Clinical Study of the Efficacy of Fluvoxamine in Women with Premenstrual Dysphoric Disorder
—A prospective cohort study, a comparative case series—

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Summary The clinical efficacy of a selective serotonin reuptake inhibitor (SSRI) on the symptoms and quality of life (QOL) in women with pre-menstrual dysphoric disorder (PMDD) was evaluated by daily diary evaluation and the use of psychological scales.

Thirty-six women diagnosed as having PMDD were enrolled in the study based on the following two inclusion criteria: 1) Women in whom the total score calculated from the Penn Daily Symptom Report (DSR) for the 5 days prior to menstruation was at least 50% higher than that for Days 5-9 of menstruation: 2) the total DSR score for the 5 days prior to menstruation was over 80 or the score on the day of the maximum symptom severity during the 5 days prior to menstruation was over 15. The changes in the type and severity of symptoms following 3 months of fluvoxamine therapy (50 mg/day, in principle) were evaluated based on the DSR, Zung Self-Rating Depression Scale (SDS), State-Trait Anxiety Inventory (STAI), and the World Health Organization Quality of Life Assessment 26 (WHO/QOL-26) scores. After fluvoxamine treatment, the DSR score was 25.1 ± 14.6 on the day of maximum symptom severity during the 5 days prior to menstruation with a total score for the 5 days prior to menstruation of 133.0 ± 72.4, which presented 79.3% and 66.9%, respectively; of the corresponding scores for the untreated period (scores prior to the start of fluvoxamine treatment: control menstruation period) (p<0.05). Significant improvement in the scores for all the domains of WHO/QOL-26, except those for the environmental domain, began to be observed as early as after one cycle of fluvoxamine treatment.

The results of this study suggest that treatment with fluvoxamine is extremely effective for obtaining early improvement of the mental symptoms and QOL of patients with PMDD.


Key words: Premenstrual dysphoric disorder, Selective serotonin reuptake inhibitor, Fluvoxamine, Daily Symptom Report, WHO/QOL-26
Introduction

Although pre-menstrual dysphoric disorder (PMDD) entity has been widely accepted as a clinical entity since its diagnostic criteria were proposed by Halbreich et al.\(^{10}\), its characteristic features have not yet been fully clarified, and no valid method for treatment of this condition has been established as yet. According to the American College of Obstetricians and Gynecologists, while 20-40% of women in the reproductive-age group experience premenstrual changes, only 2-10% report severe disruption of work and/or relationships on account of these symptoms\(^2\) and meet the criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV), for the diagnosis of PMDD\(^3\).

Recent well-designed placebo-controlled trials of progesterone and oral contraceptive agents have revealed that these interventions are no more effective than the placebo for controlling the symptoms of PMDD\(^4\). The results of placebo-controlled trials of diuretics and vitamins are mixed\(^5\)-\(^8\). It is known that anti-anxiety drugs of the benzodiazepine family and antidepressants (e.g., alprazolam and clomipramine) may show some efficacy against PMDD\(^9\). In addition, there have been some recent reports of the efficacy of SSRIs (selective serotonin re-uptake inhibitors), whose clinical use has been rapidly expanding in Europe and the U.S., are effective for this condition\(^10\)-\(^13\). Medications from this class of drugs that have been shown to be effective in double-blind, placebo-controlled studies include fluoxetine hydrochloride\(^14\), paroxetine hydrochloride\(^13\), and sertraline hydrochloride\(^15\). SSRIs therapy has been recommended as first-line therapy for premenstrual syndrome (PMS) by Dickerson et al.\(^15\) and as the first-line therapy for PMDD by Grady-Weliky\(^16\).

