Low-Dose Sertraline in the Treatment of Moderate-to-Severe Premenstrual Syndrome: Efficacy of 3 Dosing Strategies

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Objective: Many studies have demonstrated the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of premenstrual dysphoric disorder, but few studies have investigated the efficacy of SSRIs in the treatment of premenstrual syndrome (PMS). The objective of this study was to evaluate the safety and efficacy of sertraline in the treatment of moderate-to-severe PMS using 3 different dosing strategies: luteal phase (2 cycles), followed by continuous dosing throughout the month (1 cycle), followed by dosing begun at the first onset of PMS symptoms, or "symptom-onset" dosing (1 cycle).

Method: 314 women with PMS from 22 U.S. sites were randomly assigned to fixed-dose treatment with sertraline (25 or 50 mg/day) or placebo for 4 menstrual cycles after a single-blind, placebo lead-in cycle. Assessments included the Daily Symptom Report (DSR), the Clinical Global Impressions-Severity of Illness and -Improvement scales, the Patient Global Evaluation scale, the Quality of Life Enjoyment and Satisfaction Questionnaire, and the Social Adjustment Scale-Self Report.

Results: Intermittent luteal-phase dosing with low doses of sertraline (25 and 50 mg/day) produced significant improvement across 2 menstrual cycles, based on total DSR scores, compared with placebo. Continuous and symptom-onset dosing were also effective in treating PMS symptoms, particularly at the lower dose of 25 mg/day.

Conclusions: The results of the current study suggest that low doses of sertraline may be a safe, effective, and well-tolerated treatment for moderate-to-severe PMS.

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Premenstrual syndrome represents a constellation of mood, cognitive, psychomotor, vegetative (sleep and appetite disturbance), and physical symptoms that range across a spectrum of severity and disability. The syndrome is defined by its distinctive cyclical pattern, with onset in the luteal phase and remission of symptoms within the first several days after the onset of menses.

In the past decade, premenstrual disturbances have been divided diagnostically into a severe subtype, known as premenstrual dysphoric disorder (PMDD), which occurs in 2% to 9% of women of reproductive age and is characterized by severe mood symptoms causing functional impairment,[1–4] and the broader category known as premenstrual syndrome (PMS). PMS has been estimated to occur in up to 60% of women during at least some of their menstrual cycles.[5–10]

The high prevalence of PMS has raised questions concerning its nosologic validity as a distinct diagnosis. Arguing in favor of PMS as a valid syndrome is consistent genetic evidence for a 30% to 40% heritability rate and a lack of evidence for any significant contribution from environment or learning.[11–15] While PMS appears to be associated with an increased incidence of major depressive disorder,[16] evidence suggests that the vulnerability to each condition is largely independent.[15]

One of the challenges in studying PMS has been a lack of consensus diagnostic criteria. The first working defini-

tion of PMS was developed at a National Institute of Mental Health workshop in 1983.[17] This group defined PMS as "a constellation of mood, behavioral, and/or physical symptoms that have a regular cyclical relationship to the luteal phase of the menstrual cycle, are present in most if not all cycles, and remit by the end of the menstrual flow, with a symptom-free interval of at least 1 week each cycle." The tenth revision of the *International Classification of Diseases* (ICD-10) included a diagnosis of PMS that requires only 1 premenstrual symptom and no functional impairment.[18] In contrast, the American College of Obstetricians and Gynecologists (ACOG) definition[19] requires the presence of 1 symptom or more for at least 5 days prior to menses in 2 consecutive cycles. To meet ACOG criteria, PMS symptoms must be associated with some degree of functional impairment. Furthermore, the diagnosis must be confirmed by prospective charting of symptoms for at least 2 cycles. In the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), PMDD is consigned to an appendix containing diagnoses needing "further study," while PMS is only defined in contrast to PMDD as being far more common and with a less characteristic pattern of symptoms, severity, and impairment.[20]

Consistent with the lack of consensus diagnostic criteria, few adequately designed, randomized, double-blind, placebo-controlled trials have been published that rigorously evaluate treatment efficacy in a carefully defined PMS sample.[21–24] The majority of treatment studies have focused instead on PMDD,[25,26] which has clearly defined criteria but affects a relatively small subgroup of women. These PMDD treatment studies have clearly demonstrated the efficacy of serotonergic antidepressants for this condition, when given either in continuous daily dosing throughout the menstrual cycle or in intermittent luteal-phase dosing for the last 14 days of the cycle.[25] The current study was designed to provide a double-blind, placebo-controlled evaluation of the efficacy of sertraline in moderate-to-severe PMS using 3 dosing strategies: luteal-phase dosing, continuous dosing, and symptom-onset dosing (beginning at the onset of premenstrual symptoms).

