ORIGINAL ARTICLE

Time to Relapse After Short- or Long-term Treatment of Severe Premenstrual Syndrome With Sertraline

Ellen W. Freeman, PhD; Karl Rickels, MD; Mary D. Sammel, ScD; Hui Lin, MS; Steven J. Sondheimer, MD

Context: The duration of treatment after achieving a satisfactory response is unknown in the treatment of premenstrual syndrome. This information is needed in view of the improvement provided by medication vs the adverse effects and costs of drugs.

Objective: To compare rates of relapse and time to relapse between short- and long-term treatment with sertraline hydrochloride administered in the luteal phase of the menstrual cycle.

Design: Eighteen-month survival study with a randomized double-blind switch to placebo after 4 or 12 months of sertraline treatment.

Setting: Academic medical center.

Participants: One hundred seventy-four patients with premenstrual syndrome or premenstrual dysphoric disorder.

Main Outcome Measure: Relapse, defined as symptoms returning to the entry criterion level as assessed with daily ratings.

Results: The relapse rate was 41% during long-term treatment compared with 60% after short-term sertraline therapy, with a median time to relapse of 8 months vs 4 months (hazard ratio, 0.58; 95% confidence interval, 0.34-0.98; $P=.04$). Patients with severe symptoms at baseline were more likely to experience relapse compared with patients in the lower symptom severity group (hazard ratio, 2.02; 95% confidence interval, 1.18-3.41; $P=.01$) and were more likely to experience relapse with short-term treatment ($P=.03$). Duration of treatment did not affect relapse in patients in the lower symptom severity group ($P=.50$). Patients who demonstrated remission were least likely to experience relapse (hazard ratio, 0.22; 95% confidence interval, 0.10-0.45; $P<.001$). Further analysis comparing relapse in the first 6 months of placebo treatment in each group yielded similar results.

Conclusions: The relapse rate was significantly greater after short-term treatment compared with long-term treatment. The relapse rate was also high during extended drug treatment. Subjects with severe symptoms at baseline were most likely to experience relapse, and relapse occurred more swiftly regardless of treatment duration. These findings suggest that the severity of symptoms at baseline and symptom remission with treatment should be considered in determining the duration of treatment.

Trial Registration: clinicaltrials.gov Identifier: NCT00318773

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Author Affiliations: Departments of Obstetrics/Gynecology (Drs Freeman and Sondheimer) and Psychiatry (Drs Freeman and Rickels) and Centers for Clinical Epidemiology and Biostatistics (Dr Sammel) and Research in Reproduction and Women's Health (Ms Lin), University of Pennsylvania School of Medicine, Philadelphia.

PREMENSTRUAL SYNDROME (PMS) continues to be one of the most common health problems reported by women of reproductive age. The morbidity of PMS is due to the severity of the symptoms; the resulting impairment of work, personal relationships, and activities; and its chronicity over many years of menstrual cycling[1,2]; however, its etiology remains uncertain. Treatment of the severe form of PMS, termed *premenstrual dysphoric disorder* (PMDD), with sertonergic reuptake inhibitors has consistently demonstrated efficacy, and the US Food and Drug Administration has approved the use of sertraline hydrochloride, fluoxetine hydrochloride, and paroxetine hydrochloride for this indication.[3,4]

To our knowledge, clinical trials have addressed only short-term (ST) treatment of PMS and PMDD, typically for about 3 months. There is little information about the optimal duration of treatment, although anecdotal reports and small pilot investigations suggest that premenstrual symptoms return rapidly in the absence of effective medication.[5-8] How long medication should be continued after achieving a satisfactory response and the risk of relapse after discontinuing treatment are important concerns for women and clinicians, given the possible adverse effects and cost of drugs vs the benefit of medication that improves symptoms, functioning, and quality of life.[1]

The objective of the present study was to compare the rate of relapse and time to

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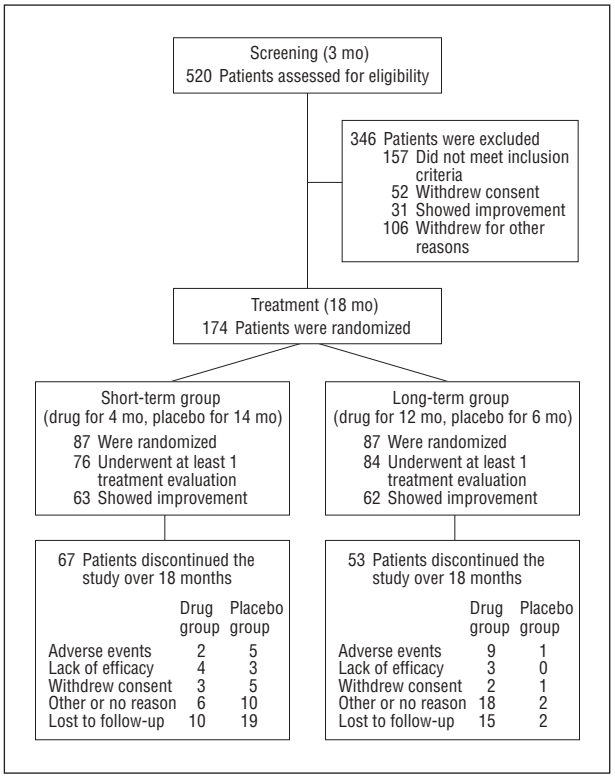

