Luteal Phase Administration of Paroxetine for the Treatment of Premenstrual Dysphoric Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial in Canadian Women

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Objective: To evaluate the efficacy and safety of intermittent, luteal phase–only administration of paroxetine (10 mg and 20 mg) in the treatment of premenstrual dysphoric disorder (PMDD).

Method: In this multicenter trial, female outpatients (aged 18–45 years) from 4 Canadian health centers meeting DSM-IV criteria for PMDD were asked to perform daily ratings of their premenstrual symptoms for 2 consecutive menstrual cycles. Those displaying the symptoms of irritability and/or depressed mood in the luteal phases but not in the follicular phases of their menstrual cycles were randomly assigned to intermittent, luteal phase–only treatment with paroxetine 10 mg or 20 mg or placebo for 4 additional cycles. The primary efficacy endpoint was the percent change from baseline at study endpoint on the visual analog scale irritability score. Treatment differences were tested using analysis of covariance ad hoc. Estimated treatment mean differences and their associated 95% confidence intervals were also calculated. Data were collected from May 1999 to November 2002.

Results: Ninety-nine patients were included in the intention-to-treat population. When compared with placebo, patients treated with paroxetine 20 mg attained a significant reduction in irritability (difference in median percent change: –23.9, 95% CI = –51.3 to –6.2, p = .014; difference in mean absolute change: –18.6, 95% CI = –32.5 to –4.6, p = .007). A statistically significant difference was not observed when the patients treated with the lower dose of paroxetine (10 mg) were compared with placebo. Treatment was well tolerated with no unexpected side effects.

Conclusion: Intermittent administration of paroxetine 20 mg significantly reduced irritability symptoms in patients with PMDD. These results are consistent with previous studies suggesting that PMDD may be treated effectively by luteal phase–only administration of a selective serotonin reuptake inhibitor.

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The majority of women of fertile age experience at least some form of mild premenstrual complaints; however, most are able to cope without treatment. This is not true for approximately 3% to 8% of North American women who meet the criteria for premenstrual dysphoric disorder (PMDD).[1–4] Premenstrual dysphoric disorder is a chronic condition, the symptoms of which typically appear within a week prior to menstruation and remit within a few days of the onset of bleeding. During this time, the impact of PMDD on a woman's work, social, and family life can be substantial. Decreased work productivity due to monthly absenteeism[5] and disruption to personal relationships with family and friends are common consequences of PMDD.[6,7] There is evidence that the impairment of psychosocial functioning of women with PMDD during luteal phases of the menstrual cycle is equal to that seen in women with major depression.[6]

The diagnostic criteria for PMDD as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) must include 1 of 4 core symptoms (irritability, tension, depressed mood, and lability of

mood) and at least 5 of 11 total symptoms during the luteal phase of a regular menstrual cycle.[8] Interference with social and occupational functioning is a key criterion for PMDD. It has been argued that, as a result of the restrictive nature of the DSM-IV criteria for PMDD, actual prevalence of PMDD among women in their reproductive years is likely to be higher than the often-cited 3% to 8% in the literature.[9]

Although the etiology of PMDD is largely unknown, it has been suggested that normal ovarian function rather than hormonal imbalance is the cyclical trigger for PMDD-related biochemical events in the central nervous system, leading to various somatic complaints and mental symptoms.[10,11] Selective serotonin reuptake inhibitors (SSRIs) have been found to be an effective treatment for PMDD. In a considerable number of clinical trials, serotonergic antidepressants, including paroxetine and paroxetine controlled release, were found to be far superior to placebo in treating PMDD when given continuously throughout the menstrual cycle and in luteal phases of the menstrual cycle.[12–26] Luteal phase administration of an SSRI is beneficial to the patient in terms of cost and duration of exposure[27] and appears more acceptable due to the on-off nature of PMDD.

This randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of intermittently administering 2 doses (20 mg and a lower dose of 10 mg) of paroxetine during luteal phases to women with PMDD over 4 menstrual cycles.

METHOD

This was a multicenter, randomized, double-blind, placebo-controlled, fixed-dose study to assess the efficacy and safety of paroxetine (10 mg and 20 mg) in women with PMDD. Data were collected from May 1999 to November 2002. Female outpatients aged 18 to 45 presenting with PMDD at 4 Canadian health centers were screened as suitable candidates against the screening inclusion and exclusion criteria. A patient was eligible if she experienced regular menstrual cycles, used an adequate form of nonhormonal contraception, and qualified for the diagnosis of PMDD according to DSM-IV criteria.[8] At least 1 of 4 core symptoms had to be prominent (irritability, depressed mood, tension, or affective lability), and the severity of these symptoms had to be rated 50% higher during the luteal phase compared with the follicular phase, as confirmed by 2 baseline reference cycles. The patient had to have a baseline luteal phase Clinical Global Impressions-Severity of Illness (CGI-S) scale[28] score ≥ 3.

Women were excluded if they were taking oral contraception, breast-feeding, pregnant, or planning to become pregnant during the study period. Women were also excluded if they met DSM-IV criteria for any Axis I disorder, were deemed a suicidal risk, had a history of SSRI use for premenstrual symptoms, were taking ongoing medication that could affect PMDD symptomatology, had a clinically significant abnormality on screening blood tests, or had a baseline Montgomery-Asberg Depression Rating Scale[29] score > 10 during the follicular phase of the menstrual cycle.

All patients gave their written informed consent prior to participation in the study. The study protocol was reviewed and approved by the institutional review boards of the participating health centers and was conducted in accordance with the Declaration of Helsinki and principles of Good Clinical Practice.

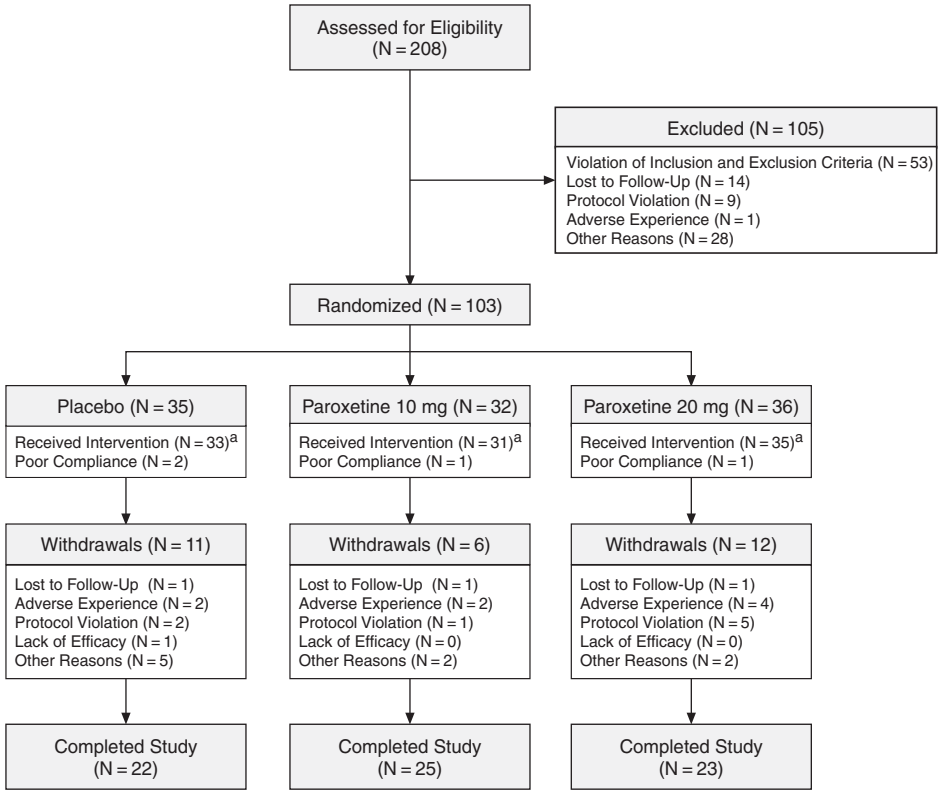
This was a 2-phase study design; the first phase consisted of a reference period and the second phase consisted of a randomized treatment period. At the screening visit, women were asked to rate the severity of their premenstrual symptoms (i.e., irritability, breast tenderness, depressed mood, etc.) prospectively in daily diaries using visual analog scales (VAS) for 2 consecutive menstrual cycles (reference cycle). Visual analog scales consist of 100-mm horizontal lines anchored by word descriptors and number values ranging from "not at all" to "extremely." Patients place a mark on the line to indicate their perception of the severity of their symptoms. Visual analog scales provide a valid and reliable measure of severity of symptoms associated with the current DSM-IV definition of PMDD.[30]