METHOD

Patient Selection

The study was conducted from February 1997 to May 1999 at 22 psychiatric and gynecological outpatient clinics in the United States. Women were recruited by means of advertisements in the media and by referrals.

Study entry criteria required women to be between the ages of 24 and 45 years inclusive, to have regular menstrual cycles lasting 24 to 36 days, and to have met criteria for PMS based on charting of symptoms using the Daily Symptom Report (DSR)[27] for 2 consecutive cycles. A total DSR score of 80 or greater for the 6 days prior to the onset of menses was required, along with at least 3 DSR items showing at least moderate severity for 2 out of 6 premenstrual days, moderate distress for at least 2 out of 6 premenstrual days, and minimal to no symptoms during the follicular phase (days 5–10).

Women were excluded for the following reasons: (1) decrease of 30% or more in DSR total score for the 6 premenstrual days during the single-blind placebo cycle (relative to the previous cycle); (2) use of oral contraceptives or other hormonal preparations within 6 months prior to screening; (3) positive human chorionic gonadotropin (β-HCG) test at screen, or currently nursing or planning pregnancy; (4) luteinizing hormone levels greater than 38 or follicle-stimulating hormone (FSH) levels greater than 20 in patients aged 38 years or older; (5) status post hysterectomy or failure to demonstrate ovulation in both cycles leading up to randomization; (6) failure to respond to an adequate trial of 2 or more antidepressants to treat premenstrual symptoms; (7) clinically symptomatic endometriosis (or treatment in past 3 months); (8) history in previous 12 months of major depressive episode or dysthymia, panic disorder, agoraphobia, generalized anxiety disorder, posttraumatic stress disorder, or substance abuse or dependence (except nicotine); (9) history in previous 2 years of an eating disorder; (10) current or lifetime history (by clinical interview) of bipolar disorder, schizophrenia or psychotic disorder, obsessive-compulsive disorder, or antisocial, schizotypal, or severe borderline personality disorder; (11) current use of any psychotropic medication; (12) positive urine drug screen; (13) current suicide risk; or (14) any acute or unstable medical illness or clinically significant laboratory abnormality.

The study was conducted in compliance with the Declaration of Helsinki (1996 revision). The study protocol and consent form were approved by the institutional review board for each study site. Study procedures were explained to patients, and written informed consent was obtained.

Prior to random assignment, each patient underwent a medical evaluation that included a physical and pelvic examination, laboratory tests (chemistry profile, thyroid panel, FSH, urine drug screen, urinalysis, and red and white blood cell counts), and a serum pregnancy test. Ovulation was confirmed by means of a urine predictor test that was completed and documented at each cycle throughout the study.

Study Design

The initial visit consisted of screening for initial inclusion and exclusion criteria, as well as instructions on how to complete the daily ratings, after which patients underwent 1 cycle of prospective ratings using the DSR to confirm the diagnosis and to establish whether there was a stable symptomatic baseline that met symptom severity

requirements. Patients were evaluated during the follicular phase, between 5 and 10 days after the onset of menses. To ensure that diagnostic criteria were met, which required 2 cycles of prospective assessment, qualifying patients then completed a second prospective cycle of charting. Luteal-phase dosing with single-blind placebo was administered during the second cycle beginning 14 days prior to the anticipated onset of menses. A baseline evaluation was made during the luteal phase, during the 3-day window prior to the anticipated onset of menses. Patients who continued to meet study entry criteria were then randomly assigned on a double-blind basis to 4 cycles of fixed-dose treatment with either 25 mg of sertraline or 50 mg of sertraline or placebo. Once assigned, patients underwent the following sequential treatment regimen: (1) 2 cycles of luteal-phase dosing, beginning on day 14 of the cycle (day 1 being the first day of menses) and continuing until the onset of menses; (2) 1 cycle of continuous dosing, beginning on day 2 of the cycle and continuing daily until the onset of menses; and (3) 1 cycle of dosing at the onset of premenstrual symptoms (as determined by the patient) and continuing until the onset of menses (symptom-onset dosing).

Patients were instructed not to self-medicate during the course of the study with any drugs that might influence their premenstrual symptomatology (e.g., hormones, diuretics, vitamins, herbal treatments, or other psychotropics).

Outcome Measures

The primary efficacy measure was the DSR[27] total score. The DSR consists of 17 common PMS symptoms rated daily on a 5-point scale (from 0 = none to 4 = severe/overwhelming/unable to function).

