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Citalopram in PMS Patients with Prior SSRI Treatment Failure: A Preliminary Study

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ABSTRACT

Objectives: **Evidence shows that the selective serotonin reuptake inhibitors (SSRIs) effectively reduce the symptoms of severe premenstrual syndrome (PMS). A placebo-controlled study of citalopram, the most selective SSRI, demonstrated that half-cycle dosing (luteal phase) was effective for DSM-IV-defined premenstrual dysphoric disorder (PMDD), a severe form of PMS. This study examined the effectiveness of half-cycle dosing of citalopram in PMS patients who did not respond to previous SSRI treatment.**

Methods: **Seventeen women with no improvement in symptoms after two menstrual cycles on an SSRI were given open-label citalopram (20–40 mg/day). Eleven subjects received half-cycle dosing, and 6 subjects received full-cycle dosing. Scores on the 17-item daily symptom report (DSR) and on each of five DSR symptom clusters were used to measure citalopram efficacy.**

Results: **Total premenstrual DSR scores were significantly improved ($p<0.001$) in both half-cycle and full-cycle dosing groups. The half-cycle group reported lower DSR scores throughout treatment compared with the full-cycle group, but the difference did not reach statistical significance in this small sample. All DSR factor scores (mood, behavioral, pain, physical symptoms, and appetite) significantly improved. Clinical improvement (≥50% decrease from baseline DSR) was reported by 76% of the subjects overall. Forty-one percent of the subjects experienced symptom remission, defined as a decrease in symptoms to postmenstrual levels.**

Conclusions: **These results from a small number of subjects with open-label treatment must be viewed as preliminary but suggest that citalopram treatment is effective for PMS patients who failed previous SSRI treatment.**

INTRODUCTION

ALTHOUGH MANY WOMEN EXPERIENCE physical changes prior to their menstrual period, these changes generally are normal and do not cause significant subjective distress or functional impairment. When premenstrual distress is dominated by emotional symptoms, such as irritability, nervousness, tension, and depressed mood, it is a powerful discriminator of treatment-seeking behavior, as shown in the Zurich Cohort Study.[1] This community-based study conducted

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in Switzerland identified 8% of menstruating women with severe premenstrual syndrome (PMS) and 14% with moderate PMS, both of which significantly correlated with functional impairment.[1] Other studies that examined criteria for premenstrual dysphoric disorder (PMDD) showed that 3%–10% of menstruating women experienced premenstrual symptoms to a degree that impaired work, relationships, or social functioning.[2–4]

Serotonin agonist antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), appear to be the treatment of choice for severe PMS at this time.[5,6] A meta-analysis of trials with SSRIs indicated that approximately 61% of PMS patients responded to serotonergic antidepressants and that they are an effective first-line treatment for this disorder.[7]

Because PMS is a chronic yet intermittent condition that appears to react swiftly to serotonergic antidepressants, researchers have investigated whether dosing on an intermittent basis (i.e., during the luteal phase) rather than continuously would provide sufficient therapeutic benefit. Several large studies[8,9] and a number of smaller preliminary studies involving sertraline,[10–12] fluoxetine,[13] citalopram,[14] and clomipramine[15] showed good response among PMS patients who underwent treatment for approximately 2 weeks preceding each menstrual period. Several of these trials[11,13,14] suggested that premenstrual dosing was more effective than continuous dosing, although more research is necessary to determine the relative value of these strategies.

To our knowledge, there has been no study of PMS patients who do not respond to initial treatment with an SSRI. Because citalopram is the most serotonin-selective of the SSRIs, we investigated whether PMS subjects who did not respond to an initial SSRI would respond to citalopram. In addition to examining the general efficacy of citalopram in this patient group, we compared half-cycle and continuous dosing regimens.

MATERIALS AND METHODS

Study design

Enrollment in this open-label study was limited to patients aged 18–45 years with severe PMS who received SSRI treatment for at least two menstrual cycles, with little or no improvement. Screening was based on subject report of previous SSRI treatment (dosing information was not systematically obtained) or on observed response after two cycles of open treatment in the PMS program. Subjects met the PMS criteria, confirmed by daily symptom ratings (DSR)[16] for two menstrual cycles. Severe PMS was confirmed by DSR for two menstrual cycles, with the premenstrual DSR score $\geq$80 and at least 50% higher than the postmenstrual scores for the average of the two screen cycles. Patients with other major psychiatric or physical disorders as assessed by the Structured Clinical Interview for DSM-IV axis 1 disorders (SCID),[17] physical examination, and laboratory blood screens were not included. Informed written consent approved by the university review board was obtained from all subjects.

