Luteal Phase Sertraline Treatment for Premenstrual Dysphoric Disorder

Results of a Double-blind, Placebo-Controlled, Crossover Study

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Objective: To test the efficacy of late-luteal phase dosing of sertraline hydrochloride in women with moderate-to-severe premenstrual dysphoric disorder. This highly prevalent disorder often causes significant psychosocial impairment.

Design: Double-blind, crossover trial of each 2-menstrual cycle of baseline, sertraline treatment, and placebo. Randomization to sertraline treatment vs placebo occurred after a 2-cycle, drug-free period.

Setting: A large outpatient multispecialty clinic in central Texas.

Patients: Fifty-seven women aged 19 to 49 years with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, diagnosis of premenstrual dysphoric disorder.

Interventions: Late-luteal phase treatment with sertraline hydrochloride in daily doses of 50 mg (cycle 1) followed by 100 mg (cycle 2) vs placebo.

Main Outcome Measures: The 22-item calendar of premenstrual experiences was completed daily and constituted the primary outcome measure, consisting of a total score and behavioral and physical factor scores.

Results: A repeated-measures analysis of variance for crossover designs found a significant beneficial effect from sertraline treatment in improving the calendar of premenstrual experiences total (P<.01), behavioral factor (P<.01), and physical factor (P<.04) scores. Most women improved when taking sertraline, 50 mg, although a dose increase to 100 mg yielded further improvement in approximately 25% of women. Use of sertraline was extremely well tolerated; the only adverse event reported by 10% or more of women was insomnia in 8 (14%) of them.

Conclusions: Luteal phase treatment with sertraline was a safe and effective treatment for moderate-to-severe premenstrual dysphoric disorder. Further controlled studies are needed to confirm the results of this preliminary study.

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PARTICIPANTS, MATERIALS, AND METHODS

STUDY POPULATION

This study was conducted at a research center associated with a large multispecialty clinic in central Texas. The participants were women volunteers recruited through advertisements and by referral from affiliated psychiatric and gynecologic clinics. The study was approved by the institutional review board of Scott & White Memorial Hospital, Temple, Tex. The benefits and risks of participation were reviewed with each patient, and written informed consent was obtained. Eligible patients were women between 19 and 49 years of age who reported regular menstrual cycles within the range of 23 to 35 days and who met DSM-IV criteria for PMDD. Women were excluded if they had a current DSM-IV Axis I psychiatric disorder based on a computerized version of the Diagnostic Interview Schedule. Also excluded were pregnant women, those with significant medical or gynecologic disorders, and those taking psychotropic or hormonal medications, including birth control pills.

Women meeting the above criteria were required to participate in a pretreatment phase of testing that involved completing a calendar of premenstrual experiences (COPE). The COPE total scores for the luteal phase needed to exceed 41 and double the follicular phase total scores during each of the 2 consecutive menstrual cycles. In addition, the follicular phase total score could not exceed 40 and the follicular-to-luteal phase increase in summed COPE ratings needed to increase by 30% for at least 5 premenstrual symptoms.

STUDY DESIGN

The study consisted of a randomized, double-blind, crossover design in which patients received 2 months of luteal phase treatment with either sertraline or placebo (cycles 3 and 4), followed by 2 months of luteal phase treatment with the other study agent (cycles 5 and 6). Randomized study treatment was preceded by a 2-cycle, drug-free, prospective assessment period (cycles 1 and 2). After randomization, luteal phase study treatment was initiated 14 days before the expected onset of menses and discontinued the day menses began. Sertraline, 50 mg, was used during the first active drug luteal phase. If the reduction in luteal phase mean COPE total score (for the last 7 days of the cycle) was less than 30%, the daily dose of sertraline or placebo during the second cycle was doubled to 100 mg or 2 pills, respectively. Compliance with study treatment was assessed by monthly pill counts.

The primary outcome measure in the study was the COPE, a 22-item patient-rated scale that assesses common behavioral and physical symptoms of PMDD on a 4-point Likert severity scale. The COPE is completed on a daily basis throughout the menstrual cycle, but results for the late-luteal phase (the last 7 days of the menstrual cycle) and the midfollicular phase (days 3-9 of the cycle) are summed to create separate scores.