Secondary efficacy parameters included the following: (1) DSR factor scores: DSR-mood (anxiety, irritability, depression, nervous tension, mood swing, feeling out of control); DSR-behavioral (poor coordination, insomnia, confusion/poor concentration, headache, crying, fatigue); DSR-pain (aches, cramps, breast tenderness); and DSR-physical symptoms (food cravings, swelling). A DSR-distress item was also included at the suggestion of the protocol design advisory board. (2) The 7-point Clinical Global Impressions-Severity of Illness (CGI-S) scale and the 7-point CGI-Improvement (CGI-I)[28] scale scores. (3) Scores on the Patient Global Evaluation scale (PGE),[28] which consists of a 7-point ordinal scale (from 1 = very much improved to 7 = very much worse) that rates the degree of overall improvement in PMS symptoms compared with pretreatment baseline. Assessments were based on the past week. (4) The total score on the short version of the Quality of Life Enjoyment and Satisfaction Scale (Q-LES-Q).[29] This scale was completed at pretreatment baseline and at each on-treatment assessment visit. The patient was asked to rate quality of life (QOL) based on the previous (luteal) week. Each item is scored on a 5-point ordinal scale from 1 = very poor to 5 = very good. A total score is computed by adding the first 14 items, dividing the sum by 70 (the maximum possible total score), and multiplying the result by 100. (5) The Social Adjustment Scale-Self Report (SAS-SR),[30] a 55-item patient-rated scale that assesses work and/or housework, interpersonal relationships, and social and leisure activities during the previous week.

At each study visit, patients were questioned and data were recorded regarding any perceived adverse effects, including start and stop dates and times and severity. Investigators were asked to distinguish treatment-emergent adverse events from a patient's typical premenstrual symptoms. Vital signs and weight were also recorded at each study visit. Electrocardiogram (ECG), laboratory tests, and physical examination were performed prior to random assignment and at the end of double-blind treatment, or earlier if the patient discontinued prematurely.

