Predictors of Response to Sertraline Treatment of Severe Premenstrual Syndromes

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Background: Serotonergic antidepressant medications have demonstrated efficacy in the treatment of severe premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). Over 60% of subjects responded well to sertraline treatment for PMS and PMDD in double-blind controlled studies. However, no studies have evaluated the predictors of treatment response for this disorder. The current study examined pretreatment demographic, medical history, and clinical symptom predictors of sertraline response in PMS and PMDD treatment.

Method: Sixty-two subjects diagnosed with severe PMS (according to the Daily Symptom Report and global ratings of functional impairment) or PMDD (DSM-IV) received sertraline treatment as part of a randomized, double-blind, placebo-controlled treatment efficacy study. All subjects completed 3 screening cycles, including a single-blind placebo washout cycle, prior to 3 cycles of double-blind treatment. Outcome was assessed across the domains of PMS symptoms and quality of life. Demographic, medical history, and symptom variables were used to predict sertraline response.

Results: Baseline postmenstrual symptom ratings were significantly and independently associated with posttreatment PMS symptoms in multivariate analysis. Premenstrual and postmenstrual ratings of depression, medical history variables, and demographic variables were not significantly predictive of response to sertraline.

Conclusion: Baseline postmenstrual symptom ratings controlled for baseline premenstrual symptoms were associated with PMS symptoms at sertraline treatment endpoint. The findings suggest that non–menstrual-related baseline characteristics other than depression may influence sertraline treatment outcome in patients with higher postmenstrual symptom levels.

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Surveys indicate that premenstrual syndrome (PMS) symptoms are among the most common health problems reported by women of reproductive age.[1,2] The American College of Obstetrics and Gynecology reports that 20% to 40% of women have difficulties with premenstrual symptoms,[3–5] and 2% to 10% of women are estimated to suffer from severe symptoms that disrupt functioning.[6,7] Severe premenstrual symptoms disrupt work productivity, interpersonal relationships, and quality of life.[8]

A number of double-blind, placebo-controlled studies[9–17] have demonstrated the efficacy of serotonergic antidepressants when given continuously in the treatment of PMS and premenstrual dysphoric disorder (PMDD). Preliminary reports[18–23] show similar efficacy when serotonergic antidepressants are given only during the luteal phase of the menstrual cycle (the symptomatic time) in the treatment of PMS and PMDD. Several studies[9,24–26] also show the superiority of selective serotonin reuptake inhibitors (SSRIs) over other antidepressant medications for the treatment of this disorder, suggesting that the effect is specifically a serotonergic treatment effect. Other evidence further suggests that serotonin may play an important role in the pathophysiology of PMS.[27–29] Serotonergic abnormalities may include both state abnormalities during the symptomatic phase of the menstrual cycle as well as trait abnormalities during the entire cycle.[27–29]

Over 60% of subjects responded well to sertraline in double-blind, controlled studies,[9,10] and trials of serotonergic antidepressants overall showed significant drug improvement ranging from 52% to 69% in treatment of PMS/PMDD.[11,12,26] However, no studies that we are aware of have examined clinical factors that might predict the response to SSRIs in PMS treatment. In contrast, several potentially prognostic variables have been identified in the treatment of mood disorders, which is the primary indication of SSRI agents. In studies of depression, single-episode patients[30] and patients with fewer past episodes of depression[31] have a more favorable response to SSRI treatment than patients with recurrent depression. Higher baseline anxiety is associated with a positive response to SSRI treatment,[32–34] although conflicting evidence has also been reported.[35] Some investigations[36,37] indicate that psychomotor retardation is predictive of a positive response to SSRI treatment of mood disorder, although an-

other study[33] found that retardation scores were a negative predictor of treatment response.

Our subjects previously participated in a double-blind, placebo-controlled comparison of sertraline and desipramine[9] designed to determine whether antidepressant efficacy in the treatment of PMS is a general antidepressant effect or a more specific serotonergic effect. The trial showed that women treated with sertraline improved significantly more than those treated with desipramine or placebo, and desipramine was not significantly better than placebo in relieving PMS symptoms. The aim of the current investigation was to evaluate whether selected demographic, medical history, and symptom variables predict response to sertraline in the treatment of PMS.

