A Preliminary Study of Luteal Phase Versus Symptom-Onset Dosing With Escitalopram for Premenstrual Dysphoric Disorder

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Objective: This preliminary study compared the efficacy and tolerability of escitalopram administered at symptom onset or throughout the luteal phase in premenstrual dysphoric disorder (PMDD).

Method: Twenty-seven women meeting DSM-IV criteria for PMDD were randomly assigned in a double-blind manner to luteal phase (N = 13) or symptom-onset (N = 14) dosing of escitalopram (10–20 mg/day) for 3 consecutive menstrual cycles. Participants were enrolled from November 2002 to July 2003, and data collection was completed in December 2003. Symptoms were assessed using the 17-item Penn Daily Symptom Report (DSR), the Clinical Global Impressions-Improvement scale, the Hamilton Rating Scale for Depression, and the Sheehan Disability Scale. Scores were compared using repeated measures analysis of covariance and t statistics.

Results: Luteal phase and symptom-onset groups received escitalopram for a mean of 13.5 and 6.0 days, respectively (mean ± SD dose = 15.2 ± 5.1 mg/day at the third treatment cycle). Total premenstrual DSR scores significantly improved from baseline ($p = .003$), with a 57% decrease in the luteal phase group and a 51% decrease in the symptom-onset group. Clinical improvement (DSR score decrease ≥ 50% from baseline) was reported by 11 of 13 patients in the luteal phase group and 9 of 14 patients in the symptom-onset group. Symptom severity differentiated the response in the symptom-onset group, with those having more severe symptoms less likely to respond. Symptom severity did not differentiate treatment response to luteal phase dosing. Escitalopram was well tolerated. Adverse events were mild and transient, with only 2 patients discontinuing due to adverse events related to the medication.

Conclusion: Premenstrual dysphoric disorder improved significantly with either luteal phase or symptom-onset dosing of escitalopram. Women with more severe PMDD may respond better to luteal phase dosing than symptom-onset dosing.

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Premenstrual dysphoric disorder (PMDD) is a chronic disorder that affects approximately 3% to 8% of women of reproductive age[1] and is characterized by its symptom pattern linked to the menstrual cycle. DSM-IV criteria for PMDD include the occurrence of at least 5 of 11 depressive, anxious, cognitive, or physical symptoms, and significant impairment in social or occupational performance.[2] Symptoms of PMDD are intermittent, with pronounced symptoms in the period preceding menses (luteal phase) and remission in the follicular phase of the cycle.[3] The level of disability of PMDD is very similar to the functional impairments reported by patients with other depressive or anxiety disorders.[4]

In previous clinical studies, serotonergic antidepressants administered throughout the menstrual cycle have been used successfully to decrease symptoms of PMDD. Currently, there is increasing evidence that the selective serotonin reuptake inhibitors (SSRIs) are effective in controlling PMDD symptoms when administered only through the luteal phase of the menstrual cycle (14 days prior to the expected onset of menstrual bleeding).[5–11] In a randomized, double-blind, placebo-controlled study of citalopram,[11] PMDD patients showed a greater reduction in

irritability, a cardinal symptom of PMDD, with luteal phase dosing compared to continuous dosing throughout the menstrual cycle. These studies with SSRIs also report low incidences of adverse events with luteal phase dosing and are comparable to those observed with continuous administration.[12] Discontinuation symptoms due to SSRI treatment have not been observed with luteal phase dosing.[12–15]

Since symptoms of PMDD are chronic but limited to the luteal phase of the menstrual cycle, further study is needed to examine the effectiveness of SSRI treatment that is restricted to the time when symptoms occur. In a preliminary study with sertraline for premenstrual syndrome (PMS),[16] luteal phase and continuous daily dosing had comparable efficacy and tolerability to symptom-onset dosing. Citalopram has demonstrated efficacy for PMDD, an off-label indication, using either luteal phase or continuous dosing.[11] Escitalopram, the therapeutically active *S*-isomer of citalopram and the most selective SRI tested to date,[17,18] has demonstrated efficacy for the labeled indications of major depression[19,20] and generalized anxiety disorder.[21] Neither citalopram nor escitalopram presently has labeled indication for PMDD. The aim of the present study was to compare the efficacy and tolerability of escitalopram administered at either symptom onset or throughout the luteal phase of the menstrual cycle.

