Treating the Overactive Bladder

As the population ages, urinary incontinence is becoming more common. Pharmacologic treatment for the overactive bladder can be successful if correctly applied.

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Urinary incontinence (UI) is the involuntary loss of urine that constitutes a social or hygiene problem. Reported prevalence rates of UI vary considerably, depending on the population studied, the definition of UI and how the information is obtained. In people between the ages of 15 and 64, the prevalence of UI ranges from 1.5% to 5% in men, and from 10% to 30% in women. The prevalence of UI increases with age, but UI is not uncommon in younger age groups (e.g., pregnant, perimenopausal or postpartum women). It has been estimated that approximately 17 million Americans and more than 1.5 million Canadians suffer from UI. The incidence (or the percentage of new events per year) of UI is more difficult to ascertain; it also increases with age, and, in the U.S., has been reported to be in the range of 1% to 20% per year.

UI has an adverse effect on quality of life. The social stigma attached to UI means that many sufferers do not even report the problem to a healthcare provider. In addition, when the problem is reported, many physicians and nurses (lacking education in this area) fail to evaluate UI. As a result, this medical problem is vastly underdiagnosed and underreported.

Types of Urinary Incontinence

Classifying UI by clinical subtypes can help guide treatment (Table 1).
1. **Stress incontinence** is the involuntary loss of urine during coughing, sneezing, laughing, walking, straining or any other physical activity that increases intra-abdominal pressure. Stress incontinence occurs when there is an increase in the intra-abdominal pressure in the absence of a bladder contraction. The most common causes of stress incontinence are urethral hypermobility due to weakness of the muscular and fascial supports of the urethra and bladder, intrinsic sphincter deficiency (ISD), or a combination of both.

2. **Urge incontinence** is the involuntary loss of urine associated with a strong desire to void; it is frequently a result of bladder overactivity, but can also result from a hypersensitive bladder.

3. **Mixed incontinence** is a combination of stress and urge. Usually one of the symptoms predominates.

4. **Overflow** is the involuntary loss of urine associated with bladder overdistension. Overflow may be caused by an underactive or noncontracting bladder, or by an urethral obstruction, causing distension and overflow. Examples of this are bladder outflow obstruction, caused by benign prostatic hypertrophy (BPH) or a weak bladder from diabetes.

5. **Functional incontinence** is caused by factors outside the lower urinary tract, and is seen in elderly, physically or cognitively impaired individuals. Immobility may interfere with toileting, and may exacerbate incontinence.

6. **Unconscious or reflex incontinence** may occur without any warning or sensation, such as in neurologically impaired patients. Extraurethral incontinence (e.g., vesico-vaginal fistula) may be continuous. Total incontinence may be seen if the bladder capacity is extremely small and/or if the urethra is nonfunctional. Enuresis means any involuntary loss of urine, and, if it occurs during sleep, may be qualified as “nocturnal.”

### Table 1: Classification of Urinary Incontinence

- Stress
- Urgency
- Mixed
- Overflow
- Functional
- Unconscious or reflex
  - continuous, total
  - nocturnal enuresis


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### Bladder Overactivity

With today’s aging population, not only is incontinence becoming more and more common, but other lower-urinary tract symptoms may also be more prevalent. The lower urinary tract changes with age, even in the absence of disease. Bladder contractility, capacity and the ability to postpone voiding appear to decline with aging in both sexes. Elderly people often excrete much of their fluid intake at night, even in the absence of venous insufficiency, renal disease, heart failure or prostatism. These changes may explain the onset of symptoms such as urinary frequency, nocturia and urgency incontinence.

According to the International Continence Society (ICS), normal bladder function during filling and storage implies no significant rise in bladder (detrusor) pressure; this is termed a stable bladder. Overactive detrusor function indicates...
the presence of involuntary contractions on the filling cystometrogram. If the involuntary contractions are due to neurologic disease, the term “detrusor hyperreflexia” is used; if not, it is termed “detrusor instability.” Very recently, the terms have been simplified. Overactive detrusor function can be either idiopathic (non-neurogenic) or neurogenic. The terms “instability” and “hyperreflexia” are being dropped.

Bladder sensation can be categorized as normal, increased or hypersensitive; decreased or hyposensitive; or absent. Bladder capacity and compliance (a change in volume/a change in pressure) are measurements that can be derived from the cystometrogram (Table 2).

