Emergence of Adverse Events Following Discontinuation of Treatment With Extended-Release Venlafaxine

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Objective: The rate of adverse events following discontinuation of treatment with extended-release venlafaxine was compared with the rate associated with discontinuation of placebo administration. Method: The subjects were 20 outpatients with major depressive disorder who had participated in a multicenter, double-blind, placebo-controlled study of the efficacy of the new extended-release formulation of venlafaxine. Results: During the 3 days after discontinuation of treatment with the study drug, seven (78%) of the nine venlafaxine-treated subjects and two (22%) of the nine placebo-treated patients reported the emergence of adverse events, a statistically significant difference. Conclusions: These results suggest that clinicians discontinuing venlafaxine treatment should consider tapering the medication dose gradually.
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There is now accumulating evidence that a substantial proportion of patients who abruptly discontinue taking selective serotonin reuptake inhibitors (SSRIs) report characteristic adverse events, such as dysphoria, anxiety, irritability, hot and cold flashes, excessive sweating, flu-like symptoms, nausea, diarrhea, fatigue, lightheadedness, dizziness, headaches, insomnia, and vivid dreams (1–3). The discontinuation-emergent symptoms that have been reported with SSRIs usually resolved with time, resumption of treatment with the SSRI, anticholinergic drug use, or the addition of an SSRI with a longer half-life, such as fluoxetine (2, 3). On the basis of these anecdotal observations, it has been recommended that clinicians discontinuing SSRI treatment consider tapering the drug dose gradually, with reinstitution of the SSRI if substantial discontinuation symptoms develop (4).

Even though venlafaxine is considered by some to be a serotonin and norepinephrine reuptake inhibitor, there is substantial evidence that its in vitro pharmacological properties and its side effect profile, at least in lower doses, are similar to those of the SSRIs (1). Following an initial case report by Farah and Lauer (5), Louie et al. (6) described the occurrence of dysphoria and gastrointestinal symptoms in three patients within 3 days after discontinuation of venlafaxine treatment. It is interesting that the symptoms experienced by two of these patients were similar to those experienced by the same subjects after they stopped taking SSRIs.

Since our site was one of 12 centers participating in a safety and efficacy study of the new extended-release formulation of venlafaxine for major depression, we decided to compare the rate of emergence of adverse events after discontinuation of venlafaxine treatment with the rate for discontinuation of placebo administration among the patients enrolled at our site. Since adverse events upon abrupt discontinuation of SSRIs are thought to occur more frequently with SSRIs that have relatively shorter half-lives than with drugs that have longer half-lives, such as fluoxetine (1), we hypothesized that withdrawal symptoms would be relatively common after discontinuation of venlafaxine, which has a relatively short half-life.

METHOD

At our site at the Depression Clinical and Research Program of the Massachusetts General Hospital, 20 outpatients 18 years of age or older participated in a multicenter, double-blind, placebo-controlled study of the efficacy of extended-release venlafaxine. Written informed consent was obtained from all patients before protocol-specified procedures were carried out. The study participants had met the DSM-IV criteria for major depressive disorder as determined by the Structured Clinical Interview for DSM-III-R—Patient Version (7) and had been required to have a score of 20 or higher on the 21-item Hamilton Depression Rating Scale (8) at screening and to have had no greater than a 20% decrease in Hamilton depression score at the baseline visit. The study included a 1-week placebo washout period followed by an 8-week double-blind treatment period, during which one-half of the patients were assigned to treatment with extended-release venlafaxine and the other one-half of the patients were assigned to placebo. During the

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first 2 weeks of double-blind treatment, the patients received either 75 mg/day of extended-release venlafaxine or placebo. After 2 weeks of treatment, if clinically indicated to improve response, the dose of extended-release venlafaxine was increased to 150 mg/day. After 4 weeks of treatment, a further increase in dose to 225 mg/day was allowed, if clinically indicated. All of the study completers taking two or three capsules per day were required to taper their study medication by reducing the dose by one capsule per week, while those taking one capsule of study medication per day (75 mg of extended-release venlafaxine or placebo) were allowed to stop taking the medication without further tapering.

The exclusion criteria included pregnancy or breast feeding; serious suicidal risk; serious or unstable medical illness; history of seizure disorder; psychotic disorders not elsewhere classified; bipolar disorder; history of drug or alcohol dependence within the previous year; previous treatment with venlafaxine; myocardial infarction within 6 months; major abnormalities in laboratory test results; use of investigational drugs, antipsychotic drugs, or ECT within 30 days; use of fluoxetine within 21 days; use of monoamine oxidase inhibitors within 14 days; and use of other psychotropic drugs within 7 days of the start of the double-blind treatment.

