Intermittent Luteal Phase Sertraline Treatment of Dysphoric Premenstrual Syndrome

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Background: Dysphoric premenstrual syndrome (PMS) has been associated with serotonergic dysregulation, and serotonergic medications have been reported to alleviate the symptoms of PMS. We investigated the effects of the serotonin reuptake inhibitor sertraline given during only the luteal phase in women with dysphoric PMS.

Method: After baseline ratings were obtained during two menstrual cycles, 15 women with dysphoric PMS who also met DSM-IV criteria for premenstrual dysphoric disorder (PMDD) entered single-blind treatment with sertraline 100 mg/day for one full menstrual cycle. Women who responded to this treatment were randomly assigned to a four-cycle double-blind placebo-controlled crossover study in which sertraline 100 mg/day or placebo was each given only during luteal phases of two consecutive menstrual cycles.

Results: Eleven (79%) of fourteen women responded to single-blind full-cycle treatment with sertraline and were randomly assigned to the double-blind crossover study. Three patients dropped out of the study while taking placebo owing to nonresponse. For the remaining patients, sertraline given during the luteal phase produced significant improvements in depression, impairment, and global ratings compared with placebo and was equivalent in efficacy to sertraline given during the entire menstrual cycle.

Conclusion: Women with dysphoric PMS who responded to continuous sertraline treatment responded equally well to sertraline treatment when it is limited to the luteal phase. Luteal phase treatment may have advantages in side effect burden and costs. Larger controlled trials are warranted to confirm this finding.

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had no past history of any mental disorder (except PMS). None of the patients had had any previous psychotropic treatment for PMS. Ten patients had used oral contraceptives in the past; 5 of them had dysphoric side effects, and 2 reported improvement of their PMS (specific type of oral contraceptives was not clear). Only 3 patients had no family history of mental disorder. Two had a family history of PMS, 2 had a family history of alcoholism, and the others had multiple relatives with mental disorders (mostly depression and alcoholism).

RESULTS

One patient dropped out during the single-blind sertraline full-cycle treatment (noncompliance). Eleven (79%) of the 14 compliant patients were considered responders to the treatment and were randomly assigned to the double-blind crossover intermittent dosing phase, which was completed by 8 patients. Three patients dropped out, all of whom were taking placebo (2 reported reappearance of premenstrual dysphoria and therefore stopped treatment before entering the sertraline phase, and 1 who had responded to the previous intermittent sertraline treatment became pregnant while taking placebo to which she did not respond). All patients who responded well to continuous sertraline reported continuation of response to intermittent sertraline (9/9), while only 2 patients responded well to placebo. In these patients, positive response to placebo was limited to the cycle immediately following the crossover from sertraline.

ANOVA comparing severity measures during the late luteal phase at baseline, full-cycle sertraline treatment, luteal phase sertraline treatment, and luteal phase placebo treatment within subjects showed a significant main effect for the HAM-D (F = 17.3, p < .0001) (Figure 1). Mean (± SD) values of outcome measures in each trial stage are presented in Table 1. Post hoc comparisons indicated significant differences between full-cycle sertraline treat-
ment and baseline, full-cycle sertraline treatment and luteal placebo treatment, and luteal sertraline treatment and luteal placebo treatment but not between full-cycle and luteal phase sertraline treatment. Similar results were obtained for the CGI ratings (F = 38.2, p < .0001); DRF depression ratings (F = 19.8, p < .0001; Figure 2); and DRF impairment ratings (F = 10.3, p < .0004; Figure 3), except that the comparison of impairment scores between the full-cycle sertraline and luteal placebo phases (p = .04) did not reach the Bonferroni-corrected significance (see Table 1).

**Concomitant and Side Effects**

During intermittent sertraline treatment, patients (N = 9) complained of headache (N = 6), dry mouth (N = 5), insomnia (N = 5), sedation (N = 4), urinary frequency (N = 4), fatigue (N = 4), nausea (N = 3), flatulence (N = 3), confusion (N = 2), and constipation, abdominal cramps, skin eruptions, light-headedness, and anxiety (N = 1 for each). None of the concomitant or adverse effects were reported as being severe. Three patients had side effects while taking placebo: headache, insomnia, flatulence, and urinary frequency (N = 1); dry mouth and fatigue (N = 1 for each).

**DISCUSSION**

This preliminary study demonstrates that patients with dysphoric PMS who respond well to continuous treatment with sertraline also respond well when this treatment is limited to the luteal phase of the menstrual cycle. These results are in accordance with a study of clomipramine and case reports of fluoxetine and might suggest that women with dysphoric PMS do not require continuous treatment for their entire reproductive life. Intermittent dosing is also less expensive and might reduce possible long-term side effects of serotonin reuptake inhibitors (SRIs) by reducing exposure to the medication.
If confirmed in larger studies, our results are intriguing from several perspectives. Because our patients started medication about a week prior to their anticipated symptoms, the beneficial effect of SRIs may be manifested much faster in patients with dysphoric PMS than in patients with major depressive disorder or anxiety disorders (in whom 2–3 weeks usually lapse before relief), an observation that might suggest a difference in the sensitivity of serotonergic systems in these patients. Intermittent treatment limited to the luteal phase also raises the question of which serotonergic systems are abnormal in PMS because it has been previously reported that some serotonergic functions are state-related and abnormal only during the dysphoric state while others are probably trait abnormalities that are detectable also during nondysphoric phases of the menstrual cycle. The distinction between state and trait effect is more apparent when a short-acting SRI (such as sertraline) is used. With a long-acting SRI, especially one with a long-acting active metabolite (such as fluoxetine), there is still active drug in plasma and serotonergic reuptake activity during the nontreatment asymptomatic follicular intervals. In contrast, each luteal treatment with a short-acting SRI is probably a de novo initiation of treatment.

These preliminary data should be confirmed in larger double-blind placebo-controlled studies that also should address the optimal timing of initiation and discontinuation of treatment, the long-term effects and possible attrition of response, and the influence of short- and long-term serotonergic agonism on the reproductive system and sexual behavior, as well as the state of the serotonergic systems during nontreatment intervals.

**Drug names:** clomipramine (Anafranil), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft).

**REFERENCES**