Figure 1. Progression of subjects throughout the study.

relapse between ST and long-term (LT) treatment with sertraline hydrochloride administered in the luteal phase of the menstrual cycle. Both treatment groups continued for the 18 months of study, using a double-blind switch to placebo when sertraline treatment was discontinued. We hypothesized that the time to relapse would be longer and the rate of relapse lower when discontinuing the drug after 12 months compared with discontinuing it after 4 months of treatment.

METHODS

PATIENT SELECTION

The study was conducted at the University of Pennsylvania Medical Center, Philadelphia, from February 2002 to December 2007. The study was approved by the institutional review board of the university, and patients provided written informed consent.

Inclusion criteria were age 18 to 45 years; regular menstrual cycles of 22 to 35 days for at least 6 months; persistent premenstrual symptoms for at least 1 year; positive findings of a urine test, indicating probable ovulation; and general good health as determined by the results of the physical and pelvic examinations and laboratory tests, including complete blood cell counts and chemistry profile.

Exclusion criteria were any major axis I psychiatric diagnosis currently or within the last year as determined by the Structured Clinical Interview for *DSM-IV* axis I disorders[9]; alcohol or substance abuse in the last year; history of psychosis or bipolar disorder; current use of psychotropic medications or any current prescription, over-the-counter, herbal, or nonmedical therapies for PMS; and pregnancy, breastfeeding, hysterectomy, symptomatic endometriosis, irregular menstrual cycles, lack of medically approved contraception, or any serious or unstable medical illness.

PMS CRITERIA

Diagnosis of severe PMS was based on prospective rating of the validated Daily Symptom Report (DSR)[10] and patient global ratings of functioning. Subjects rated the 17 DSR items daily on a scale of 0 (none) to 4 (very severe). A total premenstrual score of 80 or higher with an increase of at least 50% from the postmenstrual score was required for the mean of the screening cycles and for the third single-blind placebo-treated screening cycle. The premenstrual DSR scores were calculated by summing the 17 symptom ratings for 6 days before menses. The postmenstrual DSR scores were the sum of the 17 symptom ratings for days 5 to 10 (day 1 was the first day of menses). Patients rated functioning in work, family life, social activity, and overall interference on a 10-point scale, with at least moderate disruption (rating of $\geq$4) on 1 or more scales required for eligibility.[11] These symptom criteria are the same as those used to establish a diagnosis of PMDD, except that PMDD requires a specific number of symptoms, that is, 5 of the 11 specified PMDD symptoms.

DESIGN

This was a randomized, stratified, double-blind, placebo-controlled study conducted to examine the rate of relapse and time to relapse between ST and LT treatment with sertraline using a double-blind switch to placebo (**Figure 1**). After a 3-month screening period that included 1 month of single-blind placebo medication to confirm a stable PMS diagnosis, all eligible patients were randomized double-blind to the ST or LT treatment group and were administered sertraline in the luteal phase for 4 months. After 4 months of drug treatment, the ST group was switched to placebo and the LT group continued sertraline treatment for 8 more months. After 12 months of sertraline treatment, the LT group was switched to placebo, and the ST group continued placebo (all switches were double-blind). Both treatment groups were studied for 18 months. Symptom assessments were performed monthly and timed to the menstrual cycle.

Random allocation to the study groups was generated by computerized random number tables before the start of the study and implemented by the use of numbered containers with identical-appearing tablets. Randomization codes were kept in locked files, and neither the clinicians nor the patients knew the treatment assignments. Stratification was used to ensure equal distributions of premenstrual symptom severity in the ST and LT groups. Symptom severity was determined from the patient's average of the premenstrual DSR scores in the screening period, and patients were allocated to 1 of 3 groups at randomization: high severity of symptoms (DSR score of >169), mid severity of symptoms (DSR score of 169-122), or low severity of symptoms (DSR score of 121-80).