In addition to exploring potential patient predictive variables that might usefully guide clinicians in choosing the best treatments for PMS, another aim was to examine whether sertraline was more efficacious for patients with higher postmenstrual levels of depressive symptoms prior to treatment. (Subjects with any major Axis I diagnosis, including major depression currently or within the past year, were excluded from the study.) Postmenstrual symptom levels are assumed to reflect the "normal" and ongoing symptom level prior to the monthly premenstrual increase in symptoms that are the focus of this disorder. If patients with higher levels of depression postmenstrually responded better, it would suggest that sertraline's efficacy in PMS is linked to its antidepressant properties. A third aim was to examine not only the predictors of improvement in PMS symptoms per se but also improvement in the broader domains that describe quality of life.

METHOD

Patient Selection

After a brief screening interview, women were asked to rate their symptoms daily using the Daily Symptom Report (DSR)[38] for 2 screening months during which they participated in 2 office evaluations at premenstrual and postmenstrual times. Subjects were included in the protocol if they were between the ages of 18 and 45 years, had regular menstrual cycles lasting 22 to 35 days, showed evidence of ovulation as demonstrated by an at-home urine test kit, and experienced premenstrual symptoms for at least 6 months. Subjects were excluded if they had any major physical or psychiatric diagnosis as diagnosed by the Structured Clinical Interview for DSM-IV (SCID),[39] used any psychotropic medications, used any other prescription or nonprescription treatments for PMS, were pregnant, breast-feeding, or intending to become pregnant over the next year, had a hysterectomy or endometriosis, were not using medically approved contraception, had a risk of suicide, or had a history of alcohol or drug abuse within the past year. Eligible subjects were then administered a daily placebo capsule throughout the third screening cycle.

The presence of severe PMS was assessed throughout the screening period based on the previously validated DSR.[38] The DSR consists of 17 common PMS symptoms, including the 11 PMDD symptoms from the DSM-IV, each rated daily on a 5-point scale ranging from none to extreme. Daily DSR ratings were summed for each subject in each cycle for a premenstrual score (6 days before menses) and a postmenstrual score (cycle days 5–10). The DSR items cover the symptom clusters of mood, behavior, pain, physical symptoms, and food cravings/increased appetite, which were statistically derived by factor analysis[38] as follows: mood includes irritability/anger, mood swings, anxiety/tension, depression, feeling out of control, feeling worthless/guilty, and decreased interest; behavior includes poor coordination, insomnia, difficulty concentrating/confusion, and fatigue; pain includes aches, headache, and cramps; physical symptoms include breast tenderness and swelling/bloating; and food cravings/increased appetite is a single item.

Subjects were included in the study if they had a total premenstrual DSR score of at least 80 and demonstrated an increase of at least 50% in the total DSR score from the postmenstrual ratings to premenstrual ratings in the placebo-treated screening cycle and for the mean of all 3 screening cycles. Subjects were required to have moderate-to-severe impairment of functioning as rated on 5-point scales for work, relationships, or social activities. The SCID assessment was conducted at the postmenstrual visit (visit 1), and subjects who met DSM-IV criteria for any major mood or anxiety disorder were excluded. The 17-item Hamilton Rating Scale for Depression (HAM-D-17) scores[40] at the initial postmenstrual visit did not exceed 14. Only 4 subjects had postmenstrual HAM-D-17 scores between 10 and 14, indicating normal range scores for nearly all subjects in the postmenstrual phase of the cycle.

Whether the subjects also met the DSM-IV diagnostic criteria for PMDD was also determined. PMDD was diagnosed for subjects who met the severity criteria for 5 or more of the specific PMDD symptoms and had at least a 50% premenstrual increase in each of the 5 symptoms with confirmation in the DSR ratings. Eighty-four percent of the sertraline-treated group met the PMDD criteria. The subjects who did not meet the PMDD criteria on average met criteria for 3 rather than 5 of the specified PMDD symptoms.

Sixty-six subjects were randomly assigned to sertraline treatment. Four of these subjects immediately discontinued or were lost to follow-up, leaving 62 subjects with treatment response data. The study was approved by the institutional review board of the university, and all subjects provided written informed consent.

Design

The current report focuses solely on the patients treated with sertraline to determine the predictors of response to

this medication. The original study[9] involved double-blind randomization to 1 of 3 treatment arms: sertraline, desipramine, or placebo. Patients taking desipramine saw no more improvement than those on placebo treatment. The 3 treatment months were preceded by a 3-month screening phase. The study procedures were described previously.[9]

Dosage

Sertraline was administered in doses ranging from 50 to 150 mg/day in a flexible-dosing schedule. Subjects took 50 mg of sertraline once in the evening starting on cycle day 1 and continued daily throughout the menstrual cycle. If clear improvement was not evident, the dose was raised to 100 mg/day at the beginning of the second treatment cycle and to 150 mg/day at the beginning of the third treatment cycle unless precluded by side effects. In the third treatment cycle, the mean ± SD sertraline dose was 105 ± 37 mg/day.

