Treatment of Premenstrual Dysphoric Disorder With Sertraline During the Luteal Phase: A Randomized, Double-Blind, Placebo-Controlled Crossover Trial

Stephen A. Young, M.D., Peyton H. Hurt, M.D., David M. Benedek, M.D., and Robin S. Howard, M.A.

Background: The authors designed a randomized, double-blind, crossover study to assess the efficacy of sertraline in the treatment of premenstrual dysphoric disorder (PMDD) when given only during the luteal phase of the menstrual cycle.

Method: Thirty-one subjects were selected for a 7-month study period that included an initial 2 months of screening, 2 months of treatment with placebo or sertraline, 1 washout month, and 2 months of crossover treatment with either placebo or sertraline. Eleven subjects completed the study. Symptoms were monitored with daily reports using the Calendar of Premenstrual Experience (COPE). For each study phase, premenstrual COPE scores (7 days prior to menses) were examined using repeated measures analysis of variance. Scores were logarithmically transformed. Comparison of baseline scores between the luteal and follicular phases was examined using the paired t test.

Results: Analysis of COPE results during the treatment periods of the luteal phase showed a significant treatment effect, with higher scores during the placebo cycles compared with the sertraline-treated cycles ($p = .0052$ behavioral, $p = .014$ physical).

Conclusion: This study is the first to demonstrate a significant response to a serotonin selective reuptake inhibitor used only during the luteal phase. The authors point out the importance of this finding both in terms of economic cost to patients as well as how it may add to the growing understanding of the etiology of PMDD.

(J Clin Psychiatry 1998;59:76–80)

Received March 4, 1997; accepted Aug. 20, 1997. From the Department of Psychiatry, Walter Reed Army Medical Center, Washington, D.C.

This work was supported by the U.S. Army Research and Material Command grant number (MIPR) L3DM5541.

Presented at the 150th annual meeting of the American Psychiatric Association, May 17–22, 1997, San Diego, Calif.

The opinions, interpretations, conclusions, and recommendations contained herein are the views of the authors, and not necessarily endorsed by or are considered as reflecting the views of the Department of the Army or the Department of Defense. In the conduct of research in which humans are the subjects, the investigators adhered to the policies regarding the protection of human subjects as prescribed by 32 CFR 219 and Subparts B, C, and D.

Reprint requests to: Stephen A. Young, M.D., Clinical Assistant Professor of Psychiatry, University of Florida, Health Science Center/ Jacksonville, 653 West 8th Street, Jacksonville, FL 32209.

The existence of a premenstrual syndrome has long been debated. Recent reports have struggled with the development of reproducible diagnostic criteria,[1–3] examined various treatment regimens,[4–11] and attempted to derive etiologic theories.[1,12,13]

Today, the presence of a well-circumscribed syndrome of behavioral, affective, cognitive, and somatic changes after ovulation and prior to menses has been well described.[1,14,15] Despite concerns about the potential consequences of describing this syndrome as a psychiatric disorder (*Washington Post.* July 8, 1993:C1), late luteal phase dysphoric disorder (LLPDD) was included in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R) as a diagnosis "needing further study."[16] DSM-IV designates the disorder in the same fashion, but has simplified the name to premenstrual dysphoric disorder (PMDD).[17]

Estimates of the prevalence of PMDD vary greatly, primarily because most women note some of the symptoms on an intermittent basis. Historical reports from patients are quite unreliable,[14] and most recent studies have used various prospective self-report scales.[4–6] Of 839 women sampled in a 1986 report, 2% to 10% of women were reported to have severe symptoms of PMDD that could cause significant impairment.[2] DSM-IV states that the symptoms "must cause an obvious and marked impairment in the ability to function socially or occupationally in the week prior to menses" and occur "most months for the previous 12 months."