METHOD

Patient Selection

Twenty-seven patients were included in a randomized, parallel-group, double-blind, flexible-dose study of escitalopram for DSM-IV PMDD. Participants were enrolled from November 2002 to July 2003, and data collection was completed in December 2003. Inclusion criteria included ages 18 to 45 years; regular menstrual cycles in the normal range (22–35 days); general good health as determined by medical history, physical examination, and laboratory blood tests; evidence of ovulation as determined in the screen period by a simple at-home urine test; and signed informed consent approved by the Institutional Review Board. Exclusion criteria included any concurrent major psychiatric or physical diagnosis; psychotropic or hormonal medications including hormonal contraception; any concurrent treatment for PMS including over-the-counter, herbal, and nonmedical therapies; pregnancy, intending pregnancy, or breast feeding; hysterectomy; or symptomatic endometriosis.

Symptom Criteria

The PMDD diagnosis was confirmed with 2 cycles of prospective daily symptom ratings (17-item Penn Daily Symptom Report [DSR]).[22] The severity criteria were defined as the presence of 5 or more PMDD symptoms rated 3 (severe) or 4 (very severe) for at least 2 premenstrual days (days 23–28) for 3 screen cycles including a placebo lead-in cycle, the same symptoms rated with a mean score of ≤ 2 for cycle days 5 to 10, and moderate-to-severe functional impairment on the Sheehan Disability Scale (SDS).[23] In addition, a premenstrual DSR score ≥ 80 (sum of 6 days before menses) with a ≥ 50% increase from the postmenstrual DSR score (cycle days 5–10) was required in the screen cycles.

Dosing

After a 3-month screening phase (3 menstrual cycles, including a placebo lead-in cycle), patients meeting DSM-IV criteria for PMDD were randomly assigned to either luteal phase dosing or symptom-onset dosing for 3 menstrual cycles. All women received 2 bottles of medication in each cycle and were instructed to start bottle A 14 days before expected menses as estimated from cycle length in the preceding cycles of the study. All subjects were instructed to switch to bottle B with the onset of PMDD symptoms (or at 5 days prior to menses if bottle B had not yet been started) and continue daily through day 2 of menses. In the luteal phase group, both bottles contained escitalopram; in the symptom-onset group, bottle A contained placebo and bottle B contained escitalopram. All women took a 10-mg/day dose (or 1 placebo tablet) in the first treatment cycle. The dose was increased to 20 mg/day (or 2 placebo tablets) in the second and third cycles if symptoms of PMDD were unimproved.

Outcome Measures

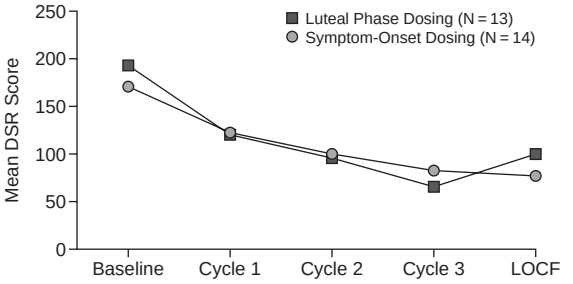
Clinical evaluations were performed in each cycle between days –4 to +3 of menses. The primary outcome measure was the premenstrual DSR score, with lower DSR scores indicative of greater improvement.[22] The 5 statistically derived DSR factors were also examined. The DSR factors included mood (irritability/anger, mood swings, anxiety/tension, depression, feeling out of control, feeling worthless/guilty, and decreased interest), behavior (poor coordination, insomnia, difficulty concentrating/confusion, and fatigue), pain (aches, headache, cramps), physical symptoms (breast tenderness, swelling/bloating), and food cravings/increased appetite. In addition to DSR scores, efficacy was evaluated at endpoint with clinical improvement defined as a DSR score decrease of ≥ 50% from baseline or a Clinical Global Impressions-Improvement (CGI-I)[24] scale score of 1 or 2. Remission was defined by premenstrual scores reduced to the postmenstrual level (using the mean postmenstrual DSR score during the screening cycles). Functioning was assessed with the SDS, which was rated by the patients on dimensions of overall interference, work, social life/leisure activities, and family life/home responsibilities. Each dimension was rated from 0 (not at all) to 10 (extremely). The clinician-rated 17-item Hamilton Rating Scale for De-

