
**Dosing by Side Effect Threshold: Two Cases of
Panic Disorder Responsive to Low-Dose Venlafaxine**

To the Editor: Current treatment guidelines for panic disorder recommend starting venlafaxine at a daily dose between 25 and 37.5 mg and then gradually titrating to a therapeutic dose between 75 and 300 mg/d.¹⁻³ In our experience, a substantial subgroup of patients will experience unacceptable side effects if dosed at these recommended levels. However, many of these same patients will respond to much lower doses that are close to, or just below, the

threshold at which they begin to experience side effects as venlafaxine is titrated upward from extremely small starting doses.

Here, we describe 2 patients with unusually low side effect thresholds who were successfully treated for panic disorder using initial and maintenance doses of venlafaxine that were only a small fraction of recommended amounts. We propose that, in the treatment of panic disorder, the side effect threshold may represent a useful guide to dosing.

Case 1. Ms A, a 51-year-old married homemaker, presented in March 2007 with an 18-year history of intermittent, spontaneous panic attacks consistent with a diagnosis of *DSM-IV* panic disorder with agoraphobia. She had a lifelong history of hypochondriacal concerns and a 2-year history of phobic avoidance of freeways that had worsened after a recent flurry of panic attacks.

Ms A was fearful of psychiatric medication because prior treatment with clonazepam had produced unacceptable sedation. Therefore, current treatment began with venlafaxine as the sole psychiatric drug at a dose of only 3.125 mg/d. This required cutting an immediate-release 25-mg tablet into 8 approximately equal parts. The dose was raised every other day by an additional 3.125 mg until, at 15.625 mg/d (five-eighths of a tablet), Ms A began to notice the onset of headaches, restlessness, and nervous tension. At that point, to minimize side effects, the daily dose was lowered to 12.5 mg. Within 3 days, Ms A's side effects disappeared, and she experienced a dramatic improvement. For the first time in 2 years, she was able to drive alone on a freeway.

Ms A continued to report virtually no psychiatric symptoms or medication side effects until 4 months later, when she experienced the abrupt return of limited-symptom panic attacks and phobic fears. In response, the dose of venlafaxine was titrated upward by an extra 3.125 mg each day until, at 25 mg/d, Ms A once again entered remission. At that point, her only side effects were vivid dreams and minor constipation, neither of which concerned her. During the first 2 months of treatment, her 17-item Hamilton Anxiety Rating Scale⁴ score decreased from 16 to 2. Until she was lost to follow-up 9 months later, she continued on treatment with 25 mg/d of venlafaxine and remained free of psychiatric complaints except for occasional mild anticipatory anxiety.

Case 2. Ms B, a 23-year-old single teacher, presented in December 2005 with a 6-week history of recurrent panic attacks consistent with a diagnosis of *DSM-IV* panic disorder without agoraphobia. Her attacks had triggered increasing problems with fatigue, insomnia, crying spells, pervasive anxiety, and obsessive worries about future attacks.

Three years earlier, when she had first been treated for panic attacks by her general physician, she had experienced unacceptable restlessness and mental confusion on treatment with citalopram 40 mg/d. To avoid adverse effects, current treatment was initiated with venlafaxine alone at a dose of only 6.25 mg/d (one-fourth of an immediate-release 25-mg tablet). The plan was to titrate upward every other day by an extra 6.25 mg until either side effects or clinical improvement intervened. Five days later, Ms B began to complain of restlessness and annoying dry mouth at a dose of 18.75 mg/d of venlafaxine. The dose was immediately lowered to 12.5 mg, and, within 2 days, Ms B was feeling much less anxious. At that point, her only side effect was a slightly dry mouth.