Power calculations before the study indicated that a sample size of 180 patients (90 per ST and LT group), assuming relapse rates of 0.65 in the ST group and less than 0.40 in the LT group, would provide greater than 90% power with $\alpha = .05$ and 2-tailed tests.

STUDY DOSAGES

Treatment was administered in the luteal phase of the menstrual cycle starting on day 14 before the expected date of menses and continuing through menstrual day 2. Sertraline and placebo tablets were prepared by the manufacturer and were identical in appearance. Medication bottles were labeled for each visit with the code number assigned at randomization. All patients started taking sertraline hydrochloride at 50 mg/d. In the

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absence of clear improvement in the second or third month of treatment (defined as premenstrual DSR scores ≥80 and Clinical Global Impressions improvement scores >2) or dosage-limiting adverse effects, the dosage was increased to 100 mg/d. The dosage in the fourth month of sertraline treatment was maintained for the remainder of the study. The equivalent number of placebo tablets was used when patients were switched to placebo. Patients with an increased dosage took 50 mg/d for the first 3 days of the dosing interval, increased to 100 mg/d until day 2 of menses, then tapered to 50 mg/d before discontinuing the dosing interval. Medication compliance was monitored by pill counts (the number used and returned at each visit) and by patient report as recorded daily in the DSR. The mean (SD) luteal-phase dose after 4 months of treatment with sertraline was 89 (21) mg/d, with no significant difference between the ST and LT groups.

DEFINITIONS OF IMPROVEMENT, RELAPSE, AND TIME TO RELAPSE

Improvement and relapse were assessed using the total premenstrual DSR scores (see the "PMS Criteria" subsection in this section). Improvement was defined by a premenstrual DSR score of less than 80 and at least a 50% decrease from the patient's average baseline DSR score. Relapse was defined as return of premenstrual DSR scores to the entry criterion of 80 or more, as documented by the daily symptom ratings for 1 or more menstrual cycles. Time to relapse was measured for 8 months, comparing the ST group receiving placebo with the LT group receiving drug in months 5 to 12 of the study. In the second analysis, time to relapse was measured for 6 months after the switch to placebo in each treatment group (months 5-10 in the ST group and months 13-18 in the LT group).

OTHER MEASURES

Possible covariates of treatment response were selected based on reports in the literature and the goals of the study and included adverse events in months 2 to 4 of sertraline treatment (yes or no); symptom remission (yes or no) as defined by premenstrual DSR score of 40 or less after 4 months of sertraline treatment (the mean postmenstrual score in previous studies[12]); perceived stress at baseline[13]; duration of PMS (<10 years or ≥10 years); history of major depression (yes or no as assessed using the Structured Clinical Interview of the DSM-IV); Hamilton Depression Rating Scale score at the postmenstrual and premenstrual screening visits[14]; and the demographic variables listed in **Table 1**.

STATISTICAL ANALYSIS

Survival analysis was used to compare the time to relapse between the ST and LT treatment groups. The time to relapse was compared between the 2 treatment groups in 2 different ways. First, we compared discontinuing drug after ST treatment vs LT treatment in the same 8-month period (model 1). Second, we addressed the research question of whether there were differences in relapse if drug was discontinued after 4 months compared with 12 months of treatment, with a direct comparison of relapse in the 6 months after the switch to placebo (months 5-10 in the ST group and months 13-18 in the LT group) (model 2).

Statistical analyses were performed using Kaplan-Meier curves,[15] log-rank tests,[16] and Cox proportional hazards models[17] to compare time to relapse between the ST and LT treatment groups. The data for all patients who showed improvement in the specified time interval were included as appropriate for each model; patients who showed no improvement were excluded. The log-rank test was used to detect differences in the distribution of time to relapse between the 2 treatment groups or multiple groups defined by the covariates of interest. Multivariable models used Cox proportional hazards models to estimate the ratio of the hazard of relapse between the groups defined by each covariate, enabling adjustment for baseline severity of symptoms and other risk factors. The hazard ratio (HR) indicates the chance of relapse in the current month provided the patient has not experienced relapse in the last month.

Bivariable associations between covariates and time to relapse were examined. The primary covariate of interest was baseline symptom severity, which was the stratification variable described in the "Design" subsection of this section. After inspection of the distributions of relapse in the 3 stratified severity groups, the mid-severity and low-severity groups were combined into a single group termed the *lower symptom severity group*.

The covariates with a bivariable association with relapse at $P \leq .15$ were entered simultaneously in the multivariable model. The final selection of covariates for multivariable models was guided by whether the variable was associated with the response variable at $P \leq .05$ or whether its inclusion in the model modified other significant associations by 15% or more.

