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 that was restricted 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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Premenstrual syndromes are quite prevalent. From 3% to 8% of women of reproductive age suffer from dysphoric premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD).[1–3] The exact pathobiology of dysphoric PMS is still unknown, but it is well established that serotonergic abnormalities play a major role in this process.[4] Accordingly, several reports indicate that serotonergic agonists are efficacious in the treatment of this disorder. Among others, fluoxetine,[5] sertraline,[6] d-fenfluramine,[7] fluvoxamine,[8] paroxetine,[9] clomipramine,[10] and nefazodone[11] all have been reported to be beneficial for women with dysphoric PMS. However, in these treatment trials, the medications were administered on a continuous basis during the entire menstrual cycle, including the nonsymptomatic phases. Several case reports of treatment with fluoxetine[12] and a preliminary placebo-controlled study of clomipramine[13] suggest that intermittent dosing limited to the luteal phase might be a sufficient and efficacious treatment for PMS.

Therefore, we tested the hypothesis that women suffering from dysphoric PMS who responded to continuous treatment with sertraline would also respond to the same treatment when it is limited to the luteal phase.

METHOD

Subjects were recruited by advertisement in local newspapers and posted notices (offering free treatment to women aged 24–45 who had regular menstrual cycles and who suffered from PMS). Responders were first screened by a structured telephone interview that covered inclusion and exclusion criteria. Women were included if they were between the ages of 24 and 45 years, had regular menstrual cycles lasting 25–34 days, had not met criteria for any DSM-IV major diagnoses for at least 6 months, and met DSM-IV criteria for PMDD[14] and criteria for dysphoric PMS.[15] Participants were physically healthy and were not taking any medications.

Premenstrual symptoms were prospectively confirmed for at least two menstrual cycles using a modified Daily Rating Form (DRF), which included the DSM-IV PMDD items.[16] Women whose DRF confirmed PMDD symptoms during the late luteal phase (severity score of at least 4 on a severity scale of 1–6 [1 = not having any symptoms at all, 6 = most severe] for at least 3 days) and no symptoms

during the mid-follicular phase (severity less than 3 = mild) were invited for a face-to-face interview during which they were evaluated with the Structured Clinical Interview for DSM-IV, Outpatient Version (SCID-OP)[17] and the Hamilton Rating Scale for Depression (HAM-D).[18] They also underwent a thorough physical examination, ECG, and blood and urine laboratory tests. Ovulation was determined by an LH-surge urine test. Study procedures were fully explained to candidates before they signed a consent form, which also included an agreement to use adequate mechanical contraception. Patients entered a single-blind treatment with sertraline 100 mg/day for one entire menstrual cycle. If they responded well (see Efficacy Evaluation) during this cycle, they were randomly assigned to a double-blind placebo-controlled crossover treatment during four menstrual cycles. During the double-blind treatment, sertraline 100 mg/day or placebo was given for two consecutive cycles each during the 14 days preceding the next expected menses (the luteal phase).

Efficacy Evaluation

Patients completed DRFs throughout the entire study. They came for office visits during each late luteal phase, during which the adverse events as well as results from Clinical Global Impressions (CGI) scale,[19] CGI-Improvement (CGI-I) scale, HAM-D, and patients' subjective reports were recorded and DRFs were evaluated. To be considered a responder, a patient had to no longer meet criteria for PMDD and dysphoric PMS, have a CGI score ≤ 3, have at least a 50% decrease in HAM-D score, and report that she was no longer dysphoric during the late luteal phase.

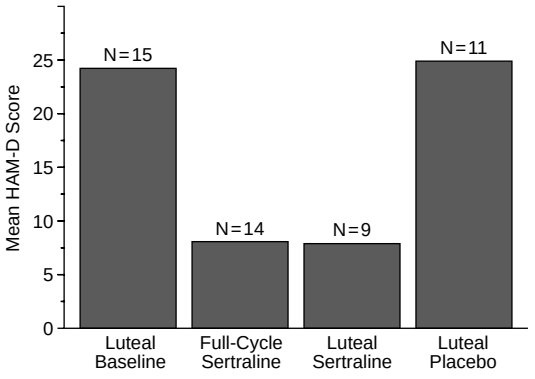
Statistical Analysis

Treatment responses during the second cycle of each treatment modality were compared to each other, to the response during the single-blind cycle, and to the baseline luteal phase, using a repeated-measures analysis of variance (ANOVA) and post hoc comparisons with a Bonferroni adjustment for an experiment-wise alpha level of < .05.

