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## FLUOXETINE IN THE TREATMENT OF PREMENSTRUAL DYSPHORIA

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**Abstract Background.** Premenstrual dysphoria shares certain features with depression and anxiety states, which have been linked to serotonergic dysregulation. We evaluated the efficacy and safety of fluoxetine (which selectively inhibits the reuptake of serotonin) in the treatment of premenstrual dysphoria.

**Methods.** The trial consisted of a single-blind, placebo washout period lasting two menstrual cycles, followed by a randomized, double-blind, placebo-controlled trial of fluoxetine at a dose of either 20 mg or 60 mg per day or placebo for six menstrual cycles. Healthy women meeting criteria for what was then called late-luteal-phase dysphoric disorder were recruited at seven university-affiliated women's health clinics in Canada. The primary outcome measure consisted of visual-analogue scales for tension, irritability, and dysphoria during the late luteal phase of each cycle.

**Results.** Of 405 women enrolled in the placebo washout period, 313 subsequently entered the randomized phase of the study, which lasted six menstrual cycles, and 180 completed it. Fluoxetine at a dose of 20 or 60 mg per day was significantly superior to placebo in reducing symptoms of tension, irritability, and dysphoria, as measured by the visual-analogue scales ( $P < 0.001$ ). The women who received 60 mg of fluoxetine per day reported significantly more side effects than those who received 20 mg per day or placebo ( $P < 0.001$ ).

**Conclusions.** Fluoxetine is useful in the treatment of premenstrual dysphoria. Treatment with fluoxetine at a dose of 20 mg per day reduces the potential for side effects while maximizing therapeutic efficacy. (N Engl J Med 1995;332:1529-34.)

LATE-luteal-phase dysphoric disorder,<sup>1</sup> currently referred to as premenstrual dysphoric disorder<sup>2</sup> (and commonly called the premenstrual syndrome), is characterized by a cluster of symptoms appearing regularly during the week before and disappearing within a few days after the onset of menstrual bleeding. Tension, irritability, and dysphoria are among the most prominent symptoms.<sup>3-5</sup> Surveys indicate that it affects up to 3 to 8 percent of North American women in their reproductive years,<sup>6-8</sup> with a substantial negative impact on health. The cause of this disorder is unknown, and it is

therefore not surprising that over the years at least 50 treatment options have been suggested to be effective, many of them based on the popular hypothesis of the moment.<sup>9-12</sup> To date, however, although some treatments, such as medical or surgical ovariectomy<sup>13-16</sup> and some anxiolytic drugs, have been found to be superior to placebo in some studies,<sup>17,18</sup> no treatments have proved consistently effective.<sup>19</sup>

Premenstrual dysphoria shares many of the features of depression and anxiety states<sup>20-22</sup> that have been linked to serotonergic dysregulation, and there is increasing evidence that serotonin may also be important in the pathogenesis of premenstrual dysphoria.<sup>23-27</sup> Clomipramine and fluoxetine (Prozac), which selectively inhibit the reuptake of serotonin, have therefore been proposed for the treatment of premenstrual dysphoria, and preliminary results of single-dose or small double-blind, placebo-controlled trials were encouraging<sup>28-30</sup> but not unanimous.<sup>31</sup> We therefore undertook a multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of fluoxetine in women with premenstrual dysphoria.

## METHODS

### Selection of Patients

Women between 18 and 45 years of age who met the diagnostic criteria for premenstrual dysphoria were enrolled in the trial after providing oral and written informed consent. The study was carried out at seven university-affiliated women's health clinics in Canada. The

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protocol was approved by the institutional ethics review committees of all the clinics. All subjects were either self-referred or referred by their physicians.

The entry requirements were a diagnosis of late-luteal-phase dysphoric disorder, as it was then called, with at least a one-year history of five (or more) symptoms attributable to the disorder (with at least one symptom being marked affective lability, irritability, tension, or depressed mood) that were present premenstrually and began to remit within a few days postmenstrually. The condition must also have been severe enough to impair activities of daily living. These criteria were confirmed prospectively by the subjects, who rated the severity of their symptoms during at least two consecutive symptomatic cycles.<sup>1</sup>

Women were excluded if they were pregnant or lactating or were taking an oral contraceptive, or if they had irregular menstrual cycles, an unstable medical illness, a history of a seizure disorder with a seizure occurring within the past year, a record of multiple adverse drug reactions, known allergies to inhibitors of the reuptake of serotonin, or a history of fluoxetine use. To minimize the inclusion of women with anovulatory cycles, the women were required to have menstrual cycles between 24 and 35 days in length.