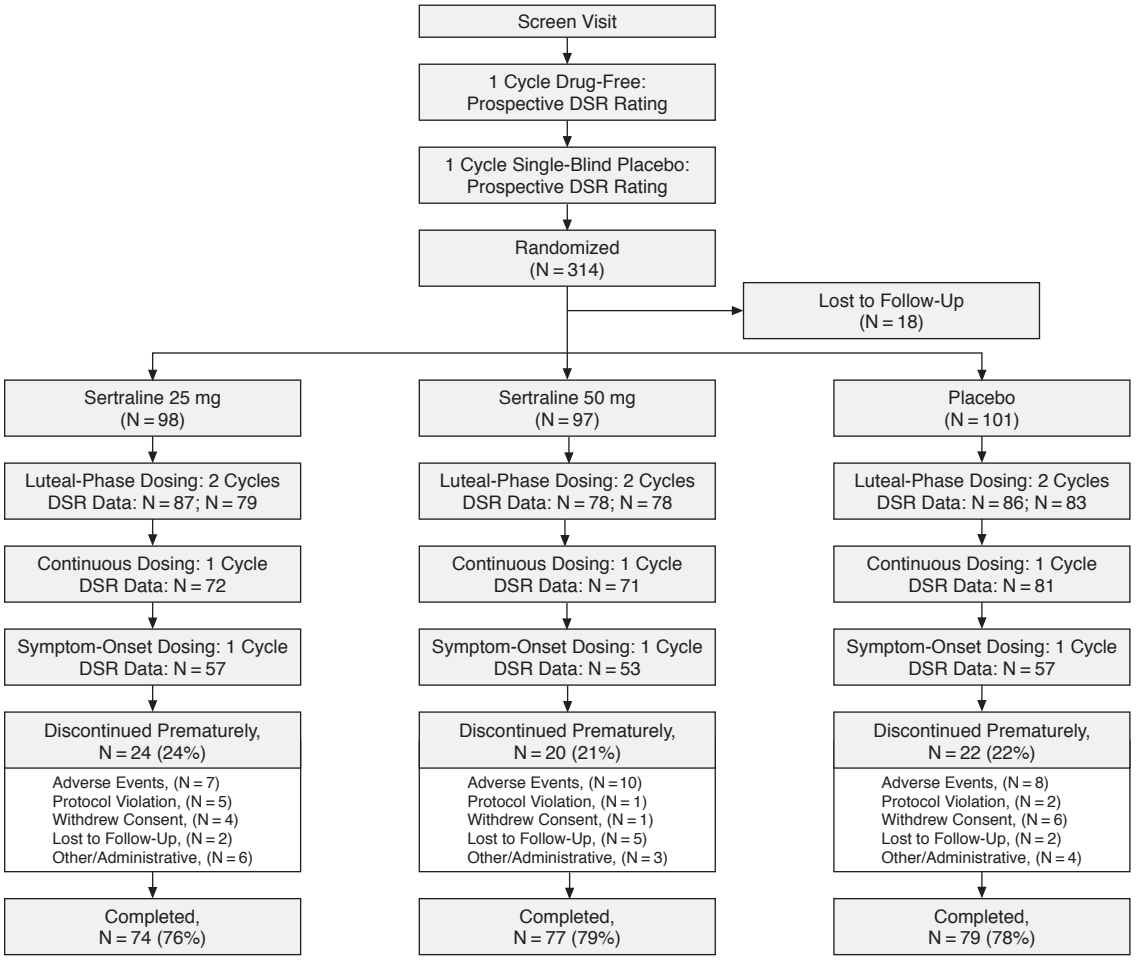
Statistical Methods

A power analysis (using SAS software, version 6.10 [SAS Institute, Inc., Cary, N.C.]) indicated that a sample size of 100 patients per treatment group provided 80% power to detect a 30-point difference in DSR 6-day total scores between sertraline and placebo groups, assuming a standard deviation of 75.

Descriptive statistical analyses were performed on baseline demographic and clinical variables. Homogeneity of key characteristics at luteal-phase baseline were investigated using analysis of variance (ANOVA) with effects for treatment and pooled center for continuous variables and generalized Cochran-Mantel-Haenszel methods for categorical responses. Distributional assumptions were examined and the equality of covariate slopes investigated prior to running analysis of covariance (ANCOVA) models. Tests for interactions using the full model were evaluated at the .10 level of significance. In the event that interactions were significant, analyses were performed to evaluate the cause of the interaction.

The primary analysis of the DSR total score used the mixed-model procedure in SAS to perform a repeated-measures analysis. Terms for treatment, pooled center, subject, cycle, and treatment-by-interaction were included in the model. The adjusted mean change from the luteal baseline DSR total score across the 2 luteal-dosing cycles (with the DSR totals averaged over the 2 cycles) was the primary a priori outcome, with comparisons of each sertraline dosage group with placebo of primary interest. The DSR total score, the 4 DSR factor totals, the DSR-distress item, the Q-LES-Q total score, the SAS-SR total and factor scores, and the CGI-S score were analyzed using ANCOVA models on the endpoint of cycles 1 and 2 (luteal cycles) and observed cases at cycles 3 and 4. ANOVA models excluding the baseline term were performed on the

Figure 1. Study Design and Patient Disposition[a]



[a]The sample size with available Daily Symptom Report (DSR) data at each cycle was smaller than the safety evaluation sample.

PGE and the CGI-I. All statistical tests were 2-sided and were performed at the .05 level of significance. No adjustments for multiple comparisons were made.

RESULTS

Patient Characteristics

Patient characteristics were similar in each of the 3 treatment groups: sertraline 25 mg (N = 103, mean ± SD age = 36.3 ± 5.4 years, 93% white, 12.6% reporting a prior history of depression), sertraline 50 mg (N = 106, mean ± SD age = 36.1 ± 5.3 years, 95% white, 16.0% reporting a prior history of depression), and placebo (N = 105, mean ± SD age = 35.4 ± 4.7 years, 92% white, 16.0% reporting a prior history of depression).

Patient Disposition

Of the 314 patients who were randomly assigned to receive study drug, 18 were lost to follow-up (Figure 1), and 91 patients taking sertraline 25 mg, 88 patients taking sertraline 50 mg, and 90 taking placebo had at least 1 postrandomization assessment and therefore met study criteria for the intent-to-treat sample (N = 269). Overall, 78% of patients completed all 4 cycles of study treatment. Premature discontinuation rates were approximately similar with sertraline 25 mg (24%), sertraline 50 mg (21%), and placebo (22%).

