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# Venlafaxine and Serious Withdrawal Symptoms: Warning to Drivers

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## Abstract

Venlafaxine is a widely used serotonin- and norepinephrine-reuptake inhibitor-type antidepressant that causes serious adverse effects in at least 5% of cases. Serious withdrawal symptoms may occur within hours of cessation or reduction of the usual dosage and may affect motor and coordination skills to such a degree that patients should be explicitly urged either to adhere to a strict medication routine or not to drive a car. Recent clinical evidence about withdrawal symptoms is presented that may indicate incidents in noradrenergic activity irrespective of dosage.

### Objective

To present clinical information and a brief review of severe venlafaxine withdrawal symptoms that may occur within hours after cessation and affect the ability to drive a motor vehicle or use heavy or dangerous machinery.

### Method

Review of own and third-party clinical records. Search in PubMed and other databases with terms: venlafaxine, discontinuation, withdrawal, syndrome, serotonin, noradrenaline, noradrenergic, serotonergic, seizures, epilepsy.

**Keywords:** Venlafaxine, withdrawal, discontinuance syndrome, serotonin, adrenaline, seizures, drivers

## Serotonin, Noradrenaline Withdrawal

Venlafaxine hydrochloride (*Effexor*, *Dobupal*) is a phenylethylamine-derivative antidepressant and anxiolytic agent that acts as a serotonin- and noradrenaline-reuptake inhibitor (SNRI). It is used primarily in major depressive disorder, with labeled uses including generalized anxiety disorder and social phobia. Nonlabeled uses include depressive symptom remission, obsessive-compulsive disorder, and chronic pain syndromes.

Most selective serotonin-reuptake inhibitors (SSRI) and SSNRIs are reported to cause serious adverse effects in approximately 5% of patients, according to its manufacturer.[1] Venlafaxine is no exception. Among the adverse effects are a number of withdrawal symptoms that form “discontinuance syndromes,” sometimes mistakenly identified with what Sternbach in 1991 proposed as the “serotonin syndrome”.[2]

Venlafaxine's half-life is only 4 hours. Its primary metabolite, O-desmethylvenlafaxine, has a half-life of 10 hours. In the past 10 years, a number of clinical reports of severe venlafaxine withdrawal symptoms have been published, and for the most part these effects are duly reflected in generally available information. Widely consulted drug information services, such as Medscape DrugInfo, American Hospital Formulary Service Drug Information, and First DataBank, list the following withdrawal symptoms as "serious": agitation, anorexia, anxiety, confusion, impaired coordination, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting.

Patient hand-outs contain several useful warnings and physicians know that, because any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that venlafaxine does not adversely affect their ability to engage in such activities. Venlafaxine is structurally similar to phencyclidine and thus should not be discontinued abruptly. If the drug has been administered for longer than 1 week, the dose should be tapered over 7 to 10 days to prevent a withdrawal syndrome (headache, nausea, dizziness, insomnia, and nervousness).[3]

However, little mention is found of the possibly severe effects of abrupt discontinuation or postponing ingestion of the daily dose for *as little as 8 to 12 hours*. Although a patient may have established that taking the drug does not noticeably affect the ability to drive a car or operate machinery, *taking the drug in the evening if it is usually taken in the morning or forgetting to take the daily dose just once* may induce sudden and severe disturbances in physical and mental condition that most definitely can impair normal functioning.

## Recent Case Histories: Withdrawal Effects Are Not Dose-Dependent

### Case 1: Standard Dose

Female, white, age 35, no other pathologies, diagnosed for major depressive disorder with anger attacks. Treated with extended-release venlafaxine 150 mg for 4 months with concurrent psychotherapy, with positive results: Beck's Depression Inventory score reduced from 38 to 14; functionality restored.