We enrolled and randomly assigned 20 subjects, 11 men and nine women, with a mean age of 36.5 years (SD=10.7). Their mean score on the Hamilton depression scale was 21.4 (SD=2.1). The primary efficacy variables were the final ratings on the total Hamilton depression scale, the Montgomery-Åsberg Depression Rating Scale (9), the Clinical Global Impression scale (10), and the depressed mood item on the Hamilton depression scale. These scales were administered at every visit by the study psychiatrists. The efficacy results are not reported here but will be the subject of a future publication based on the pooled results. Four patients did not complete the 8-week double-blind phase: two were taking placebo and two were taking venlafaxine. Only two of the dropouts were followed after discontinuation of the study medication (one taking venlafaxine and one taking placebo).

The emergence of any new symptom or adverse event during the period following discontinuation of study drug administration (posttaper period) was assessed with general inquiry (an open-ended question) by the study psychiatrists at the time of the first visit after discontinuation; this first visit occurred a mean of 5 days (SD=1) after discontinuation of venlafaxine treatment. Both the patients and study psychiatrists were blind to treatment type when the information about adverse events was obtained. This information was gathered for all of the completers and for two of the patients who stopped taking the study medication after 6 weeks of study.

The one-tailed Fisher's exact test was used to compare the rates of adverse events during the posttaper period among the patients taking venlafaxine and the patients taking placebo. The Mann-Whitney U test was used to compare the numbers of withdrawal symptoms during the posttaper period in the two groups (venlafaxine versus placebo) and to compare the Hamilton depression scores of the patients who reported withdrawal symptoms and those who did not. The Spearman rank correlation method was used to examine the relationship between Hamilton depression score at endpoint and the number of withdrawal symptoms. Finally, the multiple linear regression method was used to assess the relationship between number of withdrawal symptoms and treatment group (venlafaxine or placebo), after adjustment for endpoint Hamilton depression score.

RESULTS

During the 3 days after study drug discontinuation, seven (78%) out of the nine venlafaxine-treated subjects (95% confidence interval=0.46–0.93) and only two (22%) out of the nine placebo-treated patients (95% confidence interval=0.06–0.55) reported the emergence of adverse events (p=0.03, one-tailed Fisher's exact test). The nine patients who reported adverse events after treatment discontinuation had significantly lower endpoint scores on the Hamilton depression scale (mean=6.2, SD=3.4) than the nine patients who did not (mean=12.1, SD=5.7) ($z=2.4$, $p<0.02$). The most common adverse events after venlafaxine discontinuation were dizziness or lightheadedness (N=4), excessive sweating (N=2), irritability (N=2), dysphoria (N=2), and insomnia (N=2).

The number of adverse events during the posttaper period was significantly higher among the nine venlafaxine-treated patients (mean=2.8, SD=2.3) than among the nine placebo-treated patients (mean=0.4, SD=1.0) ($z=2.3$, $p<0.03$). In addition, among the nine venlafaxine-treated patients, the mean numbers of moderate and mild adverse events were 1.1 (SD=2.1) and 1.7 (SD=1.5), respectively. Among the nine placebo-treated patients, however, the mean numbers of moderate and mild adverse events were only 0.2 (SD=0.7) and 0.2 (SD=0.4), respectively. We also observed a statistically significant ($r=–0.5$, N=18, $p<0.05$) inverse relationship between endpoint Hamilton depression score and number of adverse events after treatment discontinuation. Finally, the number of adverse events during the posttaper period was significantly related (partial $F= 4.6$, $df=2, 15$, $p<0.05$) to treatment assignment (venlafaxine versus placebo), after adjustment for endpoint Hamilton depression score.

DISCUSSION

The results from our site showed a significantly greater number of adverse events after discontinuation of venlafaxine treatment than after discontinuation of placebo administration. Although adverse events emerged after discontinuation of antidepressant treatment mostly among patients with fewer depressive symptoms at endpoint, the relationship between number of adverse events and treatment assignment (venlafaxine versus placebo) remained statistically significant after adjustment for depression severity at endpoint. We also found that the percentage of subjects reporting adverse events after discontinuation of venlafaxine treatment was significantly higher than the percentage for placebo, despite the relatively small number of subjects.

The symptoms reported in our study after venlafaxine discontinuation (i.e., dizziness, lightheadedness, excessive sweating, irritability, dysphoria, and insomnia) are similar to those reported after discontinuation of SSRI treatment (1). The physiologic mechanism underlying the emergence of adverse events after discontinuation of venlafaxine treatment is not known yet.

The strengths of our study are that the follow-up of patients completing the double-blind trial at our site was consistent and systematic and that the clinicians assessing these adverse events were blind to treatment assignment. The main limitation of our study is the small number of subjects.

Our results suggest that discontinuation-emergent adverse events are fairly common among venlafaxine-

treated patients, and consequently clinicians should consider tapering the venlafaxine dose gradually. Larger, double-blind studies are needed to confirm our findings.

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