Primary and Secondary Efficacy Measures

The primary a priori analysis was change in the DSR total score for luteal-phase dosing analyzed by a repeated-measures ANCOVA across 2 menstrual cycles. Significant improvement was observed on this outcome with both the 25-mg and 50-mg doses of sertraline (Table 1). Significant improvement in DSR total score was also observed with the 25-mg (but not the 50-mg) dose of sertraline using both continuous and symptom-onset dosing strategies. The primary DSR analyses were based on the 6

Table 1. Treatment Response[a] on Primary and Secondary Efficacy Measures

Measure	Baseline	After Luteal-Phase Dosing[a]	After Continuous Dosing	After Symptom-Onset Dosing
DSR-total score, mean ± SE				
Sertraline 25 mg	26.5 ± 10.7	–12.6 ± 1.2*	–16.0 ± 1.1†	–14.2 ± 1.5*
Sertraline 50 mg	28.2 ± 10.0	–12.1 ± 1.2*	–13.3 ± 1.1	–13.0 ± 1.5
Placebo	26.2 ± 10.5	–8.8 + 1.2	–10.7 ± 1.1	–10.0 ± 1.5
DSR-total score on 3 most symptomatic days, mean ± SE				
Sertraline 25 mg	26.5 ± 10.7	–7.5 ± 1.2*	–10.0 ± 1.3†	–8.5 ± 1.6‡
Sertraline 50 mg	28.2 ± 10.0	–6.2 ± 1.3	–7.8 ± 1.3	–6.9 ± 1.7
Placebo	26.2 +10.5	–3.8 ± 1.2	–4.7 ± 1.2	–4.1 ± 1.7
DSR-mood factor, mean ± SE				
Sertraline 25 mg	10.7 ± 4.7	–5.9 ± 0.5*	–7.0 ± 0.5†	–5.6 ± 0.7
Sertraline 50 mg	11.4 ± 4.4	–5.3 ± 0.5	–5.9 ± 0.5	–5.8 ± 0.7
Placebo	10.7 ± 4.9	–4.5 ± 0.5	–4.8 ± 0.5	–4.1 ± 0.7
DSR-behavioral factor, mean ± SE				
Sertraline 25 mg	7.9 ± 4.1	–4.3 ± 0.3‡	–5.0 ± 0.4†	–4.5 ± 0.5*
Sertraline 50 mg	8.4 ± 4.0	–3.5 ± 0.4	–4.1 ± 0.4	–3.7 ± 0.5
Placebo	7.9 + 4.1	–3.4 ± 0.3	–3.3 ± 0.3	–3.2 ± 0.5
DSR-pain factor, mean ± SE				
Sertraline 25 mg	4.0 ± 2.4	–1.7 ± 0.2	–2.0 ± 0.2*	–2.2 ± 0.3
Sertraline 50 mg	4.2 ± 2.3	–1.5 ± 0.2	–1.7 ± 0.2	–1.8 ± 0.3
Placebo	3.8 ± 2.3	–1.6 ± 0.2	–1.5 ± 0.2	–1.6 ± 0.3
DSR-physical symptoms factor, mean ± SE				
Sertraline 25 mg	3.9 ± 1.8	–1.7 ± 0.2	–2.0 ± 0.2†	–2.0 ± 0.2*
Sertraline 50 mg	4.2 ± 2.0	–1.7 ± 0.2	–1.6 ± 0.2	–1.7 ± 0.2
Placebo	3.8 ± 1.7	–1.3 ± 0.2	–1.2 ± 0.2	–1.2 ± 0.2

[a]Least squares (LS) mean (± SE) change scores for Daily Symptom Report (DSR) total score are based on repeated-measures analysis of covariance (ANCOVA) of 2 cycles (luteal-phase dosing). The a priori analysis was performed using scores for the 6 days prior to the onset of menses (except for the analysis of the 3 most symptomatic days). The LS means for the continuous and symptom-onset dosing for all parameters were computed from an ANCOVA model using the observed-case value at each cycle. For the luteal-dosing phase, for all parameters except DSR total, the LS means are from an ANCOVA model using the endpoint of cycles 1 and 2. See Figure 1 for sample size with available DSR data at each treatment cycle.

*$p < .05$.
†$p < .01$.
‡$p < .08$.

days prior to the onset of menses. An alternative scoring method, using the 3 most symptomatic premenstrual days, was also declared a priori. Results of this analysis found significantly greater improvement versus placebo with the 25-mg (but not the 50-mg) dose of sertraline in all but the symptom-onset dosing strategies (Table 1).

Results for the secondary efficacy measures, consisting of the standard DSR-factor scores, are also summarized in Table 1. Again, significant improvement was observed, but less consistently, with sertraline 25 mg relative to placebo, while improvement was not significant with sertraline 50 mg.

Three global measures were used to evaluate overall improvement, 2 clinician-rated (CGI-S and CGI-I), and 1 patient-rated (PGE). The 25-mg dose of sertraline was significant relative to placebo on the CGI-S on continuous and symptom-onset dosing, but not on luteal-phase dosing (Table 2). In contrast, the 25-mg dose of sertraline achieved significance on the CGI-I score across all 3 dosing strategies (Table 2). On both global measures across all 3 dosing strategies, the 50-mg dose of sertraline was significant only on symptom-onset dosing on the CGI-I (Table 2). Interestingly, sertraline 50 mg was significant relative to placebo on all 3 dosing strategies on the Patient Global Improvement scale, while sertraline 25 mg was significant only on 2 of the 3 dosing strategies (luteal-phase and symptom-onset dosing).