After two screening cycles that met the criteria for severe PMS, the first 10 subjects were randomly assigned to either full-cycle or half-cycle dosing regimens, using a computer-generated random number list. All subjects after that were assigned to half-cycle dosing, which had become the primary focus of the pilot study.

Dosing

After two screen cycles that demonstrated meeting the DSR criteria for severe PMS, patients were treated with either half-cycle dosing (to start dosing at 14 days before the expected date of next menses) or full-cycle dosing with citalopram. Citalopram was initiated at 20 mg/day. Subjects who did not improve after one treatment cycle could increase to 40 mg/day in the second and third treatment cycles. Dosing compliance was assessed by clinical review at each visit, including review of the subject's daily report of pills taken and by the count of the number of pills returned at each visit.

Outcome measures

The primary outcome measure was the subject-rated premenstrual DSR score (sum of the 6 days before menses). In addition to the total premenstrual scores, the statistically derived DSR factors (mood, behavioral, pain, physical symptoms, and appetite) were evaluated. A 29-item version of the Hamilton Depression Rating Scale (HAM-D-29)[18] was rated by the clinician for the premenstrual week. The scores for the core 17 items of the HAM-D were also evaluated. Clinician ratings of symp-

TABLE 1. BASELINE CHARACTERISTICS

Characteristic	*Half cycle* (n = *11*)	*Full cycle* (n = *6*)
Age (years)	34.7 ± 7.5[a]	37.8 ± 4.5[a]
DSR, premenstrual (average 2 cycles)	153 ± 70	210 ± 77
DSR, postmenstrual (average 2 cycles)	28 ± 32	43 ± 53
HAM-D-29, premenstrual*	16.7 ± 6.1	24.8 ± 1.8
HAM-D-17, premenstrual	8.5 ± 4.7	11.8 ± 1.5

[a]Mean ± SD.
*$p = 0.05$.

tom severity and improvement were obtained at each visit using the Clinical Global Impressions (CGI).[19] Adverse event reports were obtained via clinical inquiry at each study visit.

Data analysis

Change from baseline was examined for all subjects with treatment response data using *t* statistics and the last observation carried forward (LOCF). Comparisons between half-cycle and full-cycle dosing used repeated measures analysis (LOCF), with the average baseline premenstrual scores as the covariate. Categorical data, such as improvement status, were tested with the chi-square test or Fisher s exact test. Statistical results with $p \leq 0.05$ and two-tailed interpretation were considered statistically significant. The statistical software package was SAS (SAS Institute Inc., Cary, NC).

RESULTS

Twenty-five subjects who did not respond to initial SSRI treatment enrolled in the screen phase, and 21 continued and met the symptom eligibility criteria after 2 months of daily symptom ratings. Of the 21 subjects assigned to treatment, 4 discontinued before treatment response data were collected (2 were lost to follow-up, 2 experienced side effects), leaving 17 for the efficacy analysis. Of the 17 subjects, 6 received full-cycle dosing and 11 received half-cycle dosing. Fifteen had previously received sertraline, and 2 had received fluoxetine. Safety data were available for 19 patients. Baseline characteristics of the subjects are shown in Table 1. There were no statistically significant differences between the half-cycle and full-cycle dosing groups at baseline, with the exception of the premenstrual HAM-D scores, which were higher in the full-cycle dosing group.

Total DSR scores were significantly improved ($p<0.001$) from baseline in both the half-cycle and full-cycle dosing groups. The half-cycle group had lower symptom scores throughout treatment compared with the full-cycle dosing group, but the trend did not reach statistical significance in this small sample (Fig. 1). (Based on the DSR scores at treatment end point, a sample size of 29

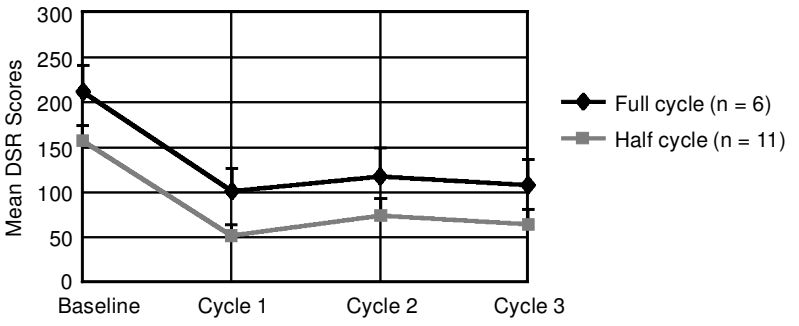

FIG. 1. Total premenstrual scores for three treatment cycles (raw means with standard error). Change from baseline with last observation carried forward (LOCF): $p<0.001$. Repeated measures analysis for treatment group, LOCF: F1, 14=2.56, $p=0.13$.

