Symptom-Onset Dosing of Sertraline for the Treatment of Premenstrual Dysphoric Disorder

A Randomized Clinical Trial

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IMPORTANCE Serotonin reuptake inhibitors (SRIs) are efficacious treatments for premenstrual dysphoric disorder (PMDD) when given daily or for half of the menstrual cycle during the luteal phase. Preliminary studies suggest that SRI treatment can be shortened to the interval from symptom onset through the beginning of menses.

OBJECTIVE To determine the efficacy of symptom-onset dosing with the SRI sertraline hydrochloride for treatment of PMDD.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, placebo-controlled, multisite, parallel-group randomized clinical trial conducted September 1, 2007, to February 29, 2012, at 3 university medical centers. In all, 252 women with PMDD started treatment at symptom onset and continued until the first few days of menses for 6 menstrual cycles. Intent-to-treat analyses were performed February 28, 2014, through April 21, 2015.

INTERVENTIONS Placebo or sertraline hydrochloride, 50 to 100 mg/d, during the symptomatic interval.

MAIN OUTCOMES AND MEASURES Premenstrual Tension Scale (PMTS) score was the primary outcome measure (score range, 0-36; 36 indicates most severe score). Secondary outcome measures included the Inventory of Depressive Symptomatology–Clinician-Rated (IDS-C) (score range, 0-84; 84 indicates most severe score), Daily Record of Severity of Problems (DRSP) (total and subscale scores; higher scores indicate most severe problems), Clinical Global Impression (CGI) scales (score range, 1-7; 7 indicates most severe symptoms and least improvement), and Michelson SSRI (Selective SRI) Withdrawal Symptoms Scale scores (range, 0-51; higher scores indicate more severe withdrawal symptoms).

RESULTS Among the participants, 125 with PMDD were randomized to sertraline, and 127 to placebo. At baseline the mean (SD) PMTS scores for sertraline and placebo were 22.3 (4.8) and 21.4 (4.5), respectively, which declined to 11.7 (6.8) and 12.0 (6.9), respectively; group mean difference, 1.88 (95% CI, 0.01-3.75; P = .06). The mean (SD) estimated difference in IDS-C scores between baseline (35.4 [10.7] for sertraline; 32.8 [10.4] for placebo) and the end point (15.3 [10.7] for sertraline; 17.8 [11.0] for placebo) favored the sertraline group by 5.14 (95% CI, 1.97-8.31) points (P = .02). Compared with the placebo group, those assigned to sertraline showed greater improvement on the total DRSP score (estimated mean difference, 1.09 [95% CI, 0.96-1.25] points; P = .02) and Anger/Irritability DRSP subscale score (1.22 [95% CI, 1.05-1.41] points; P < .01) and were more likely to respond to treatment (77 of 115 patients [67.0%] for sertraline and 65 of 124 [52.4%] for placebo; χ² = 5.23; P = .02). The mean (SD) number of symptomatic days before treatment diminished over time (sertraline, −0.7 [3.4] days; placebo, −1.0 [3.2] days), with no group differences in symptomatic days or the Michelson SSRI Withdrawal Symptoms Scale.

CONCLUSIONS AND RELEVANCE Depending on the symptom scale, women with PMDD may or may not benefit from SRI treatment during the interval from the onset of premenstrual symptoms through the first few days of menses. Abrupt treatment cessation was not associated with discontinuation symptoms.

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A wealth of evidence supports the use of serotonin reuptake inhibitors (SRIs) in the management of premenstrual dysphoric disorder (PMDD) as a daily treatment or exclusively during the luteal phase of the menstrual cycle. However, symptoms are typically present for only 4 to 7 days before the onset of menses, leading to questions about the potential efficacy of treatments that fit this shorter time frame. Small studies show that SRI administration for only 1 week or initiated at symptom onset is therapeutic. At present, to our knowledge, no large, placebo-controlled randomized clinical trials have assessed the efficacy and response parameters of symptom-onset dosing of SRIs for PMDD.

With this unique treatment format comes questions about feasibility and adverse events. Many women experience difficulty anticipating the onset of symptoms or attribute symptoms to environmental stressors rather than PMDD. This response can complicate a woman’s ability to determine the optimal time to commence treatment. In addition, a number of reports cite difficulties with abrupt cessation of SRI therapy and the emergence of a discontinuation syndrome. Intermittent treatment for PMDD, by definition, includes treatment that is abruptly stopped after a short interval. Thus, a clinical trial of an intermittent treatment would benefit from the evaluation of feasibility and the risk for discontinuation symptoms.

