Postpartum Depression Recurrence Versus Discontinuation Syndrome: Observations From a Randomized Controlled Trial

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Objective: To differentiate characteristics of a discontinuation syndrome from a recurrence of major depressive disorder in the context of a randomized trial.

Method: We performed a randomized clinical trial to compare the efficacy of sertraline versus placebo for the prevention of recurrent postpartum DSM-IV major depressive disorder. Women whose depression did not recur in the initial 17-week active treatment trial were followed through the taper phase (weeks 18–20). At week 17, 3 women assigned to placebo and 8 assigned to sertraline remained in the trial. Nine symptoms that characterize discontinuation syndrome were extracted from the 25-item Asberg Rating Scale for Side Effects (ASE) and assessed weekly during the taper phase. The 21-item Hamilton Rating Scale for Depression was used to evaluate depressive symptoms.

Results: In the taper phase, there were no significant differences between the sertraline- and placebo-treated women on the sum of the ASE-derived symptoms. Both groups had low levels of symptoms on the ASE during the weeks of taper. None of the 3 women assigned to placebo and 2 of the 8 women assigned to sertraline suffered a depressive recurrence within 6 weeks of the end of the study.

Conclusions: A gradual taper of sertraline (75 mg) over 3 weeks did not lead to discontinuation syndrome; however, the systematic dissection of symptoms resulted in our conclusion that the duration of preventive therapy should be extended to 26 weeks (about 6 months) in subsequent randomized trials, consistent with the treatment guidelines for a single episode of depression.

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The period of risk for recurrence of postpartum major depressive disorder (PMDD) defined in epidemiologic studies is 3 months (about 13 weeks).[1] Practice guidelines recommend about 6 months as the duration of treatment for a single episode of depression.[2] However, the optimum duration of treatment for the primary prevention of PMDD has not been established.

A discontinuation syndrome due to intermittent noncompliance, abrupt cessation, or rapid dosage reduction of selective serotonin reuptake inhibitor (SSRI) antidepressants has been observed.[3] A cluster of somatic and psychological symptoms that last from 7 to 14 days characterizes the syndrome.[3] Five somatic symptom clusters have been identified: (1) disequilibrium (dizziness, vertigo, ataxia); (2) gastrointestinal (nausea, vomiting); (3) flulike symptoms (fatigue, lethargy, myalgia); (4) sensory (paresthesia, electric-shock sensations); and (5) sleep disturbances (insomnia, vivid dreams). Psychological symptoms include agitation, crying, and irritability. Up to 30% of patients who discontinue treatment suffer these symptoms.[4] The incidence is highest for paroxetine, intermediate for sertraline and fluvoxamine, and lowest for fluoxetine.[4] Gradual tapering of the dose at a rate of 33% per week has been recommended to prevent discontinuation syndrome.[3,5]

The temporal relationship of symptoms is a critical factor in differentiating depressive symptom recurrence

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from SSRI discontinuation syndrome. Discontinuation syndrome occurs within 24 to 72 hours of abrupt cessation of SSRI in contrast to depression, which is unlikely to occur before 2 to 3 weeks after medication cessation.[3]

We had the opportunity to differentiate discontinuation syndrome from depressive recurrence in the context of a randomized trial. Our hypotheses were (1) during the taper phase, women who received sertraline would not differ significantly in frequency of discontinuation symptoms from women who received placebo, and (2) women who suffered recurrences would not experience depression onset during the taper phase, but following it.

METHOD

The randomized clinical trial was designed to assess the efficacy of sertraline versus placebo in the prevention of recurrent PMDD. Sertraline was chosen after an earlier identical trial with the tricyclic antidepressant nortriptyline failed to confer preventive efficacy beyond that of placebo.[6] The mean age of subjects was 32 years (SD = 3; range, 25–37). Women had had at least 1 prior episode of PMDD. Pregnant women who had recovered from this previous episode of depression were recruited.

The women were preventively medicated with sertraline or placebo immediately postbirth. We administered sertraline or identical placebo through the first 17 weeks postpartum to cover the defined 3-month period of risk for PMDD recurrence.[1] The women were evaluated weekly for 20 weeks. They received 25 mg/day of sertraline for the first 4 days, then 50 mg/day through the first 4 weeks, and 75 mg/day during weeks 5 through 17. During weeks 18 through 20, the sertraline or placebo was tapered as follows: week 18, 50 mg/day; week 19, 25 mg/day; week 20, 25 mg/day; and discontinued after week 20.

Maternal side effects were recorded with the 25-item Asberg Rating Scale for Side Effects (ASE).[7] Serum sertraline levels were obtained at 8 time points to evaluate compliance. Seven women opted to breastfeed in the postpartum period. Sertraline and N-desmethylsertraline levels were obtained from all breastfed infants to assess infant exposure from breastfeeding at week 4 postpartum.

During the randomized controlled trial (RCT), the 21-item Hamilton Rating Scale for Depression (HAM-D) was given weekly.[8] Subjects who reported symptoms of depression with a HAM-D score of ≥ 15 for 2 consecutive weeks were evaluated by the blinded principal investigator (K.L.W.) or the study psychiatrist to confirm that the clinical presentation met DSM-IV criteria[9] for major depressive disorder. A 1-year follow-up phase began immediately after the RCT, with assessments for depression recurrence every 2 months. The institutional review board approved the study, and all subjects provided written informed consent.

Drug assignment was known only to the study research pharmacist, the nonblinded medical monitor, and the study statistician (B.H.H.). The medication monitoring function was separate from (and blinded to) the mood symptom monitoring. The blind was continued until all subjects completed the year-long protocol.