Analysis of symptom levels used the premenstrual DSR scores and the *t* test or analysis of variance to compare treatment groups at the end of each study phase. All randomized patients with treatment response data were included, using the last obser-

Table 1. Participant Characteristics at Baseline

Variable[a]	Short-term Treatment Group (n=87)	Long-term Treatment Group (n=87)
Duration of PMS, mean (SD), y	12.4 (7.8)	12.5 (8.0)
DSR score, mean (SD)[b]		
Premenstrual	166 (57)	159 (56)
Postmenstrual	39 (36)	39 (31)
HAM-D score, mean (SD)		
Premenstrual	21.9 (7.0)	22.3 (7.8)
Postmenstrual	5.2 (5.3)	6.4 (5.4)
Perceived stress score, mean (SD)	31.6 (4.5)	31.7 (4.0)
History of depression, No. (%)	44 (51)	41 (47)
Premenstrual dysphoric disorder, ≥2 cycles, No. (%)	49 (56)	50 (57)
Age, mean (SD), y	32.1 (7.4)	33.6 (7.1)
Currently employed, No. (%)	29 (33)	24 (28)
Educational achievement level, ≥high school, No. (%)	72 (83)	71 (82)
Living with a partner, No. (%)	28 (32)	39 (45)
Currently using oral contraception, No. (%)	22 (25)	22 (25)
Race/ethnicity, No. (%)		
White	52 (60)	48 (55)
African American	28 (32)	31 (36)
Other	6 (7)	8 (9)
Children, No. (%)		
0	39 (45)	33 (38)
1-2	36 (41)	36 (41)
≥3	11 (13)	18 (21)

Abbreviations: DSR, Daily Symptom Report; HAM-D, Hamilton Depression Rating Scale; PMS, premenstrual syndrome.

[a] There were no significant differences between the short- and long-term treatment groups.

[b] Average of 3 screening cycles. Symptom severity rated on a scale of 0 (none) to 4 (very severe). Premenstrual scores are the sum of ratings for 6 days before menses. Postmenstrual scores are the sum of ratings for days 5 to 10 after onset of menses.

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Table 2. Relapse Compared Between Placebo and Sertraline Therapy and Symptom Severity at Baseline Over 8 Months[a]

Variable	Total No. of Improved Patients	Patients With Relapse, No. (%)	Median Time to Relapse, mo	HR (95% CI)	*P* Value
Treatment					
Placebo	53	32 (60)	4.0	0.58 (0.34-0.98)	.04
Sertraline	58	24 (41)	>8.0		
Symptom severity					
High	37	26 (70)	2.0	2.02 (1.18-3.41)	.01
Low	74	30 (41)	>8.0		

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Relapse in months 5-12, comparing placebo after 4 months of sertraline hydrochloride therapy vs long-term sertraline treatment.

Table 3. Relapse in Treatment Groups Adjusted for Symptom Severity Over 8 Months[a]

Group[b]	Total No. of Improved Patients	Patients With Relapse, No. (%)	Median Time to Relapse, mo
High symptom severity[c]			
ST, placebo	18	15 (83)	1.0
LT, sertraline hydrochloride	19	11 (58)	6.0
Low symptom severity[d]			
ST, placebo	35	17 (49)	8.0
LT, sertraline	39	13 (33)	>8.0

Abbreviations: LT, long term; ST, short term.
[a] Relapse in months 5 to 12; ST switched to placebo; LT continued sertraline.
[b] Overall, $P = .001$, log-rank test.
[c] ST vs LT, $P = .03$, log-rank test.
[d] ST vs LT, $P = .19$, log-rank test.

vation in each phase for study dropouts (intent-to-treat analysis). A second analysis included only patients who remained active throughout the phase.

Baseline characteristics of all randomized patients were compared between the treatment groups using *t* tests or χ^2 tests as appropriate for the data. In all analyses, results with $P \leq .05$ for a 2-tailed interpretation were considered statistically significant. Commercially available software (SAS version 9.1; SAS Institute, Inc, Cary, North Carolina) was used for analyses.

RESULTS

One hundred seventy-four patients were randomly assigned to the ST (n=87) or LT (n=87) group. Figure 1 shows patient progression and dropouts throughout the study. There were no significant differences in discontinuation rates between the ST and LT groups. At baseline, clinical and demographic variables did not differ between the 2 treatment groups (Table 1).