Herein we report the results of a randomized clinical trial that evaluated symptom-onset dosing of sertraline hydrochloride for the treatment of PMDD. Sertraline hydrochloride is an effective treatment when given only in the luteal phase at doses of 50 to 100 mg/d. Our a priori hypothesis was that sertraline hydrochloride given at flexible doses of 50 to 100 mg/d during the symptomatic interval would be feasible and more effective than placebo in the treatment of PMDD. Our assessment includes secondary outcome data on improvement according to emotional and physical domains. Process outcomes, including the interval from symptom onset, initiation of treatment during the course of the trial as a measure of feasibility, and possible discontinuation symptoms are also reported.

**Methods**

**Study Design and Eligibility**

This double-blind, placebo-controlled, multisite, parallel-group randomized clinical trial included a minimum 2-month pretrial assessment to confirm a diagnosis of PMDD. Participants were randomized to receive sertraline or placebo in a 1:1 ratio. The study pills were taken daily during the symptomatic interval for 6 menstrual cycles (Figure). Women who did not achieve a Clinical Global Impression scale Severity (CGI-S) rating of 2 or less, indicating a reduction in severity of symptoms, after 2 months at a dosage of 100 mg/d or the highest tolerated dosage were offered removal from the trial and daily sertraline rescue treatment. Participants who completed the trial were also offered 3 months of open-label, daily continuation treatment. Ratings during rescue and continuation treatments were not included in the efficacy analysis. The full study protocol can be found in Supplement 1. This study was approved by the human subjects’ boards at the Yale School of Medicine, Cornell Weill Medical Center, and Virginia Commonwealth University. All participants provided written informed consent.

**Participants**

Women were eligible if they were 18 to 48 years of age, had menstrual cycles of 21 to 35 days, and met criteria for PMDD. Women were ineligible if they currently met criteria for a major depressive episode, bulimia, or a substance use condition other than tobacco use; had lifetime bipolar disorder or a psychotic illness; had severe suicidal thoughts; were undergoing treatment with a psychotropic medication; were using an oral contraceptive that included drospirenone (an effective treatment for PMDD); were receiving a depot hormonal preparation or using an intrauterine device that could stop menses; used any oral contraceptive for less than 6 months before screening or did not plan to continue the same hormonal contraceptive use throughout the study; used an inadequate birth control method; had a history of hypersensitivity to sertraline; were pregnant or lactating; were planning on relocating during the study period; or were unable or unwilling to provide informed consent.
Randomization and Masking
Recruitment occurred from September 1, 2007, through February 29, 2012. Randomization and preparation of study pills occurred at the Yale University School of Medicine. We used a computer-generated randomization list that stratified assignment into block sizes of 6 and 6 strata based on the study site and participant use (yes or no) of an oral contraceptive. A research assistant who had no contact with the participants prepared sequentially numbered stock bottles that had no information about the test drug. Sites were sent 2 lists (yes or no for oral contraceptives) specific for their center and stock bottles. A research assistant who was part of the study team took stock bottles in sequence from the appropriate list, filled a smaller bottle, and added a medication event-monitoring system cap. The prepared bottle was given to the participant. The research assistant replaced pills from the stock bottle at monthly visits as needed. In this way, the masking of study medication was maintained.

Procedures
This study was conducted in New Haven, Connecticut; New York, New York; and Richmond, Virginia. Participants were recruited via flyers, newspaper advertisements, and direct mail sent to women aged 18 to 40 years in local zip codes. Respondents completed a brief prescreening telephone interview that included verbal consent to participate. Provisionally eligible women attended a screening office visit wherein we obtained information about premenstrual symptoms, concurrent medical conditions, and use of medications. Study staff gave respondents daily symptom rating forms that were returned weekly. Respondents were allowed to chart symptoms for an additional cycle if 1 of 2 cycles did not meet criteria. Participants were reimbursed $15 for the study visit and $50 for completion of daily ratings. Women who did not meet criteria were given treatment referrals.

We used the Daily Record of Severity of Problems (DRSP)
 to establish a diagnosis of PMDD prospectively. The DRSP consists of 21 items that reflect the 11 candidate symptoms for PMDD according to the DSM-IV and DSM-5. Some symptoms are broken into several component items. Each item is scored from 1 to 6 points, with 6 indicating the most severe problems. As in past studies, a diagnosis of PMDD required a minimal mean luteal-phase score of mild (≥3 on a 6-point scale) for at least 5 PMDD symptoms, including at least 1 mood symptom, during the 5 most symptomatic days of the final luteal phase and the first 2 days of menses onset; we required that a mean follicular-phase score be less than 2 on these same items.