Fluvoxamine is one of the three SSRIs authorized for clinical use in Japan. Its elimination half-life from the blood is 9-14 hours, and its metabolites are almost inactive; the drug is therefore expected to disappear from the blood rapidly after dosing and is, therefore, convenient for use in women of the reproductive-age females who desire to become pregnant. In the light of this background, we recently evaluated the efficacy of fluvoxamine in women of the reproductive-age group with PMDD. The study was aimed at (1) evaluating the clinical efficacy of SSRIs (fluvoxamine) on the symptoms observed in patients with PMDD, and (2) examining the extent to which the quality of life of the patients is altered by fluvoxamine therapy.

Materials and Methods

This study was conducted as a prospective cohort study, a comparative case series. Women were recruited by referral from five psychiatric and gynecological outpatient clinics and two outpatient clinics of university-affiliated gynecological departments in Japan. Seventy-eight women, 15-46 years of age (mean 31.2 ± 8.9), who were diagnosed to have PMDD according to the DMS-IV diagnostic criteria\(^3\) (Table 1) were enrolled in this study. The menstruation-related inclusion criterion adopted for enrollment in the study was that each woman had to have a regular menstrual cycle (24-36 days). We used two major inclusion criteria for enrollment in this study designed to evaluate the response of PMDD to treatment: 1) The total DSR score for the 5 days prior to menstruation was at least 50% higher than that for Days 5-9 of menstruation (this criterion was used to balance the distribution of the severity among the patients). 2) to avoid inclusion of cases of premenstrual syndrome (PMS) and cases with mild PMDD, the cutoff level mentioned below was adopted based on the results of the clinical study reported by Freeman et al.\(^17\)-\(^18\); the total DSR score for the 5 days prior to menstruation was over 80 or the score on the day of maximum
Table 1  Proposal diagnostic criteria of PMDD for clinical research

- A. Symptoms must occur during the week before menses, and remit a few days after onset of menses
- Five of following symptoms must be present at least one must be 1, 2, 3, or 4
  1. Depressed mood or dysphoria
  2. Anxiety or tension
  3. Affective lability
  4. Irritability
  5. Decreased interest in usual activities
  6. Concentration difficulties
  7. Marked lack of energy
  8. Marked change of appetite, over-eating, or food craving
  9. Hypersomnia or insomnia
  10. Other physical symptoms: ie. Breast tenderness, bloating
- B. Symptoms must interfere with work, school, usual activities, or relationships
- C. Symptoms must not merely be an exacerbation of another disorder
- D. Criteria A, B, and C must be confirmed by prospective daily ratings for at least two consecutive symptomatic menstrual cycles

Table 2  Clinical characteristics of study participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fluvoxamine (n = 36)</th>
<th>Control group (n = 25)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (S.D.)</td>
<td>30.1 (9.7)</td>
<td>31.6 (8.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Body Mass Index (Kg/m²) (S.D.)</td>
<td>23.0 (3.0)</td>
<td>23.5 (3.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean duration of illness (years) (S.D.)</td>
<td>3.8 (3.2)</td>
<td>4.0 (3.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Daily Symptom Report total score (S.D.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score of the five-day period in the late luteal phase</td>
<td>133.0 (72.4)</td>
<td>128.0 (79.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Score on the day of most intense symptoms in the late luteal phase</td>
<td>31.5 (15.0)</td>
<td>30.7 (13.4)</td>
<td>NS</td>
</tr>
<tr>
<td>SDS total score (S.D.)</td>
<td>51.5 (8.3)</td>
<td>50.2 (8.7)</td>
<td>NS</td>
</tr>
<tr>
<td>STAI total score (S.D.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trait-form</td>
<td>54.2 (12.4)</td>
<td>51.4 (13.1)</td>
<td>NS</td>
</tr>
<tr>
<td>State-form</td>
<td>56.3 (8.8)</td>
<td>53.8 (9.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

symptom severity during the 5 days prior to menstruation was 15. Women who fulfilled the criteria for mood disorder, anxiety disorder, or eating disorder within the previous 6 months, a history of alcohol or other drug abuse or dependence within the previous 12 months, or a life-long history of organic mental syndrome, psychotic disorder or severe borderline personality disorder were excluded from the study. Other women who were excluded were those with clinical symptomatic endometriosis, hysterectomy, a follicle stimulating hormone level of more than 20 mIU/ml (reflective of a peri-menopausal status), neurological disease, or any other severe or unstable general medical illness.