Using standard CGI-I response criteria (CGI-I score ≤ 2; "much" or "very much" improved), treatment with both doses of sertraline was significant relative to placebo when using luteal-phase dosing (Figure 2). On continuous and symptom-onset dosing, responder rates were significant relative to placebo only with the 25-mg dose of sertraline. There was a notable increase in placebo response in the third and fourth menstrual cycle compared with the first 2 cycles.

Results for secondary QOL and social-adjustment measures are summarized in Table 2. Significant efficacy relative to placebo in QOL and social adjustment was only occasionally achieved, most notably with the 25-mg dose using a continuous-dosing regimen.

Improvement in PMS Subgroup: Post Hoc Comparison of Outcome

Though patients met screening criteria for PMS at study entry, a subgroup reported sufficient symptom

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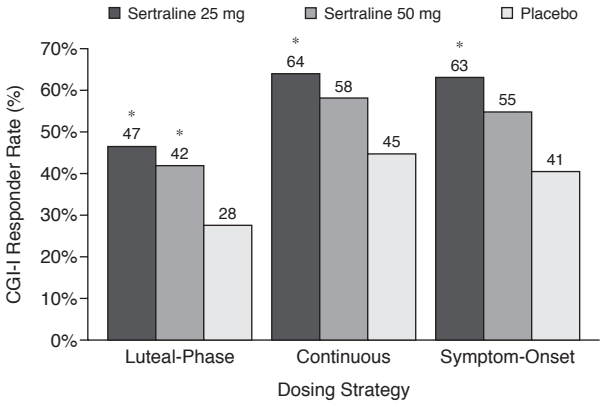
Table 2. Treatment Response on Functional, Quality-of-Life, and Global Measures[a]

Measure	Baseline	After Luteal-Phase Dosing[a]	After Continuous Dosing	After Symptom-Onset Dosing
DSR-distress score, mean ± SE				
Sertraline 25 mg	2.4 ± 0.7	–1.0 ± 0.1‡	–1.2 ± 0.1†	–1.1 ± 0.1‡
Sertraline 50 mg	2.4 ± 0.7	–0.9 ± 0.1	–1.1 ± 0.1*	–1.0 ± 0.1
Placebo	2.4 ± 0.8	–0.8 ± 0.1	–0.7 ± 0.1	–0.8 ± 0.1
Q-LES-Q score, mean ± SE				
Sertraline 25 mg	66.2 ± 12.3	10.5 ± 1.3	11.9 ± 1.4†	9.4 ± 1.3
Sertraline 50 mg	65.5 ± 10.8	9.4 ± 1.3	9.7 ± 1.4‡	9.9 ± 1.3
Placebo	64.4 ± 12.8	8.5 ± 1.3	6.1 ± 1.4	6.7 ± 1.3
SAS-SR total score, mean ± SE				
Sertraline 25 mg	1.1 ± 0.4	–0.3 ± 0.1	–0.4 ± 0.1*	–0.3 ± 0.1
Sertraline 50 mg	1.2 ± 0.5	–0.3 ± 0.1	–0.2 ± 0.1	–0.3 ± 0.1
Placebo	1.2 ± 0.4	–0.2 ± 0.1	–0.2 ± 0.1	–0.2 ± 0.1
CGI-S score, mean ± SE				
Sertraline 25 mg	4.4 ± 0.8	–1.4 ± 0.1	–1.7 ± 0.1*	–1.7 ± 0.2*
Sertraline 50 mg	4.5 ± 0.8	–1.5 ± 0.1	–1.6 ± 0.1‡	–1.6 ± 0.1‡
Placebo	4.4 ± 1.0	–1.2 ± 0.1	–1.2 ± 0.1	–1.2 ± 0.1
CGI-I score, mean ± SE				
Sertraline 25 mg		2.4 ± 0.1*	2.3 ± 0.1†	2.3 ± 0.1†
Sertraline 50 mg		2.5 ± 0.1	2.5 ± 0.1‡	2.4 ± 0.1†
Placebo		2.7 ± 0.1	2.8 ± 0.1	2.9 ± 0.1
PGE score, mean ± SE				
Sertraline 25 mg		2.5 ± 0.1*	2.5 ± 0.1	2.4 ± 0.1†
Sertraline 50 mg		2.3 ± 0.1†	2.3 ± 0.1*	2.3 ± 0.1†
Placebo		2.8 ± 0.1	2.7 ± 0.1	2.9 ± 0.1

[a]The least squares means for the continuous and symptom-onset dosing were computed from an analysis of covariance model using the observed-case value at each cycle. For luteal-phase dosing, the endpoint of cycles 1 and 2 were used.
*p < .05.
†p < .01.
‡p < .08.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, DSR = Daily Symptom Report, PGE = Patient Global Evaluation scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SAS-SR = Social Adjustment Scale-Self Report.