Women who remained eligible after the reference cycle were randomly assigned by a computer-generated randomization code to paroxetine 10 mg, paroxetine 20 mg, or placebo at a ratio of 1:1:1 for 4 menstrual cycles (treatment cycles), during which they continued to record daily symptoms in their diaries. Patients were instructed to take their first pack of medication (containing placebo) on the first day of menstrual bleeding until the estimated day of ovulation (follicular phase). Thereafter, they were instructed to begin the second pack of medication (containing active paroxetine 10 mg or 20 mg for the 2 treatment groups) until the first day of bleeding (luteal phase). This pattern was repeated for 3 menstrual cycles. The fourth cycle consisted of 4 days of 10 mg/day of paroxetine beginning on the first day of menstrual bleeding, allowing the patient to downtitrate prior to stopping treatment.

The study duration was 6 menstrual cycles and involved 3 telephone contacts and 6 study visits. Study visits were scheduled within 5 days prior to menstruation in order to collect diaries, conduct other efficacy assessments, and verify laboratory data, vital signs, and adverse events.

The primary objective was to compare the efficacy of intermittent treatment with paroxetine (10 mg and 20 mg) administered during the luteal phase of the menstrual cycle with placebo for the treatment of PMDD. The secondary objective was to evaluate the safety of intermittent

Figure 1. Study Flowchart



[a]Intent-to-treat population.

treatment with paroxetine. The primary efficacy variable for this study was the percent change from baseline in the luteal phase VAS irritability score at study endpoint. Secondary outcome measures included change from baseline in luteal phase VAS individual scores and change from baseline to study endpoint in the Premenstrual Tension Scale (PMTS-O)[31] total score, CGI-S score, and Sheehan Disability Scale[32] scores (work life, social life, family life). The overall proportion of responders was defined as a $\geq 50\%$ reduction from baseline to study endpoint for each of the VAS mood items, and the proportion of responders was determined by a score of 1 (very much improved) or 2 (much improved) on the CGI.

Statistical Methods

Sample size determination was based on detecting a 35% difference between the treatment and placebo groups on the primary efficacy variable, VAS irritability score. A sample size of 26 evaluable patients in each of the 3 study arms provided 90% power for each comparison between placebo and paroxetine (10 mg and 20 mg), given a normal significance level of 5%. This accounted for adjusting for multiple comparisons. The estimated standard deviation was 38.5. In order to allow for a 20% attrition rate, 99 patients were targeted for recruitment so as to obtain 33 patients per treatment arm.

Primary inferences concerning the efficacy of each paroxetine group (10 mg and 20 mg) were made using the intention-to-treat (ITT) population, which consisted of all patients randomly assigned to study medication who received at least 1 dose of treatment and had a baseline measurement and at least 1 postbaseline efficacy evaluation.