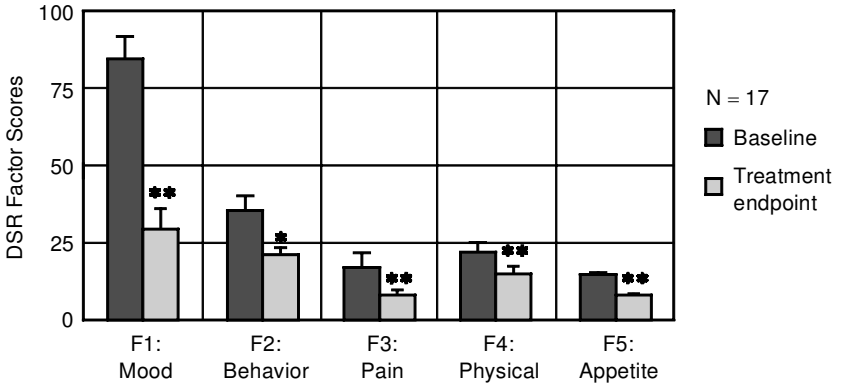

FIG. 2. Premenstrual DSR factor scores at baseline and treatment end point (raw means with standard error) with last observation carried forward (LOCF), $n = 17$: Change from baseline: $^{**}p<0.001$; $^{*}p<0.01$.

in each group would have 80% power to detect a difference between the two means with a common standard deviation [SD] of 60, using a t test with a 0.05 two-sided significance level.) Symptom improvement with citalopram was swift. Decreases in total DSR scores occurred within the first treatment cycle. Each of the five DSR symptom clusters (mood, behavioral, pain, physical symptoms, and appetite) were significantly improved from baseline at end point (Fig. 2).

HAM-D-29 scores were significantly improved ($p<0.001$) in both treatment groups. The half-cycle dosing group had lower HAM-D scores throughout treatment compared with the full-cycle dosing group, but the difference did not reach significance (Fig. 3). Results of the 17-item HAM-D were similar.

Using a clinical definition of improvement (≥50% decrease in DSR from baseline), 76% (13 of 17) of the study subjects responded to citalopram treatment (Fig. 4). Of these responders, 9 received half-cycle dosing and 4 received full-cycle dosing. Forty-one percent (7 of 17) achieved remission (defined as the premenstrual DSR reduced to the postmenstrual level). Of those achieving remission, 6 received half-cycle dosing and 1 received full-cycle dosing. Fifty-nine percent of the subjects experienced a decrease of 50% or more in premenstrual HAM-D-29 scores, and all of these improved scores were ≤7, a level considered to indicate symptom remission. CGI indicated that 14 of the 17 subjects (82%) were improved or very improved.

The citalopram dose remained low. At treatment end point, the mean doses were 23 ± 9 mg/day in half-cycle treatment and 25 ± 10 mg/day in full-cycle treatment. The majority of subjects (59%) remained at the starting dose of 20 mg/day throughout the study. Mean dose in the unimproved group was 25 ± 6 mg/day compared with 23 ± 10 mg/day in the improved group ($p=0.65$).

Citalopram was well tolerated, and adverse events generally were mild and transient. Twelve of 19 subjects reported adverse events in the first treatment cycle, most frequently nausea, insom-

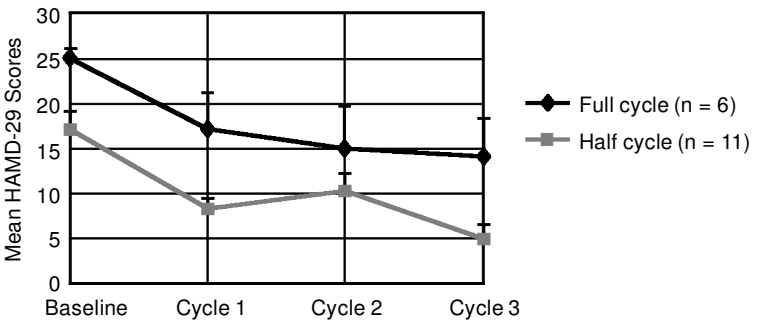

FIG. 3. Premenstrual HAM-D-29 scores for three treatment cycles (raw means with standard error). Change from baseline: $p<0.002$ for half-cycle group and $p<0.03$ for full-cycle group. Repeated measures analysis for treatment group with last observation carried forward (LOCF): F1, 13=3.48, $p=0.09$.

