# Venlafaxine and Bladder Function

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**Background:** Occasional case reports describe urinary incontinence in patients taking the selective serotonin and norepinephrine reuptake inhibitor antidepressant venlafaxine.

**Objective:** In this study the authors investigated the possible effect of venlafaxine on urinary function in a series of 9 patients with urinary retention resulting from spinal cord lesions. They primarily sought to understand whether the reported venlafaxine-induced urinary incontinence was a specific drug-induced effect and, if so, whether venlafaxine might be an effective treatment of urinary retention.

**Methods:** During a 1-week baseline period, patients measured postvoiding residual volume through a catheter and recorded the number of micturitions within 24 hours. At the end of the baseline period, venlafaxine 75 mg extended-release on a once-daily evening administration schedule was added to their therapy for 1 week.

**Results:** None of the patients reported severe/uncontrollable side effects while taking venlafaxine. Extended-release venlafaxine (75 mg/day) significantly reduced the postvoiding residual volume and increased the micturition rate; the volume diminished on the first day of treatment and remained stable over the ensuing days.

**Conclusion:** These findings suggest that venlafaxine could be useful to improve voiding in patients with spinal cord disease.

Key Words: SNRI, venlafaxine, postvoiding residual volume, vesicosphincteric dyssynergia

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Venlafaxine is a selective serotonin and noradrenaline reuptake inhibitor (SNRI) used for its antidepressant action. It inhibits the uptake of biogenic amines and exerts its most potent action on serotonin, followed by norepinephrine and dopamine.<sup>1</sup> Conversely, venlafaxine has no significant activity on cholinergic receptors.<sup>2</sup> Its major metabolite, O-desmethylvenlafaxine, has a pharmacologic profile similar to venlafaxine.<sup>3,4</sup> Venlafaxine and O-desmethylvenlafaxine are cleared by the kidney and excreted in the urine after 48 hours.<sup>5</sup> The half-life of venlafaxine is  $5 \pm 2$  hours; the half-life of O-desmethylvenlafaxine is  $11 \pm 2$  hours. The extendedrelease (XR) formulation reaches a peak plasma concentration at 6 hours after dosing.<sup>4</sup>

In clinical trials, venlafaxine proved to be well tolerated in both depressed and anxious patients.<sup>6,7</sup> Unlike the classic tricyclic antidepressants, venlafaxine lacks the muscarinic– cholinergic receptor affinity<sup>3</sup> that is usually responsible for tricyclic-induced adverse effects, such as dry mouth, constipation, urinary retention, glaucoma, orthostatic hypotension, and sedation.

Nevertheless, several case reports unexpectedly described venlafaxine-induced anticholinergiclike side effects, including bilateral acute angle closure glaucoma,<sup>8,9</sup> dry mouth, and constipation.<sup>3</sup> In their clinical trials database analysis, Rudolph and Derivan<sup>3</sup> suggested that these anticholinergiclike events resulted, not from a direct cholinergic blockade, but from an adrenergic effect secondary to a noradrenaline reuptake blockade. Despite these general data showing a nonsignificant venlafaxine-induced urinary effect, others reported urinary incontinence in patients treated with venlafaxine.<sup>10</sup> Previous studies in animals showed that venlafaxine altered detrusor muscle contraction and bladder capacity.<sup>2</sup>

Prompted by these findings, we wondered whether the adverse urinary effects induced by venlafaxine might be exploited to improve urinary problems in patients with urinary retention from various causes, including spinal cord lesions. Spinal cord lesions result in incomplete bladder emptying caused by a combination of vesicosphincteric dyssynergia (detrusor contraction without pelvic floor relaxation) and decreased detrusor contraction during micturition resulting from the absence of supraspinal voiding control.<sup>11</sup>

Our aim in this study was to determine whether and how venlafaxine changes vesicosphincteric function in patients with urinary retention. To understand whether the reported venlafaxine-induced urinary incontinence was a specific druginduced effect, we administered oral venlafaxine for 1 week and measured postvoiding residual volume and micturition frequency in patients with documented spinal cord lesions who lack supraspinal voiding control.