Forty-three women who satisfied the inclusion criteria, and did not fulfill any of the exclusion criteria described above and gave informed consent for the study according to the principles of the Declaration of Helsinki were enrolled in the study. After ethical consent they were designed to evaluate the response to treatment. Of the 43 women registered, the study could be completed in 36 women. Twenty-five age-matched women fulfilling the inclusion criteria were selected randomly as the untreated control group (Table 2).
Fluvoxamine, an SSRI (50-75 mg) was administered to the study subjects, as a rule, at an initial dose level of 25 mg/day. The dose level was increased to 50 mg/day seven to fourteen days after the start of treatment. If no alleviation of symptoms was observed after one cycle of treatment, the daily dose was increased further to 75 mg. The changes in the severity of symptoms after 3 cycles (months) of fluvoxamine therapy (50 mg/day, in principle) were evaluated based on the changes in the DSR, Zung Self-Rating Depression Scale (SDS), and State-Trait Anxiety Inventory (STAI) scores. Evaluation for each cycle of treatment was made by collecting the records for each cycle. The DSR was analyzed with regard to four items: (1) degree of good feeling, (2) disruption of social activities, including at the workplace and personal relationships, (3) presence/absence of pain, and (4) type and severity of physical symptoms. As indicators of anxiety, the state and trait anxiety scores according to the STAI were evaluated. The SDS was used to evaluate depression. Using the WHO/QOL-26, the quality of life (QOL) was investigated in relation to four domains (physical, psychological, social and environmental). In each of the four domains, the QOL was evaluated using a five-grade scale (higher scores indicating a higher QOL; maximum score = 5). The length of follow-up of the study patients was three months after the start of fluvoxamine administration. The changes in the type and severity of the symptoms in the 36 patients of the treatment group and 25 patients of the untreated control group were evaluated based on the DSR, SDS, STAI, and WHO/Quality of Life (QOL)-26 scores at the start of the study, and after 1, 2, and 3 months of treatment.

Data were expressed as the mean ± SD. The Wilcoxon-signed rank test was employed for analysis of the data. A values P < 0.05 were considered to be statistically significant.

Results

1. Changes in the DSR scores

There were no significant differences in the baseline data, namely, age, body mass index, mean duration of illness, or any of the evaluated parameters between the SSRI treatment group and the untreated control group. When the total scores for the 5 days prior to menstruation during the first cycle of treatment were analyzed, the DSR scores for mood, behavior, and pain were significantly lower (58.7%, 85.3% and 60.5%, respectively) than the corresponding scores prior to the start of treatment (32.0 ± 27.2, 35.9 ± 27.9 and 9.8 ± 11.6 vs 55.0 ± 31.4, 49.2 ± 26.8 and 16.7 ± 15.5, respectively; P < 0.05 for all). When the DSR scores on the day of the maximum symptoms severity during the 5 days prior to menstruation were analyzed during the first cycle of treatment, the DSR score for mood was significantly lower (65.4%) than that prior to the start of the treatment (9.9 ± 6.4 vs 13.5 ± 6.5; P < 0.05). No significant changes of the DSR scores for behavior, pain or physical symptoms were observed during the first cycle of fluvoxamine treatment. However, after the second cycle of treatment, the DSR score for behavior decreased from the pre-treatment score of 12.0 ± 6.0 to 8.2 ± 6.0 (70.5%), that for pain decreased from the pre-treatment score of 3.8 ± 3.5 to 2.8 ± 2.9 (75.1%), and that for physical symptoms decreased from the pre-treatment score of 2.6 ± 2.6 to 1.7 ± 2.0 (66.6%) (P < 0.05 for all). No significant changes of the DSR scores for any of the 4 symptom categories were observed in the untreated control group (Fig. 1).