The VAS score was calculated as the mean of the daily scores for the 5 days prior to the onset of continuous bleeding. Baseline scores were calculated as the mean of the 2 reference cycles, and the study endpoint score was constructed from each patient's third treatment cycle using last observation carried forward (LOCF) to handle missing data. Percent change in individual luteal phase VAS scores was calculated as the value at a particular treatment visit minus patient's baseline, multiplied by 100, and divided by baseline (i.e., [treatment – baseline] × 100/baseline).

The data of percent change from baseline in individual VAS luteal phase scores were not normally distributed. Therefore, a nonparametric method of Wilcoxon's rank sum test adjusting for center was used, as planned at the stage of study design, to test the difference in percent

change from baseline in VAS luteal phase score between each paroxetine group and the placebo group at study endpoint. The statistical analysis for the primary endpoint was adjusted using Bonferroni for multiple comparisons (p = .025). Point estimates and their 95% confidence intervals for the differences were calculated using van Elteren's method. Safety data were summarized by calculating the frequency of adverse events for each study arm.

Given the limitation of Wilcoxon's rank sum test (i.e., unable to control any imbalance at baseline across randomized arms), a parametric method of analysis of covariance on endpoint scores with baseline scores as covariate adjusting for center and age was also performed to validate the findings from the nonparametric method.[33,34] Dunnett's procedure was used to keep the overall type 1 error at 0.05 for multiple comparisons.

Many techniques could be used for the imputation of missing data, but none are considered the gold standard for every situation. The LOCF analysis used in this study seems to be the most receptive strategy by many regulatory agencies (i.e., U.S. Food and Drug Administration).[35] However, a sensitivity analysis using random-effect regression modeling to impute missing values was performed to test the robustness of the results from the LOCF approach.

RESULTS

A total of 208 patients were screened, of whom, 103 were randomly assigned to the study. A total of 99 of the randomized patients represented the ITT population (placebo: N = 33, paroxetine 10 mg: N = 31, paroxetine 20 mg: N = 35). In total, 70 patients completed the study (placebo: N = 22, paroxetine 10 mg: N = 25, paroxetine 20 mg: N = 23). Details on the number of participants through each stage and reasons for withdrawal are shown in Figure 1.

Thirty percent (30/99) of the ITT population had protocol violations, and the proportion was similar across the 3 treatment groups (placebo: 30% [N = 10], paroxetine 10 mg: 29% [N = 9], paroxetine 20 mg: 31% [N = 11]). The most common reason for protocol violation among randomized patients was missing more than 3 days of study medication (placebo: 20% [N = 2], paroxetine 10 mg: 56% [N = 5], paroxetine 20 mg: 73% [N = 8]), completing less than 1 active treatment cycle (placebo: 50% [N = 5], paroxetine 10 mg: 22% [N = 2], paroxetine 20 mg: 18% [N = 2]), and completing less than the 2 qualifying reference cycles (placebo: 20% [N = 2], paroxetine 10 mg: 22% [N = 2], paroxetine 20 mg: 18% [N = 2]).

All 3 treatment groups in the ITT population were well matched on demographic characteristics. Age, race, and age at onset of PMDD are reported in Table 1. Psychiatric, obstetric, and gynecological history was similar across treatment groups.

Table 1. Baseline Characteristics and Luteal Phase Scores in the Intent-to-Treat Population