At the baseline visit, participants were administered the Mini International Neuropsychiatric Interview to determine the presence of exclusionary diagnoses. Premenstrual symptom severity was captured through administration of the Premenstrual Tension Scale (PMTS) and the Inventory of Depressive Symptomatology–Clinician-Rated version (IDS-C). A clinician (K.A.Y., S.G.K., or M.A.) assigned a CGI-S score and obtained urine samples for a pregnancy test.

Follow-up visits were 5 to 7 days after the onset of men- mena wherein we administered measures of premenstrual symp- toms, collected daily ratings, assigned CGI-S and CGI scale Improvement (CGI-I) scores, and obtained samples for urine pregnancy tests. Visits 5 and 6 were completed by telephone, whereas the other visits were face-to-face. Information on adverse events was collected at all visits. At face-to-face visits, the research assistant conducted pill counts and reconciled pill use with the menstrual chart and the medication event-monitoring system cap.

The starting dose of sertraline hydrochloride was 50 mg/d (two 25-mg capsules) to be taken once per day during the symptomatic interval. Daily ratings were reviewed at each visit with the participant to estimate when premenstrual symptoms were likely to occur. Participants were instructed to begin taking sertraline when they first noticed onset of their typical premenstrual symptoms and were asked to cease taking pills within a few days of their menstrual flow, around the time that these symptoms typically ended. The medication event-monitoring system cap recorded whether the bottle was opened, and participants recorded the days they took pills.

Participants who had an inadequate response (CGI-S, >2) were instructed to increase their daily dose to a maximum of 4 capsules (100 mg of sertraline hydrochloride). Participants were instructed to titrate the dose by 2 capsules every 2 days to the final dose of 4 capsules and follow the reverse schedule to end dosing. Women who reported moderate to severe adverse effects were allowed to reduce the daily dose to 1 capsule (25 mg of sertraline hydrochloride) but to increase the dose at the next cycle unless rate-limiting adverse effects continued. Participants were reimbursed $65 for time, transportation, and completion of daily symptom ratings.

Outcome Measures
The primary outcome measure was the PMTS; secondary outcomes included the IDS-C, DRSP, and Michelson SSRI (Selective SRI) Withdrawal Scale. The PMTS is a 10-item scale (range of possible scores, 0-36, with 36 indicating the most severe score) that includes items for irritability and/or hostility, tension, efficiency, dysphoria, motor coordination, mental and/or cognitive function, eating habits, social impairment, sex drive, and physical symptoms. The IDS-C has 28 items (range of possible scores, 0-84, with 84 indicating the most severe score) and detects appropriate variations in mood between the follicular and luteal phases in patients with PMDD. The PMTS and IDS-C were rated for the 7 days before menses. The DRSP total score was generated by computing the mean of each item during the final 5 days of the luteal phase and summing the 21 items.

Secondary outcomes also included global change in illness severity and improvement according to the CGI-S and CGI-I ratings, respectively. The possible ranges for both were 1 to 7, with 7 denoting the most severe symptoms and least improvement. In addition, treatment response was designated as 1 or 2 on the CGI-I scale; remission was indicated by a 1.

We evaluated possible discontinuation symptoms by adding items from the Michelson SSRI Withdrawal Scale to the daily charting form that contained the DRSP. The mean of each Michelson SSRI Withdrawal Scale item was summed for the 3 days after treatment ended for each menstrual cycle. Scores
Table 1. Demographic Characteristics of Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sertraline Hydrochloride (n = 125)</th>
<th>Placebo (n = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>33.7 (6.7)</td>
<td>34.6 (6.9)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>86 (68.8)</td>
<td>89 (70.1)</td>
</tr>
<tr>
<td>Black</td>
<td>19 (15.2)</td>
<td>20 (15.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15 (12.0)</td>
<td>13 (10.2)</td>
</tr>
<tr>
<td>Asian, mixed, or other</td>
<td>5 (4.0)</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College, graduate, or professional school</td>
<td>73 (58.4)</td>
<td>94 (74.0)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>51 (40.8)</td>
<td>42 (33.1)</td>
</tr>
<tr>
<td>Living with partner</td>
<td>14 (11.2)</td>
<td>20 (15.7)</td>
</tr>
<tr>
<td>Divorced or separated</td>
<td>11 (8.8)</td>
<td>14 (11.0)</td>
</tr>
<tr>
<td>Never married</td>
<td>49 (39.2)</td>
<td>51 (40.2)</td>
</tr>
<tr>
<td>Past psychiatric status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>35 (28.0)</td>
<td>43 (33.8)</td>
</tr>
<tr>
<td>Baseline length of menstrual cycle, mean (SD), d</td>
<td>27.9 (5.1)</td>
<td>27.0 (4.6)</td>
</tr>
<tr>
<td>Baseline luteal-phase DRSP score, mean (SD)</td>
<td>61.2 (20.1)</td>
<td>60.4 (17.4)</td>
</tr>
</tbody>
</table>

