Venlafaxine in the Treatment of Postpartum Depression

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Background: Although postpartum depression is a highly prevalent illness, antidepressant treatment studies of postpartum depression are sparse. Incomplete recognition and treatment of puerperal illness place women at risk for chronic depression and may have adverse effects on child development.

Method: An 8-week, flexible-dose, open study of venlafaxine (immediate release; mean dose = 162.5 mg/day) was performed in a group of 15 women who met DSM-III-R criteria for major depressive disorder with onset within the first 3 months postpartum. Patients were assessed at baseline and every 2 weeks across the study. Measurements of outcome included the 17-item Hamilton Rating Scale for Depression (HAM-D), the Kellner Symptom Questionnaire, and the Clinical Global Impressions scale (CGI).

Results: Despite baseline scores of depression that were particularly high, response to treatment was robust. Twelve of 15 patients experienced remission of major depression (HAM-D score ≤ 7 or CGI score ≤ 2). Dramatic decrease in anxiety paralleled the decrease in depression across the sample.

Conclusion: Venlafaxine is effective in the treatment of postpartum major depression. Early identification of women who suffer from postpartum mood disturbance is critical to minimize the morbidity associated with untreated mood disturbance and the effect of depression on children and families.

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Postpartum depression is a highly prevalent disorder, with estimated prevalence rates of 10% to 15%.[1–4] The postpartum period has been acknowledged by many investigators as a period of substantial risk for development of mood disorder. Women with histories of past depression and specifically postpartum depression appear to be at particular risk for postpartum mood disturbance. Despite the high prevalence estimates of postpartum depressive illness and studies that also describe attendant morbidity associated with untreated puerperal psychiatric illness,[5,6] well-controlled treatment studies of postpartum depression are sparse. Published studies evaluating the efficacy of pharmacologic and nonpharmacologic therapies for the treatment of this disorder[7–11] are finite when compared with the numerous clinical trials that have described the efficacy of antidepressants for nonpuerperal depression.

Two trials reporting efficacy of antidepressant treatment of postpartum depression have included an open study of sertraline[7] and a double-blind, placebo-controlled study of fluoxetine.[8] Although studies of the potential role of hormonal therapies such as progesterone[12] and estrogen[9] for the treatment of postpartum depression have also been reported, these studies have not been consistently repli-

cated and their role in the treatment of puerperal mood disturbance remains unclear.

Despite the efficacy of the varied approaches to treatment of postpartum depression, it has been our observation that many clinicians tend to treat women who suffer from postpartum depression with lower doses and for shorter periods of time than those suffering from nonpuerperal depression. However, there are no controlled treatment data to suggest that treatment of postpartum major depression should be different than depression noted in any other clinical setting. Inadequate intensity of somatotherapy puts women at risk for chronic depression and its attendant morbidity. The current study was designed to evaluate the efficacy of venlafaxine (immediate-release preparation) in the treatment of major depression with onset of symptoms within the first 3 months postpartum. Given the abundant data supporting efficacy and tolerability of venlafaxine for treatment of nonpuerperal depression,[13–15] we hypothesized that this antidepressant would be efficacious for the management of postpartum depression.

METHOD

Fifteen women meeting DSM-III-R criteria for major depressive disorder with onset within the first 3 months postpartum were recruited, having been referred from community psychiatrists and obstetricians, into an 8-week open-label clinical trial of venlafaxine (immediate-release preparation). Advertisements were also placed in several area magazines geared toward new families. Patients who met DSM-III-R criteria for substance abuse disorders, psychotic disorders, bipolar disorder, and anxiety disorders or who were breastfeeding were excluded from the study. The study protocol was approved by the institutional review board at the Massachusetts General Hospital. After a complete description of the study was provided to participants, written informed consent was obtained. Diagnosis of major depression was confirmed using the Structured Clinical Interview for DSM-III-R,[16] and baseline assessment of depressive symptoms included the 17-item Hamilton Rating Scale for Depression (HAM-D)[17] and the Kellner Symptom Questionnaire.[18] The Clinical Global Impressions scale (CGI)[19] was also administered (scale from 1 to 7: 1 = "normal, not ill at all"; 4 = "moderately ill"; and 7 = "among the most extremely ill patients").