Figure 2. CGI-I Responder Rates



*p < .05.
Abbreviation: CGI-I = Clinical Global Impressions-Improvement scale.

severity to qualify symptomatically for a diagnosis of PMDD. A comparison was made (Table 3) between the "pure" PMS subgroup (excluding women meeting criteria for PMDD) and the total sample in terms of 2 DSR-derived metrics: drug versus placebo effect size for each treatment cycle and percent improvement from baseline. The latter outcome was included in an attempt to capture the magnitude of improvement over baseline, while effect size provided a measure of drug-specific effect. The results suggest that patients with "pure" PMS have levels of improvement comparable with the more severely symptomatic total sample.

Treatment Tolerability

Sertraline was safe and generally well-tolerated at doses of 25 mg and 50 mg per day. Sertraline tolerability exhibited a modest dose effect, with comparable adverse event rates with the 25-mg dose of sertraline and placebo and a somewhat higher adverse event rate with the 50-mg dose (Table 4). In all 3 treatment groups, the majority of adverse events were mild or moderate in intensity. Adverse events reported in the current sample were similar to those reported in sertraline trials in other indications. Rates of discontinuation due to treatment-emergent adverse events were also similar for sertraline 25 mg (7%) and placebo (8%) and modestly higher for sertraline 50 mg (10%). One serious adverse event (a miscarriage) was reported with sertraline 25 mg. After 15 days of luteal-phase dosing with sertraline 25 mg during the first blinded treatment cycle, 1 patient developed a positive serum β-HCG test 16 days after the last dose of sertraline; a miscarriage occurred 18 days after the last dose.

Table 3. Magnitude of Treatment Effect by Treatment Strategy and Dose Used: Comparison of the "Pure" PMS Subgroup With the Total Sample (Daily Symptom Report-total score data)

	Sertraline 25 mg				Sertraline 50 mg				Placebo	
	Total Sample (N = 87)		PMS Subgroup (N = 74)		Total Sample (N = 78)		PMS Subgroup (N = 71)		Total Sample (N = 86)	PMS Subgroup (N = 75)
Treatment Strategy	Effect Size[b]	Improved, %	Effect Size[b]	Improved, %	Effect Size[b]	Improved, %	Effect Size[b]	Improved, %	Improved, %	Improved, %
Luteal-phase dosing[a]	0.32	53	0.33	52	0.14	43	0.18	42	41	40
Continuous dosing	0.55	60	0.60	61	0.27	47	0.29	45	41	39
Symptom-onset dosing	0.37	54	0.37	56	0.26	46	0.21	45	39	40

[a]Cycle 2 data only.
[b]Effect size was calculated as the sertraline vs. placebo Daily Symptom Report-total difference score divided by the mean standard deviation.
Abbreviation: PMS = premenstrual syndrome.

Table 4. Treatment-Emergent Adverse Events by Dose[a]

Event	Sertraline 25 mg (N = 98), %	Sertraline 50 mg (N = 97), %	Placebo (N = 101), %
Insomnia	14	20	9
Nausea	10	21	6
Upper respiratory tract infection	6	10	7
Headache	13	6	8
Patients with ≥ 1 adverse event	69	80	62

[a]All causality, incidence ≥ 10%.

The proportion of patients with clinically significant abnormalities on laboratory tests, vital signs, body weight, or ECG was similar for both doses of sertraline and placebo.

DISCUSSION

To our knowledge, this is the first study to evaluate the efficacy of low-dose antidepressant medication for the treatment of moderate-to-severe PMS, and also the first placebo-controlled study evaluating the symptom-onset dosing strategy. The results of the current study support the conclusion that intermittent, luteal-phase dosing with low doses of sertraline (25 and 50 mg/day) is an effective treatment for PMS. The primary a priori efficacy parameter, improvement in DSR total score, was significant for both doses of sertraline across 2 menstrual cycles. Secondary analyses indicate that both of the alternative dosing strategies (continuous and symptom-onset dosing) are also effective in treating the symptoms of PMS, more consistently so for the lower dose of 25 mg per day. For example, the 25-mg/day dose of sertraline demonstrated significantly greater improvement on the CGI-I scores on all 3 dosing strategies, and on 2 of 3 dosing strategies (continuous and symptom-onset) on the CGI-S. In contrast, treatment with the 50-mg/day dose of sertraline was associated with significantly greater global effect than placebo only on continuous dosing as measured by the CGI-I scale.