A number of reports have examined the somatic treatment of PMDD. These have employed alprazolam,[4] fluoxetine,[5,6,8,18–21] valproate,[7] danazol,[9] nortriptyline,[10] bright light,[11] buspirone,[22] and a gonadotropin-releasing hormone (GnRH) agonist (specifically, D-Trp^6-Pro^9-NEt-GnRH)[23] among others. While danazol and the GnRH agonist have both shown promise, side effects pose significant problems with both regimens.[14] Fluoxetine treatment has clearly been shown to be beneficial, demonstrating statistically significant improvement in the majority of patients studied. These studies have primarily treated

the subjects during the entire menstrual cycle. There is one case report of the use of fluoxetine in a single dose given 7 days prior to the onset of menses.[8] At the time of the report, the subject had been treated for four cycles and reported significant improvement in each. The excessive half-life of fluoxetine combined with the long-term cost of the regimen makes daily indefinite treatment a potentially limited tool in clinical settings. The present study employed sertraline, a serotonin selective reuptake inhibitor (SSRI) with a much briefer half-life (24 hours as opposed to 7 days for fluoxetine). Additionally, patients were treated only during the luteal phase of the cycle, thus lessening cost and long-term exposure to psychotropic medication. Sertraline has been demonstrated to be effective in treating PMDD when used on a daily basis.[24]

METHOD

A randomized, double-blind, placebo-controlled crossover trial was conducted at the Walter Reed Army Medical Center, Washington, D.C., from October 1994 to July 1995. Thirty-one study subjects between the ages of 18 and 45 years were selected from approximately 50 responders to advertisements in local military newspapers and posted in gynecology clinics. They were not paid. DSM-IV criteria[17] were used to screen potential subjects by telephone. Those who had a history of any mental health treatment in the previous 18 months or were taking psychotropic medication were excluded. After the study was completely described to the subjects, written informed consent was obtained. This protocol was reviewed and approved by the Human Use Committee/Institutional Review Board through the Walter Reed Army Medical Center Department of Clinical Investigation.

This initial group then entered the assessment phase of the study, a 2-month period of daily symptom reporting utilizing the Calendar of Premenstrual Experiences (COPE),[25] a PMDD assessment instrument that has been tested for validity and reliability. The COPE has been shown to be significantly correlated with corresponding scales of the Profile of Mood States and the Beck Depression Inventory and has a high test-retest reliability from cycle to cycle.[25] While some studies have employed a battery of various psychometric tests,[4] this instrument has been effective in differentiating PMDD patients from controls[25] and assessing improvement in response to treatment.[6] The COPE asks subjects to self-rate 22 symptoms grouped into behavioral (angry outbursts, crying easily, forgetfulness, etc.) and physical (acne, breast tenderness, bloatedness, etc.) categories. Symptoms are rated daily on a 0 (none) to 3 (severe) scale.

Once this initial screening period was completed, subjects were assessed for entry into the treatment phase of the study. Subjects with a documented overall COPE score 30% greater during the last 7 days of the cycle (late luteal phase) compared with the first 7 days of the cycle were allowed to continue. National Institute of Mental Health diagnostic criteria[26] require the 30% differential between the immediate premenstrual scores (last 6 days) and the intermenstrual scores (Days 5 to 10). Inclusion criteria for the present study were more strict, given that many of the subjects continued to have moderate symptoms during the initial days of menses. Additionally, a thyroid panel, general serum chemistries, serum beta–human chorionic gonadotropin level, and a complete blood count were performed at this phase. Any diagnosis of active disease that required further evaluation or treatment (e.g., hypothyroidism, hepatitis, pregnancy) resulted in exclusion from the study.

The 17 remaining subjects were randomly assigned to receive either sertraline or placebo in the first treatment phase. Of these subjects, 11 completed the protocol over the seven-cycle study period. Three women dropped out secondary to medication side effects. Of these, two experienced significant nausea, and the third complained of significant hyperstimulation ("nervousness" and tremulousness). This latter patient was taking placebo when she experienced those effects. One subject moved from the area, and two discontinued for undetermined reasons. The initial treatment group received a daily dose of sertraline 50 mg or placebo from Day 15 to the initial day of menses for two cycles. All subjects then underwent a washout cycle. Finally, the two groups were crossed over for the final two cycles of the study. Subjects completed the COPE calendar daily during the entire study period.