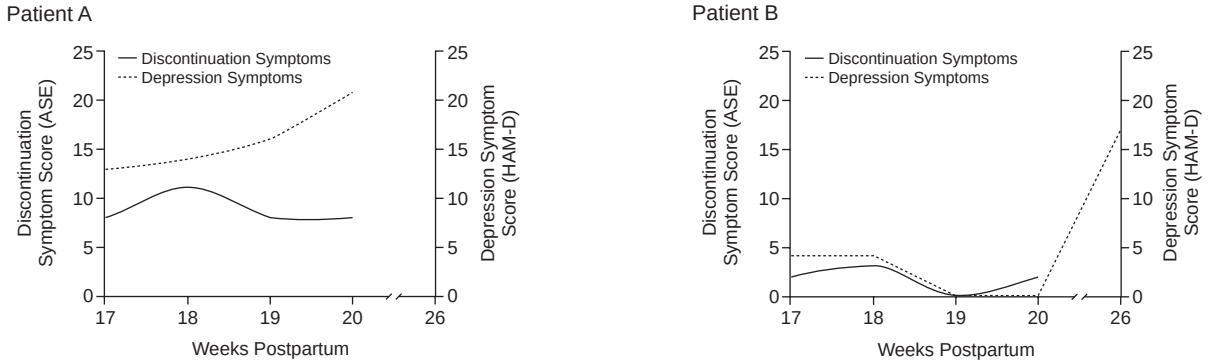
Data for the parent study were derived from 22 subjects (8 subjects received placebo and 14 received sertraline). A subset of data was used to evaluate the hypotheses related to the occurrence of discontinuation syndrome. In the 8 women assigned to placebo, 4 experienced recurrence in the 17-week trial, 1 withdrew, and 3 women completed the trial without recurrence. In the 14 women assigned to sertraline, 1 experienced recurrence at week 17, 4 withdrew, 1 was removed from the trial due to hypomania, and 8 completed the trial without recurrence. Therefore, 8 women who took sertraline and 3 women who took placebo entered the tapering phase (the focus of this report) of the original randomized trial.

The 25-item ASE was used to construct a measure of the symptoms characteristic of discontinuation syndrome. Nine items from the somatic and physical symptom profile of SSRI discontinuation syndrome proposed by the Discontinuation Consensus Panel[3] were included: physical tiredness, sleep disturbance, headaches, dizziness, tremor, nausea/vomiting, nervousness, agitation, and confusion. The 9-item score from the ASE could range from 0 to 27. Comparisons across the weeks of taper were carried out with mixed models that assessed drug and drug-by-week interactions and were based on log-likelihood statistics.

RESULTS

At the end of each week of taper (weeks 18–20), low levels of symptoms from the ASE in both the sertraline- and placebo-treated groups were observed. There was no significant difference between sertraline- and placebo-treated women on the 9-item subset of the ASE (for the drug-by-week interaction, $\chi^2 = 0.44$, df = 3, p = .3; for the drug, $\chi^2 = 0.00$, df = 1, p = .96). Two women who had taken sertraline became depressed as the drug was being discontinued (week 20) or shortly thereafter (week 26). None of the 3 women in the placebo group suffered recurrence during the same time frame. Displayed in Figure 1 are discontinuation symptom scores and the HAM-D scores for the 2 women who experienced recurrence. The first patient (Figure 1A) showed a mild, brief increase in discontinuation symptoms 1 week after the taper of the sertraline dose began, then reached consistent symptom levels. Her depression symptoms increased immediately after cessation of sertraline treatment. She passed our criteria of 2 weeks of elevation of symptoms at week 20. The second patient (Figure 1B) showed no change in discontinuation symptoms but became depressed 6 weeks after stopping sertraline.

Figure 1. Discontinuation Symptom Scores and Depression Symptom Scores for 2 Subjects Whose Depression Recurred After Sertraline Treatment Ended at Week 17



The women were compliant with their medication. Maternal mean sertraline and N-desmethylsertraline levels ranged from 23 to 48 ng/mL and 36 to 66 ng/mL, respectively, across the study. Consistent with previous reports,[10] all infant sertraline levels were ≤ 2 ng/mL and N-desmethylsertraline levels were ≤ 12 ng/mL. The limit of reliable quantifiability was 2 ng/mL, and none of the infants had adverse clinical effects.

DISCUSSION

In this study we found that a gradual taper of sertraline from 75 mg/day over 3 weeks did not result in clinically significant discontinuation symptoms. Two of the 8 study subjects assigned to sertraline became depressed after it was tapered. The later onset of depressive disorder is typical of the time course of a recurrence, in contrast to discontinuation syndrome.[3]

The importance of directly questioning patients about specific symptoms during drug discontinuation is critical. In clinical practice, systematic inquiry about the most frequently reported discontinuation symptoms (dizziness, lethargy, nausea, and headache)[3] and their relationship to sustained depressed mood and/or anhedonia is important in the differential diagnosis of depressive disorder versus discontinuation syndrome.[3] This systematic dissection of symptoms resulted in our conclusion that the duration of preventive therapy was insufficient in our initial trial, rather than the rate of drug tapering. The length of preventive therapy has been extended to 26 weeks (about 6 months) in our subsequent randomized trial, consistent with the treatment guidelines for a single episode of depression.[2]

Drug names: fluoxetine (Prozac and others), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil and others), sertraline (Zoloft).

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