# MATERIALS AND METHODS

#### **Patient Selection and Assessment**

From June 2004 to September 2004 we recruited for the study 9 consecutive patients (age,  $57 \pm 4$  years [SE]; 6 men and 3 women) attending our neurologic outpatient department for investigation of spinal cord lesions. Patients underwent medical interview, physical and neurologic examinations, electrocardiogram, neuroimaging, neurophysiologic testing,

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and laboratory tests. All eligible patients had a diagnosis of incomplete spinal cord lesion. They presented with spastic paraparesis, but were able to walk, and had sensory loss and lower limb hyperreflexia. To enter the study, patients had to have a stable neurologic lesion (at least 6 months after the spinal cord injury). Before entering the study, all patients underwent uroflowmetry, cystometry and a pressure/flow study that documented overactive neurogenic bladder and vesicosphincteric dyssynergia with secondary urinary retention. Patients were already trained to self-assess their postvoiding residual volume level with a sterile in-and-out Nelaton 6-Ch catheter (Porges-La Boursidiére, France), and the postvoiding residual volume was checked at outpatient visits. Only patients whose postvoiding residual volume remained higher than 80 mL were considered eligible to enter the study. Exclusion criteria were systemic contraindications for venlafaxine, previous successful treatment of urinary retention, nonstabilized spinal cord lesion, residual urine less than 80 mL/day, dementia and cognitive disorders, and a history of substance abuse or dependence.

All participants gave their written informed consent to the study and the local ethical committee approved the procedures.

### **Baseline and Treatment Period**

During a 1-week baseline period patients measured postvoid residual volume through a catheter and recorded the number of micturitions in 24 hours. At the end of the baseline period, venlafaxine 75 mg XR on a once-daily evening administration schedule was added to their therapy for 1 week. During the baseline and treatment periods, none of the patients was taking drugs acting on voiding function, and no new medications were allowed. Patients were not hospitalized and were seen at the outpatient service.

Measures of effectiveness were the reduction in postvoiding residual volume and the increase in micturition frequency. Patients were instructed to measure and record residual urine at the same time in the morning of each day. Postvoiding residual volume was measured in milliliters. Patients also had to report any adverse effects. Patients' daily ratings were tabulated by study researchers and mean weekly residual measures were calculated.

### Statistical Analysis

Unless otherwise indicated, all data are expressed as means  $\pm$  SE. Mean weekly micturition frequency scores before treatment and during venlafaxine administration were analyzed by the nonparametric Wilcoxon test. A repeated-measures analysis of variance (ANOVA) with "drug" and "time" as main factors was used to exclude a time-related bias and to confirm whether the reported effect was specifically related to venlafaxine treatment. *P* values less than 0.05 were considered to indicate statistical significance.

#### RESULTS

All 9 recruited patients entered the study and completed the 1-week baseline and treatment period. None reported severe adverse reactions during venlafaxine treatment.



**FIGURE 1.** Effects of venlafaxine on postvoiding residual volume. The graph shows changes in residual volume induced by oral venlafaxine in patients with spinal cord lesions. Venlafaxine significantly decreases postvoiding residual volume after the first day of treatment (P = 0.001 by ANOVA).

During the 1-week baseline period the mean postvoiding residual volume was  $231.55 \pm 43.91$  mL/micturition. Venlafaxine significantly reduced urinary residual volume. ANOVA showed a main effect of factor "drug" (F = 23.51; *P* = 0.001) and a nonsignificant effect of factor "time" (F = 0.33; *P* = 0.9). Postvoiding residual volumes diminished on the first day of treatment and remained stable during the ensuing 7 days (Fig. 1).

Once-daily XR venlafaxine significantly increased the frequency of micturition (predrug,  $2.5 \pm 0.2$  micturitions/day vs postdrug,  $4 \pm 0.4$  micturitions/day; P = 0.008, Wilcoxon test).