Using a CGI-I score of "much" or "very much" improved as a criterion for response, both doses of sertraline achieved significantly higher responder rates than placebo. Statistical significance was maintained for the 25-mg/day dose of sertraline on subsequent cycles of continuous and symptom-onset dosing, but not for sertraline 50 mg/day. The loss of significance with the 50-mg/day dose was not due to a loss of treatment effect over time but appeared to be largely due to a notable increase in the placebo response rate in the last 2 treatment cycles. The explanation for this phenomenon is uncertain, but it is commonly seen in other PMS and PMDD studies and may be attributable to nonspecific therapeutic effects of daily ratings and study participation over time.[31] Alternatively, the high placebo response rate could be attributable to naturalistic fluctuation in illness severity among individuals with PMS. In the current study, the high placebo response rate may also be due to the intrinsically lower symptom severity of PMS compared with PMDD, since some studies suggest that placebo response may be inversely related to illness severity at pretreatment baseline.[31–33]

Improvement in PMS symptoms with sertraline was associated with parallel improvement in quality-of-life and social-functioning measures, but the degree of improvement was only intermittently significant relative to placebo. This disparity is likely attributable to a "floor effect": when the current PMS study is compared with typical PMDD treatment studies,[34,35] the degree of baseline impairment is notably less on both quality-of-life measures (baseline Q-LES-Q score: 66 vs. 60–63) and on social-adjustment measures (baseline SAS-SR score: 1.1 vs. 2.2–2.4). The presence of greater impairment in the latter studies is consistent with DSM-IV criteria requiring functional impairment to qualify for a PMDD diagnosis.

As expected given the low doses administered, sertraline was very well-tolerated in the current sample of women with PMS. The most effective dose, sertraline 25 mg, was similar to placebo in the incidence of adverse events.

The efficacy of luteal-phase treatment with sertraline in the current study extends, to a milder part of the PMS

spectrum, the results of a previous study that reported benefit from luteal-phase sertraline in patients meeting DSM-IV criteria for PMDD.[35] Several luteal dosing studies with other antidepressants for PMDD have also shown efficacy.[36–39]An exploratory post hoc analysis in the current study evaluated the efficacy of the 3 dosing strategies in a "pure" PMS subgroup, which excluded patients (~20%) whose symptomatology was sufficiently severe that it was in the PMDD range of severity. The effect size of sertraline was similar, across all 3 dosing strategies, in the milder "pure" PMS subgroup when compared with the more severe total sample.

In addition to luteal-phase dosing, the current study also explores 2 alternative antidepressant treatment strategies, continuous and symptom-onset dosing. While many previous studies have demonstrated the efficacy of continuous daily dosing,[25] to our knowledge this is the first placebo-controlled study to be published that examines the use of symptom-onset dosing. A recent study suggested that symptom-onset escitalopram was equivalent in efficacy to luteal-phase escitalopram in women with PMDD.[38] The current study differs from the study with escitalopram in the inclusion of women with PMS, the use of low-dose antidepressant medication, and the inclusion of a placebo control. Since patients prescribed intermittent luteal dosing may forget to begin their antidepressant until they become symptomatic, symptom-onset dosing may prove to be a practical treatment regimen. In addition, this regimen offers less medication exposure and lower cost than the other 2 strategies.

The main limitations of the current study include the homogeneity of the sample in terms of absence of medical and psychiatric comorbidity, which reduces the generalizability of the results to broader clinical settings, and the short duration of the study, which did not permit us to evaluate whether efficacy for each treatment strategy would be sustained over time. An additional important limitation was the use of a sequential design, which did not control for the possibility of a treatment effect over time. This is an important confound to be aware of when evaluating the results of continuous and symptom-onset dosing. As a result, it is possible that the benefit of symptom-onset dosing in this study might be largely attributable to its ability to sustain efficacy initially achieved with luteal-phase or continuous dosing.

Clearly, more research is needed to more fully characterize which patients with PMS might benefit from use of antidepressant treatment, which dosing regimen yields maximal benefit, and what is the optimal duration of treatment.

Drug names: escitalopram (Lexapro), sertraline (Zoloft and others).

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