Assessments were repeated at weeks 2, 4, 6, and 8. Anxiety symptoms were assessed using the anxiety subscale of the Kellner Symptom Questionnaire.[18] Subjects were treated in an open fashion with venlafaxine using a flexible dosing schedule, with dosages up to a maximum dose of 225 mg/day. All subjects were started at a dose of 37.5 mg/day of venlafaxine. Medication dosage was adjusted by the study clinician after the first 2 weeks on the basis of the presence of residual depressive symptoms and side effects.

Remission of major depression was assessed at endpoint. Remission was defined as either a HAM-D score less than or equal to 7 or a CGI score less than or equal to 2 (2 = "borderline mentally ill" and 1 = "normal, not at all ill"). Statistically significant change was assessed by comparing rating scale scores at baseline and endpoint using t tests of mean differences.

RESULTS

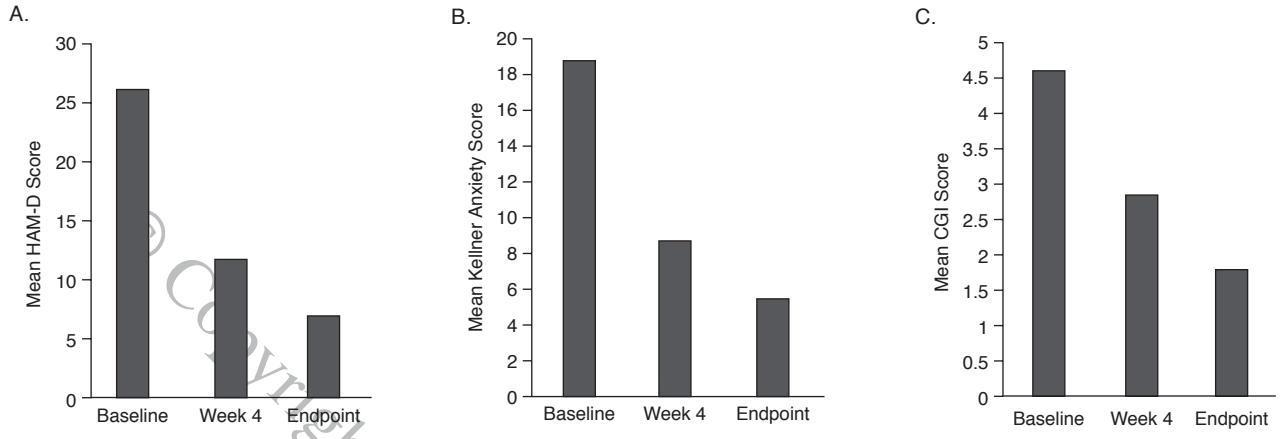
Nineteen subjects were enrolled, and 15 of these women completed at least the 2-week visit of the open-label study. Two subjects dropped out of the study after signing an informed consent form because of an unwillingness to take medication, and an additional 2 did not return after signing the informed consent form and were lost to follow-up. Fifteen subjects were thus included in the analysis with last observation carried forward (LOCF). Of these 15 subjects, 10 subjects completed the full 8-week course of the study, 2 subjects completed the 6-week visit, 2 subjects completed the 4-week visit, and 1 subject completed the 2-week visit. Reasons for removal for the 5 patients who were dropped from the study after the 2-week visit included initiation of nonpsychiatric medications that were prohibited by the study protocol (i.e., oral contraceptives) (N = 2), alcohol abuse (N = 1), refusal to take medication (N = 1), and emergence of hypomanic symptoms (N = 1). The most common adverse events during the trial were sweating (N = 7), dry mouth (N = 6), nausea (N = 6), decrease in or loss of libido (N = 3), and lightheadedness (N = 3). Other reported adverse symptoms included insomnia, blurred vision, constipation, and decreased appetite. For the majority of subjects, these symptoms resolved by week 2 of the study.

Sample Characteristics

The mean age of the sample was 30.4 years (range, 21–39 years). Most patients were married (93.3%; N = 14) and had at least a 2-year college education (66.7%; N = 10). Forty percent of the women were primiparous (N = 6), with the remaining women being multiparous. For 67% of the women (N = 10), the episode of postpartum depression represented a recurrence of major depression. For the balance (N = 5), the postpartum episode of major depression was the index depressive episode. The mean ± SD duration of illness for the postpartum depressive episode prior to entry in the study was 2.47 ± 2.15 months. The mean dose of venlafaxine used across the sample was 162.5 mg/day (range, 75–225 mg/day).