Abbreviation: DRSP, Daily Record of Severity of Problems.

a Unless otherwise indicated, data are expressed as number (percentage) of patients.

b Each of 21 items is scored from 1 to 6 points, with 6 indicating the most severe problems.

ranged from 0 to 51, with higher scores indicating more severe withdrawal symptoms.

The subscales from the DRSP and secondary outcomes were scored using the days and methods outlined above for the full DRSP. Items were grouped into a Depressive Symptoms subscale (ie, felt depressed, felt hopeless, felt worthless or guilty, slept more, had trouble sleeping, and felt overwhelmed), a Physical Symptoms subscale (ie, breast tenderness, bloating, headache, and joint or muscle pain), and an Anger/Irritability subscale (ie, anger and/or irritability and conflicts with people). In prior work, internal consistency of these subscales (Cronbach α) was found to be 0.90, 0.76, and 0.90, respectively.26,31 Interrater reliability was maintained throughout the trial via videotapes. The intraclass correlation coefficient was 0.8 or greater.

Statistical Analysis

Data from the intent-to-treat population were analyzed from February 28, 2014, through April 21, 2015. The distributions of all continuous variables were examined before analysis. No transformations were necessary. For the comparison of the sertraline and placebo groups, we used linear mixed-effects models for the dependent measures of PMTS, IDS-C, DRSP total and subscale, and the Michelson SSRI Withdrawal Symptoms Scale scores. We used generalized estimating equations for the ordinal CGI scales. In each repeated-measures model, fixed effects included treatment group (sertraline or placebo), time (months 1-7), the interaction between group and time, site (New Haven, New York City, or Richmond), and oral contraceptive use (yes or no). Interactions among the stratification variables, condition, and time were considered but dropped from the models when the results were nonsignificant. The best-fitting correlation structure was selected for each model based on the Schwartz Bayesian information criterion.38 Time was treated as a categorical variable, but linear effects of time were tested within each model. Post hoc comparisons of least squares means were performed to explain significant interactions and main effects. For the responder and remission (CGI-I) analysis, we used the observation from the last visit carried forward and the χ² statistic to compare the number of responders by group.

An α level of .05 was used for all overall tests of main effects and interactions. The sample size calculation was based on the PMTS. We estimated that with 143 participants per group and a dropout rate of 30%, we had 80% power to detect a medium effect size (Cohen d = 0.4) for the difference in mean change from baseline to end point between groups. Such a difference is considered clinically meaningful.

We conducted an exploratory analysis to determine changes in the interval between symptom onset and initiation of treatment during the course of the trial. We computed the mean number of symptomatic days from the DRSP after applying the following conventions. A day was considered symptomatic if a woman had at least 3 symptoms, each with a severity score of at least 3. We conducted sensitivity analyses that used 5 symptoms, but the results were not substantially different. The mean number of symptomatic days before treatment in each cycle was compared for groups over time using linear mixed-effects models. Adverse events experienced by participants were tabulated, and groups were compared with the χ² test and Fisher exact test if the cell size was less than 5.

Results

Recruitment occurred from September 1, 2007, through February 29, 2012, and included 252 participants. The first randomization occurred on November 6, 2007; the last randomization, February 20, 2012; and the final visit, July 9, 2012. Screening, randomization, and retention are illustrated in the Figure. Participant characteristics are provided in Table 1. We note a slight imbalance between groups in the percentages of participants with at least a college education.

Overall, 188 participants (74.6%) completed the trial or were moved to rescue treatment. Groups had similar retention, although more participants in the placebo (n = 9) than the sertraline (n = 3) groups were moved to rescue treatment.

