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A Case of Interdose Discontinuation Symptoms With Venlafaxine Extended Release

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To the Editor: Venlafaxine extended release (XR) is a serotonin-norepinephrine reuptake inhibitor that, like many other antidepressants, may be associated with a discontinuation syndrome. Discontinuation syndromes are, in part, related to drugs with short half-lives[1] (eg, for venlafaxine and its metabolite, 5 and 11 hours, respectively). Venlafaxine XR discontinuation symptoms have been clinically reported as soon as 6 hours[2] and as long as 9 days[3] after discontinuation of the drug, but typically emerge in 1–4 days.[4] In one study, the prevalence of typical discontinuation symptoms with venlafaxine XR (eg, dysphoria, headaches, nausea, irritability, emotional lability, sleep disturbance) was 27%.[5] However, discontinuation symptoms may be severe[6,7] in up to 5% of cases.[8] In addition, unexpected symptoms may emerge such as "shock-like sensations,"[9] gait difficulties,[10] palinopsia (persistent visual images),[11] delirium,[12] suicidal ideation,[13] and hypomania[14] or mania.[14,15] In the following case, we describe a patient who experienced routine venlafaxine XR discontinuation symptoms within hours of daily dosing.

Case report. In December 2009, Ms A, a 41-year-old white woman with a history of hypertension and palpitations, was prescribed venlafaxine XR 37.5 mg/d by another primary care provider for the treatment of depression. With a change in primary care providers in January 2011, Ms A promptly discussed her concerns with venlafaxine XR. According to the patient, approximately 2 months after the onset of the venlafaxine XR trial, she began to experience a number of side effects in the absence of any other changes in medication, including nausea, irritability, emotional lability, and, most troublesome, "electrical brain shocks." Oddly, all of these symptoms occurred on a daily basis, and they consistently emerged approximately 8–10 hours after the administration of the daily dose of venlafaxine XR. Symptoms would

then promptly resolve after Ms A took the next dose of venlafaxine XR.

Because the patient seemed to be experiencing discontinuation symptoms, she was switched to regular-release venlafaxine 37.5 mg in January 2011, which was dosed twice per day. The regular-release venlafaxine was well tolerated. Within 2 weeks, the patient confirmed that most, if not all, of her symptoms had subsided.

Although discontinuation symptoms from venlafaxine XR have been clinically described by one author in as few as 6 hours after the last dose,[2] we are unaware of any actual case reports of venlafaxine XR interdose discontinuation symptoms. This phenomenon may be related to individual genetics and the cytochrome P450 isoenzyme system. Specifically, venlafaxine XR is metabolized by the 2D6 isoenzyme, which is subject to broad genetic polymorphism. In this regard, Zhou[16] has described 4 genetic variants: ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers, and poor metabolizers, which constitute 3%–5%, 70%–80%, 10%–17%, and 5%–10% of white individuals, respectively. It is possible that our patient was an ultrarapid metabolizer and briskly eliminated venlafaxine XR through the 2D6 isoenzyme, resulting in interdose discontinuation symptoms.

As for clinical approaches to interdose discontinuation symptoms, venlafaxine XR or regular-release venlafaxine may be dosed twice per day, or a patient might be switched to an antidepressant that is less dependent on 2D6 metabolism, such as sertraline, citalopram, or mirtazapine.[17] To conclude, to our knowledge, this is the first case report of interdose discontinuation symptoms with venlafaxine XR.

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