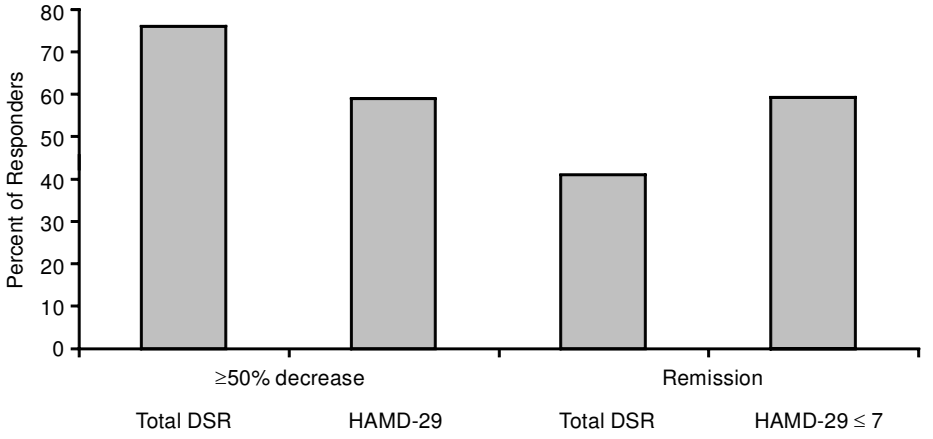

FIG. 4. Responders (%) at treatment end point with last observation carried forward (LOCF), total sample, $n=17$.

nia, dry mouth, and gastrointestinal symptoms ($n=4$ each). These adverse events are consistent with the citalopram package insert, where the most frequent treatment-emergent events are nausea (21%), other gastrointestinal symptoms (20%), dry mouth (20%), somnolence (18%), and insomnia (15%). The frequency of adverse events did not differ between half-cycle (64%) and full-cycle (63%) dosing. The transience of the adverse events was shown by their decrease to 28% (5 of 19) of the subjects in the second cycle and to only 2 subjects in the third cycle, who reported insomnia, constipation, diarrhea, and flatulence. Two subjects discontinued because of side effects (insomnia and vivid dreams, $n=1$; fatigue, body aches, and weight gain, $n=1$). Although 4 subjects had complained of decreased libido in their previous SSRI treatment, there were no reports of sexual side effects during 3 months of citalopram treatment.[20] (The incidence of decreased libido for citalopram in the package insert is 2%.)

Because of the intermittent dosing regimen, with abrupt discontinuation of the medication in each treatment cycle,[21] we also examined the DSR to determine if symptoms worsened following discontinuation of citalopram in the half-cycle dosing group. Comparison of the scores for DSR symptoms on cycle days 3–7 with the pretreatment baseline for the same days showed no worsening of any symptom. No subject reported any difficulties following discontinuation of citalopram.

DISCUSSION/CONCLUSIONS

Switching to an alternate SSRI after failed initial treatment with an SSRI has been shown to be an effective strategy in the treatment of depression,[22–24] but there have been no reports of this method in the treatment of PMS. Our results suggest that citalopram is effective for PMS patients who did not respond to an initial SSRI treatment. The findings of this study also support luteal phase dosing with an SSRI in the treatment of PMS. Furthermore, citalopram worked swiftly and at low doses, which adds support to previous data suggesting that low doses and rapid onset of action may characterize the use of some SSRIs in the treatment of PMS.[14,25–27] Finally, citalopram was well tolerated in this study, with low attrition due to adverse events, few adverse events reported by the third treatment cycle, and no reports of decreased libido in this small sample.

Interpretation of these results must be considered in light of the limits imposed by study design. A small study group makes extrapolation of the findings problematic. Furthermore, the open-label and naturalistic dosing of citalopram means that this trial was uncontrolled and unblinded. The previous SSRI failure in this pilot study was determined in uncontrolled conditions and based on subject report. The present data cannot say whether previous SSRI failure was due to inadequate dosing, overdosing, or patient noncompliance and cannot determine relationships between previous SSRI dosing and response in the present study. However, the evidence of effectiveness of citalopram administered only in the luteal phase is in agreement with the results of a previous controlled trial of citalopram in treatment of PMDD.[14] Further controlled study is warranted to support or refute these findings, which indicate that citalopram treatment is effective in PMS

patients who failed previous SSRI treatment and that half-cycle dosing is effective for these patients.