IMPROVEMENT

One hundred twenty-five of 174 patients (72%) showed improvement (defined by a decrease of 50% or more in the premenstrual DSR score from the average at baseline to a score below the entry criterion of 80). Nearly all improvement occurred in the first months of treatment: 37% of patients showed improvement in the first month, 62% in the second month, 69% in the third month, and 70% in the fourth month of sertraline treatment. Only 3 additional patients showed improvement during extended sertraline treatment in months 5, 6, and 9, respectively. There was no significant difference between the ST and LT groups in the percentage of patients who showed improvement.

RELAPSE

Model 1

We first compared time to relapse between the ST group that switched to placebo and the LT group that continued sertraline treatment (months 5-12 of the study). In this 8-month period, 60% (32 of 53) experienced relapse in the ST group vs 41% (24 of 58) in the LT group. The median time to relapse was 4 months vs more than 8 months, respectively. The chance of relapse was significantly lower in the LT group receiving sertraline treatment compared with the ST group receiving placebo in this 8-month period (HR, 0.58; 95% confidence interval [CI], 0.34-0.98; $P = .04$) (**Table 2**).

Baseline symptom severity was strongly associated with relapse independent of treatment. In the high symptom severity group, the relapse rate was 70% (26 of 37) compared with 41% (30 of 74) in the lower symptom severity group, with a median time to relapse of 2 months vs more than 8 months, respectively. The chance of relapse was 2-fold greater in the high severity group compared with the lower severity group in this 8-month period (HR, 2.02; 95% CI, 1.18-3.41; $P = .01$) (Table 2).

Table 3 gives the significant differences in relapse across the 4 strata of treatment and severity ($P = .001$, log-rank test). In the high severity group, 83% (15 of 18) in the ST group experienced relapse after switching to placebo compared with 58% (11 of 19) in the LT group who continued sertraline treatment. In the low severity group, 49% (17 of 35) in the ST group experienced relapse after switching to placebo compared with 33% (13 of 39) in the LT group who continued sertraline treatment. In patients with severe symptoms, the rate of relapse was significantly greater in the ST group compared with the LT group ($P = .03$). In the low severity group, the rate of relapse did not differ between ST and LT treatment ($P = .19$) (Table 3 and **Figure 2**A and B).

Model 2

We examined time to relapse for the first 6 months of placebo in each treatment group (months 5-10 in the ST

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group and months 13-18 in the LT group). The results were consistent with model 1. In the LT group, 33% (13 of 39) experienced relapse vs 51% (27 of 53) in the ST group. The median time to relapse was more than 6 months and 4 months, respectively. The chance of relapse was lower in the LT group compared with the ST group in the first 6 months after discontinuing the drug (HR, 0.55; 95% CI, 0.28-1.11; $P=.09$) (**Table 4**).

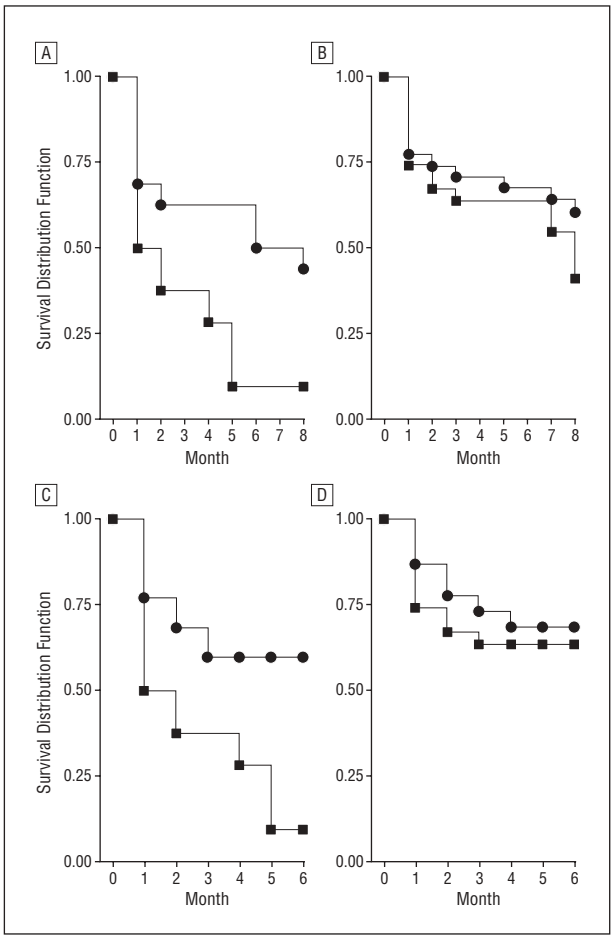

Figure 2. Time to relapse in long-term (circles) and short-term (squares) treatment groups. Data shown over 8 months in the groups with high severity of symptoms (A) and low severity of symptoms (B) (Tables 2 and 3; n=111). The short-term treatment group switched to placebo; the long-term treatment group continued sertraline hydrochloride treatment. Data shown over 6 months in the groups with high severity of symptoms (C) and low severity of symptoms (D) (Table 4; n=92). Both groups were receiving placebo: the short-term treatment group switched to placebo after 4 months of sertraline therapy; the long-term treatment group switched to placebo after 12 months of sertraline therapy.