Subjects were seen by a physician investigator at regular monthly intervals throughout the initial and treatment phases of the study. These brief visits were structured to include assessment of side effects (a preprinted form listing the most common side effects was administered), collection of COPE calendars, and performance of a serial serum pregnancy test during each of the treatment cycles. No psychotherapy was performed at these visits. The physicians were not aware of which treatment was being received by the patients.

For each reporting day, responses for the 22 symptoms on the COPE (each response measured on a four-point Likert scale of 0–3) were subdivided into a score for 8 physical symptoms and a score for 14 behavioral symptoms. For each month, total scores for the late luteal phase (last 7 days of the menstrual cycle) and for the initial follicular phase (first 7 days of cycle) were calculated. Average COPE scores for physical symptoms and behavioral symptoms were then obtained for each study period (e.g., baseline, first treatment, washout, second treatment). Data were examined using repeated measures analysis of variance for the within-subject factor (study period) and the between-subject factor (study drug order). Comparison of baseline scores between the luteal and follicular phases was examined using the paired t test. To satisfy as-

Table 1. Calendar of Premenstrual Experiences (COPE) Score Results for Each Study Period for 11 Women

Study Period	Behavioral COPE Scores				Physical COPE Scores			
	Luteal		Follicular		Luteal		Follicular	
	Median	Range	Median	Range	Median	Range	Median	Range
Baseline	128	36–286	27	0–199	42	11–162	26	0–133
Washout	103	34–273	25	0–115	45	15–158	30	0–168
Placebo	88	18–153	62	0–192	45	7–98	30	0–114
Sertraline	27	7–139	31	1–228	24	1–84	19	0–136

sumptions of normality and homogeneity of variance for the model, scores were logarithmically transformed. Data were analyzed using the Statistical Package for the Social Sciences 5.0 version for Windows (SPSS, Chicago, Ill).

On the basis of previous placebo-controlled studies of treatment of PMDD with fluoxetine and controlling the probability of a type I error at alpha = .05, a sample of nine subjects was expected to have at least 80% power to detect a 70% difference in efficacy (90% for fluoxetine vs. 20% for placebo).[19]

RESULTS

The mean age of the 11 women who completed the study was 36.9 years (range, 23–43). Four subjects received placebo in the first treatment cycle and seven subjects received sertraline initially. COPE score results for each study period are presented in Table 1.

Baseline behavioral COPE scores in the luteal phase were significantly higher compared with scores in the follicular phase (t = 2.4, df = 10, p = .038), and there was a similar trend for physical symptoms (t = 2.0, df = 10, p = .074). In the follicular phase, there was no significant difference in COPE scores between any of the four study periods (F = 0.6, df = 3,27; p = .60 for behavioral symptoms; F = 0.9, df = 3,27; p = .44 for physical symptoms), and the factor of study drug order had no significant effect on COPE scores (F = 1.6, df = 1,9; p = .24 for behavioral symptoms; F = 2.4, df = 1,9; p = .16 for physical symptoms).

In the luteal phase, there was a significant difference between the four study periods (F = 8.8, df = 3,27; p = .00031 for behavioral symptoms; F = 4.4, df = 3,27; p = .012 for physical symptoms). There was no significant difference between baseline and washout cycles (F = 0.5, df = 1,9; p = .49 for behavioral symptoms; F = 0.2, df = 1,9; p = .71 for physical symptoms) and the order in which the subject received the treatment did not significantly affect COPE scores in the untreated cycles (F = 0.2, df = 1,9; p = .65 for behavioral symptoms; F = 0.003, df = 1,9; p = .96 for physical symptoms).

