Sertraline and Venlafaxine-Induced Nocturnal Enuresis
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ABSTRACT:
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Nocturnal enuresis is defined as the involuntary discharge of urine after the age of expected continence that occurs during sleep at night. Although there are a few reports in adults for nocturnal enuresis associated with serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), the mechanism or frequency of this side effect have not been identified yet. We report here a case of nocturnal enuresis associated with both sertraline and venlafaxine in different major depressive episodes in an adult patient that resolves after the discontinuation of the medications and continuation with escitalopram. To our knowledge, in literature there have been no reports about nocturnal enuresis caused by those two agents in the same patient. This case is discussed in detail for the recurrence of nocturnal enuresis, the importance of detailed assessment of even rare side effects and for their possible mechanisms.

Keywords: nocturnal enuresis, venlafaxine, sertraline, depression

INTRODUCTION
Nocturnal enuresis due to selective serotonin reuptake inhibitors (SSRIs) is a rare but disturbing side effect that may result in discontinuation of the treatment. Although several studies suggest that serotonin (5HT) and norepinephrine (NE) reuptake might be the reason for the dysfunction of the lower urinary tract, the mechanism still remains unclear1,2. In the literature, there are only a few case reports about enuresis with SSRIs in adults that are found to be associated with paroxetine, sertraline, and citalopram1-3,4. Venlafaxine, which is a serotonin norepinephrine reuptake inhibitor (SNRI), is also reported for nocturnal enuresis in 4 publications1,2,5,6. The majority of the cases are reported as dose-dependent and defined for only one SSRI or SNRI side effect1-6.

In this report, a case is described with nocturnal enuresis that developed with both sertraline and venlafaxine in lower doses during different episodes and resolved after discontinuation of the medication. To our knowledge, this is the first such case that was reported in the literature.

CASE
The patient is a 21-year-old male who presented to our outpatient clinic with the diagnosis of major depressive disorder. This was not the first episode, as he described another episode developed about two years earlier, and sertraline 50 mg/day had been initiated. However, after a month he discontinued his medication himself
due to the occurrence of nocturnal enuresis, and he never experienced enuresis again. Although his depressive symptoms continued for about 6 months, he did not use any medication during that episode. Two years later, in the current episode, he was firstly prescribed venlafaxine 37.5 mg/day for four days, then increased to 75 mg/day, but nocturnal enuresis occurred again within a month with a frequency of 4 nights a week, so that he could not continue the medication. He was not taking any drugs during the visit to our clinic, and after he discontinued venlafaxine, enuresis completely stopped within a week. We decided to start escitalopram 5 mg/day and increased to 10 mg/day after four days for his depression. The patient was also referred to urology and neurology clinics, but all his examinations, including urinalysis, ultrasonography, electroencephalography (EEG), were normal. After a month, his depression had subsided and he had no complaints about nocturnal enuresis.

**DISCUSSION**

We report a case of nocturnal enuresis associated with both sertraline and venlafaxine for the same patient in lower doses. Enuresis resolved after the cessation of medication and did not occur with escitalopram. The mechanism of nocturnal enuresis due to antidepressants still remains unclear and complicated. Reports are contradictory about whether this side effect is due to the central nervous system or receptors on the bladder muscles. Human bladder muscles have three different serotonin (5-HT) receptor sites, 5HT-4, 5HT-7 and 5HT1A. 5HT-4 and 5HT-7 are excitatory receptors for acetylcholine which is suggested to be related with dose-dependent effects of sertraline in nocturnal enuresis.5HT-4 agonists like cisapride are known to increase the urination frequency, and SSRIs may have a similar effect. It has also been shown that spinal 5HT1A receptor activation would increase bladder contraction at spinal level. On the other hand, sertraline is known to have some α-adrenergic blockade and dopamine reuptake inhibition properties in the central nervous system that can lead to urinary incontinence by decreasing internal bladder sphincter tone. Venlafaxine was the other medication that caused nocturnal enuresis in our patient. Venlafaxine is an SNRI that inhibits the uptake of serotonin, norepinephrine and dopamine. Previous animal studies showed that venlafaxine might alter the contraction of detrusor muscle and bladder capacity. Inghilleri et al. reported in 9 patients that venlafaxine might be efficacious in patients with urinary retention resulting from spinal cord lesions by reducing the post-voiding residual volume and increasing the urination rate. In the same study, they suggested that venlafaxine was effective at spinal level and modulated bladder detrusor muscle contraction through the segmental loop. In another study, Polimeni et al. reported a case characterized by the occurrence of urinary incontinence with venlafaxine but not with sertraline and suggested a possible relation with noradrenergic mechanism. However, our case is in contrast to this finding, considering other mechanisms.

Our patient had nocturnal enuresis with both sertraline and venlafaxine but not with escitalopram. Although it is difficult to describe the etiology with only one case, this situation leads us to consider the similarities and differences in the patterns of these drugs. Firstly, in previous cases, antipsychotic-induced enuresis was explained by decreased dopamine transmission in the basal ganglia or an imbalance between dopamine and norepinephrine within the basal ganglia and venlafaxine and sertraline both have some dopaminergic effects in the central nervous system. Venlafaxine weakly inhibits the reuptake of dopamine, and recent evidence shows that the norepinephrine transporter transports some dopamine as well, and dopamine is inactivated by norepinephrine reuptake in the frontal cortex. Therefore, venlafaxine is suggested to increase dopamine neurotransmission in this part of the brain. Sertraline also has some ability to block the dopamine reuptake pump (dopamine
transporter), which may increase dopamine neurotransmission\(^\text{16}\). In a recent study, Kiatichi et al. have reported the increase of dopamine in the nucleus accumbens and striatum of rats caused by sertraline\(^\text{17}\). Secondly, sertraline and venlafaxine may both increase the urination frequency, which may be another reason for nocturnal enuresis\(^\text{12,8}\).

Escitalopram has some properties that differ from venlafaxine and sertraline for their receptor affinity. Escitalopram is extremely selective for serotonergic transport proteins when compared with other antidepressants such as fluoxetine, paroxetine, fluvoxamine, and sertraline. Besides, escitalopram has little or no binding affinity for many receptor or binding sites tested in vitro, including \(\alpha\)-adrenergic (\(\alpha_1\)) receptors, muscarinic (M1) receptors, and histamine (H1) receptors\(^\text{18}\). In contrast to the dopaminergic effects of sertraline and venlafaxine, which might be the underlying mechanism of enuresis, escitalopram has no effect on dopamine uptake and also has no or very low affinity for serotonergic (5-HT1-7) receptors found on bladder muscles, which might be another reason for the non-occurrence of nocturnal enuresis\(^\text{16}\).

The main limitation of this case report is that the results cannot be generalized due to the presentation of a single case. In this case, we highlight that nocturnal enuresis may be a serious side effect resulting in the discontinuation of the medication, which may be more frequent than we expect: hence, clinicians should be aware of all side effects. Nocturnal enuresis may be a recurrent symptom both for SSRIs and SNRIs. Therefore, further research is needed to elucidate the frequency, recurrence, and etiology of nocturnal enuresis to define a treatment process.

**References:**