In model 2, symptom severity was significantly associated with relapse independent of treatment duration. In the high symptom severity group, 66% (21 of 32) of patients experienced relapse compared with 32% (19 of 60) of patients in the lower symptom severity group, with a median time to relapse of 2 months and more than 6 months, respectively. The chance of relapse in the first 6 months after switching to placebo was more than 2-fold greater in the high severity group compared with the low severity group (HR, 2.22; 95% CI, 1.15-4.29; $P=.02$).

In model 2, the differences in relapse across the 4 strata of treatment and severity were significant ($P=.001$, log-rank test) and consistent with model 1. In the high severity group, 83% of patients experienced relapse after ST treatment compared with 43% after LT treatment, with a median time to relapse of 1 month vs more than 6 months, respectively. In the lower severity group, 34% of patients experienced relapse after ST treatment compared with 28% of patients after LT treatment, with a median time to relapse of more than 6 months in both groups (Figure 2C and D). In patients with severe symptoms, the rate of relapse was significantly lower in the LT group ($P=.02$). In patients in the lower symptom severity group, the rate of relapse did not differ between the ST and LT groups ($P=.50$).

EFFECT OF REMISSION ON RELAPSE

We defined symptom remission as a premenstrual DSR score of 40 or less, which was the mean postmenstrual score in previous studies. Forty-one of 174 subjects (24%) reported remission after 4 months of sertraline treatment. The rate of remission did not differ significantly between the high vs lower symptom severity groups ($P<.14$). In model 1, 22% (9 of 41) of patients who demonstrated remission experienced relapse compared with 67% of patients with less complete recovery (HR, 0.22; 95% CI, 0.10-0.45; $P<.001$). In model 2, 16% (6 of 37) of patients who demonstrated remission experienced relapse compared with 62% of the remaining patients who showed improvement (HR, 0.22; 95% CI, 0.09-0.52; $P<.001$). The median time to relapse extended beyond the observation periods in both models. There was no interaction between remission and treatment groups, in-

Table 4. Relapse Compared Between Short-term and Long-term Treatment and Symptom Severity at Baseline Over 6 Months in Model 2[a]

Variable	Total No. of Improved Patients	Patients With Relapse, No. (%)	Median Time to Relapse, mo	HR (95% CI)	*P* Value
Treatment, placebo				0.55 (0.28-1.11)	.09
Short term	53	27 (51)	4.0		
Long term	39	13 (33)	>6.0		
Symptom severity				2.22 (1.15-4.29)	.02
High	32	21 (66)	2.0		
Low	60	19 (32)	>6.0		

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Relapse during the first 6 months of placebo treatment after 4 months (short term) or 12 months (long term) of sertraline hydrochloride treatment.

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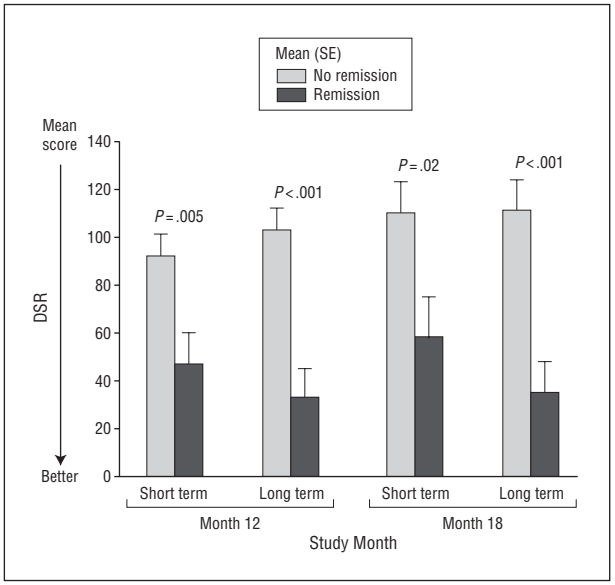

Figure 3. Premenstrual Daily Symptom Report (DSR) scores for short- and long-term treatment groups at 12 and 18 months according to remission or no remission. Main effect of remission, $P<.001$; main effect of short- or long-term treatment, $P>.87$; all pairwise comparisons with remission, $P<.001$. At month 12, the short-term treatment group was receiving placebo and the long-term treatment group was receiving sertraline hydrochloride treatment. At month 18, both treatment groups were receiving placebo. SE indicates standard error.

dicating that relapse was not different in the 2 treatment groups when remission was taken into account.

