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## VENLAFAXINE WITHDRAWAL SYNDROME

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### SUMMARY

Dual-action antidepressants serotonin–norepinephrine reuptake inhibitors (SRNIs) are widely used to treat depression. Owing to its efficiency and safety, venlafaxine holds a prominent place in this group of depressants. Abrupt venlafaxine discontinuation involves a high risk of withdrawal syndrome. Mechanism of its development is similar to that of selective serotonin reuptake inhibitors (SSRIs), but of higher intensity. Venlafaxine withdrawal symptoms may include several somatic symptoms as well as several psychiatric symptoms. In some cases, symptoms may look like a stroke. A treatment option is re-inclusion of venlafaxine or a SSRI antidepressant.

The paper presents the case of a 70-year-old patient who discontinued of her own accord to take venlafaxine, which she had been taking regularly at a daily dose of 225 mg for more than a year. A few hours after taking the last dose, withdrawal syndrome occurred with severe symptoms resembling a stroke. The patient was examined by a neurologist and the CT and laboratory parameters showed no irregularities. Diagnosis was made after psychiatric observation. Venlafaxine, 150 mg per day, was prescribed, the symptoms disappeared relatively quickly, and the patient fully recovered.

Withdrawal syndrome is a real risk for each venlafaxine treated patient. The possibility of its occurrence should be always kept in mind and patients should be timely informed about it. In this way, the risk of venlafaxine withdraw syndrome could be reduced, unnecessary stress to patients prevented and the costs of medical treatment lowered.

**Key words:** venlafaxine – withdrawal syndrome – dual-action antidepressants

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### INTRODUCTION

Venlafaxine is a widely applicable dual-action antidepressant from the serotonin–norepinephrine reuptake inhibitor class (SRNIs). At lower doses (up to 150 mg) it acts as a serotonin reuptake inhibitor, at doses from 150 to 300 mg it is a dual-action antidepressant, while at higher doses it also acts on the dopamine and neurotransmitter systems. Its good therapeutic effect, higher therapeutic potentials compared to SSRI and its favorable side effect profile (Golden et al. 2000, Benazzi et al. 1998, Gutierrez et al. 2003) make venlafaxine one of the most prescribed antidepressants today. According to its pharmacokinetic characteristics, venlafaxine is a short half-life antidepressant (5 hours+/- 2 hours). In the case of sudden discontinuation of venlafaxine treatment, this fact may, together with the effect of dual uptake inhibition, raise a significant risk of developing a severe withdrawal syndrome (Fava et al. 1997, Parker et al. 1998). Mechanism of the withdrawal syndrome development is unknown but is associated with electrophysiological changes in brain, particularly 5-HT receptors. The mechanism is thus of the same nature as the withdrawal syndrome associated with SSRIs, but the effect may be stronger in the case of venlafaxine. Withdrawal syndrome can occur in patients who have abruptly discontinued the use of venlafaxine as well as in patients who have missed one venlafaxine dose (Haddad et al. 2001) or in cases of too rapid dose reduction (Fava et al. 1997). Abrupt discontinuance of

venlafaxine may lead to a withdrawal syndrome, which usually lasts 3 days (Reeves et al. 2003).

Venlafaxine withdrawal symptoms may include somatic symptoms such as irritability, headache, nausea, sweating, restlessness, elevated blood pressure, paresthesia and vertigo. Psychiatric symptoms may include dysphoria, visual and auditory hallucinations, delirium, weird and bizarre dreams, impaired concentration, agitation, worsening of depression, electric shock-like sensations and transient narcolepsy-cataplexy (Fava et al. 1997, Haddad et al. 2001, Parker et al. 1998, Reeves et al. 2003). Studies of Haddad et al. 2001, Reeves et al. 2003, reported cases of venlafaxine withdrawal symptoms that may look like a stroke.

There are several options to treat venlafaxine withdrawal syndrome. A venlafaxine dose prior to discontinuation could reverse withdrawal symptoms and fluoxetine or some other SSRI can suppress symptoms (Haddad et al. 2001).

### CASE REPORT

Female patient, 70 years old, married, no children, retired school teacher. The patient was always the dominant partner in her marriage, resolute, with an authoritative and rigorous approach to her job. She was mainly physically fit, with occasionally elevated blood pressure and blood fat levels. She took no medication for the said disturbances and had her blood pressure and lipidogram controlled only sporadically by her general practitioner.

The first psychiatric disturbances started fourteen years ago with the clinical picture of a depression anxiety disorder (F 41.2). Anxiety symptoms such as tension, nervousness, insomnia interchanged with symptoms of depression. She complained of apathy, loss of energy and initiative, but no depressive disorder was diagnosed because her everyday functioning was not affected. The patient periodically took anxiolytics over subsequent seven years and they had a good effect. The first antidepressant (fluoxetine) was prescribed in 2004 during the first diagnosed depressive episode (F32.1).