Outcome Measures

The primary outcome measure for the present report was premenstrual daily symptom scores at treatment endpoint as rated on the DSR (described above). Higher DSR scores indicate more severe symptom levels.

The secondary outcome measure for the evaluation of prediction of treatment response was the Quality of Life Enjoyment and Satisfaction Questionnaire[41] (Q-LES-Q). The short form of the Q-LES-Q contains 14 items, which are the summary scales of various aspects of daily living plus a global assessment of overall life satisfaction during the past week. Each item is rated on a 5-point scale ranging from very poor to very good. Higher scores indicate a better quality of life. This measure has demonstrated validity as a measure of quality of life independent of changes in depressive symptoms.[41,42]

Demographic, medical history, and symptom variables were selected from pretreatment medical and PMS history data. The demographic variables included age, education (coded as greater than high school degree or not), and the number of children. The medical history variables included a history of major depressive disorder, the number of years the subject suffered from PMS, the diagnosis of PMDD (yes/no), the length of the menstrual cycle, and the use of oral contraceptives. The clinical symptom variables included the baseline DSR ratings and the baseline HAM-D-17 scores, each with postmenstrual and premenstrual assessments.

Statistical Analysis

Data analyses were conducted on all subjects with treatment assessments in the sertraline-treatment arm using the last observation carried forward. Analysis of covariance (ANCOVA) was used to evaluate whether the demographic, medical history, or symptom measures predicted change in PMS symptoms from the premenstrual baseline ratings to the premenstrual ratings at treatment endpoint. Data were reviewed for influential observations using plots and Student t test residuals; all subjects were included in the final models. Preliminary analyses were conducted using either multiple regression or ANCOVA models that included the pretreatment premenstrual DSR scores (averaged for 3 screen cycles) and one additional variable with the premenstrual DSR score at treatment endpoint as the dependent variable. Only variables with $p < .20$ in these 2-variable models were entered in the final multivariate models. Analysis of the secondary outcome measure was conducted in a similar fashion. Slight differences in numbers are due to missing data. Statistical significance was defined as $p < .05$ (2-tailed).

Table 1. Baseline Clinical and Demographic Variables[a]

Variable	Study Population (N = 62)
Clinical variables	
Postmenstrual DSR total score, mean (SD)[b]	39 (37)
Premenstrual DSR total score, mean (SD)[b]	170 (60)
Postmenstrual HAM-D-17 score, mean (SD)	5 (4)
Premenstrual HAM-D-17 score, mean (SD)	18 (6)
Length of PMS, mean (SD), y	12 (8)
Length of cycle, mean (SD), d	28 (3)
History of MDD, %	32
Meets criteria for PMDD, %	84
Uses oral contraception, %	27
Demographic variables	
Age, mean (SD) y	34 (6)
Education beyond high school, %	87
No. of living children, mean (SD)	1 (1)

[a]Abbreviations: DSR = Daily Symptom Report, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MDD = major depressive disorder, PMDD = premenstrual dysphoric disorder, PMS = premenstrual syndrome.
[b]Average of 3 screen cycles.

RESULTS

Baseline Clinical and Demographic Characteristics

Table 1 summarizes the baseline clinical and demographic characteristics of the sertraline-treated subjects.

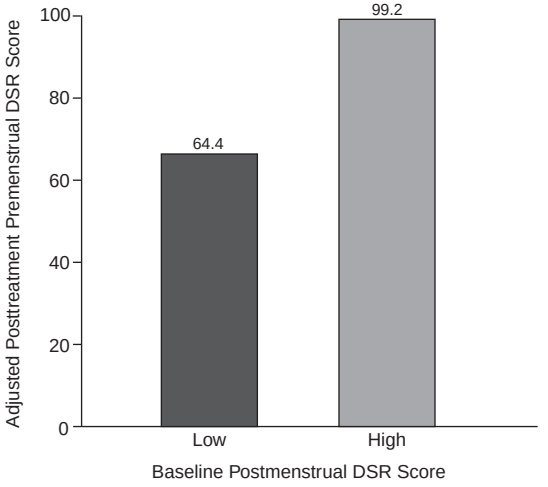
The baseline premenstrual DSR scores were positively and highly correlated with premenstrual DSR scores at treatment endpoint ($r = 0.43$, $p = .0006$). To control for baseline differences in the response variable, the baseline premenstrual DSR scores were included in the multiple regression or ANCOVA models. Only 2 of the study variables were associated with premenstrual DSR scores at treatment endpoint in the ANCOVA models at $p < .20$: baseline postmenstrual DSR scores ($r_{partial} = 0.49$, $p = .0001$) and the presence or absence of PMDD diagnosis (least squares adjusted difference = 39, $p = .11$). None of the remaining variables shown in Table 1 were significantly associated with the premenstrual DSR scores at treatment endpoint.