The percent changes in COPE scores from baseline for behavioral and physical symptoms in the luteal phase according to treatment sequence are presented in Figures 1 and 2. During treatment periods of the luteal phase, the

Figure 1. Percent Change in Luteal Phase Behavioral COPE Scores Between Baseline and Treatment With Placebo and Sertraline

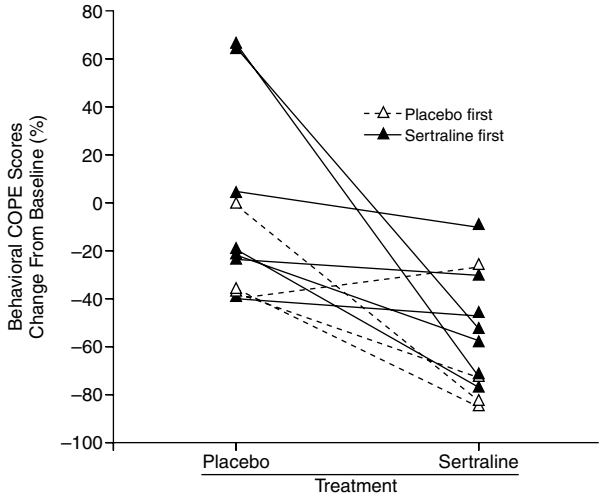
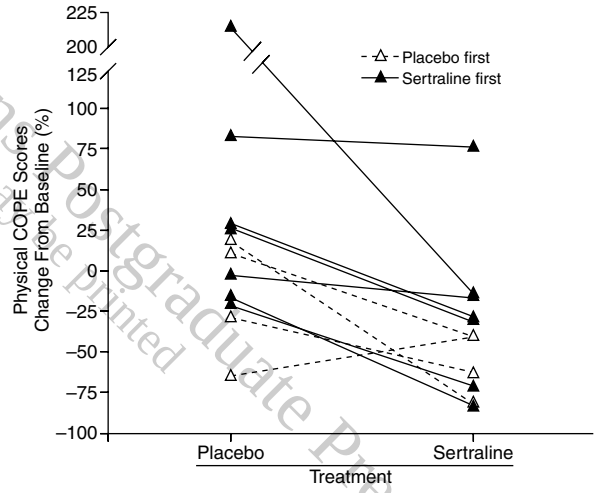


Figure 2. Percent Change in Luteal Phase Physical COPE Scores Between Baseline and Treatment With Placebo and Sertraline



COPE scores for the placebo cycles were significantly higher compared with the sertraline-treated cycles (F = 13.4, df = 1,9; p = .005 for behavioral symptoms; F = 9.3, df = 1,9; p = .014 for physical symptoms). The order in which the treatments were administered was not statistically significant (F = 1.4, df = 1,9; p = .27 for behavioral symptoms; F = 0.3, df = 1,9; p = .58 for physical symptoms).

Behavioral COPE scores during treatment with placebo tended to decline from baseline levels, but the change was not statistically significant (t = 1.3, df = 10; p = .22); scores improved by a median of –22% (range, –40% to 67%) from baseline values during treatment with

placebo, compared with –58% (range, –85% to –10%) improvement for patients treated with sertraline. The change in physical scores from baseline during the placebo period was not statistically significant ($t = 0.3$, $df = 10$; $p = .74$), and fewer physical symptoms were reported during sertraline treatment ($t = 3.1$, $df = 10$; $p = .011$). During treatment with placebo, 8 women (73%) showed improvement from baseline in behavioral symptoms, and 5 (45%) had lower physical COPE scores. When treated with sertraline, all 11 women (100%) had lower behavioral COPE scores compared with both the baseline and placebo periods, and 10 subjects (91%) had improved physical scores.

DISCUSSION

The efficacy of SSRIs in PMDD has been established in a number of previously cited studies. This is the first study to our knowledge that has treated PMDD patients solely during the luteal phase. We feel this approach raises important ideas from both etiologic and clinical perspectives.