REFERENCES

1. Angst J, Sellaro R, Merikangas KR, et al. The epidemiology of perimenstrual psychological symptoms. Acta Psychiatr Scand 2001;104:110.
2. Ramcharan S, Love E, Fick G, et al. The epidemiology of premenstrual symptoms in a population-based sample of 2650 urban women: Attributable risk and risk factors. J Clin Epidemiol 1992;45:377.
3. Logue CM, Moos RH. Perimenstrual symptoms: Prevalence and risk factors. Psychosom Med 1986;48: 388.
4. Deuster PA, Adera T, South-Paul J. Biological, social, and behavioral factors associated with premenstrual syndrome. Arch Fam Med 1999;8:122.
5. Endicott J, Amsterdam J, Eriksson E, et al. Is premenstrual dysphoric disorder a distinct clinical entity? J Wom Health Gender-Based Med 1999;8:663.
6. Yonkers KA, Clark RH, Trivedi MH. The psychopharmacological treatment of nonmajor mood disorders. Mod Probl Pharmacopsychiatry 1997;25:146.
7. Dimmock PW, Wyatt KM, Jones PW, et al. Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: A systematic review. Lancet 2000; 356:1131.
8. Halbreich U, Bergeron R, Freeman E, et al. Intermittent luteal phase dosing of sertraline effective in PMDD. Int J Neuropsychopharmacol 2000;3:S249.
9. Judge R, Brown E, Miner C, et al. Intermittent fluoxetine dosing in premenstrual dysphoric disorder. Arch Wom Ment Health 2001;3/4:37.
10. Jermain DM, Preece CK, Sykes RL, et al. Luteal phase sertraline treatment for premenstrual dysphoric disorder. Results of a double-blind, placebo-controlled, crossover study. Arch Fam Med 1999;8:328.
11. Freeman EW, Rickels K, Arredondo F, et al. Full- or half-cycle treatment of severe premenstrual syndrome with a serotonergic antidepressant. J Clin Psychopharmacol 1999;19:3.
12. Halbreich U, Smoller JW. Intermittent luteal phase sertraline treatment of dysphoric premenstrual syndrome. J Clin Psychiatry 1997;58:399.
13. Steiner M, Korzekwa M, Lamont J, et al. Intermittent fluoxetine dosing in the treatment of women with premenstrual dysphoria. Psychopharmacol Bull 1997;33: 771.
14. Wikander I, Sundblad C, Andersch B, et al. Citalopram in premenstrual dysphoria: Is intermittent treatment during luteal phases more effective than continuous medication throughout the menstrual cycle? J Clin Psychopharmacol 1998;18:390.
15. Sunblad C, Hedberg MA, Eriksson E. Clomipramine administered during the luteal phase reduces the symptoms of premenstrual syndrome: A placebo-controlled trial. Neuropsychopharmacology 1993;9:133.
16. Freeman EW, DeRubeis RJ, Rickels K. Reliability and validity of a daily diary for premenstrual syndrome. Psychiatry Res 1996;65:97.
17. Spitzer RL, Williams JB, Gibbon M, et al. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 1992;49:624.
18. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56.
19. Guy W. ECDEU assessment manual for psychopharmacology. Washington, DC: Superintendent of Documents, U.S. Government Printing Office, U.S. Department of Health, Education, and Welfare Publication No. 76-338; 1976.
20. Norton JW. Citalopram inpatients with SSRI-induced sexual dysfunction. Primary Psychiatry 2000;7:78.
21. Markowitz JS, DeVane CL, Liston HL, et al. An assessment of selective serotonin reuptake inhibitor discontinuation symptoms with citalopram. Int Clin Psychopharmacol 2000;15:329.
22. Thase ME, Blomgren SL, Birkett MA, et al. Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. J Clin Psychiatry 1997;58:16.
23. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? J Clin Psychiatry 1995;56:30.
24. Thase ME, Ferguson J, Wilcox C. Citalopram treatment of paroxetine intolerant patients. Presented at the New Clinical Drug Evaluation meeting, Boca Raton, FL, 1999.
25. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group [see Comments]. N Engl J Med 1995; 332:1529.
26. Diegoli MS, da Fonseca AM, Diegoli CA, et al. A double-blind trial of four medications to treat severe premenstrual syndrome. Int J Gynaecol Obstet 1998;62: 63.
27. Yonkers KA, Halbreich U, Freeman E, et al. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. A randomized controlled trial. Sertraline Premenstrual Dysphoric Collaborative Study Group [see Comments]. JAMA 1997; 278:983.

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