The patient ran out of medication on a Thursday and could not get in touch with her doctor until the next Monday. On Friday, only 12 hours after the usual time of taking the medication, she felt a noticeable change in mood, dizziness, and nausea. She experienced a sensation in her head as if electrical discharges "popped" and could not concentrate to the extent that she was unable to drive her car back from where she had gone. By Friday evening (18 hours after cessation), the "popping" in her head had become worse and she vomited after dinner. Depression symptoms reappeared acutely, and she could not stop crying. At first, she did not equate these symptoms to the missed dose of venlafaxine, but thought she might have contracted the flu. However, the symptoms continued and intensified over the weekend and only reduced when, on Monday, she started again on venlafaxine. She was inadvertently given the lower dose of 75 mg, which did not quite restore her mood to the previous level, although the "electrical popping" sensation in her head stopped and the nausea was reduced.

### Case 2: High Dose

(Provided by J. Garcia Campayo, MD, PhD, Dept of Psychiatry, Miguel Servet Hospital, University of Zaragoza, Spain)

Female, white, age 43, first diagnosis of major depressive disorder of moderate intensity; maternal history of depressive disorder. Successfully treated with 225 mg of venlafaxine (75-75-75) for 12 months with no adverse effects. The patient decided she could do without the medication and stopped taking it abruptly.

Withdrawal effects appeared within a day and included headaches, dizziness, and instability, with a sense of losing balance (although she did not actually fall down), sense of sparks and electrical discharges in her head, and intense anxiety. When treatment at the original level was reinstated and progressively reduced over a period of 2 weeks, the symptoms disappeared.

### Case 3: Low Dose

(Provided by N. Mjellem, MD, PhD, CEO World Federation of Biological Psychiatry, Oslo, Norway)

Physician (psychiatrist), female, white, age 54, major depressive disorder (recurrent). Took 37.5 mg venlafaxine daily for 3 weeks. Experienced side effects while taking the low doses of the medication, such as aggressive and paranoid behavior after limited consumption of alcohol, frequent headaches, and tinnitus. The last symptom made her work situation difficult, so she tapered the medication at 18.75 mg over a 2-week period. Neurologic symptoms appeared during the tapering phase, including lasting severe dizziness and short, intense feelings of electrical currents in her head, causing disorientation.

The symptoms disappeared, only to reappear 2 weeks after termination was complete and persisted for some weeks more.

These cases illustrate 2 important aspects of venlafaxine medication that warrant specific warning to patient and physician:

1. Several of the documented withdrawal effects do not fit with a “serotonin-discontinuance syndrome,” but point to a “noradrenaline-mediated withdrawal syndrome.”
2. Venlafaxine withdrawal symptoms can be severe. Even a relatively short delay in taking the daily dose could severely impair motor skills.[4–8] At present this is insufficiently reflected in patient handouts and the physician may not sufficiently point out the need for a strict adherence to a fixed medication routine.

## As regards 1: A Role for Noradrenaline

Sternbach's review and interpretation of the data concentrated on a toxic and potentially fatal condition that commonly results from the interaction between serotonergic agents and monoamine-oxidase inhibitors. Later reports indicate that co-administration of other psychotropic and nonpsychotropic agents that influence the serotoninergic system can cause the serotonin syndrome.[9] This interaction is hypothesized to hyperactivate central (1A) serotonin (5-hydroxytryptamine [5-HT]) receptors, causing changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, and tremor. In the early stages, this toxic state can be resolved by discontinuing the serotonergic agent or through use of 5-HT receptor antagonists. Cyproheptadine and chlorpromazine have been suggested for more severe cases.[10] A recent animal study[11] found limited efficacy of pretreatment with 5-HT (2A) antagonists, although such therapy is considered clinically effective.[12] The former study found that noradrenaline levels increased along with increased serotonin, but to a significantly lower level in the animals pretreated with the 5-HT (2A) antagonists. The results of the study[11] may also suggest that increased noradrenaline levels contribute to the severity of the condition. However, during withdrawal of venlafaxine, both serotonin and noradrenaline levels decrease instead of increase, ruling out toxic levels of serotonin and noradrenaline as a probable cause of the withdrawal symptoms, that can be hypothesized to result from a (too) rapid deprivation of neurotransmitter levels. Which neurotransmitters apart from 5-HT (2A) antagonists are involved may be deduced from some of the less often-reported withdrawal symptoms, such as the “electrical discharges in the head.” These symptoms are similar to preseizure symptoms in epilepsy, and there is now evidence of the relevant role of the noradrenergic system in modulating seizures,[13] providing further evidence that noradrenergic and/or serotonergic deficits may contribute to epilepsy and depression.[14] Although this does not necessarily establish a link between epileptiform manifestations