The Beck Depression Inventory (BDI) is another 22-item patient-rated scale that assesses the common features of depression, which are rated on a 4-point severity scale anchored to written descriptions of thoughts or behaviors. The BDI has been widely used in both drug and psychosocial treatment studies of depression.

Patients were seen at monthly intervals throughout the 2 cycles of drug-free baseline assessment and the 4 cycles of study treatment. At each study visit, the completed COPEs and BDIs were collected and reviewed for completeness. Adverse events were assessed by open-ended inquiry.

STATISTICAL ANALYSIS

The primary outcome measure was the sertraline vs placebo difference in mean change from baseline in luteal phase COPE total score. Secondary outcomes included similar change from baseline comparisons for the COPE behavior factor (angry outbursts, anxiety and tension, confusion and concentration, crying, depression, food cravings, forgetfulness, irritability, increased appetite, mood swings, oversensitivity, and the wish to be alone), the COPE physical factor (acne; bloatedness; breast tenderness; dizziness; fatigue; headache; hot flashes; nausea, constipation, and diarrhea; palpitations; and swelling of hands, ankles, and breasts), and the BDI total score.

For analysis, the follicular phase scores on the COPE were derived by computing the sum score for days 3 through 9 of each cycle. For the luteal phase, the COPE scores were the sum of the last 7 days of the cycle. For the BDI, the first available score during the last 5 days of the cycle was used. For all scales during the nontreatment phase (cycles 1 and 2), the mean score was used. All demographic information is summarized using descriptive statistics. The mean luteal phase results for the COPE total and factor scores and the BDI were compared using a repeated-measures analysis of variance. The treatment and period effects were tested using the F statistic. The mean change from baseline for the luteal phase COPE total score and factor scores and the BDI after 1 and 2 cycles of treatment were compared using a paired t test. Differences between the proportions of women with various characteristics (ie, adverse effects, adverse events, or treatment response) during the treatment phase of sertraline vs placebo were compared using the McNemar test. All statistical testing was 2 tailed, with a 5% criterion level required for significance.
a large, placebo-controlled, multicenter study\textsuperscript{14} suggest that sertraline, administered throughout the menstrual cycle, has significant efficacy in reducing the core symptoms of PMDD and in improving luteal phase psychosocial functioning.

The present study was undertaken to test the efficacy and tolerability of a late-luteal phase dosing strategy with sertraline.

### RESULTS

#### PATIENT CHARACTERISTICS

Of 189 women who met the initial entrance criteria and were screened, 57 had sufficiently large increases in their COPE total score to be assigned to the study. The women were randomized for the 2 treatment phases into groups, the characteristics of which are shown in Table 1. Of the 16 characteristics examined, only 2 differed significantly between groups: age (\(P = .03\)) and baseline midfollicular phase COPE total score (\(P = .02\)). No outcome measure differed between groups during the baseline test.

#### CLINICAL OUTCOMES

Figure 1 shows the average changes from follicular to luteal phases in COPE total scores for each of 6 trial cycles (cycles 1 and 2 are baseline, 3 and 4 are first treatment interventions, and 5 and 6 are second treatment interventions).
Participants and excluded 7 women who withdrew before the end of the first month of drug treatment. A statistically significant treatment effect was found for the COPE total (P = .01), behavioral factor (P < .01), and physical factor (P = .03) scores. The BDI (P = .09) was not different because of treatment. Table 2 presents the change in scores related to study treatments and statistical comparisons.

Administration of placebo also produced a decrease in COPE scores. However, 70% (31/44) of participants showed at least a 30% reduction in luteal phase COPE total score after the first cycle of sertraline treatment compared with 50% (22/44) of participants after the first cycle of placebo administration (P < .05).

The effect of the order of administering placebo and sertraline was examined by comparing the differential carry-over effect during the crossover portion of the study. No statistical differences were found for the luteal phase COPE total (P = .61), behavioral factor (P = .75), or physical factor (P = .49) score or the BDI (P = .97).