Ms B remained virtually free of psychiatric complaints until 2 weeks later, when she began to notice the gradual return of anxiety. Her dose was again raised every other day by an additional 6.25 mg. Upon reaching 25 mg/d, she experienced a full remission, again with no side effects other than a slightly dry mouth. During the first 2 months of treatment, her 17-item Hamilton Anxiety Rating Scale score decreased from 12 to 1. She remained in remission on 25 mg/d until she switched her care to her general

physician and was lost to follow-up 16 months later. At that point, she had not had a single panic attack since starting venlafaxine.

We are unaware of previous reports of successful treatment of panic disorder using initial doses of venlafaxine as low as 3.13 to 6.25 mg or therapeutic doses as low as 12.5 to 25 mg. These remarkably low doses were an outgrowth of efforts to avoid dosing above each patient's side effect threshold.

Observations gleaned from previous reports provide examples of patients who experienced annoying side effects at recommended doses. Of 5 published randomized, double-blind, placebo-controlled trials of venlafaxine in panic disorder,⁵⁻⁹ only 1 reported no withdrawals because of adverse reactions,⁵ and this trial was also the only one to use an initial dose as low as 12.5 mg, an amount well below the recommended initial dosage range of 25 to 37.5 mg/d. In a separate open-label study that allowed variable dosing,¹⁰ venlafaxine was started at 25 mg/d, but the mean daily dose during the first week of treatment turned out to be only 16.6 mg, suggesting that the dose had to be adjusted downward because some patients were uncomfortable at the 25-mg starting dose.

None of the 5 published randomized double-blind, placebo-controlled trials of venlafaxine in panic disorder allowed doses below 75 mg/d after the opening phase of treatment, making it difficult to gauge how often patients with panic disorder may be helped by lesser amounts. The open-label study that allowed variable dosing up to 250 mg/d¹⁰ reported an effective mean daily dose of venlafaxine of only 46.9 mg, a dose less than two-thirds as large as the "minimum effective dose" of 75 mg recommended by treatment guidelines. A case series comprising 4 patients treated for panic disorder with venlafaxine found that only 1 of the 4 required a dose as high as 75 mg/d to achieve remission.¹¹ Moreover, 1 of these 4 patients experienced the immediate onset of generalized anxiety after starting venlafaxine at 18.5 mg bid but improved rapidly once the dose was lowered to 9.375 mg bid. Taken together with the present report, these observations argue for further consideration of venlafaxine at initial daily doses below 25 mg and maintenance doses below 75 mg/d.

Both of our patients showed clinical improvement at doses only a few milligrams below those doses at which they began to experience annoying side effects. To account for this, we propose that there may exist a linkage between side effects and therapeutic effects in panic disorder such that, as the dose of an antidepressant is titrated upward, therapeutic effects often occur at, or just below, the threshold at which side effects begin to appear. Here, we refer to side effects such as agitation or sedation that tend to occur early in treatment and can be removed quickly by dosage reduction. Dosing venlafaxine in accordance with this hypothesis requires repeated titrations targeting the individual's evolving side effect threshold, keeping side effects to minimal or nonexistent levels throughout the course of treatment, and largely ignoring the notion of a "minimum effective dose." Our approach is consistent with guidelines that recommend starting treatment at low doses and titrating according to the patient's tolerance¹⁻³ but at odds with recommendations encouraging patients to persevere in the face of side effects¹² in order to ascend to the "therapeutic range."³ The present hypothesis is analogous to the neuroleptic threshold hypothesis, which holds that neuroleptic doses at the side effect threshold afford the schizophrenic patient maximum antipsychotic benefit with the least possible unwanted side effects.¹³

Our patients improved quickly, both within less than 2 weeks of starting venlafaxine. Taken together with Geraciotti's¹¹ observation of an almost immediate remission of panic symptoms in several patients started on low doses of venlafaxine, these observations raise the possibility that a low-dose approach, by minimizing interference from adverse reactions, may sometimes facilitate rapid improvements.

Controlled trials comparing threshold doses to more standard doses are needed to provide a fuller understanding of the dose response relationship of venlafaxine in panic disorder.

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