Introduction

In the last several years, multiple new “bladder medications” have received approval by the Food and Drug Administration. Most of these drugs are designed to treat patients suffering from detrusor overactivity. This chapter will review both old and new pharmacologic treatments for detrusor overactivity and stress urinary incontinence. This chapter will not offer a comprehensive review, but instead will focus on the practical advantages and disadvantages of the most commonly used medications. Before using the drugs mentioned in this chapter, practitioners should familiarize themselves in detail with the relevant clinical pharmacology.

Background: Normal Bladder Physiology

No pharmacologic agents offer pure selectivity for the lower urinary tract. Therefore, all medications designed to alleviate lower urinary tract symptoms have side effects caused by their activity in other organ systems. Understanding the normal physiology of bladder activity makes it easy to understand the drugs we use to treat bladder dysfunction.

The bladder is a muscular reservoir that rests in the retropubic space in an extra-peritoneal position. As urine fills the bladder, stretch receptors are activated. These receptors send impulses along pelvic nerve afferent fibers to the spinal cord and on to the sympathetic nucleus, where the hypogastric nerve is activated. The resulting impulse is carried down the hypogastric nerve to the bladder, where beta-adrenergic receptors cause bladder relaxation, and alpha-adrenergic receptors cause increased urethral smooth muscle tone. Urethral skeletal muscle tone is maintained through a different complimentary system that originates in the sacral spinal cord (in Onuf’s nucleus). Activity from Onuf’s nucleus is conveyed along the pudendal nerve, which releases acetylcholine to stimulate excitatory nicotinic receptors and contraction of the striated urethral sphincter.

When the bladder becomes distended to the point at which micturition should occur, activity from the pelvic nerve is carried up to the pontine micturition center, which causes activation of sacral parasympathetic neurons whose axons traverse the pelvic nerve and cause release of acetylcholine to stimulate excitatory muscarinic receptors and contraction of the detrusor. Of course, the cerebral cortex comes into play as well, because one should be able to suppress these stimuli if one’s social situation does not lend itself to micturition.

Drugs for Stress Incontinence

General Considerations

To date, there are no drugs with an FDA approved indication for the treatment of stress urinary incontinence. The medications listed below all
work by increasing either smooth or striated muscle tone within the urethra.

**Imipramine Hydrochloride**

Imipramine hydrochloride is a tricyclic antidepressant that produces systemic anticholinergic effects as well as direct inhibitory effects on bladder smooth muscle. This drug also has alpha-adrenergic effects in the urethra. Therefore, imipramine hydrochloride decreases bladder contractility and increases outlet resistance. Use of this drug for lower urinary tract symptoms is considered “off-label” by the U.S. FDA, so any practitioner contemplating use of this drug to alleviate bladder symptoms should be thoroughly familiar with potential side effects and relative precautions—some of which are discussed below.

The usual adult dosage is 25 mg to 75 mg once daily. Due to its propensity to cause drowsiness, this drug is taken at bedtime. Usually, patients should be started on 25 mg, and the dosage should be increased by 25 mg increments on a weekly basis (i.e., 25 mg the first week, 50 mg the second week, and 75 mg thereafter). The most common side effects include dry mouth, constipation, CNS effects, postural hypotension, fatigue, and generalized weakness. Patients who want to discontinue this drug due to unpleasant side effects should be weaned slowly (using the reverse of the weekly dosing schedule). Coming off this drug too quickly can produce confusion and disorientation.

Patients with moderate to severe nocturia and mild stress incontinence tend to be the best candidates for imipramine hydrochloride. Significant symptomatic improvements can be expected in approximately 30% of these patients.1

**Pseudoephedrine**

Pseudoephedrine is a common ingredient in over-the-counter cold remedies (e.g., Sudafed) that produces an alpha-adrenergic effect in the urethra. Use of this drug for stress incontinence is considered off-label. Potential side effects include blood pressure elevation, anxiety, insomnia, palpitations, and cardiac dysrhythmias.

The usual dosage is 30 mg to 60 mg QID in patients with mild stress incontinence. Moderate to severe stress incontinence usually does not respond to this medication. Stress incontinent patients who become dry on this medication should be screened for urinary retention via a post-void residual measurement. A recent Cochrane review suggests only weak evidence that alpha-agonists perform better than placebos in the treatment of stress urinary incontinence.2

**Duloxetine Hydrochloride**

A combination norepinephrine and serotonin re-uptake inhibitor, duloxetine hydrochloride produces increased skeletal muscle tone by activating receptors in Onuf’s nucleus. This drug is currently available in the U.S. for the treatment of depression; however, it is approved for use in Europe as either an antidepressant or treatment for stress urinary incontinence. After years of clinical trials in the U.S., duloxetine was recently removed from the FDA pipeline by its manufacturer. Therefore, use of this drug for stress incontinence in the U.S. will likely always be considered off-label. Interestingly, the dosage used in clinical trials for stress incontinence was actually higher than currently approved dosages for depression. The dosage for depression is 20 mg to 30 mg BID, and the most likely dosage for stress incontinence would be—if approved—40 mg BID. At that dosage, duloxetine reduced incontinence episode frequency by 59% compared with 40% in a placebo group. In those studies, the most common side effects of this drug seemed to be very much like those of serotonin re-uptake inhibitors—namely, nausea and diarrhea.3,4,5

**Drugs for Detrusor Overactivity**

**General Considerations**

Once the diagnosis of detrusor overactivity has been established, there are multiple pharmacologic treatment options. In the last few years, several new agents for the treatment of detrusor overactivity have been approved by the FDA. The clinical trials required for FDA approval typically pit the active molecule against a placebo. Unfortunately, there are very few randomized trials