## DISCUSSION

In this study, oral venlafaxine (75 mg XR/day) effectively improved urinary retention resulting from vesicosphincteric dysfunction secondary to spinal cord lesion. The drug improved voiding by decreasing postvoiding residual volume and increasing micturition frequency. The venlafaxine-induced changes we observed in patients with spinal cord lesions suggest that previously reported venlafaxine-induced urinary incontinence<sup>10</sup> is a specific drug-induced effect.

Several hypotheses might explain how venlafaxine decreased postvoiding residual volume and increased the micturition frequency in patients with spinal cord lesions. Venlafaxine modulates serotonergic and noradrenergic systems<sup>1</sup> with receptors that are widely present in the peripheral and central nervous systems.

Venlafaxine presumably acts on voiding systemically through the plasma and not through the urine. Indeed, venlafaxine and O-desmethylvenlafaxine are cleared by the kidneys and excreted in the urine after 48 hours,<sup>4</sup> whereas in our patients postvoiding residual volume decreased already after 8 to 10 hours of treatment. Hence, we excluded a local effect on the bladder wall due to a direct effect of venlafaxine and/or its metabolites through the urine.

Because spinal cord lesions rendered our patients functionally devoid of central supralesional influences, we consider a descending effect improbable.

The hypothesis of an action through the plasma directly at the bladder level could also be excluded. Indeed, a study in vitro, using animal detrusor strips exposed to venlafaxine, showed that venlafaxine decreased contraction of detrusor strips and increased sphincter contraction,<sup>2</sup> whereas in our study the decrease in postvoiding residual volume suggests that, during micturition, venlafaxine does not alter bladder contraction.

Current knowledge and our findings in this study therefore suggest that venlafaxine acts at the spinal level and modulates bladder detrusor muscle contraction through the segmental loop. The main regions that might be involved are the lumbosacral sympathetic and parasympathetic autonomic nuclei, as well as the urethral sphincter motor nucleus (the Onuf nucleus). Theoretically, venlafaxine could modulate the lumbosacral spinal region through 2 possible mechanisms. Venlafaxine could increase detrusor muscle contraction without altering vesicosphincteric dyssynergia, concordantly our patients reported an increase in micturition rate. Supporting this hypothesis, Burgard et al<sup>12</sup> reported that spinal 5HT1A receptor activation causes bladder contraction. An other possibility is that venlafaxine promotes bladder contraction by improving the synaptic gain of the micturition reflex. Hence, venlafaxine probably improves voiding by reestablishing the synergism between detrusor contraction and pelvic floor inhibition.

Another SNRI similar to venlafaxine that has been reported to modulate voiding function is duloxetine. A clinical trial with patients with urinary stress incontinence suggested that duloxetine might be used to control voiding dysfunction. During bladder filling, duloxetine increases bladder capacity by inhibiting detrusor muscle contraction and increases the outer sphincter activity, whereas during micturition duloxetine produces a large-amplitude bladder contraction simultaneously inhibiting the sphincter.<sup>13</sup>

To our knowledge, duloxetine was not previously studied in overactive bladder due to spinal cord lesion. Accordingly, our data cannot be directly compared with previous studies with duloxetine. However, Thor<sup>13</sup> reported that duloxetine promotes bladder–sphincter synergy, which supports our findings with venlafaxine.

Because our patients reported that micturition frequency increased and postvoiding residual volume decreased after venlafaxine, we suggest that venlafaxine acts during the micturition contraction phase. In this way it might reestablish the synergism between detrusor contraction and pelvic floor inhibition. Large, randomized, double-blind studies using urodynamic evaluations are needed to confirm our preliminary results.

In conclusion, venlafaxine appeared to reduce postvoiding residual volume in patients with spinal cord lesion. This effect may be due to a decrease of vesicosphincteric dyssynergia, probably by acting directly on 5HT1 subtype receptors and indirectly on  $\alpha$ -1 adrenoreceptors.

If confirmed in further studies, our data suggest that in patients with vesicosphincteric dyssynergia, venlafaxine could be an interesting new therapeutic tool to reduce postvoiding residual volume.

Finally, it should be noted that in patients with voiding dysfunction, venlafaxine needs to be used with caution because it could induce urinary incontinence.

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