Table 2. Multivariate Analysis of Variables Associated With Premenstrual Response to Sertraline on 2 Outcome Measures[a]

	DSR			Q-LES-Q		
Predictor	Regression Coefficient	SE	p Value	Regression Coefficient	SE	p Value
Baseline postmenstrual DSR score	0.89	0.22	.0002	–0.09	0.04	.01
Baseline premenstrual DSR score	0.32	0.14	.03	–0.01	0.02	.62
PMDD diagnosis	–16.40	22.52	.47	1.84	3.55	.61

[a]Abbreviations: DSR = Daily Symptom Report (high scores indicate more severe symptoms), PMDD = premenstrual dysphoric disorder, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire (high scores indicate better quality of life). The Pearson correlation of premenstrual DSR and Q-LES-Q scores at endpoint is r = –0.69. The partial correlations with DSR are 0.49 for baseline postmenstrual DSR and 0.29 for baseline premenstrual DSR.

Figure 1. Adjusted Premenstrual Daily Symptom Report (DSR) Scores at Treatment Endpoint for Patients With High and Low Scores (Median Split) on Postmenstrual DSR Before Treatment[a]



[a]Higher DSR scores indicate more symptoms.

Table 2 presents the associations of the variables (each controlled for all others) with the measures of treatment outcome. Baseline postmenstrual DSR scores had the strongest association with treatment response. Patients with higher postmenstrual scores at baseline had higher PMS symptom scores at endpoint. High premenstrual DSR scores at baseline were also associated with higher DSR scores at endpoint. Figure 1 presents the adjusted premenstrual DSR scores at treatment endpoint for subjects with high postmenstrual DSR ratings versus subjects with low postmenstrual DSR scores based on a median split. This figure illustrates that subjects with high baseline ratings on the postmenstrual DSR remained more symptomatic at treatment endpoint adjusted for premenstrual DSR scores over the screening period than did those with low ratings.

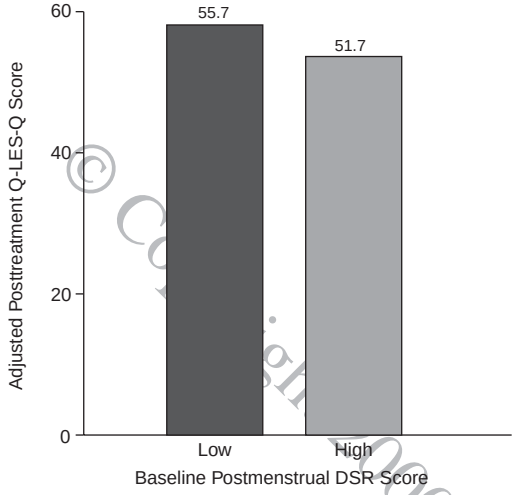
We also examined the component factors of the DSR to determine whether specific symptom clusters were associated with PMS symptoms at treatment endpoint. The correlations of baseline postmenstrual DSR factor scores with total DSR score at treatment endpoint were significant (p = .0001) for the factors of mood (r = 0.53), behavior (r = 0.54), pain (r = 0.57), and physical symptoms (r = 0.51). When the baseline postmenstrual factors were entered in the model in place of the total postmenstrual DSR score, only the pain factor (aches, headache, cramps) reached statistical significance (p = .0009) because of high colinearity of the factor scores with each other. The correlations of scores for baseline premenstrual DSR factors of mood, behavior, pain, and physical symptoms with total DSR score at treatment endpoint were r = 0.32, 0.44, 0.32, and 0.36, respectively. Substituting the baseline premenstrual factor scores in the model in place of the total baseline premenstrual DSR score showed that none of the factor scores reached statistical significance as predictors of response, again because of high colinearity of the factor scores with each other. These results indicate that the total symptom severity at both the postmenstrual (r = 0.58, p = .0001) and premenstrual (r = 0.43, p = .0006) baseline assessments predicted endpoint severity as well as any specific symptom cluster.

