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Fluoxetine versus *Vitex agnus castus* extract in the treatment of premenstrual dysphoric disorder

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Clinical trials have demonstrated that serotonin reuptake inhibitors (SRIs) and the extract of *Vitex agnus castus* are effective for the treatment of premenstrual dysphoric disorder (PMDD). However, to the best of our knowledge, there has been no study comparing the efficacy of the SRIs with *Vitex agnus castus* (AC) extract. Therefore, the aim of the present study was to compare the efficacy of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), with that of the AC extract, a natural choice. After a period of 2 screening months to screen the patients for suitability, 41 patients with PMDD according to DSM-IV were recruited into the study. The patients were randomized to fluoxetine or AC for 2 months of single-blind, rater-blinded and prospective treatment period. The outcome measures included the Penn daily symptom report (DSR), the Hamilton depression rating scale (HAM-D), and the clinical global impression-severity of illness (CGI-SI) and -improvement (CGI-I) scales. At endpoint, using the clinical criterion for improvement, a similar percentage of patients responded to fluoxetine (68.4%, $n = 13$) and AC (57.9%, $n = 11$). There was no statistically significant difference between the groups with respect to the rate of responders. This preliminary study suggests that patients with PMDD respond well to treatment with both fluoxetine and AC. However, fluoxetine was more effective for psychological symptoms while the extract diminished the physical symptoms. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — premenstrual dysphoric disorder; fluoxetine; *Vitex agnus castus*; efficacy; SSRI

INTRODUCTION

Premenstrual dysphoric disorder (PMDD) is characterized by markedly depressed mood, marked anxiety, affective lability and decreased interest in daily activities during the last week of luteal phase in most menstrual cycles during the past year (APA, 1994). It has been previously mentioned that premenstrual complaints are triggered by decreases in serum progesterone and oestradiol levels during the late luteal phase, and therefore PMDD has been considered as a consequence of steroid withdrawal (Schmidt *et al.*, 1998). Both animal experiments and clinical studies suggest that androgens may exaggerate irritability and aggression. So it has been suggested that PMDD may be partly due to enhanced androgenicity because irritability is the main symptom of PMDD. Preliminary support for this assumption has been obtained (Eriksson *et al*., 1994). However, opposite results have also been reported (Bloch *et al*., 1998). Because the main symptoms of PMDD such as irritability, anger, depressed mood and carbohydrate craving are also believed to be regulated by serotonergic neurotransmission, the assumption that PMDD may be related to the serotonergic system is not far fetched. Moreover, it has been shown to be an interaction between steroid hormones and the serotonergic system (Eriksson *et al*., 1999).

A variety of treatment strategies have been used for the treatment of PMDD including hormones, diuretics, vitamins, and recently *Vitex agnus castus* extract and serotonergic antidepressants. The fruits of *Vitex agnus castus* (AC) contain a mixture of irodoids and flavonoids and some compounds similar in structure to the sex hormones have been isolated from the leaves and flowers (Schellenberg *et al*., 2001). The mechanism of action has been reported to be related to a modulation of stress-induced prolactin secretion

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through dopamine (Sliutz *et al*., 1993). The extract of this plant has been found to be effective in PMDD (Schellenberg *et al*., 2001). On the other hand, both non-selective and selective serotonin reuptake inhibitors (SSRIs) have been reported to be useful in the treatment of PMDD (Halbreich and Smoller, 1997; Young *et al*., 1998). To the best of our knowledge, there has been no study comparing the efficacy of SSRIs and AC.

The present study reports a preliminary, double-blind study to compare the response to fluoxetine and AC in patients who met the criteria for PMDD.

METHODS

Patients

The study consisted of 42 patients (aged 18–49 years) who had applied to Firat University School of Medicine Departments of Gynecology or Psychiatry and were diagnosed with PMDD according to DSM-IV criteria. After complete description of the study to the subjects, written informed consent was obtained from each patient. Ethical permission was approved by the Local Ethics Committee of Firat University School of Medicine. Females were included if they were between the ages of 24 and 45 years, had regular menstrual cycles lasting 25–34 days, and met DSM-IV criteria for PMDD. Exclusion criteria included the presence of a severe physical illness, pregnancy, irregular menstrual cycles, a history of hysterectomy, breastfeeding, the presence of mental retardation and meeting criteria for any DSM-IV major diagnoses for at least 6 months. PMDD criteria were based on Penn daily symptom reports (DSR) rated by the subjects for two menstrual cycles prior to 8-week single-blind, rater-blinded, randomized treatment period. The aim of this screening period for two menstrual cycles was to screen the patients for suitability and to confirm the diagnosis of PMDD. The DSR have 17 common PMDD symptoms, including the 11 symptoms of the research criteria for PMDD in DSM-IV. Each item was rated by on a five-point scale daily (0 = none to 4 = extreme). Scores were calculated by summing the ratings of cycle days 5–10 for postmenstrual score (day 1 was the first day of the menses) and the ratings of cycle days 23–28 for the premenstrual score. DSR criteria for this 2 month open-label screening period were severe premenstrual symptoms, as indicated by a premenstrual DSR score of at least 80 and an increase of 30% or over in total premenstrual DSR scores (days 23–28) compared with the postmenstrual scores (days 5–10). After the 2-month screening period, all the patients except one who became pregnant continued to meet the PMDD criteria and were randomized to receive 8 weeks of treatment with either fluoxetine ($n = 21$) or AC ($n = 20$) in a computer-generated schedule. Hamilton depression rating scale (HAM-D) (Hamilton, 1960) and clinical global impression scale-severity of illness (CGI-SI) and -improvement (CGI-I) scales were administered by a trained psychiatrist in addition to DSR. The dose range was 20–40 mg/day in the fluoxetine group and 20–40 mg/day in the AC group, with a flexible dosing. Medication was initiated on menstrual cycle day 1. The use of concomitant medications was prohibited.