2. Changes in the STAI and SDS scores

Analysis of the STAI scores revealed a slight decrease of the state anxiety score and the trait anxiety score (by 9.6% and 4.6%, respectively) during the third cycle of treatment, but neither showed any statistically significant changes associated with fluvoxamine treatment. The percent
Fig. 1  Percent change in the score of each DSR element on the pre-menstrual day of most intense symptoms in PMDD patients treated with fluvoxamine
(A) : DSR score on the day of most intense symptoms in the treated group,
(B) : total DSR score for the 5 pre-menstrual days in the treated group,
(C) : DSR score on the day of most intense symptoms in the untreated group,
(D) : total DSR score for the 5 pre-menstrual days in the untreated group

decrease in the SDS score was about 5% after each of the three cycles of treatment, as compared with the scores prior to the start of treatment, however, none of these differences were statistically significant. On the other hand, the mean scores for 4 of the 20 SDS items, i.e., the scores for "I feel down-hearted and blue", "I get tired for no reason", "I am restless and can’t keep still" and "I am more irritable than usual", were significant lower than the corresponding pre-treatment scores after 2 cycles of treatment (P < 0.01 for all). No significant changes of the STAI and SDS scores were observed in the untreated control group either (Table 3).

3. Changes in the mean WHO/QOL26 scores
   After one cycle of fluvoxamine treatment, the WHO/QOL-26 scores for the mental, physical and social domains rose by 18.8%, 14.2% and 11.7%, respectively, relative to the corresponding pre-treatment scores, which were 2.18 ± 0.58, 2.32 ± 0.66 and 2.66 ± 0.69 (P < 0.01, P < 0.01 and P < 0.05, respectively). No significant changes in the mean WHO/QOL26 scores were observed in the untreated control group. A significant increase in
the scores continued to be seen throughout until the third cycle of treatment (Table 4). The score for the responses to questions about the overall QOL ("How do you appraise the quality of your life?" and "Are you satisfied with your present health status?") increased by 21.4% after one cycle of fluvoxamine treatment (P < 0.05) and by 27.4% after the third cycle of treatment (P < 0.01), relative to the pre-treatment scores.

Adverse events

Adverse events associated with the treatment (epigastric pain, nausea, rash and staggering gait) were observed in 5 patients, but none of these events necessitated discontinuation of the drug. Subjective symptomatic alleviation was noted in 75.0% of all the patients.

Discussion

The results of this study conducted using the evaluation scales described above indicate that treatment with fluvoxamine can alleviate the mental distress associated with PMDD in women of the reproductive age group and also improve the social life and QOL of these patients.

Primary anti-anxiety drugs, gonadotropin releasing hormone agonists, etc have been recommended by various researchers for the treatment of PMDD\(^9\). Anti-anxiety drugs of the benzodiazepine family and anti-depressants are known to be effective against the pathological condition of PMDD\(^9\). Previous studies have also shown the beneficial effects of treatment with SSRIs in women with premenstrual dysphoria\(^10\). In a study of the SSRI paroxetine, 64% of the women assigned to paroxetine but only 38% of those given maprotiline were "enormously or much improved"\(^10\). In a clinical trial of sertraline, the overall severity of the symptoms was markedly reduced in 62% of the sertraline-treated patients, but in only 34% of the placebo-treated patients\(^14\). Although, recent studies showed global clinical improvement following treatment with several SSRIs in patients with PMDD detailed evaluation of the effects of SSRIs using a daily diary and QOL scores has not been conducted before.

This study showed that while the DSR score for mood was significantly lower as compared to
the baseline score (65.4% relative to the pre-treatment score) during the first cycle of the treatment with fluvoxamine, no significant changes of the DSR scores for behavior, pain or physical symptoms were observed during the first cycle of the treatment. On the other hand, during the second cycle of treatment, significant decreases of the DSR scores for behavior, pain and physical symptoms were observed relative to the corresponding pre-treatment scores (70.5%, 75.1% and 66.6% of the scores, respectively). While the total SDS score showed no significant decrease following fluvoxamine treatment, the scores for some SDS items, namely, those pertaining to depressed mood irritability and easy fatigability, showed a significant decrease after 2 cycles of treatment. This finding is consistent with the significant reduction in the DSR scores for mood and physical symptoms. These results suggest that fluvoxamine treatment is suitable for patients with PMDD who present with relatively severe symptoms. Furthermore, it appeared that fluvoxamine caused an earlier improvement of mood disturbances than of physical disturbances.