Women were also excluded if they met diagnostic criteria for a major psychiatric syndrome other than late-luteal-phase dysphoric disorder, expressed suicidal ideation or intent, had used psychoactive medications or investigational drugs within two months before the study, or were taking any other medication to treat premenstrual symptoms.

### Study Design

The two-phase study design consisted of a single-blind washout period, during which the women received placebo for two menstrual cycles, followed by a randomized, double-blind, placebo-controlled trial lasting six menstrual cycles. Women who remained eligible after the placebo washout phase were randomly assigned to receive placebo, fluoxetine at a dose of 20 mg per day, or fluoxetine at a dose of 60 mg per day beginning on the first day of cycle 3. The study drugs were to be taken each morning. No other psychoactive medications were permitted.

The women were required to visit the clinics twice during each menstrual cycle throughout the study. Visits and assessments coincided with the follicular and late luteal phases of each cycle. The study involved a total of 18 visits: 1 prescreening visit, 4 visits during the two-cycle placebo washout phase, 12 visits during the six cycles in the randomized controlled trial, and 1 follow-up visit after the trial ended.

### Measurements

The primary outcome was defined as the reduction in the raw luteal-phase score (reported as the percent change from the base-line score) for premenstrual symptoms, as measured by the mean score on three visual-analogue scales — one each for tension, irritability, and dysphoria. Visual-analogue scales have been found to be an effective tool in measuring changes over time in response to treatment for the symptoms of mood disturbance, and their reliability and validity have been well documented.<sup>32-34</sup> The participants were prompted to rate how they were feeling each day using 100-mm scales in which the descriptors ranged from “no symptoms” (0 mm) to “severe or extreme symptoms” (100 mm). The mean of these three scales was calculated to determine the total psychological-symptom score. Secondary outcome measures included the premenstrual tension syndrome scales, which consist of a 36-item scale completed by the patient and a 10-item scale completed by the therapist.<sup>3,35</sup> Both scales rate premenstrual symptoms for a particular day; the total score can range from 0, indicating no symptoms, to 36, indicating all symptoms present and severe. Tertiary outcome measures included visual-analogue scales for physical symptoms of headache, bloating, and breast tenderness, as well as a modified Prospective Record of the Impact and Severity of Menstrual Symptomatology calendar, which was completed daily.<sup>36</sup> A standardized questionnaire was used at each visit to determine whether the subjects had had any side effects. All these data were collected at each visit.

Compliance was monitored through monthly pill counts, by the subjects' own assessments, and, for 15 percent of the study popula-

tion, by measuring serum concentrations of fluoxetine and norfluoxetine (the principal active metabolite of fluoxetine). Blood was drawn after a minimum of two cycles of the study medication and assayed after the completion of the study.<sup>37</sup> Subjects who missed more than six consecutive doses of study medication during any cycle were withdrawn from the trial.<sup>38</sup> On completion of six cycles of treatment, the subjects stopped the study medication and were allowed to pursue independent treatment with their own physicians.

### Statistical Analysis

Analysis of efficacy for all study participants who completed at least one cycle of the randomized trial was conducted with BMDP5V unbalanced repeated-measures models with structured covariance matrixes. Akaike's Information Criterion was used to select the most appropriate covariance structure.<sup>39</sup> In order to perform this analysis, changes in the raw scores of the visual-analogue scales within subjects were recalculated to obtain the percent change from base-line scores within subjects according to the following formula: (base-line luteal-phase score – treatment luteal-phase score)/base-line luteal-phase score × 100. These values ranged from –100 percent (worsening) to +100 percent (improvement). Parametric base-line characteristics were analyzed by one-way analysis of variance. All continuous efficacy variables for those who completed all six cycles of the protocol were analyzed with repeated-measures multivariate analysis of variance.<sup>40,41</sup> The frequency of side effects and other nonparametric data were analyzed with Fisher's exact test or the chi-square test for association where appropriate. Pearson's correlation coefficients were used to ensure the validity of the primary outcome data as compared with the secondary and tertiary outcome measures. P values of 0.01 or less were considered to indicate statistical significance; all tests were two-tailed.

The safety analysis included all subjects who underwent randomization. Side effects were classified according to their frequency and their occurrence in combination with other events.