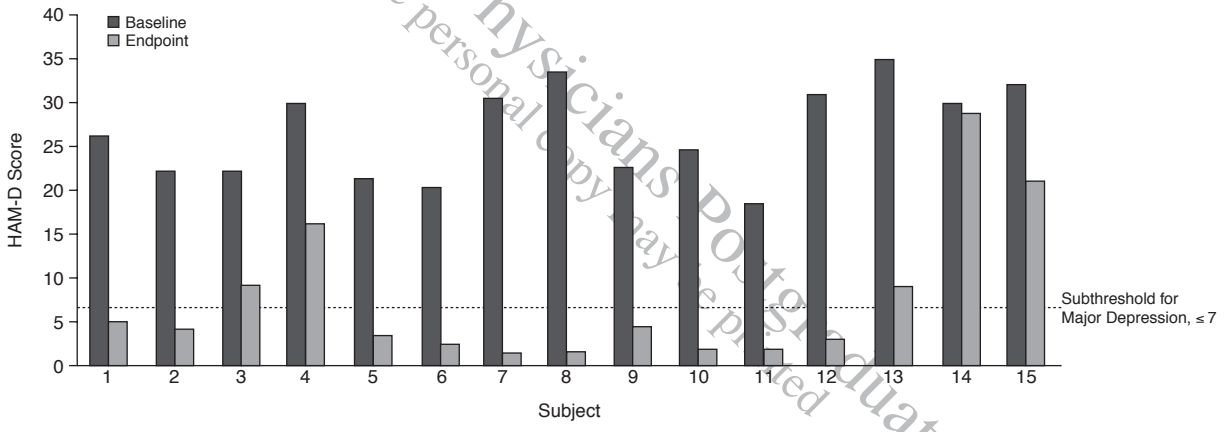
The mean ± SD baseline HAM-D score for the study sample was 26.13 ± 5.15 (range, 18–34); 26.7% of the sample (N = 4) endorsed suicidal ideation at baseline. The

Figure 1. Mean (A) 17-Item Hamilton Rating Scale for Depression (HAM-D), (B) Kellner Symptom Questionnaire Anxiety Subscale, and (C) Clinical Global Impressions Scale (CGI) Scores at Baseline, Week 4, and Endpoint[a]



[a]For the purposes of analysis, endpoint was calculated as the last observation carried forward for those subjects who did not complete all 8 weeks of the trial.

Figure 2. Hamilton Rating Scale for Depression (HAM-D) Scores at Baseline and Endpoint for Subjects With Postpartum Major Depression (N = 15)[a]



[a]For the purposes of analysis, endpoint was calculated as last observation carried forward for those subjects who did not complete all 8 weeks of the trial.

mean ± SD baseline Kellner anxiety subscale score was 18.8 ± 3.8 (range, 12–23), and the mean ± SD baseline CGI score was 4.6 ± 0.6 (range, 4–6).

Treatment Response

Data for 15 subjects were included in the analysis. Overall response to treatment as determined by HAM-D, Kellner anxiety subscale, and CGI scores is summarized in Figure 1. Individual response to treatment as determined by the HAM-D is summarized in Figure 2. By endpoint, 12 (80%) of 15 subjects had remitted (HAM-D score ≤ 7 or CGI score ≤ 2). Ten of the 15 subjects had a HAM-D score less than or equal to 7 and a CGI score less than or equal to 2; 2 subjects had a HAM-D score of greater than 7, but a CGI score of less than or equal to 2. Of the 3 subjects who did not have a 50% reduction in HAM-D score, 1 had a greater reduction (47%) than the other 2.

Patients demonstrated statistically significant improvement in mean 17-item HAM-D score from baseline to endpoint (26.13 ± 5.15 vs. 7 ± 8.14, respectively; $p < .01$) as well as in mean Kellner anxiety subscale score (18.8 ± 3.8 vs. 5.6 ± 6.71; $p < .01$) and CGI score (4.6 ± 0.63 vs. 1.79 ± 1.12; $p < .01$). Of note, this statistically significant improvement was evident by week 2 in both mean HAM-D score (week 2 score = 13.47 ± 5.98; $p < .01$) and Kellner anxiety subscale score (week 2 score = 12.46 ± 6.16; $p < .05$) and by week 4 in CGI score (week 4 score = 2.86; $p < .01$).