and venlafaxine withdrawal, it does suggest that some of the venlafaxine-withdrawal symptoms are more likely to be caused by a lack of noradrenergic than of serotonergic action, contrary to the commonly accepted theory.[15] A hypothesis worth investigating is whether the "electrical discharges in the head" are the result of a "bursting" activity of noradrenergic receptors in the absence of a hitherto customary neurotransmitter presence. Among the few case reports available, a recent report again attributes this symptom to a serotonin effect, possibly confounding the withdrawal effects of venlafaxine with a serotonin syndrome.[5] In this case, the authors refer to the "buzz" noted upon withdrawal in approximately 5% of patients treated with SSRIs and hypothesize that the sensations may be a form of paresthesias. However, the clinical evidence they provide gives contradictory information. Their patient no.1 was taken off venlafaxine but given fluoxetine, whereupon the brain shocks started, so the symptoms appeared to be caused either by venlafaxine withdrawal or by an unlikely serotonin syndrome. Their patient no.2 was gradually tapered from venlafaxine but given citalopram and also experienced the shocklike sensations. Finally, they cite the case of a 72-year-old woman in whom venlafaxine withdrawal symptoms were readily relieved by sertraline, but not by maprotiline, and 3 other cases that were "treated successfully by fluoxetine." The authors rightfully indicated that "an unexplained aspect of our two patients is that the addition of an SSRI, which theoretically would result in an increase of serotonin, did not alleviate withdrawal symptoms…"

The 3 case reports presented here suggest that this specific venlafaxine withdrawal symptom appears irrespective of dosage. Although venlafaxine in the lower daily dose range (18.75 to 75 mg) blocks reuptake of serotonin more than reuptake of noradrenaline, all SSRIs and SSNRIs affect both serotonin and noradrenaline levels, depending on their specificity. The particular withdrawal effect discussed here compares more closely to preseizure signs than to paresthesias, and thus could be attributed to noradrenergic more than serotoninergic action.

## As regards 2: The Need for a Warning to Drivers

As discussed, withdrawal symptoms occur in patients who have received both low and high doses of venlafaxine and result in a discontinuance syndrome with several manifestations, especially severe dizziness and disorientation, that are incompatible with driving a car or using heavy or dangerous machinery. Although standard warnings are given that taking the drug may affect those abilities, and patients are also generally advised not to stop the medication abruptly, severe withdrawal symptoms, such as confusion, impaired coordination, sensory disturbances, vertigo, delirium, strokelike symptoms, and depersonalization, may occur only hours after reduction or cessation and should warrant a specific "warning to drivers." Whenever venlafaxine is not taken at the usual time or in the usual quantity, special caution is warranted. Even when the dosage is being tapered, the physician should instruct the patient to beware of these symptoms, because the recommended tapering period of 2 weeks is not necessarily sufficient. Cases have been documented in which even tapering over a period of 3 months was insufficient.[16]

## Conclusions

Venlafaxine is a widely used antidepressant. The World Health Organization asserts that SSRI and SSRNI antidepressants cause dependence and that discontinuation symptoms can be troublesome and persist notwithstanding taper therapy.[17] The specific symptoms that can result from venlafaxine reduction or discontinuation as reviewed here seriously impair driving ability and should be prevented by strict dosage discipline and adequate warnings.

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