While no significant changes in the WHO/QOL-26 score for the environmental domain were observed following fluvoxamine treatment, the WHO/QOL-26 scores for the other domains (mental, physical and social) showed marked improvement even during the first cycle of treatment. We may, therefore, say that fluvoxamine therapy in patients with PMDD showing high DSR scores may be expected to achieve not only alleviate the various mental symptoms but also improvement in the quality of life of the patients. We propose to conduct a long-term study of PMDD patients to investigate the long-term prognosis, etc., of these patients.

In conclusion, fluvoxamine is suitable for patients with PMDD who present with relatively severe symptoms, and alleviates the mood disturbances in these patients even from the early stage of treatment. In addition, marked improvements in the QOL scores for the mental, physical and social domains were also observed as early as during the first cycle of treatment.

**Study limitations**

The first limitation of this study was that the number of patients examined (n = 36) was small and the age range was quite wide. Studies including larger populations of women are thus needed to confirm our results. It would also be desirable to evaluate the drug efficacy in relation to the patient age. Second, this study did not control for the efficacy of a psychological clinical approach in the drug treatment group. Third, this study did not compare the results of treatment with various SSRIs were not compared. Fourth, after three cycles of treatment with fluvoxamine, no significant changes in the STA1 or SDS scores were noted although some slight changes were observed. We cannot rule out the possibility that the study duration was too short to allow detection of significant changes in these scores. Furthermore, we did not compare the findings in relation to changes in the endocrinological status, e.g., changes in the estradiol level in the late luteal phase, nor did we take into consideration the patient’s life history and social environment. A long-term trial including several SSRIs and a placebo as well as a comparative trial between fluvoxamine and other therapeutic agents in patients with PMDD are needed.

**Acknowledgment** : The authors thank Hideyo Machida and Takashi Kudo for preparation of the manuscript.

**References**

Clinical Efficacy of Fluvoxamine in PMDD


月経前不快障害（PMDD）に対する daily symptom report（DSR）を用いたプルボキサミンの治療成績の評価と quality of life 向上への効果
—前向き比較研究—

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概要　DSM-IV により pre-menstrual dysphoric disorder（PMDD）と診断された 61 例に対し、十分なインフォームド・コンセントの後、36 例にプルボキサミンを連続投与し、症状の変化を daily symptom report（DSR）、STAI、SDS および WHO QOL26 にて評価し、薬剤投与群（コントロール）と比較した。
プルボキサミン投与 1 周期目に、気分（32.0±27.2）、行動（35.9±27.9）および痛み（9.8±11.6）の黄体後期の5日間平均 DSR スコアは、投与前（それぞれ55.0±31.4、49.2±26.8、および16.7±15.5）に比べ有意に低下した（P<0.05）。一方、コントロールではスコア変化はなかった。WHO QOL26 では、プルボキサミン投与により、精神的項目（18.8%）、身体的項目（14.2%）および社会的項目（11.7%）において有意に（それぞれ P<0.01、P<0.01 および P<0.05）スコアの増加（QOL 向上）が観察された。特に、「生活の質について」、「健康状態について」の質問項目では、プルボキサミンの服用で前者は 1 周期目に 21.4% P<0.05）、後者は 3 周期目に 27.4% のスコアの増加（QOL 向上）が認められた（P<0.01）。
PMDD に対するプルボキサミンの連続投与は、黄体後期の気分、行動および痛みの症状を軽減させ、低下している QOL を向上させる効果が期待できることができた。