DISCUSSION

This study represents the third pharmacologic treatment study of women with postpartum onset of major depression. Although the study had obvious methodological limitations associated with an open design, several important findings were apparent. First, venlafaxine appeared to be effective for the treatment of postpartum depression of clinically significant severity. Mean ± SD HAM-D scores at baseline were high (26.13 ± 5.15; range, 18–34). Second, the majority of patients experienced statistically significant improvement in depression scores and overall functioning as assessed by the CGI after only 4 weeks of treatment. Improvement in depressive symptoms was associated with a paralleled decrease in anxiety symptoms. Lastly, by the conclusion of the study, 12 (80%) of 15 subjects had achieved remission of major depression.

These findings are consistent with our clinical observation that many women, including those with particularly severe depression with postpartum onset, especially when identified and treated early in the course of an episode, demonstrate a significant and rapid response to antidepressant treatment. In the current sample, response to treatment was rapid, with signs of improvement occurring as early as the first 2 weeks of treatment, consistent with findings from previous published reports.[7,8,20] This finding of rapid and robust response to antidepressant treatment among women suffering from postpartum depression suggests that puerperal mood disturbance, particularly when identified early, is no more refractory to treatment than nonpuerperal depression. The impression that postpartum depression is a more refractory type of mood disturbance[21] may be more a function of delay in recognition and treatment of the disorder than of anything intrinsic to postpartum depression per se.

Delay in treatment of postpartum depression is not uncommon. Women with postpartum depression have been noted to report the persistence of depressive symptoms for many months before finally receiving treatment; many remain depressed even at 1 year after childbirth.[2,22] Reasons for delay in diagnosis and treatment of postpartum depression may be secondary to multiple factors, including denial, fear of stigmatization, and difficulty distinguishing neurovegetative symptoms (i.e., sleep disturbance, decreased energy) from the normative experiences of the postpartum period. In addition, absence of data about the extent of infant exposure to antidepressants, including venlafaxine, frequently is responsible for this delay in treatment of postpartum depression. In one small case series, for example (N = 3), venlafaxine, like SSRIs in other studies, was noted in the plasma of infants whose mothers received this drug during lactation.[23] The impact of untreated postpartum depression on both mother and infant may be significant, with multiple reports describing the emotional, cognitive, and social difficulties associated with untreated maternal mood disorder.[24–27] Untreated depression may also be associated with the development of more chronic and refractory mood disorder in the mother,[28–30] with its attendant morbidity. Given the robust response to treatment observed in the current sample and the risks associated with failure to treat postpartum depression, raising awareness of the prevalence of this disorder and available treatment options is an issue with significant public health consequences.

The observation of paralleled improvement in anxiety and depressive symptoms in the current study deserves comment along several lines. Although studies have not demonstrated clear phenomenologic differences between puerperal and nonpuerperal depression, several investigators have noted the presence of both anxiety and obsessionality[5,31,32] as particular characteristics of postpartum depression. One might hypothesize that the decrease in anxiety associated with postpartum depression found with venlafaxine treatment may catalyze the response to antidepressant treatment in women who suffer from puerperal mood disorder. This hypothesis would be consistent with the clinical practice of frequently using benzodiazepines adjunctively with antidepressants to treat postpartum depression.[33,34] The improvement in anxiety and depressive symptoms seen in the current study may derive from the dual mechanism of venlafaxine as opposed to the more singular action of the SSRIs in general.[35,36] Our clinical experience suggests that lysis of postpartum anxiety associated with postpartum mood disturbance modulates the momentum of clinical deterioration seen in this population. Further systematic study is needed to delineate which aspects of puerperal mood disturbance may be more responsive to certain classes of antidepressants. Such pharmacologic dissection may prove to be helpful in maximizing the probability of treatment response to particular antidepressants when used in certain subtypes of depressed patients. In addition, given the limited data regarding the extent of infant exposure while breastfeeding compared with other antidepressants, further studies are necessary to clarify the relative safety of venlafaxine use during lactation.

CONCLUSION

Venlafaxine, like other antidepressants,[7,8] appears to be efficacious in the treatment of postpartum depression. Improvement in symptoms of postpartum depression in response to treatment with venlafaxine was rapid and was associated with remission of illness and marked decrease in anxiety symptoms. Further research is necessary to delineate the phenomenologic differences (if any) between puerperal and nonpuerperal depression and whether differential treatment response exists when therapy includes antidepressants with varying and distinct pharmacologic properties.

Drug names: fluoxetine (Prozac), sertraline (Zoloft), venlafaxine (Effexor).

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