Table 1. Baseline Characteristics of the Luteal Phase and Symptom-Onset Dosing Groups[a]

Characteristic	Luteal Phase (N = 13)	Symptom-Onset (N = 14)
Age, y		
Mean (SD)	32.8 (7.6)	36.1 (4.3)
Range	20–44	27–40
DSR score, mean (SD)[b]		
Premenstrual	193 (57)	170 (59)
Postmenstrual	40 (34)	26 (28)
SDS overall score, mean (SD)	7.25 (1.48)	7.29 (2.13)
Duration of PMS, mean (SD), y	15.4 (20.2)	15.5 (22.0)

[a]There were no statistically significant differences between treatment groups.
[b]Average of 3 cycles.
Abbreviations: DSR = 17-item Penn Daily Symptom Report, PMS = premenstrual syndrome, SDS = Sheehan Disability Scale.

Figure 1. Total Premenstrual DSR Scores at Baseline and During 3 Treatment Cycles[a]



[a]Treatment, p = .749; cycle, p = .003; treatment by cycle, p = .634.
Abbreviations: DSR = 17-item Penn Daily Symptom Report, LOCF = last observation carried forward.

pression (HAM-D-17) was also administered.[25] Adverse events were assessed at each visit using a patient self-report questionnaire that included a question on the presence or absence of adverse events and instruction to list all adverse events experienced. The semistructured interview questionnaire used by the clinician at each visit also elicited adverse events and rated their severity.

Statistical Analysis

Primary analyses were performed on the intent-to-treat population (defined as patients with any treatment response data) using repeated-measures analysis of covariance, with unstructured covariance fit using SAS Proc Mixed (SAS Version 8.0; SAS Institute Inc, Cary, N.C.). The primary outcome variables were the premenstrual DSR scores. The model used all available data and included treatment (2 dosing groups), time as measured by cycle (3 menstrual cycles), and baseline symptoms (average of the premenstrual DSR scores for 3 screen cycles). Interactions between treatment and cycle were examined. Secondary outcomes using clinical definitions of improvement, interference with functioning, and symptom severity were examined with last observation carried forward (LOCF) and used t statistics, χ^2, or Fisher exact test as appropriate for the data. Statistical results with $p \leq .05$ and 2-tailed interpretation were considered significant.

RESULTS

A total of 73 women enrolled in the study, with 37 entering the placebo lead-in cycle. Twenty-seven were randomly assigned to either the luteal phase dosing group (N = 13) or the symptom-onset dosing group (N = 14). Reasons for the 46 women who discontinued during the screening phase were ineligibility (N = 17), loss to follow-up (N = 14), personal reasons or withdrawal of consent (N = 12), placebo response (N = 2), and adverse events (N = 1). During the treatment phase, 1 woman discontinued in the luteal phase group (adverse event, not treatment related), and 3 women discontinued in the symptom-onset group due to adverse events (N = 1), poor response (N = 1), and noncompliance (N = 1).