Characteristic	Placebo (N = 33)	Paroxetine 10 mg (N = 31)	Paroxetine 20 mg (N = 35)
Age, y			
Mean	34.6	38.3	36.5
Median (range)	36 (22–45)	38 (29–45)	37 (18–47)
Race, N (%)			
White	32 (97)	31 (100)	34 (97)
Black	0	0	0
Asian	1 (3)	0	0
Other	0	0	1 (3)
Age at onset of premenstrual dysphoric disorder, y			
Mean	25.7	29.5	28.5
Median (range)	25 (11–42)	32 (15–43)	30 (12–44)
Luteal phase scores, median			
Visual analog scale (mm)			
Irritability	57.1	44.0	48.5
Depressed mood	37.5	27.2	27.1
Tension	56.5	44.1	44.6
Affective lability	47.5	36.0	24.9
Mood swings	58.9	38.3	39.4
Bloatedness	59.8	37.8	40.0
Breast tenderness	38.0	38.0	28.3
Lack of energy	43.2	43.1	27.4
Food craving	44.3	41.3	28.0
CGI-S	4.0	4.0	4.0
Premenstrual Tension Scale	21.9	21.5	21.8
Sheehan Disability Scale			
Work	4.8	4.6	4.4
Social life	5.0	4.7	5.0
Family life	6.8	6.1	6.0

Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale.

Baseline luteal phase scores indicated the presence of marked PMDD with substantial functional impairment. Although the baseline luteal phase VAS scores in the placebo group were similar to those found among patients in other PMDD studies,[12–14,26] the VAS scores on several items in the paroxetine treatment groups were lower (Table 1). Baseline luteal phase PMTS-O scores, CGI scores, and Sheehan Disability Scale scores were similar across treatment groups.

Results for the primary efficacy analysis are shown in Table 2. At study endpoint, all 3 treatment groups showed improvement in irritability symptoms. The ad hoc analysis of endpoint scores was conducted using analysis of covariance (ANCOVA) by adjusting for baseline score, study center, and age. When compared with placebo, a difference of 18.6 (p = .007) versus placebo was observed in favor of paroxetine 20 mg on VAS irritability. Paroxetine at a dose of 10 mg failed to show a statistically significant advantage over placebo with respect to VAS irritability. The results from the ANCOVA are consistent with the originally planned nonparametrical analysis for VAS irritability for the 20-mg group and the 10-mg group (Table 2). These results were also consistent with those derived from repeated-measurement analysis using

Table 2. Summary of Luteal Phase Individual Visual Analog Scale Scores (mm) at Baseline and Study Endpoint Among Patients With Premenstrual Dysphoric Disorder (intent-to-treat population)[a,b,c]