Functionally classifying voiding dysfunction as the failure to store or the failure to empty (popularized by Wein) simplifies the treatment approach. Storage failure (Table 3) is caused by bladder or outlet abnormalities, or a combination of both of these factors. Bladder abnormalities may include involuntary contractions, low compliance and hypersensitivity. Although in pharmaceutical trials most therapy for overactive bladders has been directed against involuntary contractions or decreased compliance, many patients with symp-
Clinically Managing the Patient with Bladder Overactivity

All patients with UI should undergo a basic evaluation that includes a history, physical examination and urinalysis. Measurement of postvoid residual urine (PVR) (by in- and out-catheterization or ultrasound) is also considered important, especially in patients with symptoms and signs of incomplete bladder emptying, neurologic disease or failure of previous medical or surgical therapy. Risk factors that are associated with such symptoms and signs should be identified, and attempts should be made to modify these factors.

Figure 1 illustrates the physician’s approach to the patient with overactive bladder symptoms. The basic approach is to initially manage the nonurologic causes, and then treat the bladder causes. Treatment may then be directed toward other factors (e.g., benign prostatic hyperplasia [BPH]), or may include medications and/or lifestyle and behavioral modifications (e.g., fluid restriction, avoidance of caffeinated foods and beverages). At any point, the patient may be referred to a specialist for additional evaluation, such as imaging, cystoscopy and urodynamics.

Pharmacologic Agents

Anticholinergics. The major portion of the neurohumoral stimulus needed for contraction of the bladder is the stimulation of postganglionic parasympathetic muscarinic (cholinergic) receptors on the bladder’s smooth muscle, caused by the release of acetylcholine from the preganglionic nerve endings. Most anticholinergics have antimuscarinic activity, but some have

toms of bladder overactivity do not manifest filling abnormalities on cystometrogram. Additionally, many patients with symptoms of bladder overactivity do not undergo cystometrograms, especially when treated in the primary-care setting. As a result, medication is frequently used solely for the symptoms of overactivity. The term “overactive bladder” simply means a condition in which the patient complains of the symptoms of urgency, frequency, nocturia, with or without urge incontinence.

Table 3

Failure to Store as an Explanation for Bladder Dysfunction

<table>
<thead>
<tr>
<th>Because of the Bladder:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrusor Hyperactivity</td>
</tr>
<tr>
<td>Involuntary contractions (which may be secondary to):</td>
</tr>
<tr>
<td>• Neurologic disease, injury or degeneration</td>
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<tr>
<td>• Bladder-outlet obstruction</td>
</tr>
<tr>
<td>• Inflammation</td>
</tr>
<tr>
<td>• Idiopathic</td>
</tr>
<tr>
<td>Decreased compliance (which may be secondary to):</td>
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<tr>
<td>• Neurologic disease</td>
</tr>
<tr>
<td>• Fibrosis</td>
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<tr>
<td>• Idiopathic</td>
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<tr>
<td>Detrusor Hypersensitivity</td>
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<tr>
<td>• Inflammatory</td>
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<td>• Infectious</td>
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<td>• Psychologic</td>
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<td>• Idiopathic</td>
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parasympathetic ganglionic blocking activity (i.e., outside the bladder) where specified.

Atropine is a naturally occurring antimuscarinic alkaloid of the Belladonna plant, and is available in both oral and parenteral forms. The oral 0.5 mg tablet is rapidly absorbed from the gastrointestinal (GI) tract, but its short half-life (2.5 hours) and diffuse effect on muscarinic receptors make it impractical. Synthetic analogues of atropine are more poorly absorbed, but have longer durations of action; they also have a ganglionic blocking effect because of the greater potency on nicotinic receptors. These agents are rarely used.6

Propantheline bromide is an inexpensive quaternary ammonium compound with ganglionic blocking and antimuscarinic activity. Dosage is 7.5 mg to 30 mg, administered three to five times daily. Propantheline bromide is a second-line drug used for the treatment of bladder instability.2 Methantheline has a higher ratio of ganglionic blocking activity. Other agents have sim-
Hyoscyamine has similar action to propantheline, while glycopyrrolate is another synthetic atropine-like drug that can be administered both orally and parenterally. These agents are, likewise, rarely used.

Side effects are due to the lack of selectivity of anticholinergics. Antimuscarinic side effects include narrow-angle glaucoma, obstructive or atonic diseases of the GI tract, and myasthenia gravis.6

Tolterodine is a relatively new antimuscarinic agent that, when tested in anesthetized cats, shows more in vivo selectivity for the bladder than for the salivary glands.7 In phase-three randomized trials, tolterodine showed efficacy in reducing the frequency of micturition and incontinent episodes, and in increasing bladder capacity. The main side effect of tolterodine is dry mouth.8 Dosage is 2 mg twice daily. Tolterodine was released in Canada about two years ago. A long-acting, once daily formulation of tolterodine has been shown to have a similar action, with a slightly better side-effect profile. It is not yet available in Canada.9

Musculotropic Relaxants. All of these agents relax smooth muscle in vitro, and all possess variable amounts of anticholinergic and local anesthetic properties. The amount of atropine-like activity in the clinical efficacy of these drugs is unknown.10 Side effects are common and are similar to those of anticholinergic agents. Dosage reduction is frequently necessary, and treatment drop-outs are common if used at the full dose.