ADVERSE EVENTS AND ATTRITION

In general, sertraline treatment was well tolerated. Only 1 adverse event—inomnia—was reported by 10% or more of participants. This occurrence, in 8 participants (14%) taking sertraline vs 4 (7%) taking placebo, was

| Table 2. Baseline Luteal Phase Scores and Change From Baseline for Efficacy Measures* |
|---------------------------------|-----------------|-----------------|
|                                  | Sertraline       | Placebo         | P†               |
| Adjusted baseline COPE total score | 127 ± 67        |                 |                 |
| Change from baseline             |                 |                 |                 |
| After 1 cycle of treatment       | −61 ± 46        | −36 ± 72        | .11              |
| After 2 cycles of treatment      | −79 ± 65        | −43 ± 82        | .01              |
| Adjusted baseline COPE behavior factor score | 78 ± 43        |                 |                 |
| Change from baseline             |                 |                 |                 |
| After 1 cycle of treatment       | −47 ± 33        | −28 ± 48        | .08              |
| After 2 cycles of treatment      | −55 ± 45        | −30 ± 58        | .01              |
| Adjusted baseline COPE physical factor score | 50 ± 27        |                 |                 |
| Change from baseline             |                 |                 |                 |
| After 1 cycle of treatment       | −14 ± 19        | −8 ± 28         | .27              |
| After 2 cycles of treatment      | −24 ± 26        | −13 ± 27        | .02              |
| Adjusted baseline Beck Depression Inventory total score | 11 ± 8        |                 |                 |

*Scores are given as mean ± SD. Negative scores imply reduction (improvement) from baseline scores. Baseline values are computed by taking the mean pretreatment score for all 57 patients across cycles 1 and 2. COPE indicates calendar of premenstrual experiences.

†Based on a paired t test on the difference between the mean change for sertraline and placebo.
The results of this double-blind, placebo-controlled, crossover study provide solid evidence that moderate-to-severe PMDD can be effectively treated with sertraline using a late-luteal phase dosing strategy. The behavioral and physical symptoms of PMDD responded significantly to sertraline treatment, although improvement with sertraline treatment was somewhat greater for the behavioral symptoms. Improvement began to be observed after the first cycle of treatment but was greater after the second cycle of treatment.

Most women responded well to administration of sertraline, 50 mg, but approximately 1 in 4 seemed to benefit more from a dose of 100 mg. At these doses—administered during the latter half of the menstrual cycle—sertraline treatment was well tolerated, with no notable adverse effects compared with placebo except increased insomnia in 8 (14%) of women. Despite abrupt discontinuation of sertraline use at the onset of menses, there were no reports of withdrawal symptoms.

The magnitude of improvement in the present study, using a late-luteal phase dosing strategy, was comparable to that reported for continuous treatment with sertraline throughout the menstrual cycle. Yonkers and colleagues also found notable improvement in psychosocial functioning after sertraline treatment. Psychosocial outcome was not assessed in the present study.

It is of interest to speculate as to why sertraline treatment, limited to the late-luteal phase, would be equally effective as treatment throughout the menstrual cycle. There is indirect evidence for altered serotonergic activity in the late-luteal phase in women with PMDD. It has been hypothesized that this may be caused, at least in part, by the effect of gonadal hormones on the serotonin system. Augmentation of serotonergic activity because of short-term sertraline treatment may be sufficient to correct serotonergic hypofunctioning, even without eliciting the changes in postsynaptic receptors that seem to be necessary for typical antidepressant drug response. For this reason, late-luteal phase dosing is likely to have less efficacy in patients with PMDD complicated by comorbid dysthymia or with other forms of affective illness.

Late-luteal phase use of sertraline seems to be a promising treatment strategy for management of PMDD. It offers some financial advantages over daily dosing throughout the menstrual cycle. Whether late-luteal phase dosing offers any advantages in terms of increased compliance is uncertain. A larger, confirmatory trial is indicated that should include quality-of-life and psychosocial measures and a maintenance phase to assess the long-term outcome of late-luteal phase sertraline treatment.

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REFERENCES