Visual Analog Scale Domains	Placebo (N = 33)	Paroxetine 10 mg (N = 31)	p Value	Paroxetine 20 mg (N = 35)	p Value
Primary outcome					
Irritability					
Patients available for analysis, N	29	24		27	
Raw score at baseline, mean (SD)	62.0 (20.5)	47.0 (16.8)		49.7 (19.1)	
Raw score at endpoint, mean (SD)	36.8 (28.9)	22.1 (20.4)		15.0 (16.4)	
Difference in scores at endpoint vs placebo (95% CI)		–10.8 (–25.4 to 3.8)	.176	–18.6 (–32.5 to –4.6)	.007
Percent change from baseline to endpoint, median	–46.1	–67.0		–74.4	
Difference in median percent change vs placebo (95% CI)		–10.7 (–42.3 to 9.9)	.403*	–23.9 (–51.3 to –6.2)	.014*
Secondary outcome					
Depressed mood					
Patients available for analysis, N	28	20		25	
Raw score at baseline, mean (SD)	39.8 (26.2)	29.7 (20.4)		32.1 (25.9)	
Raw score at endpoint, mean (SD)	22.6 (26.2)	10.4 (13.6)		7.3 (10.5)	
Difference in treatment vs placebo mean score (95% CI)		–9.8 (–21.7 to 2.2)	.124	–13.4 (–24.5 to –2.2)	.016
Tension					
Patients available for analysis, N	28	23		25	
Raw score at baseline, mean (SD)	58.6 (24.9)	44.3 (17.8)		42.5 (23.4)	
Raw score at endpoint, mean (SD)	35.5 (32.8)	21.8 (20.0)		12.2 (12.9)	
Difference in treatment vs placebo mean score (95% CI)		–8.8 (–23.9 to 6.3)	.323	–17.7 (–32.7 to –2.7)	.018
Affective lability					
Patients available for analysis, N	27	21		24	
Raw score at baseline, mean (SD)	47.3 (26.0)	34.1 (20.7)		32.6 (25.3)	
Raw score at endpoint, mean (SD)	31.7 (27.6)	15.8 (18.1)		5.7 (8.9)	
Difference in treatment vs placebo mean score (95% CI)		–11.5 (–24.1 to 1.2)	.081	–21.1 (–33.4 to –8.8)	< .001
Mood swings					
Patients available for analysis, N	27	23		25	
Raw score at baseline, mean (SD)	56.4 (26.5)	39.6 (17.2)		37.3 (25.1)	
Raw score at endpoint, mean (SD)	34.6 (30.0)	17.6 (19.6)		8.7 (12.5)	
Difference in treatment vs placebo mean score (95% CI)		–12.0 (–26.3 to 2.3)	.110	–20.1 (–34.3 to –6.0)	.004
Bloatedness					
Patients available for analysis, N	28	25		26	
Raw score at baseline, mean (SD)	51.5 (26.9)	38.3 (22.4)		37.1 (26.0)	
Raw score at endpoint, mean (SD)	34.9 (27.0)	24.3 (24.5)		19.1 (22.0)	
Difference in treatment vs placebo mean score (95% CI)		–4.4 (–18.4 to 9.6)	.696	–9.1 (–23.0 to 4.9)	.250
Breast tenderness					
Patients available for analysis, N	28	23		25	
Raw score at baseline, mean (SD)	41.4 (29.7)	40.3 (26.5)		33.1 (26.4)	
Raw score at endpoint, mean (SD)	25.4 (25.2)	29.8 (23.5)		16.3 (22.8)	
Difference in treatment vs placebo mean score (95% CI)		4.9 (–8.61 to 18.3)	.634	–5.5 (–18.8 to 7.8)	.553
Lack of energy					
Patients available for analysis, N	29	23		27	
Raw score at baseline, mean (SD)	45.2 (26.9)	44.4 (20.1)		37.6 (27.0)	
Raw score at endpoint, mean (SD)	34.2 (28.8)	26.9 (21.5)		25.9 (25.5)	
Difference in treatment vs placebo mean score (95% CI)		–6.9 (–21.5 to 7.7)	.467	–4.7 (–18.9 to 9.4)	.673
Food craving					
Patients available for analysis, N	29	24		25	
Raw score at baseline, mean (SD)	47.8 (26.4)	41.7 (21.5)		32.3 (26.5)	
Raw score at endpoint, mean (SD)	30.5 (24.7)	21.8 (20.2)		12.3 (18.6)	
Difference in treatment vs placebo mean score (95% CI)		–7.2 (–20.2 to 5.8)	.362	–14.1 (–27.3 to –0.9)	.035

[a]A negative number indicates improvement, while a positive number indicates worsening.
[b]Differences in mean score (95% CIs) and p values are calculated by analysis of covariance, adjusting for center and baseline score.
[c]Subjects with ≥ 3 missing scores in the luteal phase were excluded from the analysis.
*Wilcoxon's rank sum test.

a random-effect regression modeling technique to impute missing data (data not shown here).

Results of the primary efficacy analysis were confirmed by those of the secondary efficacy analyses. Paroxetine 20 mg (and not 10 mg) was significantly superior to placebo on several individual VAS item scores. At study endpoint, a statistically significant difference was observed in favor of paroxetine 20 mg when compared with placebo for depressed mood (–13.4, p = .016), tension (–17.7, p = .018), affective lability (–21.1, p < .001), mood swings (–20.1, p = .004), and food cravings (–14.1, p = .035) (Table 2). These results are consistent with those derived from Wilcoxon analysis (p = .03 for depressed mood, p < .001 for affective lability, p = .013 for mood swings, and p = .015 for food cravings). In addition, compared with placebo, patients randomly assigned to paroxetine at a dose of 20 mg had greater odds of achieving a ≥ 50% reduction from baseline on 2 of 4 core VAS mood items:

Table 3. Summary of Changes From Baseline to Study Endpoint in Sheehan Disability Scale Scores Among Patients With Premenstrual Dysphoric Disorder (intent-to-treat population)

Variable	Placebo (N = 33)	Paroxetine 10 mg (N = 31)	p Value	Paroxetine 20 mg (N = 35)	p Value
Sheehan Disability Scale					
Work					
Patients available for analysis, N	26	22		23	
Change from baseline to study endpoint, mean	–1.9	–2.4		–2.7	
Difference in mean change vs placebo (95% CI)		–0.64 (–2.20 to 0.93)	.42	–1.13 (–2.50 to 0.23)	.10
Social life					
Patients available for analysis, N	26	22		24	
Change from baseline to study endpoint, mean	–1.9	–2.4		–3.5	
Difference in mean change vs placebo (95% CI)		–0.79 (–2.49 to 0.91)	.14	–1.67 (–3.10 to –0.25)	.02
Family life					
Patients available for analysis, N	26	22		24	
Change from baseline to study endpoint, mean	–2.9	–3.6		–4.1	
Difference in mean change vs placebo (95% CI)		–1.25 (–2.94 to 0.44)	.14	–1.74 (–3.26 to –0.22)	.03

Table 4. Summary of Adverse Events (≥ 5% in any treatment group) and Severe Adverse Events Among Patients With Premenstrual Dysphoric Disorder

Variable, %	Placebo (N = 33)	Paroxetine 10 mg (N = 31)	Paroxetine 20 mg (N = 35)
Adverse events			
At least 1 event	85	81	83
Nausea	27	26	54
Dry mouth	9	16	17
Fatigue	0	3	14
Decreased appetite	6	13	9
Influenza symptoms	9	13	3
Exacerbation of fatigue	3	13	11
Coryza	21	10	9
Exacerbation of insomnia	3	10	3
Weight gain	3	10	3
Constipation	6	10	0
Dizziness	3	6	9
Yawning	0	6	9
Diarrhea	6	3	9
Decreased libido	9	0	9
Light-headedness	0	0	9
Heartburn	0	0	9
Cold symptoms	0	6	6
Exacerbation of headache	9	3	6
Back pain	6	3	6
Painful period (dysmenorrhea)	6	0	6
Cramps (not site specific)	3	0	6
Severe adverse events			
At least 1 event	3	6	0
Pregnancy	3	3	0
Tonsillitis	0	3	0

VAS irritability (78% vs. 48%) (OR = 4.7, 95% CI = 1.3 to 16.9, p = .02) and VAS tension (72% vs. 46%) (OR = 3.9, 95% CI = 1.1 to 14.3, p = .04).

Results also showed statistically significant differences in favor of paroxetine 20 mg when compared with placebo on change from baseline to study endpoint in Sheehan Disability Scale social life score (1.7, p = .02) and family life score (1.7, p = .03) (Table 3).

There were no statistically significant differences posttreatment between patients randomly assigned to paroxetine 10 mg and 20 mg and patients randomly assigned to placebo on the PMTS-O (p = .27 and p = .06, respectively) and CGI and CGI-S (p = .78 and p = .25, respectively).

In general, paroxetine was well tolerated with no unexpected adverse events reported (Table 4). Overall, 81% of the patients in the paroxetine 10-mg group and 83% in the paroxetine 20-mg group experienced at least 1 adverse event in the treatment phase compared with 85% in the placebo group. The most common adverse events (≥ 5% in either paroxetine group and at least twice the rate of placebo) were nausea, fatigue, decreased appetite, exacerbation of fatigue, exacerbation of insomnia, weight gain, dizziness, yawning, heartburn, light-headedness, cold symptoms, and cramps. The only severe adverse events to occur were pregnancy and tonsillitis. A total of 8 patients from the ITT population were withdrawn from the study due to adverse events (placebo: 2, paroxetine 10 mg: 2, paroxetine 20 mg: 4).