Oxybutynin chloride has been shown to be superior to placebo in six randomized trials of middle-aged outpatients.2 Its efficacy compared to propantheline is suggested by two studies. It has also been shown to be equivalent to or better than placebo.2 Dosage is 2.5 mg to 5 mg, two to four times daily. Oxybutynin chloride has been recommended as first-line therapy for patients with detrusor instability, and has also been effective and well tolerated when instilled into the neurogenic bladders of patients with troublesome incontinence.2

A new long-acting once daily formulation of oxybutynin has recently been released in Canada.
It has been shown to have an equal efficacy to regular oxybutynin, but with a better side-effect profile. The dosage is 5 mg to 30 mg once daily.\(^\text{11}\)

*Dicyclomine hydrochloride* has similar properties to oxybutynin chloride, and two trials have shown its efficacy when compared to placebo.\(^\text{2}\) Dosage is 10 mg to 20 mg, three to four times daily.

*Flavoxate hydrochloride* is a tertiary amine with smooth-muscle relaxant properties and weak anticholinergic activity. Favorable clinical effects have been shown in some studies, but four randomized trials showed no significant benefit over placebo. Dosage is 200 mg three to four times daily.\(^\text{2}\)

**Tricyclic Antidepressants (TCAs).** These agents have multiple effects on the lower urinary tract. While the mechanisms of TCAs are not completely understood, such mechanisms may be a result of the agents’ sedative and antihistaminic properties. TCAs block the active transport of noradrenaline into the adrenergic nerve terminal, potentiating contraction of the bladder base and the proximal urethra (and possibly beta-receptor-induced relaxation of the bladder body). There may also be a direct inhibitory effect on the bladder muscle.\(^\text{7}\) TCAs are not recommended as first-line therapy.\(^\text{2}\)

*Imipramine hydrochloride* is useful alone or in combination with other anticholinergics, but the side effects may be additive. Dosage is 10 mg to 25 mg one to four times daily. *Doxepin* has also been used at 50 mg every hour of sleep +/- 25 mg every morning.

Side effects are commonly anticholinergic, but may include postural hypotension, fine tremor and cardiac arrhythmias.

**Alpha-adrenergic antagonists.** When parasympathetic decentralization occurs (e.g., in patients with sacral injuries), a sympathetic hyperinnervation or an alteration in the beta-receptor function may occur, with an exaggerated alpha-adrenergic response. In addition, the alpha response (rather than the beta response) has been demonstrated *in vitro* in the bladder dome muscle in patients undergoing operations for BPH. Clinical use of alpha-adrenergic antagonists has been reported in patients with neurogenic bladders.\(^\text{10}\)

**Calcium channel blocking agents.** The influx of extracellular calcium is important for detrusor muscle contraction, and can be blocked by these agents. Clinical reports on current drugs (e.g., verapamil) are limited in this regard, and patients commonly experience side effects.

**Antidiuretic hormone-like agents.** The synthetic antidiuretic hormone peptide analogue called 1-deamino-8-D-arginine-vasopressin has been used to treat nocturnal enuresis in both children and adults.\(^\text{12}\) This drug can be administered at bedtime by intranasal spray in doses of 10 µg to 40 µg, and suppresses urine production for seven to 10 hours. A number of studies have supported the use of DDAVP in patients with refractory nocturnal frequency and incontinence.\(^\text{13}\) Side effects are occasionally seen, and may include headache, rhinitis, nasal discomfort, epistaxis and abdominal pain. Water retention may be caused by overdosage.

**Reasons for the lack of efficacy of anticholinergic agents.** The most commonly used drugs for symptoms of bladder overactivity are not always effective, even if the patient complies with therapy. The reasons for this ineffectiveness are seen in Table 4.\(^\text{14}\) This incomplete patient response is spurring the search for improved drugs and new classes of drugs that can alter abnormal bladder behavior.

**Conclusions**

The prevalence of urinary incontinence and the frequency of lower-urinary-tract symptoms is...
increasing as the bulk of the population ages. Both types of urinary problems have a detrimental impact on the patient’s quality of life. Pharmacologic treatment for overactive bladder dysfunction may be successful if correctly applied. This may involve combining therapy with behavioral measures and lifestyle intervention, such as fluid alterations and Kegel exercises or urge suppression. Many drugs are available and should be used according to current guidelines. Since these drugs are not completely effective and have side effects (which may limit their use), alternatives and combinations of drugs may be necessary to improve lower-urinary-tract symptoms.

References