When remission was included in the multivariable analysis, only remission remained significantly and inversely associated with relapse, and treatment and baseline severity had no significant association with relapse. This indicated that the patients who demonstrated remission were significantly less likely to experience relapse regardless of the duration of treatment or the severity of symptoms. **Figure 3** shows that the DSR scores were significantly lower in the remission group at 12 and 18 months regardless of whether they were receiving drug or switched to placebo.

EFFECT OF OTHER VARIABLES ON RELAPSE

All baseline characteristics (Table 1) and a variable for adverse events (yes or no) during initial sertraline treatment were examined with relapse in bivariable analysis. Only 3 of these variables were associated with relapse at the level of $P \leq .15$: PMDD, history of depression, and oral contraceptive (OC) use. Patients with PMDD demonstrated a higher rate of relapse at bivariable analysis in model 1 ($P=.02$). However, PMDD was highly correlated with symptom severity (correlation = 0.51) and could not be retained in the multivariable model. History of depression was significantly associated with relapse in the bivariable analysis in model 2 ($P=.005$). Patients with a history of depression were nearly twice as likely to experience relapse after switching to placebo regardless of the duration of sertraline treatment (HR, 1.92; 95% CI, 1.00-3.66; $P=.05$). The addition of OC use (25% in each treatment group) reduced the estimated association between treatment group and relapse, indicating confounding in model 1. However, there was no significant interaction between OC use and treatment, indicating that the response to sertraline treatment was not different in users of OC.

PREMENSTRUAL SYMPTOM SCORES

To determine whether symptom scores differed after ST or LT treatment, we compared the premenstrual DSR scores for all available patients at the beginning of each study phase using the last observation of the study dropouts during the phase. We had hypothesized that patients who continued through LT treatment would have lower symptom scores; however, we found no significant difference in the premenstrual DSR scores between the ST and LT groups after 4, 12, or 18 months in this analysis. When only those who completed the study were examined in each phase, the mean (SE) DSR scores were significantly lower at 12 months in the LT group that continued drug compared with the ST group receiving placebo (22 [7] vs 62 [9]; $P=.03$). However, at 18 months when both groups were receiving placebo, there was no significant difference in DSR scores for the completers (25 [5] in the LT group vs 38 [8] in the ST group; $P=.17$).

ADVERSE EVENTS

Adverse events were reported at each visit in response to general clinical questioning and patient reports on the DSR. There were no serious adverse events from treatment that required medical intervention or withdrawal from the study. There were no reports of withdrawal symptoms that resulted in medication adjustments. Seventeen of 174 randomized patients stated that adverse effects were the reason for withdrawing from the study (Figure 1).

The most frequent adverse effects were insomnia (23%), nausea (22%), fatigue (18%), headache (13%), decreased libido or orgasm (10%), and changes in appetite (9%). Adverse effects usually diminished with time and adjustment to the medication. For example, 60% (105/174) of the patients reported adverse effects in the first 2 months of sertraline treatment; however, only 16 patients reported adverse effects in month 4. Of the 17 patients who reported decreased libido or orgasm during the 12 months of sertraline treatment administered in the luteal phase, only 1 patient reported this adverse effect at more than 1 visit, and none stated that discontinuation occurred because of this adverse effect.

COMMENT

Approximately half of the patients who demonstrated improvement experienced relapse within 6 to 8 months after discontinuing sertraline treatment. Overall, longer treatment was marginally better in preventing relapse. More important, both the rate of relapse and time to relapse were highly associated with symptom severity at baseline. Patients with severe symptoms at baseline were significantly more likely to experience relapse after discontinuing drug, experienced relapse after a shorter pe-

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riod, and were significantly more likely to experience relapse during extended drug treatment compared with patients in the lower symptom severity group. The patients with lower symptom severity at baseline were less likely to experience relapse regardless of treatment duration, and the time to relapse was significantly longer.

The rate of relapse during extended drug treatment was high. Forty-one percent of patients who showed improvement experienced relapse during months 5 to 12 of drug continuation. The reasons for relapse during drug treatment are unclear.[18] Maintenance therapy was at the improvement dosage, and patients took the medication as prescribed in the protocol and as confirmed by pill counts. We observed that in this group, the sertraline dosage was more likely to have been increased in the initial treatment period (54% vs 18% of patients who continued with the lower sertraline dosage), possibly indicating that their initial improvement was less stable or less responsive to sertraline treatment and, thus, more susceptible to relapse. Another possible reason for the loss of treatment response is loss of a placebo response, as has been identified in maintenance studies of depression.[19,20] The present study was not designed to determine loss of placebo effects; however, the findings suggest that the true drug effect of sertraline in treatment of PMS may be lower than observed in ST clinical trials.[4] A third possibility is that luteal-phase dosing may be insufficient in patients with severe symptoms, who were the most likely to experience relapse. Although luteal-phase dosing is a current standard of treatment in PMS and PMDD, these findings suggest that further studies are needed to examine the role of symptom severity in treatment response.