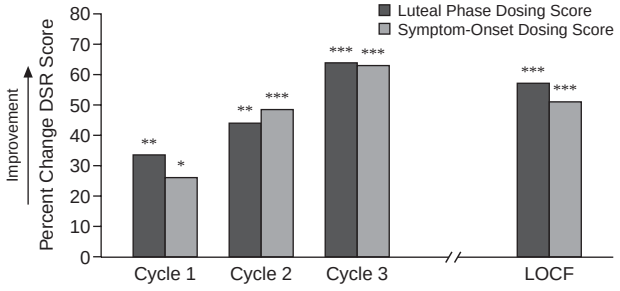
There were no statistically significant differences in baseline characteristics between the 2 treatment groups in terms of demographics and severity of illness metrics (Table 1). The mean duration of active medication was 13.5 days in the luteal phase group and 6.0 days in the symptom-onset group. The mean ± SD daily dose of escitalopram in the third treatment cycle was 15.2 ± 5.1 mg/day for the total group, with 17.5 ± 4.5 mg/day and 12.2 ± 4.4 mg/day ($p = .015$) in the luteal phase and symptom-onset dosing groups, respectively.

Total premenstrual DSR scores significantly improved from baseline ($F = 7.48$, $df = 2,24$; $p = .003$). There was no difference in improvement compared between the 2 dosing groups and no significant interaction of dosing group with time, as shown in Figure 1. All DSR factors significantly improved from baseline in both dosing groups, with no significant differences between the 2 dosing groups (data not shown). At endpoint (LOCF), the total premenstrual DSR scores decreased from baseline by 57% in the luteal phase group and 51% in the symptom-onset group (Figure 2).

Using the clinical improvement criterion (decrease in total premenstrual DSR ≥ 50% from baseline), 11 of 13 patients in the luteal phase group and 9 of 14 patients in the symptom-onset group improved at endpoint ($p = .23$). Additionally, 7 patients in the luteal phase group and 4 patients in the symptom-onset group achieved remission at endpoint ($p = .18$). Endpoint analysis of improvement as shown by CGI-I scores of 1 or 2 indicated that 10 patients in the luteal phase group and 9 patients in the symptom-onset group improved ($p = .66$).

Symptom interference with overall functioning as assessed by the SDS significantly improved in both dosing groups, decreasing from marked interference before treatment to a mild level at endpoint, with no significant dif-

Figure 2. Percent Change From Baseline in Mean Total Premenstrual DSR Scores[a]



[a]There are no significant differences between the 2 dosing groups.
*p < .05 for change from baseline (paired t test).
**p < .01 for change from baseline (paired t test).
***p < .001 for change from baseline (paired t test).
Abbreviations: DSR = 17-item Penn Daily Symptom Report, LOCF = last observation carried forward.

ference between the 2 dosing groups (mean ± SD scores: luteal phase group = 7.25 ± 1.48 at baseline to 2.85 ± 2.97 at endpoint, 95% CI = 2.08 to 6.02; symptom-onset group = 7.29 ± 2.13 at baseline to 4.07 ± 3.02 at endpoint, 95% CI = 1.33 to 5.10; p = .30 for comparison of the 2 groups at endpoint). The subject-rated dimensions of interference with family life, work, and leisure activities each followed the same pattern of improvement. The HAM-D-17 premenstrual ratings were subclinical before treatment (mean = 12.0) and decreased to normal levels at endpoint (mean = 4.0 in both dosing groups). However, improvement was swifter in the luteal phase dosing group, which had a lower mean score over all treatment cycles (p = .097).

We examined the effect of symptom severity at baseline on improvement, using the median split of the premenstrual DSR scores of 185 as the cutoff point for severity and ≥ 50% decrease in DSR score from baseline as the definition of improvement. Premenstrual symptom severity was not associated with improvement in the luteal phase dosing group (6 of 8 high-severity patients and 5 of 5 low-severity patients improved, p = .36). In the symptom-onset dosing group, the patients with lower premenstrual symptom severity were more likely to improve than the patients with high symptom severity (1 of 5 high-severity patients and 8 of 9 low-severity patients improved, p = .02).