Etiologic theories have focused on the similarities of PMDD to other psychiatric syndromes, including affective disorders, anxiety disorders, and opiate withdrawal. This latter theory stems from the fact that (1) there appears to be a link between β-endorphins and gonadal steroids,[13,27] (2) β-endorphin neuronal cell bodies are concentrated in the arcuate nucleus where GnRH and dopamine are also found,[27] and (3) PMDD symptoms bear a number of similarities to opiate withdrawal. Studies of endorphin activity in PMDD patients have tended to demonstrate a potential abnormality,[28–30] although these findings are preliminary in nature and have not been consistently replicated.[31] This model of a possible disruption in receptor activity due to an acute change in gonadal steroid levels was of particular interest to us, given the acute onset of PMDD symptoms, suggesting an etiology different from the much more gradually occurring affective disorders. Our observation of the effectiveness of an SSRI taken only during the luteal phase supports this idea of an acute change, which can also be reversed on an acute basis. It is possible that an acute increase in serotonergic tone at least partially offsets changes in endogenous opiate binding caused by the rapid decrease in gonadal steroids typical of the luteal phase.

It is likely that symptom expression in PMDD involves a number of different steps at a central as well as peripheral level. The linking of ovarian hormones to neurotransmitter function,[27] as well as clinical effects of prostaglandin inhibitors (mefenamic acid),[14] points to what is likely a chain of events that can be affected by manipulating various links.

Given the decline in behavioral COPE scores during the placebo period, this study reaffirms that placebo-controlled trials are required to evaluate prospective treatments for this condition. Although the order in which treatment was received did not produce a statistically significant difference in the COPE scores, the lack of significance may be due to the small number of subjects in each sequence. Subjects were queried at the end of this study to assess the effectiveness of blinding of the treatment order, and all were able to correctly identify which treatment was received in each period.

Recent studies have shown some evidence of serotonin abnormalities in patients with PMDD,[32] including significantly lowered whole blood serotonin, as compared with controls during the last 10 days of the menstrual cycle[12] and exacerbation of symptoms with tryptophan depletion.[33] Fluoxetine may not be the best agent to increase serotonergic tone in this population. Sertraline is also an effective SSRI, but has a half-life of approximately 24 hours, compared with 7 days for fluoxetine (and the active metabolite norfluoxetine), is more specific than fluoxetine, and of the available SSRIs in this country, has the least effect on the P450 2D6 system.[34,35]

The potential advantages of sertraline in PMDD include a much shorter washout period if the drug needs to be discontinued (this may be of particular importance in women considering pregnancy) and less drug-drug interaction due to sertraline's higher specificity and minimal effect on hepatic enzymes. While the use of SSRI agents solely during the luteal phase needs further investigation, the practice may be important in terms of medication costs for the patient. In addition, this approach may be more attractive to patients and physicians dealing with the possibility of daily medication use for a large portion of a woman's reproductive years.

This trial provides preliminary evidence that use of sertraline during the luteal phase is a viable treatment for PMDD. The study is limited by the small number of subjects, and further research with larger cohorts is warranted.

Drug names: alprazolam (Xanax), buspirone (BuSpar), danazol (Chronogyn, Danocrine), fluoxetine (Prozac), nortriptyline (Pamelor and others), sertraline (Zoloft).

REFERENCES

1. Tucker JS, Whalen RE. Premenstrual syndrome. Int J Psychiatry Med 1991;21:311–341
2. Logue C, Moos R. Perimenstrual symptoms: prevalence and risk factors. Psychosom Med 1986;48:388–414
3. Severino SK, Moline ML. Premenstrual syndrome. Obstet Gynecol Clin North Am 1990;17:889–903
4. Schmidt PJ, Grover GN, Rubinow DR. Alprazolam in the treatment of premenstrual syndrome. Arch Gen Psychiatry 1993;50:467–473
5. Elks ML. Open trial of fluoxetine therapy for premenstrual syndrome. South Med J 1993;86:503–507
6. Wood SH, Mortola JF. Treatment of premenstrual syndrome with fluoxetine: a double blind, placebo controlled, crossover study. Obstet Gynecol 1992;80:339–344
7. Jacobsen FM. Low-dose valproate: a new treatment for cyclothymia, mild rapid cycling disorders, and premenstrual syndrome. J Clin Psychiatry