### RESULTS

Of the 405 women screened for entry during the placebo washout period, 92 did not enter the second phase of the trial for the reasons listed in Table 1. Thus, 313 eligible women were randomly assigned to the treatment groups. The study participants were between 20 and 45 years of age (mean [±SD], 36±5); all were high-school graduates; 55 percent were married; and 70 percent had at least one child. At base line the mean (±SD) follicular-phase score for the visual-analogue scales was 14.9±13.4 mm, and the mean luteal-phase score was 56.1±18.2 mm. Base-line demographic and clinical characteristics were comparable in the three treatment groups.

Of the 313 women who underwent randomization, 277 completed cycle 1 of phase 2 and were included in the efficacy analysis (Table 2). The raw follicular-phase scores for primary and secondary outcome measures throughout the trial were stable, with minimal variation between groups or over time (P=0.57). Scores on the visual-analogue scales for tension, irritability, and dysphoria were similar within subjects (P=0.42), allowing the use of the mean scores of the three visual-analogue scales to represent the total premenstrual-symptom score at each visit for the primary efficacy analysis.

Fluoxetine at a daily dose of either 20 mg or 60 mg proved to be superior to placebo in reducing psychological symptoms within the first cycle of treatment, as demonstrated by both the primary and secondary outcome measures (Table 2). Despite a high dropout rate

Table 1. Classification of the Study Subjects According to How Much of the Trial They Completed.

PHASE OF STUDY/REASON FOR WITHDRAWAL OR NOT COMPLETING STUDY	TOTAL NO. OF SUBJECTS			
Phase 1, entry into placebo washout period	405			
Did not meet criteria	22			
Response to placebo	12			
Withdrawal				
Side effects	15			
Lost to follow-up	20			
Personal reasons	23			
Total withdrawals	92			
Phase 2, entry into randomized study	313			
Withdrawal				
Side effects	8	11	35	54
Lack of efficacy	27	4	2	33
Lost to follow-up	5	2	2	9
Personal reasons	6	9	4	19
Protocol violation	7	7	4	18
Total withdrawals	53	33	47	133
Total no. completing protocol	52	69	59	180

in the placebo group and the group that received 60 mg of fluoxetine per day, regression analysis identified a statistically significant effect of the group ( $P<0.001$ ) and of the change from base line ( $P<0.001$ ). The mean percent improvement in the luteal-phase score from base line was four to six times greater in the fluoxetine groups than in the placebo group, as measured by the total visual-analogue scale and by the subject-rated premenstrual tension syndrome scale, and two to three times greater as measured by the observer-rated premenstrual tension syndrome scale. In the first cycle alone, the raw scores on the luteal-phase visual-analogue scale were reduced to one half the base-line score in 46 of the 96 women receiving 20 mg of fluoxetine per day and 49 of the 86 women receiving 60 mg of fluoxetine per day, as compared with 21 of the 95 women receiving placebo ( $P<0.001$ ). The significant difference in the scores on the visual-analogue scale between women receiving fluoxetine and women receiving placebo was maintained during the six cycles of the trial in the 180 women who completed the protocol ( $P<0.001$ ) (Fig. 1). This improvement over time was corroborated by an analysis of the secondary outcome measures ( $P<0.001$ ).

To define clinically relevant changes throughout this trial, we considered 50 percent improvement from base line to represent moderate improvement and 75 percent to represent marked improvement. With the

use of these criteria, 52 percent of the women receiving fluoxetine at either dose had at least moderate improvement in their symptoms within the first cycle of active treatment, as compared with 22 percent of the women receiving placebo ( $P<0.001$ ). These proportions remained consistent throughout the trial: 53 percent of all cycles involving fluoxetine therapy (437 of 832) were associated with at least moderate improvement, as compared with 28 percent of the cycles involving placebo (113 of 410,  $P<0.001$ ). The proportion of cycles in which there was marked improvement was also significantly different between groups (266 of 832 cycles involving fluoxetine therapy vs. 56 of 410 cycles involving placebo,  $P<0.001$ ). The results were combined because the rates of response were very similar in the two groups of women who received fluoxetine (20 mg per day or 60 mg per day).

Of the 313 women included in the safety analysis, the study medication was discontinued in 133 (Table 1). The rate of withdrawal was similar in the three groups for the first three cycles of the randomized trial but became significantly different by cycle 6 ( $P<0.028$ ) as a result of the high rate of withdrawal of women from the group receiving 60 mg of fluoxetine per day (35 of 106) and from the placebo group (27 of 105), the former because of side effects and the latter because of lack of efficacy. It is important to note that 97 percent of the withdrawals due to side effects in the group given 60 mg of fluoxetine per day occurred during the first three cycles of the trial.