The difference between the sertraline and placebo groups in rates of change for the PMTS scores was not statistically significant (F₆,₄₄₈ = 2.11 [P = .06]), with an estimated mean group difference in change from baseline to the end point of 1.88 (95%
CI, 0.01-3.75) points. Compared with the placebo group, participants in the sertraline group showed greater improvement in IDS-C scores over time (F(6,447) = 13.181 (P < .001); for the group × time interaction, F(6,447) = 2.1 (P = .06)). The estimated mean difference (95% CI) from baseline to the end point, sertraline vs placebo, was 1.88 (0.01-3.75).

Secondary outcomes showed that groups did not differ on the CGI-I ratings, although the CGI-I scale favored sertraline (χ² = 6.7 (P = .01)). The mean changes in the total and Anger/Irritability subscale scores of the DRSP were greater for the sertraline than the placebo groups, with an estimated mean difference for change from baseline to the end point for the total DRSP (1.09 [95% CI, 0.96-1.25]; P = .02) and the Anger/Irritability subscale (1.22 [95% CI, 1.05-1.41]; P < .01) scores, but we found no differences between conditions in the Depressive Symptoms and Physical Symptoms subscales (Table 3).

Seventy-seven of 115 participants in the sertraline group (67.0%) and 65 of 124 participants in the placebo group (52.4%) responded to treatment (χ² = 5.23 (P = .02)); remission was attained by 48 of 115 participants in the sertraline group (41.7%) and 39 of 124 participants in the placebo group (31.5%) (χ² = 2.73 (P = .10)). We found no interaction between treatment response and hormonal contraceptive use on any of the continuous outcome measures. The number of symptomatic days between symptom onset and the initiation of treatment shortened significantly for both groups (mean [SD] change, −0.7 [3.4] days for the sertraline group vs −1.0 [3.2] days for the placebo group) during the course of the trial (Table 4). The time effect was not significant between groups.

Both groups acknowledged fewer and similar symptoms on the Michelson SSRI Withdrawal Symptoms Scale as the trial progressed (eTable 1 in Supplement 2), suggesting that these scores do not represent medication withdrawal. Adverse events were similar between groups with the following exceptions: 35 participants in the sertraline group (28.0%) and 15 participants in placebo group (11.8%) acknowledged nausea (χ² = 6.7 (P = .01); with time as the fixed effect, χ² = 29.9 (P < .001). The estimated mean difference (95% CI) at the end point, sertraline vs placebo, was 0.55 (0.30-1.02).

* Represents mean change from cycle 1 to the end point.
Abbreviation: DRSP, Daily Record of Severity of Problems.

Table 3. Total and Subscale Scores for the DRSP Ratings by Study Group

<table>
<thead>
<tr>
<th>Visit</th>
<th>No. of Participants</th>
<th>Total DRSP Score, Mean (SD)b</th>
<th>DRSP Subscale Score, Mean (SD)</th>
<th>Physical Symptomsd</th>
<th>Depressive Symptoms c</th>
<th>Anger/Irritability e</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sertraline Hydrochloride Group</td>
<td>Placebo Group</td>
<td>Sertraline Group</td>
<td>Placebo Group</td>
<td>Sertraline Group</td>
<td>Placebo Group</td>
</tr>
<tr>
<td>Baseline</td>
<td>113</td>
<td>115</td>
<td>60.3 (19.5)</td>
<td>59.5 (17.3)</td>
<td>7.5 (4.0)</td>
<td>7.2 (3.5)</td>
</tr>
<tr>
<td>Cycle</td>
<td>1</td>
<td>104</td>
<td>110</td>
<td>43.7 (17.4)</td>
<td>46.1 (17.2)</td>
<td>5.5 (3.0)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>95</td>
<td>104</td>
<td>38.7 (15.6)</td>
<td>44.4 (17.5)</td>
<td>4.8 (2.7)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>87</td>
<td>89</td>
<td>36.8 (15.7)</td>
<td>40.7 (14.7)</td>
<td>4.6 (2.7)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>81</td>
<td>74</td>
<td>35.3 (12.2)</td>
<td>36.9 (11.3)</td>
<td>4.3 (1.9)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>76</td>
<td>64</td>
<td>31.7 (10.5)</td>
<td>35.2 (12.7)</td>
<td>3.9 (1.6)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>58</td>
<td>51</td>
<td>32.2 (10.4)</td>
<td>36.1 (13.6)</td>
<td>3.9 (2.0)</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>55</td>
<td>49</td>
<td>−29.7 (18.8)</td>
<td>−22.4 (16.0)</td>
<td>−4.0 (4.0)</td>
<td>−2.7 (3.0)</td>
</tr>
</tbody>
</table>

Abbreviation: DRSP, Daily Record of Severity of Problems.

