ≤30 mL/min (0.5 mL/sec)	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/sec) or moderate hepatic impairment; avoid in severe hepatic impairment	Swallow whole
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/sec); 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/sec) or moderate hepatic impairment; avoid in patients with ESRD or severe hepatic impairment	Swallow whole

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.

Oxybutynin

- **Oxybutynin immediate-release** (IR) is the oldest and least expensive treatment for UUI.
- Many patients discontinue oxybutynin IR because of adverse effects due to antimuscarinic effects (eg, dry mouth, constipation, vision impairment, confusion, cognitive dysfunction, and tachycardia), α-adrenergic inhibition (eg, orthostatic hypotension), and histamine H_1 inhibition (eg, sedation and weight gain).
- **Oxybutynin extended-release** (XL) is better tolerated than oxybutynin IR. Maximum benefits may take up to 4 weeks after dose initiation or escalation.
- **Oxybutynin transdermal system** (TDS) has similar efficacy but is better tolerated than oxybutynin IR presumably because this route avoids first-pass metabolism in the liver, which generates the metabolite thought to cause adverse events, especially dry mouth.
- **Oxybutynin gel** causes significantly less dry mouth than oxybutynin IR, but patients must be monitored for anticholinergic affects during long-term therapy, particularly frail patients.

Tolterodine

- **Tolterodine**, a competitive muscarinic receptor antagonist, is as effective as oxybutynin IR in efficacy outcomes with lower drug discontinuation rates.
- Tolterodine undergoes hepatic metabolism involving cytochrome (CYP) 2D6 and 3A4 isoenzymes. Therefore, elimination may be impaired by CYP 3A4 inhibitors, including **fluoxetine, sertraline, fluvoxamine**, macrolide antibiotics, azole antifungals, and grapefruit juice.
- Tolterodine's most common adverse effects include dry mouth, dyspepsia, headache, constipation, and dry eyes. The maximum benefit of

tolterodine is not realized for up to 8 weeks after starting therapy or dose escalation.

- **Tolterodine long acting** (LA) offers once-daily dosing and may also take up to 8 weeks after starting therapy or dose escalation to see maximum benefit.
- **Fesoterodine fumarate** is a prodrug for tolterodine and is considered an alternative first-line therapy for UI in patients with urinary frequency, urgency, or urge incontinence.

Other Pharmacologic Therapies for Urgency Urinary Incontinence

- **Trospium chloride IR**, a quaternary ammonium anticholinergic, was shown to be noninferior to oxybutynin IR but was associated with less dry mouth. It causes the expected anticholinergic adverse effects with increased frequency in patients age 75 years or older. An extended-release product is also available.
- **Solifenacin succinate** and **darifenacin** are second-generation antimuscarinic agents. Both have been shown to improve urinary symptoms and quality-of-life. Drug interactions are possible if CYP 3A4 inhibitors are given with solifenacin succinate or CYP 2D6 or 3A4 inhibitors with darifenacin.
- **Mirabegron** is a β_3-adrenergic agonist alternative to anticholinergic/antimuscarinic drugs for managing UUI. It has modest efficacy as compared with placebo. Hypertension, nasopharyngitis, urinary tract infection, and headache are the most common adverse effects. It is a moderate inhibitor of CYP2D6.
- Use of other agents, including tricyclic antidepressants, **propantheline**, **flavoxate**, **hyoscyamine**, and **dicyclomine hydrochloride**, is not recommended. They are less effective, not safer, or have not been adequately studied.
- A systematic review of 94 randomized controlled trials with antimuscarinic drugs for UUI showed similar, small benefits for all drugs studied. Selection of initial drug therapy depends on side-effect profile, comorbidities, concurrent drug therapy, and patient preference in drug delivery methods (**Table 82-4**).
- **Botulinum toxin A** temporarily paralyzes smooth or striated muscle. It is indicated for the treatment of detrusor overactivity associated with neurologic conditions and OAB.
- Adverse effects of botulinum toxin A include dysuria, hematuria, urinary tract infection, and urinary retention (up to 20%). Therapeutic and adverse effects are seen 3–7 days after injection and subside after 6–8 months.

TABLE 82-4

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

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

Urethral Underactivity: Stress Urinary Incontinence

- Treatment of SUI is aimed at improving urethral closure by stimulating α-adrenergic receptors in smooth muscle of the bladder neck and proximal urethra, enhancing supportive structures underlying the urethral epithelium, or enhancing serotonin and norepinephrine effects in the micturition reflex pathways.

Estrogens

- Historically, local and systemic **estrogens** have been the mainstays of pharmacologic management of SUI.
- A meta-analysis of 34 trials evaluating the use of local or systemic estrogen therapy on UI in postmenopausal women found that systemic administration of estrogen alone or in combination with progesterone resulted in UI worsening. There was some evidence that vaginal estrogen may improve UI, and reduce urgency and frequency.
- A 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.
- Based on the results of these analyses, only topical estrogen products should be used for treatment of UI or OAB in postmenopausal women.

α-Adrenergic Receptor Agonists

- Many open trials support the use of a variety of α-adrenergic receptor agonists in SUI. Combining an α-adrenergic receptor agonist with an estrogen yields somewhat superior clinical and urodynamic responses compared with monotherapy.
- Contraindications to these agents include hypertension, tachyarrhythmias, coronary artery disease, myocardial infarction, cor pulmonale, hyperthyroidism, renal failure, and narrow-angle glaucoma.

Duloxetine

- **Duloxetine**, a dual inhibitor of serotonin and norepinephrine reuptake indicated for depression and painful diabetic neuropathy, is approved in many countries for the treatment of SUI, but not in the United States. Duloxetine is thought to facilitate the bladder-to-sympathetic reflex pathway, increasing urethral and external urethral sphincter muscle tone during the storage phase.
- Six placebo-controlled studies showed that duloxetine reduces incontinent episode frequency and the number of daily micturitions, increases micturition interval, and improves quality-of-life scores. These benefits were statistically significant but clinically modest.
- Monitor patients taking concurrent CYP 2D6 and 1A2 substrates or inhibitors closely.
- The adverse event profile might make adherence problematic. Adverse events include nausea, headache, insomnia, dizziness, constipation, and dry mouth.

Overflow Incontinence

- Overflow incontinence secondary to benign or malignant prostatic hyperplasia may be amenable to pharmacotherapy (see Chapters 64 and 80).

EVALUATION OF THERAPEUTIC OUTCOMES

- Total elimination of UI signs and symptoms may not be possible. Therefore, realistic goals should be established for therapy.
- In the long-term management of UI, the clinical symptoms of most distress to the individual patient need to be monitored.
- Survey instruments used in UI research along with quantitating the use of ancillary supplies (eg, pads) can be used in clinical monitoring.
- Therapies for UI frequently have nuisance adverse effects, which need to be carefully elicited. Adverse effects can necessitate drug dosage adjustments, use of alternative strategies (eg, chewing sugarless gum, sucking on hard sugarless candy, or use of saliva substitutes for xerostomia), or even drug discontinuation.

See Chapter 101, Urinary Incontinence, authored by Eric S. Rovner, Jean Wyman, and Sum Lam, for a more detailed discussion of this topic.