The first major depressive episode occurred in 2006. The patient complained of severe hypobulia, depressiveness, inertness, and was especially affected by the decline in everyday functioning. Treatment with several antidepressants did not have the expected effects (fluvoxamin, mirtazapine, escitalopram). Antidepressants were combined with anxiolytics (alprazolam, diazepam) and a hypnotic (nitrazepam).

Venlafaxine therapy was introduced towards the end of 2007 at a daily dose of 150 mg (2x75 mg), along with mirtazapine 30 mg in the evening and alprazolam as needed. After six months of therapy and moderate therapeutic effects, venlafaxine dose was raised to 225 mg, with 30 mg mirtazapine in the evening. This therapy led to appreciable improvement of the patient's mental state in two subsequent months. Satisfactory remission was achieved and the patient largely resumed her everyday activities. This state was unchanged until the end of 2009; the patient was in stable remission. The patient took venlafaxine regularly (225 mg/day), while mirtazapine was gradually down-titrated and then discontinued. She periodically took alprazolam 0.25 mg in the evening.

At the beginning of 2010, the patient suddenly stopped taking venlafaxine without consulting her psychiatrist. She decided to discontinue venlafaxine therapy because she had been feeling well for two years. Later on, she said that she did it because her husband was "very sick" (cardiac ailment) and she wanted to help him with her "healthy condition".

Problems started in the evening hours, as a sudden onset of weakness, several hours after the last dose of venlafaxine. The patient could not walk straight, was swerving from side to side and got terrified. Her blood pressure was elevated (160/100) and pulse was 100 beats per minute. She soon started to sweat, felt nausea, palpitations and heat waves. A niece brought her to the ER unit. After examination, the neurologist diagnosed potential stroke or transient ischemic attack (TIA). Blood pressure rose additionally to 180/110, pulse to 110/min. Laboratory findings were generally normal, body temperature slightly elevated - 37.5 °C. Brain CT scan was normal for the patient's age. As the patient was treated for depression over several years, the possibility of deliberate self-poisoning with drugs was considered. Diazepam was administered through intravenous infusion. Psychiatric examination did not

reveal greater irregularities in the patient's mental state. Her physical condition gradually improved though she still walked unsteadily and had vertigo and heat wave sensations. On the following day, she was moved to the psychiatric unit. It was established that the patient of her own accord discontinued taking venlafaxine at the medium high dose of 225 mg /day, so we suspected development of a withdrawal syndrome after abrupt drug cessation. Venlafaxine 150 mg was prescribed in combination with alprazolam 1.5 mg/day. The patient fully recovered in the following 24 hours. Psychological remission continued. After 3 months, venlafaxine was gradually withdrawn from therapy in such a way that the dosage was weekly reduced by 75 mg; the patient was given 37.5 mg venlafaxine in the last week. There were no withdrawal reactions to gradual discontinuation of venlafaxine. Since then, the patient has been taking lower doses of alprazolam from time to time and as needed.

## DISCUSSION

Withdrawal syndrome may occur after intentional or unintentional discontinuation of venlafaxine therapy. In our case, the patient discontinued taking venlafaxine at a daily dose of 225 mg at her own discretion and a severe withdrawal syndrome developed. Clinical manifestations resembled stroke symptoms as described by Haddad et al. (2001). The patient was initially diagnosed with potential stroke, transient ischemic attack (TIA) or drug ingestion in our ER, as well as by the neurologist. All parameters, including brain CT and laboratory blood tests, were normal, with the exception of elevated blood pressure and pulse. Proper diagnosis of venlafaxine withdrawal syndrome due to abrupt discontinuation of therapy was made in the psychiatric unit. Symptoms appeared within a few hours upon drug cessation, which was probably caused by the short half-life of venlafaxine (5 hours +/-2 hours) (Fava et al., 1997). Symptoms were of severe intensity, the patient ended up in the ER, was examined by several consulting specialists, all of which caused considerable distress to the patient as well as costs to the hospital and the health system. At her own request she was observed in the psychiatric unit, though no significant psychiatric side effects were noticed. According to the authors' recommendations (Pinzani et al. 2000), venlafaxine therapy was prescribed again, at a daily dose of 150 mg. Problems disappeared within two days after abrupt discontinuation of therapy and did not reappear until full recovery. Based on experience, very slow down-titration of venlafaxine was applied in further treatment. This case has shown that it is essential to know that withdrawal syndrome symptoms can develop after abrupt discontinuation of venlafaxine; their intensity may range from mild to severe. The experience gained from this case will help recognize similar events in the future and thus reduce unnecessary stress to patients as well as the costs of medical treatment.

## CONCLUSION

Besides its beneficial effects, daily venlafaxine therapy can also have adverse effects in terms of a withdrawal syndrome, which was the case of our patient. Diversity of clinical symptoms similar to brain stroke resulted in extensive treatment and unnecessary costs. Findings showed no irregularities, and the correct diagnosis was made on the basis of anamnestic data. Psychiatric interventions resulted in fast recovery. Withdrawal syndrome is a real risk for each venlafaxine treated patient and therefore should be constantly kept in mind. Patients should be timely informed of its potential occurrence.

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