Analysis using the Q-LES-Q as the outcome measure with the same set of predictor variables showed that only the postmenstrual DSR scores predicted the quality of life outcome. Higher postmenstrual DSR scores at baseline significantly predicted poorer quality of life (see Table 2). Figure 2 illustrates that subjects with high postmenstrual DSR scores prior to treatment reported a lower quality of life at treatment endpoint (lower Q-LES-Q scores controlling for initial levels).

DISCUSSION

The results show that higher levels of postmenstrual and premenstrual DSR scores at baseline were significant predictors of higher symptom levels at sertraline-treatment endpoint. Total DSR scores predicted endpoint symptom levels as well as any specific symptom cluster of mood, behavior, pain, or physical symptoms. These results, particularly the association of higher baseline postmenstrual symptom levels with higher premenstrual symptom levels at endpoint (controlling for baseline premenstrual DSR scores) were unexpected. We had postulated that postmenstrual symptoms that were not of sufficient severity to meet criteria for an Axis I diagnosis indicated undiagnosed dysphoric mood disorder such as dysthymia or minor depression, which would respond well to daily sertraline treatment as administered in the study. Sertraline has

Figure 2. Adjusted Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) Scores at Treatment Endpoint for Patients With High and Low Scores (Median Split) on the Postmenstrual Daily Symptom Report (DSR) Before Treatment[a]



[a]Higher Q-LES-Q scores indicate better quality of life.

established efficacy in the treatment of both dysthymia[43] and chronic depression.[44] Further arguing against comorbid or subclinical depression as the primary explanation for the subjects with higher postmenstrual DSR scores is that previous research showed that the efficacy of sertraline in chronic depressive states was not reduced by the presence of comorbidity.[45]

Inasmuch as the serotonergic antidepressant did not successfully treat the subjects with higher postmenstrual symptom levels, symptoms other than depressive symptoms might account for the higher DSR scores. It is underscored that postmenstrual depression ratings as assessed by the HAM-D-17 overall were in the normal range (mean ± SD = 5 ± 4), and a comparison between the high and low postmenstrual DSR groups showed no difference in postmenstrual HAM-D-17 scores. In the higher DSR group, the highest ratings postmenstrually were for the symptoms of fatigue, anxiety, irritability, and mood swings (in decreasing order of severity). These anxiety symptoms may have been less responsive to treatment, as suggested in a previous study by Silverstone et al.,[46] who showed that the SSRI fluoxetine was less effective for anxiety symptoms in depression. These same symptoms were the highest rated in premenstrual DSR scores as well and possibly accounted for the association of high baseline premenstrual DSR scores with high DSR scores at treatment endpoint. From the clinical perspective, an important question for further study is whether nonresponders to the serotonergic antidepressant would respond more favorably to other medications such as anxiolytics or other classes of antidepressants, although these medications have shown little efficacy in PMS treatments overall.[9,24–26,47]

The results suggest that some sort of persistent trait characteristic, which is not menstrual-cycle specific,[48–50] may influence treatment response. For example, previous assessment with the Tridimensional Personality Questionnaire showed that subjects with PMS had higher scores compared with normative samples, and the personality dimensions were moderately correlated with the baseline premenstrual symptom scores,[50] suggesting the possibility that personality factors could have a role in treatment response, albeit undefined at this time.

Limitations of this study include the possibility that other variables not assessed here may predict sertraline response. Also, the present study did not address the issue of whether any pretreatment subject variables are differentially associated with response to specific SSRI medications. The sample size in the current study provided statistical power to detect moderate effects. With $N = 62$, $\alpha = 0.05$, and $r = 0.30$ (medium effect size), the power is 0.86, but the power is reduced to 0.60 for $r = 0.20$. A number of variables may predict response with only a small effect, but it is possible that their cumulative effect may be clinically meaningful. Finally, we are unaware of any placebo-controlled studies that have been analyzed to identify predictors of response in PMS/PMDD treatment. Until additional predictor analyses are conducted that confirm these results, they should be viewed as preliminary.

CONCLUSION

Response to sertraline was broadly effective and not differentiated by demographic or medical history factors in this treatment group with moderate-to-severe premenstrual symptoms and no other current major psychiatric or physical diagnoses. High postmenstrual symptom levels were the strongest predictor of high premenstrual symptom scores at treatment endpoint. These unexpected results point to the possible diversity of underlying mechanisms in this disorder as well as the need for additional therapies for those who do not respond to first-line treatments.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac), sertraline (Zoloft).

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