Escitalopram was well tolerated, and adverse events were generally transient and mild in nature. Ten (37%) of 27 patients reported no adverse events. Only 2 patients discontinued the study due to adverse events of the medication, and 1 subject withdrew due to the adverse event of shoulder pain that was not treatment related. There was a statistical trend toward more adverse events in the symptom-onset dosing group than in the luteal phase dosing group (79% [11/14] vs. 46% [6/13], respectively; p = .07). The following adverse events were reported by 2 or more patients with an incidence at least twice that in the placebo lead-in phase and were reported in both dosing groups: fatigue (6/27, 22%), nausea (4/27, 15%), decreased libido or anorgasmia (4/27, 15%), insomnia (4/27, 15%), dizziness or light-headedness (4/27, 15%), headache (2/27, 7%), dry mouth (2/27, 7%), and vivid dreams (2/27, 7%). There were no reports of withdrawal symptoms. We examined the *postmenstrual* DSR scores (cycle days 5–10) in the 3 treatment cycles, but found no significant increases for any symptom, factor, or the total postmenstrual DSR score.

DISCUSSION

Both symptom-onset and luteal phase dosing regimens reduced PMDD symptoms and improved functioning in this preliminary study. The results are consistent with those of previous studies that demonstrated the efficacy of luteal phase dosing with SSRIs for the treatment of PMDD[3,11,14] and suggest that symptom-onset dosing may be similarly effective for some women, particularly those with less severe premenstrual symptoms. In both dosing groups, improvement in DSR scores was reported in the first treatment cycle and continued to increase in the subsequent cycles, consistent with previous reports that the onset of action of a serotonergic antidepressant is more rapid in PMDD treatment than in treatment of major depressive disorder.[12] However, these results were not studied under double-blind, placebo-controlled conditions and must be interpreted with caution, inasmuch as a placebo response or effects of nonsymptomatic cycles during the treatment interval cannot be dismissed.

Escitalopram was well tolerated in both dosing regimens, although fewer adverse events were reported in the luteal phase dosing group after 3 months of treatment. Only 2 patients attributed their study discontinuation to adverse events of the medication. Symptom-onset dosing may offer a more favorable treatment modality that limits drug exposure to only those times when symptoms are experienced, reduces the possibility of ongoing side effects, reduces the cost of medication, and ultimately improves patient functioning.

Although the 2 dosing groups did not differ overall in treatment response, the severity of premenstrual symptoms was associated with improvement. In the symptom-onset dosing group, the women with greater symptom severity were less likely to improve than those with lower severity. This differential response was not observed in the luteal phase dosing group.

The data do not indicate why the patients with more severe symptoms in the symptom-onset dosing group were less improved. Although the patients were instructed to switch to the second bottle of medication with the "onset" of symptoms, it may be that the "switch" was too late,

and that symptoms had developed before receiving active medication. This was also suggested in the results from Miner et al.,[26] who found that 2 doses of weekly enteric-coated fluoxetine 90 mg taken 14 and 7 days before menses effectively treated PMS, while a single dose taken 7 days before menses did not. While dosing is not comparable in these 2 studies, the earlier study similarly suggested that dosing only in the week prior to menses is not sufficient for improvement of PMS. Su et al.[27] found little evidence for luteal phase–specific serotonergic dysfunction, suggesting that the serotonin system is a modulating but not causal factor in PMS. It may be that effectiveness of the SSRI requires that the serotonergic effects be linked to gonadal hormone activity earlier in the menstrual cycle, possibly around ovulation.

The better response in the symptom-onset group of patients with a lower symptom level may indicate a placebo response that is particularly difficult to separate from drug response in patients with less severe symptoms. Other speculations for the observations in the present study are the possibility that the dose was too low in the symptom-onset group for patients with more severe symptoms (dose increases were less likely in the symptom-onset group, resulting in a significantly lower mean daily dose compared to the luteal phase group). Possibly the high-severity patients had other undetected depressive disorders that do not respond as rapidly to SSRIs, although the lack of association between symptom severity and improvement in the luteal phase dosing group suggests this is unlikely.

These preliminary results showing efficacy and tolerability of escitalopram for symptom-onset compared to luteal phase dosing in PMDD merit further study in a larger and extended controlled trial. Whether these findings are replicated, whether similar responses are maintained with long-term escitalopram treatment, and whether either premenstrual or postmenstrual symptom severity can serve as a predictor of response to the dosing regimen are important clinical questions that need to be addressed.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro), fluoxetine (Sarafem and others), sertraline (Zoloft).

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