* For DRSP ratings, each of 21 items is scored from 1 to 6 points, with 6 indicating the most severe problems.

b For the difference between groups with treatment as the fixed effect, F1,273 = 0.1 (P = .83); with time as the fixed effect, F6.901 = 79.5 (P < .001); for the group × time interaction, F6.901 = 2.5 (P = .02). The estimated mean difference (95% CI) from baseline to the end point, sertraline vs placebo, was 1.09 (0.96-1.25).

f Includes felt depressed, felt hopeless, felt worthless or guilty, slept more, had trouble sleeping, and felt overwhelmed. For the difference between groups with treatment as the fixed effect, F1,292 = 0.8 (P = .37); with time as the fixed effect, F6.940 = 3.18 (P < .001); for the group × time interaction, F6.940 = 0.6 (P = .73). The estimated mean difference (95% CI) from baseline to the end point, sertraline vs placebo, was 1.08 (0.91-1.28).

The efficacy signal in this study was not as large as that of PMDD trials using continuous and full luteal-phase sertraline dosing.5,31 The following 4 reasons may explain this finding: (1) we included symptomatic days before the onset of treatment in the luteal phase each month; (2) a true lack of effect on depression and somatic symptom dimensions included in the PMTS, IDS-C, and total DRSP scales may have been detected; (3) the repeated counseling regarding dosage, timing, and expectation of effects of starting treatment each month...
could have increased the nonspecific response levels, which at 52.4%, was 10% to 25% higher than the rates reported in many full- and half-cycle dosing SRI trials; and (4) we may have seen significant differences in the PMTs and depression and somatic measures with a larger sample.

The effect of the Anger/Irritability subscale symptoms in this study is in line with the results from complete luteal-phase dosing studies and the hypothesis that symptoms of anger and irritability are the hallmark of the condition. The higher SD for the DRSP subscale scores for depression and somatic symptoms suggest that these symptoms were less consistently severe than irritability.

A strength of this study is the 6-cycle duration, which allowed us to demonstrate the persistence of response and increased accuracy of the treatment over time. Clinicians and patients may have concerns about determining when to initiate treatment. Daily ratings of PMDD symptoms are likely to familiarize women with their temporal pattern of symptom emergence and enable them to improve recognition of their symptomatic days. We cannot say whether the accuracy of treatment would have improved without the necessary vigilance that accompanies keeping a daily symptom rating log.

Limitations of the study include the labor and attention involved in charting symptoms that may not be easily replicated in clinical settings, the maximum dose of 100 mg of sertraline hydrochloride, and the cohort size that did not quite achieve our power estimates.

Our data support the rapid therapeutic action of SRIs for PMDD symptoms. Although a partial response can be seen in major depressive episodes within 1 week, this response is not the norm, and no evidence suggests that a response occurs within a few days, as seen in PMDD. Suggested mechanisms of a rapid response are greater sensitivity among patients with PMDD to the acute increased availability of synaptic serotonin or the increased production of allopregnanolone, an anxiolytic neurosteroid produced in greater amounts after SRI treatment. Animal studies demonstrate that SRIs increase the activity of 3α-hydroxysteroid dehydrogenase, the rate-limiting enzyme for allopregnanolone synthesis, independently of serotonin reuptake.

Treatment at symptom onset was well tolerated. Attrition rates did not differ between groups, and the rates of adverse events were generally similar, except that the sertraline group had higher rates of nausea and insomnia. We found no evidence of withdrawal symptoms after cessation of sertraline treatment each month.

Conclusions

This large, double-blind, placebo-controlled, multisite, parallel-group randomized clinical trial finds that symptom-onset dosing of sertraline demonstrated efficacy for treatment of PMDD in some of the secondary outcomes. Irritability symptoms were most responsive to symptom-onset treatment. Abrupt treatment cessation at the end of each cycle did not increase the risk for discontinuation symptoms.

ARTICLE INFORMATION
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Author Contributions: Dr Yonkers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yonkers, Kornstein, Gueorgueva, Alttemus. Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Yonkers, Kornstein, Gueorgueva, Merry, Alttemus. Critical revision of the manuscript for important intellectual content: All authors.
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