DISCUSSION

The results of this multicenter, randomized, double-blind, placebo-controlled clinical trial demonstrated that paroxetine administered during the luteal phase of the menstrual cycle is effective in treating PMDD. In particular, significant improvements were seen in the psychological symptoms associated with PMDD such as irritability, depressed mood, and tension. Women treated with paroxetine also experienced improvement regarding their social/family life functioning. This latter finding is important, as impaired social functioning is a key feature of PMDD.[5–8] As demonstrated by their baseline scores, the women in this study may have had mild-to-moderate PMDD symptoms, less severe than women studied in other trials. This fact may explain why differences were not detected between women treated with paroxetine and those administered placebo on the global measures including PMTS-O and CGI.

This trial failed to demonstrate efficacy of intermittent paroxetine at a dose of 10 mg for the treatment of PMDD. Limitations of the data, including a high noncompliance rate, may account for these results. The differences between the 10-mg and 20-mg groups versus placebo were smaller than those found in a similar study.[25] This was most likely due to the fact that this trial saw a 30% protocol violation rate, mostly due to women missing more than 3 days of study medication. In addition, based on an analysis of long-term treatment with paroxetine controlled release for PMDD,[36] it has been suggested that response to lower doses of paroxetine may be progressive over time.[13] The final consideration that should be taken into account is that a 10-mg dose of paroxetine may be too low to treat PMDD.

Study limitations, including the high protocol violation rate and small sample size, should be kept in mind when interpreting the data. Baseline scores in the paroxetine groups suggest that they may experience less severe PMDD symptoms than patients randomly assigned to placebo. Any differences in baseline scores among treatment groups were adjusted for when calculating the primary efficacy variable (i.e., percentage change from baseline) and therefore did not likely impact the final results. The efficacy conclusions are further supported by a series of secondary and ad hoc analyses.

Evidence from previous trials supports the efficacy of intermittent treatment with an SSRI including sertraline,[21–23] fluoxetine,[19,20,37] clomipramine,[24] citalopram,[18,38] and escitalopram.[27,39]

Landén et al.[25] showed that the efficacy of intermittent administration of paroxetine at a dose of 20 mg/day reduced all VAS-rated symptoms (with the exception of lack of energy and food craving) when compared with continuous administration of paroxetine and placebo. Consistent with the findings in this trial, Cohen et al.[13,19] demonstrated superior efficacy with the higher paroxetine dosage compared with lower dosage. Steiner et al.[26] demonstrated the efficacy of paroxetine controlled release administered intermittently at high and low doses when compared with placebo. With respect to safety, fewer adverse events have been reported with the intermittent dosing regimen with paroxetine.[25] In this trial, intermittent treatment with paroxetine was well tolerated, and side effects were consistent with previous findings.[40] Very few patients dropped out due to adverse events, most side effects were mild, and the proportion identifying side effects as severe was similar across treatment groups.

The implications of these findings suggest that clinicians may be more flexible in their approach to treating PMDD in terms of the choice of drug, dose, and administration regimen. According to recently published expert guidelines for the treatment of PMDD, an intermittent dosing regimen is an appropriate choice for patients who wish to limit the amount of medication they take, can adhere to the on/off dosing regimen, have no mood symptoms in the follicular phase, or are concerned about long-term side effects.[7]

In summary, intermittent paroxetine at a dose of 20 mg administered during the luteal phase of the menstrual cycle is superior to placebo in treating symptoms of PMDD. These results are consistent with those reported in previous studies suggesting that PMDD may be treated effectively by the luteal phase–only administration of an SSRI.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil), escitalopram (Lexapro and others), fluoxetine (Prozac, Sarafem, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft).

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