The side effects reported during the trial were dose-related, with significantly fewer events occurring in the placebo group and the group receiving 20 mg of fluoxetine per day than in the group given 60 mg of fluoxetine per day ( $P<0.001$ ). In addition, statistically significant differences were found across the three groups for

Table 2. Scores on Primary and Secondary Outcome Measures for the 277 Women Who Completed Cycle 1 of the Randomized Trial.\*

OUTCOME MEASURE	PLACEBO (N = 95)	FLUOXETINE, 20 mg (N = 96)	FLUOXETINE, 60 mg (N = 86)	P VALUE
Visual-analogue scales				
Base line (mm)	56.0±16.9	57.2±16.6	56.3±20.0	0.889
Cycle 1 (mm)	51.1±29.1	32.4±27.2	26.6±23.5	<0.001
Percent change	6.7±54.0	43.9±45.8	52.4±40.8	<0.001
Premenstrual tension syndrome scale (assessed by the subjects)†				
Base line	20.3±6.2	19.9±6.7	19.9±7.2	0.885
Cycle 1	17.9±9.5	11.4±9.8	10.5±8.9	<0.001
Percent change	9.5±45.2	42.9±44.6	44.4±44.2	<0.001
Premenstrual tension syndrome scale (assessed by an observer)†				
Base line	19.8±5.2	18.9±5.8	18.9±6.0	0.459
Cycle 1	16.7±8.2	11.4±8.5	9.7±7.7	<0.001
Percent change	14.9±40.6	39.7±41.1	48.8±35.8	<0.001

\*Plus-minus values are means ±SD.

†Scores on this scale can range from 0 (no symptoms) to 36 (all symptoms present and severe).

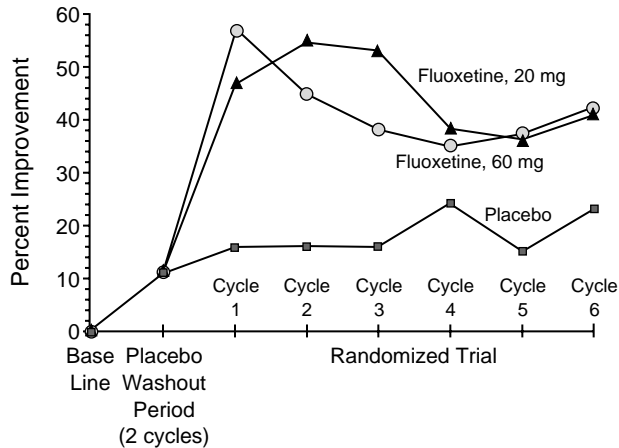


Figure 1. Percent Improvement in the Total Luteal-Phase Scores of the Visual-Analogue Scale for the 180 Women Who Completed the Protocol ( $P < 0.001$ ).

The degree of improvement recorded during the placebo washout period did not differ between groups (mean improvement, 11.2 percent).

the 12 most frequently identified types of events, as listed in Table 3. These events were reported alone or in various combinations, and they occurred more frequently in the group given 60 mg of fluoxetine per day than in the other two groups. No serious or life-threatening events were reported during the trial.

## DISCUSSION

We compared two doses of fluoxetine with placebo in women with severe premenstrual dysphoria. Fluoxetine at doses of 20 mg or 60 mg per day proved significantly superior to placebo in reducing symptoms associated with this disorder, as measured by visual-analogue scales for tension, irritability, and dysphoria. These results were corroborated by an analysis of secondary outcome data.

The primary outcome measure was the percent im-

Table 3. Most Frequently Reported Side Effects.

SIDE EFFECT	PLACEBO (N = 105)	FLUOXETINE, 20 mg (N = 102)	FLUOXETINE, 60 mg (N = 106)	P VALUE*
Insomnia or disturbed sleep	7	10	28	0.001
Nausea	8	14	25	0.005
Tremor or shakiness	1	5	21	0.001
Fatigue or lethargy	6	10	20	0.009
Dizziness	2	8	15	0.005
Anorexia or disturbed appetite	5	5	15	0.016
Somnolence or decreased ability to concentrate	2	9	15	0.005
Sweating	3	4	12	0.020
Visual disturbance	3	3	12	0.010
Dry mouth	3	4	11	0.040
Minor cardiovascular symptoms	0	4	11	0.002
Yawning	0	1	6	0.012