Subjects

Thirty-two patients were eligible for the face-to-face assessment (over 60 were screened). Twenty-seven patients were eligible for the study, of whom 15 actually entered the single-blind phase. The 12 patients who did not enter the single-blind phase dropped out owing to time demands (7 patients), refusal of gynecologic or mammographic examination (2 patients), noncompliance with appointments (1 patient), and being prescribed sertraline by their family physician (2 patients). Mean ± SD age of patients who completed the single-blind phase was 33.6 ± 6.9 years. Nine had children (2 or 3 offspring each), and 5 had a past history of postpartum depression, 2 of whom also had a past history of major depressive disorder. One patient had a lifetime history of a severe grief reaction, and 8 patients 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).

Figure 1. Hamilton Rating Scale for Depression Ratings During the Late Luteal Phase in Patients at Baseline and During Treatment With Sertraline and Placebo



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-

Table 1. Outcome Measure Ratings During the Late Luteal Phase in Patients at Baseline and During Treatment With Sertraline and Placebo[a]

	HAM-D[b]		CGI[c]		DRF-D[d]		DRF-I[e]	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A: Luteal baseline	25.13	7.38	4.86	0.69	4.07	1.11	3.99	1.59
B: Full-cycle sertraline	6.13	6.06	1.57	0.79	1.30	0.49	1.29	0.50
C: Luteal sertraline	7.75	5.18	1.86	0.90	1.40	0.49	1.57	0.76
D: Luteal placebo	24.88	7.16	4.14	0.38	3.34	1.23	3.61	1.73
Pairwise Comparisons								
A vs B	$p < .0001$*		$p < .0001$*		$p < .0001$*		$p = .0008$*	
A vs C	$p < .0001$*		$p < .0001$*		$p < .0001$*		$p < .0001$*	
B vs C	$p = .94$		$p = .16$		$p = .59$		$p = .36$	
B vs D	$p < .0001$*		$p < .0001$*		$p = .001$*		$p = .04$	
C vs D	$p < .0001$*		$p < .0001$*		$p = .0004$*		$p = .007$*	

[a]Abbreviations: HAM-D = Hamilton Rating Scale for Depression; CGI = Clinical Global Impressions Scale; DRF-D = Daily Rating Form for depression; DRF-I = Daily Rating Form for impairment.
[b]HAM-D main effect: $F = 17.26$, $p < .0001$.
[c]CGI main effect: $F = 38.20$, $p < .0001$.
[d]DRF-D main effect: $F = 19.76$, $p < .0001$.
[e]DRF-I main effect: $F = 10.25$, $p < .0004$.
*Significant at .05 level with Bonferroni correction.

Figure 2. Daily Rating Form (DRF) Depression Ratings During the Late Luteal Phase in Patients at Baseline and During Treatment With Sertraline and Placebo

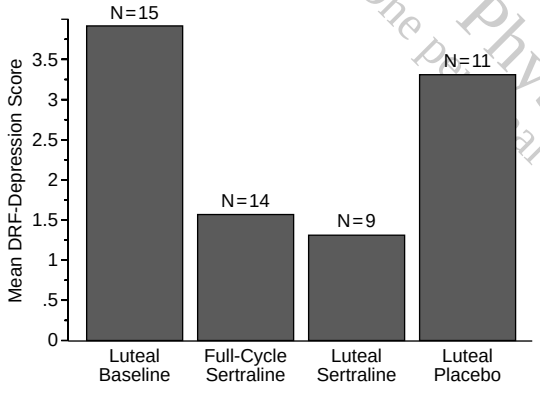
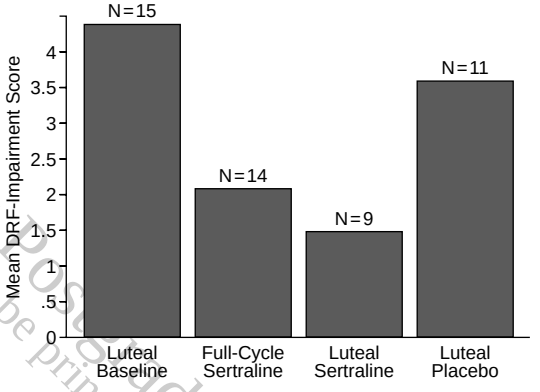


Figure 3. Daily Rating Form (DRF) Impairment Ratings During the Late Luteal Phase in Patients at Baseline and During Treatment With Sertraline and Placebo



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[13] and case reports of fluoxetine[12] 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[4,20] 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,[21] 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).

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