THE CASE
A 57-year-old African American woman was being treated at our clinic for neurogenic urinary incontinence (UI). The UI, which occurred day and night, began 2 years earlier following a laminectomy of vertebrae C3 to C6 with spinal fusion of C3 to C7 for cervical spinal stenosis. The UI persisted despite physical therapy and trials of oxybutynin and imipramine. Since the surgery, the patient had also been experiencing chronic (debilitating) neuropathic pain in both legs, and the sensation of incomplete bladder emptying. She denied bowel incontinence or saddle anesthesia. Her prescription medications included hydrocodone-acetaminophen 7.5/325 mg every 6 hours as needed for pain and lisinopril 20 mg/d for essential hypertension. The patient’s body mass index (BMI) was 23.3.

A urine culture initially grew *Klebsiella pneumoniae*, which we successfully treated with ciprofloxacin. A urinalysis was unremarkable, and blood urea nitrogen and creatinine levels were within normal limits.

We started the patient on oral duloxetine 30 mg/d for her neuropathic pain. The patient hadn’t undergone a urologic evaluation before starting duloxetine, so no urodynamic studies or measurements had been conducted. At that point, we sent the patient to a urologist for an evaluation.

At a follow-up visit with one of our clinic providers <3 months later, the patient reported that the duloxetine was providing her with some pain relief and that she was “waking up dry” in the mornings and having fewer UI symptoms throughout the day, as well as at night. The patient denied any adverse effects such as nausea, gastrointestinal upset, weight changes, xerostomia, fatigue, insomnia, headaches, or dizziness. Duloxetine was titrated up to 60 mg/d for better control of her neuropathic pain. At the next follow-up visit at our clinic 3 months later, her UI was 80% to 90% improved and she was able to stop her opioid pain medications.

DISCUSSION
UI is a significant problem in the United States and around the world. For women, the prevalence of UI ranges from 15% to 69%; among men, the prevalence is 5% to 24%.1-3 The economic burden of UI includes both medical and nonmedical (eg, pads, diapers, laundry, and dry cleaning) care. The total national cost was estimated at $66 billion in 2007: $49 billion for direct medical costs, $2 billion for direct nonmedical costs, and $15 billion for indirect costs.4 And those costs are expected to increase 25% by 2020, mainly because of the aging population.

Risk factors for UI other than gender include advancing age, obesity, non-Hispanic white race, depression, hypertension, type 2 diabetes mellitus, neurologic disease, and...
functional limitations/general poor health. Comorbid depression and BMI >30, as well as the presence and duration of diabetes, increase the odds for developing UI.

Risk factors for women include hysterectomy, increasing parity, and delivery of at least one infant >9.5 pounds; the risk is the same for both vaginal and cesarean-section delivery. Specific risk factors for men include prostate cancer, prostate surgery, and prostate radiation.

Significant, chronic comorbidities of UI include depression and chronic pain. While quality of life is negatively affected by UI alone, the coexistence of depression and UI produces an additive negative effect on quality of life.

Types and treatment of UI

There are 5 types of UI: urge, stress, overflow, functional, and mixed.

- **Urge** incontinence is the leakage of urine following a sensation of sudden urgency to void.
- **Stress** incontinence is urine leakage associated with increased intra-abdominal pressure such as with coughing or sneezing and is typically associated with weakened pelvic floor musculature.
- **Overflow** incontinence is more common in men, and is typically caused by prostatic disease. The urethral outlet is obstructed leading to increased pressure within the bladder and subsequent leakage of urine.
- **Functional** incontinence is caused by physical or cognitive impairment leading to a decreased ability to get to a bathroom quickly enough to void.
- **Mixed** incontinence is when symptoms of stress and urgency incontinence are present.

There are 3 broad categories of treatment methods for urinary incontinence: behavioral, pharmacologic, and surgical. Behavioral interventions are subdivided into caregiver-dependent (prompted voiding, habit retraining, and timed voiding) and patient-directed (bladder training, pelvic floor muscle training, strategies for bladder control, education, and self-monitoring) techniques. Pharmacologic treatment typically consists of antimuscarinics (eg, oxybutynin, tolterodine, solifenacin) and tricyclic antidepressants (eg, imipramine). Injections of onabotulinumtoxinA into the detrusor muscle have also been shown to reduce the symptoms of urinary incontinence. Surgical options for treatment of UI include retropubic suspension, slings, and, in some instances, artificial urethral sphincters.

A novel treatment for neurogenic UI?

Despite the many treatments available for UI, none comprehensively addresses UI and its common comorbidities.

- **The role of duloxetine.** Normal micturition is regulated by the somatic nervous system and an autonomic reflex arc; the neurotransmitters serotonin and norepinephrine play an important role in the neural regulation of micturition and urinary continence. Duloxetine, alone or as an adjunctive treatment, is a potential novel therapy that treats 2 common comorbidities of UI—chronic pain and depression.

As a selective serotonin norepinephrine reuptake inhibitor (SNRI), duloxetine acts at the molecular level to block the reuptake of serotonin and norepinephrine from synaptic clefts. Specifically, the medication blocks the 5-hydroxytryptamine (5-HT) reuptake transporters, as well as the norepinephrine transporters, of pre-synaptic neurons. Thus, the concentrations of 5-HT and norepinephrine increase in the synaptic cleft.

Functionally, the accumulation of norepinephrine inhibits micturition by relaxing the detrusor muscle and constricting the urethral smooth muscle. In addition, a higher concentration of 5-HT at the neuromuscular junction leads to constriction of the external urethral sphincter.

Duloxetine has been shown to be effective for the treatment of stress and mixed urinary incontinence. This case suggests it may be useful for neurogenic urinary incontinence, as well.
THE TAKEAWAY

Duloxetine is a potential novel drug choice for the treatment of neurogenic UI. Its effects on serotonin and norepinephrine at the synaptic cleft and neuromuscular junction could provide relief for those who have not found relief from other therapies. Further research—particularly a prospective, randomized controlled trial—is needed to determine if duloxetine is, in fact, more than just a theoretical candidate to treat UI and, if so, the most effective dosing.

Offering duloxetine for the treatment of neurogenic UI would potentially address coexisting conditions—such as pain or depression—thus improving patient compliance and reducing health care spending. Before beginning therapy, urodynamic studies to identify the type of UI should be completed, or, at a minimum, post-void residual volume should be measured.

References