\*For the differences between the three groups.

provement from base line in luteal-phase symptom scores. This approach is similar to that taken in other clinical trials and allows some comparisons between studies regardless of differences in the primary outcome measure used. An analysis of the clinical relevance of our study showed that moderate and marked improvement was twice as common in cycles involving fluoxetine as in cycles involving placebo. This rate of improvement was similar to that found in studies that defined outcome according to the percent change from base line in luteal-phase symptom scores.<sup>16,42-44</sup>

Reports of the occurrence of a preoccupation with suicide during fluoxetine treatment<sup>45</sup> garnered much media attention and affected our ability to recruit and retain subjects, since many potential candidates refused to participate. Fortunately, this association has since been refuted.<sup>46</sup> None of the women we studied had any suicidal or homicidal tendencies during the trial. Our study as well as other large-scale studies, in which fluoxetine was prescribed for psychiatric disorders other than depression, seem to offer further support for the notion that there is no direct link between this medication and the risk of suicide.<sup>38,47,48</sup>

The dropout rate for this trial was substantial: 42 percent of the women who underwent randomization did not complete the protocol. Reported side effects were an important contributor to this high rate of withdrawal. There is a clear delineation in the event profiles between women receiving 60 mg of fluoxetine per day and those receiving 20 mg of fluoxetine per day or placebo. Thirty-three percent of the women who received 60 mg of fluoxetine per day dropped out of the study because of side effects, and of those who remained in the study, 86 percent reported one or more side effects attributable to the drug. Although the use of a 60-mg daily dose of fluoxetine may be appropriate and efficacious in other psychiatric disorders, there seems to be no indication to use such a high dose in patients with this disorder. The use of a daily dose of 20 mg resulted in rates of side effects that were more similar to those of the placebo group. Side effects attributable to the drug that were reported most frequently were typical of those reported in other clinical trials of fluoxetine.<sup>38,44,49,50</sup> The high dropout rate in the placebo group due to a lack of efficacy (26 percent) indicates the perceived severity of symptoms associated with this diagnosis. Since most of the women were referred by their family physicians and had not responded to more conservative treatments for premenstrual dysphoria, this dropout rate may be taken as an indication of the appropriateness of and necessity for the use of selective inhibitors of serotonin reuptake to treat the mood-disturbance symptoms associated with this disorder.

The mechanism of action of fluoxetine in premenstrual dysphoria remains uncertain, but it probably differs from the mechanisms by which the inhibitors of serotonin reuptake alleviate symptoms of depression. There is some question whether by blocking reuptake, fluoxetine augments the action of serotonin only at

brain synapses where it is already being released (the synaptic information-transmission mechanism)<sup>51</sup> or whether the primary mechanism of action is of the non-synaptic diffusion-neurotransmission type.<sup>52</sup> The clinical observation that a lag of three to six weeks is required before the inhibitors of serotonin reuptake (as well as most other antidepressant drugs) become effective in depression further suggests that the synaptic model may not be as relevant in premenstrual dysphoria, where the response seems to be more immediate. In our study, active medication was given for approximately three weeks before the first luteal phase of the randomized trial, and the improvement at that time was already significantly better for fluoxetine at both doses than for placebo.

When this study was begun there were only three reports in the literature of the use of inhibitors of serotonin reuptake in premenstrual dysphoria.<sup>28-30</sup> The results of several additional drug trials have since been published,<sup>43,44,50,53,54</sup> further establishing a role for specific serotonin-reuptake inhibitors in the treatment of this disorder.

Our study did not address whether fluoxetine is required on a daily basis throughout the menstrual cycle to treat premenstrual dysphoria. At the time the study was initiated, the use of doses of 20 mg or 60 mg per day was the accepted practice (without gradual or flexible dosing), and no problems had been reported with the use of a similar schedule in other trials in North America.<sup>55</sup> A recent case study suggests that a single dose of fluoxetine during the early luteal phase may be as effective as daily doses.<sup>56</sup> At the end of one study, once the medications were discontinued, the improvement realized during the trial was not maintained, and most women opted to resume taking medication.<sup>57</sup> We are in the process of analyzing data from an open study in which women who met the criteria for premenstrual dysphoria responded to treatment with fluoxetine given during the late luteal phase alone.<sup>58</sup>

It thus appears that fluoxetine in doses of 20 mg per day or lower may be effective in decreasing the psychological symptoms of tension, irritability, and dysphoria in women who have premenstrual dysphoric disorder.

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