CASE REPORT

THE PATIENT

57-year-old African American woman

THE CLINICAL QUESTION

Could duloxetine, which we prescribed for our patient's neuropathic leg pain, also provide relief from her neurogenic urinary incontinence?

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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.[5-7] Comorbid depression and BMI >30, as well as the presence and duration of diabetes, increase the odds for developing UI.[7,8]

Risk factors for women include hysterectomy,[7] increasing parity, and delivery of at least one infant >9.5 pounds; the risk is the same for both vaginal and cesarean-section delivery.[6] Specific risk factors for men include prostate cancer, prostate surgery, and prostate radiation.[5]

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.[9]

Types and treatment of UI

There are 5 types of UI: urge, stress, overflow, functional, and mixed.[10]

- *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).[11] Injections of onabotulinumtoxinA into the detrusor muscle have also been shown to reduce the symptoms of urinary incontinence.[12] Surgical options for treatment of UI include retropubic suspension, slings, and, in some instances, artificial urethral sphincters.[13]

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.[14] 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 in the treatment of other types of UI, such as stress UI[15] and mixed UI.[16] Additionally, it was found to be effective when compared with placebo in women with overactive bladder syndrome[17] and in women with multiple sclerosis and depression.[18] However, we are

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.

not aware of any cases using duloxetine for the treatment of neurogenic UI.

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. JFP

Offering duloxetine for the treatment of neurogenic urinary incontinence would potentially address coexisting conditions, such as pain or depression.

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References

1. Markland AD, Richter HE, Fwu CW, et al. Prevalence and trends of urinary incontinence in adults in the United States, 2001 to 2008. *J Urol*. 2011;186:589-593.
2. Buckley BS, Lapitan MC; Epidemiology Committee of the Fourth International Consultation on Incontinence, Paris, 2008. Prevalence of urinary incontinence in men, women, and children—current evidence: findings of the Fourth International Consultation on Incontinence. *Urology*. 2010;76:265-270.
3. Gorina Y, Schappert S, Bercovitz A, et al. Prevalence of incontinence among older Americans. *Vital Health Stat 3*. 2014;1-33.
4. Coyne KS, Wein A, Nicholson S, et al. Economic burden of urgency urinary incontinence in the United States: a systematic review. *J Manag Care Pharm*. 2014;20:130-140.
5. Shamliyan TA, Wyman JF, Ping R, et al. Male urinary incontinence: prevalence, risk factors, and preventive interventions. *Rev Urol*. 2009;11:145-165.
6. Matthews CA, Whitehead WE, Townsend MK, et al. Risk factors for urinary, fecal, or dual incontinence in the Nurses' Health Study. *Obstet Gynecol*. 2013;122:539-545.
7. Danforth KN, Townsend MK, Lifford K, et al. Risk factors for urinary incontinence among middle-aged women. *Am J Obstet Gynecol*. 2006;194:339-345.
8. Lifford KL, Curhan GC, Hu FB, et al. Type 2 diabetes mellitus and risk of developing urinary incontinence. *J Am Geriatr Soc*. 2005;53:1851-1857.
9. Avery JC, Stocks NP, Duggan P, et al. Identifying the quality of life effects of urinary incontinence with depression in an Australian population. *BMC Urol*. 2013;13:11.
10. National Kidney and Urologic Diseases Information Clearinghouse. Urinary incontinence in women. Available at: http://kidney.niddk.nih.gov/KUDISEASES/pubs/uiwomen/UI-Women_508.pdf. Accessed January 2, 2015.
11. Ontario Medical Advisory Secretariat. Behavioural interventions for urinary incontinence in community-dwelling seniors: an evidence-based analysis. *Ontario Health Technology Assessment Series*. 2008:8. Available at: http://www.hqontario.ca/Portals/0/Documents/evidence/reports/rev_aic_ui_20081002.pdf. Accessed November 30, 2015.
12. Cox L, Cameron A. OnabotulinumtoxinA for the treatment of overactive bladder. *Res Rep Urol*. 2014;6:79-89.
13. Dmochowski RR, Blaivas JM, Gormley EA, et al. Update of AUA guideline on the surgical management of female stress urinary incontinence. *J Urol*. 2010;183:1906-1914.
14. Duloxetine. US National Library of Medicine: National Center for Biotechnology Information. 2015. Available at: http://pubchem.ncbi.nlm.nih.gov/compound/duloxetine. Accessed October 20, 2015.
15. Li J, Yang L, Pu C, et al. The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. *Int Urol Nephrol*. 2013;45:679-686.
16. Bent AE, Gousse AE, Hendrix SL, et al. Duloxetine compared with placebo for the treatment of women with mixed urinary incontinence. *Neurourol Urodyn*. 2008;27:212-221.
17. Steers WD, Herschorn S, Kreder KJ, et al; Duloxetine OAB Study Group. Duloxetine compared with placebo for treating women with symptoms of overactive bladder. *BJU Int*. 2007;100:337-345.
18. Di Rezze S, Frasca V, Inghilleri M, et al. Duloxetine for the treatment of overactive bladder syndrome in multiple sclerosis: a pilot study. *Clin Neuropharmacol*. 2012;35:231-234.