The patients who demonstrated remission as defined in the study were significantly less likely to experience relapse than were patients who demonstrated improvment with less complete recovery regardless of the duration of treatment or the severity of symptoms at baseline. These findings indicate that partial recovery is associated with rapid return of symptoms, whereas a more complete recovery, in which symptoms are reduced to approximately the normal postmenstrual level, is associated with a longer delay in symptom recurrence, similar to findings of previous studies in patients with depression.[21,22]

Numerous clinical and demographic variables were examined for an association with relapse; however, only 2 variables retained significance at multivariable analysis. Patients with a history of depression, which was reported by approximately half of the sample, were about twice as likely to experience relapse within 6 months of discontinuing sertraline treatment compared with those with no history of depression. This association has been previously observed in patients with depression when both the chronicity and the severity of depression predict relapse after treatment with selective serotonin reuptake inhibitors.[18] Current OC users were less likely to experience relapse, and the treatment association with relapse became nonsignificant when OC use was included in the multivariable model. However, there was no significant interaction between OC use and treatment, indicating that the response to sertraline treatment was not different in OC users. Nevertheless, the indication that OC use is a potential confounder of treatment warrants further studies.

Several limitations of the present study were considered. There are no established definitions of improvement, remission, and relapse in treatment of PMS or PMDD, and results may vary according to the definitions of these conditions. Our definition of improvement yielded results consistent with the percentages of patients who demonstrated improvement in other clinical trials of treatments for PMS and PMDD. Our definition of relapse is conservative in requiring that symptoms return to the study eligibility level and may underestimate the rate of relapse if less stringent definitions were used.

Our prestudy estimates for the sample size assumed a 25% difference in relapse between the 2 treatment groups, with 90% power and α at $P = .05$. However, the observed difference in the relapse rate between ST and LT treatment was only 18% to 19%, which resulted in a marginal P value for treatment in model 2.

Although the considerable relapse that was observed with continued drug treatment clearly affects the number of survivors in the LT treatment group, there is no direct way to account for this when the primary objective of the study is to compare discontinuing drug after different durations of treatment. However, our hypothesis that discontinuing drug after longer treatment would delay relapse was tested in 2 different ways and yielded consistent results. Both models favored LT treatment, in particular for patients with severe symptoms.

The patients were without comorbidities, in their late 20s to mid-30s, and predominantly white, and results may not be generalizable to all women with premenstrual symptoms. The study did not address alternative dosing regimens or other treatment strategies in the patients who experienced relapse or demonstrated no improvement, and further studies that examine treatment approaches for these conditions are needed.

The strengths of this study include randomized placebo-controlled comparisons of ST and LT treatment of PMS using luteal-phase administration of a selective serotonin reuptake inhibitor, which is the current criterion standard for treatment of this disorder. Both improvement and relapse were systematically identified in DSRs that were maintained by the patients throughout the study. The findings indicate that there is a high likelihood of relapse when medication is discontinued, in particular in patients with severe premenstrual symptoms at baseline. Inasmuch as the patients with severe symptoms were less likely to experience relapse with LT treatment compared with ST treatment, patients with severe symptoms might be advised to continue medication for at least 1 year after initial improvement. However, the considerable relapse during continued drug treatment raises an important question as to whether luteal-phase dosing is sufficient in patients with severe symptoms and should be further evaluated. Relapse was not associated with the duration of treatment in patients in the lower symptom severity group, which suggests that in these patients, the continued use of medication could be evaluated after initial improvement. Although the premenstrual symp-

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toms may eventually return, a medication-free interval that reduces the adverse effects and costs of drugs may be an acceptable benefit in patients with less severe symptoms. Patients who demonstrated remission were much less likely to experience relapse regardless of treatment duration or the severity of symptoms at baseline. This is a compelling indication of the importance of seeking remission as the goal of treatment of PMS.

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Correspondence: Ellen W. Freeman, PhD, Department of Obstetrics/Gynecology, University of Pennsylvania Health System, 3701 Market St, Ste 820 (Mudd), Philadelphia, PA 19104-5509 (freemane@mail.med.upenn.edu).
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