1993;54:229–234
8. Daamen MJ, Brown WA. Single-dose fluoxetine in management of premenstrual syndrome [letter]. J Clin Psychiatry 1992;53:210–211
9. Derzko CM. Role of danazol in relieving the premenstrual syndrome. J Reprod Med 1990;35(suppl 1):97–102
10. Harrison WM, Endicott J, Nee J. Treatment of premenstrual depression with nortriptyline: a pilot study. J Clin Psychiatry 1989;50:136–139
11. Parry BL, Mahan AM, Mostofi N, et al. Light therapy of late luteal phase dysphoric disorder: an extended study. Am J Psychiatry 1993;150: 1417–1419
12. Rapkin AJ, Edelmuth E, Chang LC, et al. Whole-blood serotonin in premenstrual syndrome. Obstet Gynecol 1987;70:533–537
13. Seifer DB, Collins RL. Current concepts of β-endorphin physiology in female reproductive dysfunction. Fertil Steril 1990;54:757–771
14. Chihal HJ. Premenstrual syndrome: an update for the clinician. Obstet Gynecol Clin North Am 1990;17:457–479
15. Lurie S, Borenstein R. The premenstrual syndrome. Obstet Gynecol Surv 1990;45:220–228
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987:367–369
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994:715–718
18. Menkes DB, Taghavi E, Mason PA, et al. Fluoxetine treatment of severe premenstrual syndrome. BMJ 1992;305:346–347
19. Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1991;52:290–293
20. Rickels K, Freeman EW, Sondheimer S, et al. Fluoxetine in the treatment of premenstrual syndrome. Current Therapeutic Research 1990;48: 161–166
21. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. N Engl J Med 1995;332:1529–1534
22. Rickels K. Buspirone in treatment of premenstrual syndrome [letter]. Lancet 1989;1:777
23. Muse KN, Cetel NS, Futterman LA, et al. The premenstrual syndrome: effects of "medical ovariectomy." N Engl J Med 1984;311:1345–1349
24. Yonkers KA, Halbreich U, Freeman E, et al. Sertraline in the treatment of premenstrual dysphoric disorder. Psychopharmacol Bull 1996;32:41–46
25. Mortola JF, Girton L, Beck L, et al. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: the Calendar of Premenstrual Experiences. Obstet Gynecol 1990;76:302–307
26. Hamilton JA, Parry BL, Alagna S, et al. Premenstrual mood changes: a guide to evaluation and treatment. Psychiatric Annals 1984;14:426–435
27. Ferin M, Jewelewicz R, Warren M. The Menstrual Cycle: Physiology, Reproductive Disorders, and Infertility. New York, NY: Oxford University Press; 1993:20–23
28. Giannini AJ, Melemis SM, Marin DM, et al. Symptoms of premenstrual syndrome as a function of beta-endorphin: two subtypes. Prog Neuropsychopharmacol Biol Psychiatry 1994;18:321–327
29. Facchinetti F, Fioroni L, Martignoni E, et al. Changes of opioid modulation of the hypothalamo-pituitary-adrenal axis in patients with severe premenstrual syndrome. Psychosom Med 1994;56:418–422
30. Chuong CJ, Hsi BP, Gibbons WE. Periovulatory beta-endorphin levels in premenstrual syndrome. Obstet Gynecol 1994;83(5 pt 1):755–760
31. Chuong CJ, Hsi BP. Effect of naloxone on luteinizing hormone secretion in premenstrual syndrome. Fertil Steril 1994;61:1039–1044
32. Halbreich U, Tworek H. Altered serotonergic activity in women with dysphoric premenstrual syndrome. Int J Psychiatry Med 1993;23:1–27
33. Menkes DB, Coates DC, Fawcett JP. Acute tryptophan depletion aggravates premenstrual syndrome. J Affect Disord 1994;32:37–44
34. Preskorn S. Recent pharmacologic advances in antidepressant therapy for the elderly. Am J Med 1993;94(suppl 5A):2–12
35. Murdoch D, McTavish D. Sertraline: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depression and obsessive-compulsive disorder. Drugs 1992;44:604–624