Procedure

The patients' sociodemographic and clinical data were recorded at the first interview. All patients were evaluated using HAM-D, DSR and CGI-SI scales at baseline and week 8 and CGI-I at week 8. The main outcome measure was the premenstrual score from the DSR, HAM-D and CGI-SI. In addition, the patients were asked for adverse effects via an instrument designed by authors. This instrument included all reported side effects related to AC, fluoxetine and other SSRIs. All adverse events were designed as a semi-structured questionnaire form by the authors, which was able to be understood by the patients. Thus, side effects were recorded as 'present' or 'absent'. The study was an 8-week, randomized, single-blind, rater-blinded, prospective and parallel-group trial. The patients and raters were blind to drug assignment, although the prescribing physician was open to assignment. At each evaluation point, the patients were assessed by raters blind to drug assignment via the standardized scales and semistructured side effect instrument.

In order to determine the response to the treatment period of 2 months, the following criteria were used; (1) criteria for PMDD no longer being met, (2) having ratings of 'much' or 'very much improved' on CGI-I, (3) having at least a 50% decrease in HAM-D scores, (4) having at least a 50% decrease in DSR, and (5) the agreement of two authors (M.A. and S.K.) that the patient was improved sufficiently.

Statistical analysis

Statistical analysis was performed using the statistical package for social sciences (SPSS/PC 9.05 version, 1998). To compare the values of repeated measures at the different time points within the treatment groups, repeated measures analysis of variance

(MANOVA) following Bonferroni's correction test for four pairwise comparisons, and between the groups *t*-test were used. The χ^2 test was used to compare the side effects experienced and the rate of responders. The confidence interval was accepted as $p < 0.05$.

RESULTS

Except for three patients (two from the fluoxetine and one from the AC group) all patients completed the study. The mean age was 32.7 (SD = 10.8) years in the fluoxetine group and 34.1 (SD = 12.5) years in the AC group. The mean duration of illness for the fluoxetine and AC groups was 8.4 (SD = 4.8) and 9.6 (SD = 5.2) years, respectively. There were no significant differences between groups in the mean age or the duration of illness ($p > 0.05$).

At baseline, the mean HAM-D scores were 15.9 (SD = 5.6) in the fluoxetine group and 15.2 (SD = 4.7) in the *Vitex agnus castus* group. The mean HAM-D scores at last assessment were 7.1 (SD = 3.8) in the fluoxetine group and 7.4 (SD = 4.3) in the AC group. There was no significant difference between groups in the mean reductions of HAM-D from baseline to last assessment ($p > 0.05$), with no significant changes in the HAM-D scores between the start of treatment and week 4 or 8 between the groups (Table 1).

At baseline, the mean DSR scores were 177.4 (SD = 62.8) in the fluoxetine group and 171.7 (SD = 58.1) in the AC group. The mean DSR scores at last assessment were 85.6 (SD = 55.3) in the fluoxetine group and 82.8 (SD = 49.5) in the AC group. There was no considerable difference between the groups in the mean reductions of DSR from baseline to last assessment ($p > 0.05$), with no significant changes in the DSR scores between the start of treatment and week 4 or 8 between the groups (Table 1).

Table 1. Scale scores at each evaluation point in the groups

	Fluoxetine ($n = 19$)	AC ($n = 19$)	*p*
DSR			
Pretreatment	177.4 ± 62.8	171.7 ± 58.1	> 0.05
Month 1	108.8 ± 60.4[a]	117.1 ± 54.5[a]	> 0.05
Month 2	85.6 ± 55.3[b]	82.8 ± 49.5[b]	> 0.05
HAM-D			
Pretreatment	15.9 ± 5.6	15.2 ± 4.7	> 0.05
Month 1	9.7 ± 3.1[a]	12.9 ± 2.9	< 0.05
Month 2	7.1 ± 3.8[b]	7.6 ± 4.3[b]	> 0.05
CGI-SI			
Pretreatment	4.3 ± 1.6	4.1 ± 1.4	> 0.05
Month 1	2.5 ± 1.1[a]	2.6 ± 1.2[a]	> 0.05
Month 2	1.5 ± 0.6[b]	1.2 ± 0.7[b]	> 0.05

[a]Statistically significant difference from baseline (test with contrast in MANOVA); $p < 0.05$.
[b]Statistically significant difference from baseline (test with contrast in MANOVA); $p < 0.01$.

The mean CGI-SI scores were 4.3 (SD = 1.6) in the fluoxetine group and 4.1 (SD = 1.4) in the AC group at baseline ($p > 0.05$), compared with 1.5 (SD = 0.6) and 1.2 (SD = 0.7) at last assessment in the fluoxetine group and in the AC group, respectively ($p > 0.05$). There were no statistically significant differences between the groups with respect to the reductions in CGI-SI scores ($p > 0.05$).

At endpoint, using the clinical criterion for improvement, a similar percentage of patients responded in the fluoxetine (68.4%, $n = 13$) and in the AC group (57.9%, $n = 11$). There was no statistically significant difference between the groups with respect to the rate of responders ($p > 0.05$). When analysing each symptom of the DSR, the patients treated with fluoxetine experienced a decrease of 50% or over of the seven premenstrual symptoms including depression, irritability, insomnia, nervous tension, feeling out of control, breast tenderness and aches, being largely psychological symptoms. In patients treated with the AC, five symptoms diminished 50% or more: irritability, breast tenderness, swelling, food cravings and cramps, being largely physical symptoms.

Both drugs were well tolerated. Treatment-related adverse events were reported by 17 patients (nine patients from the fluoxetine group and eight from the AC group). There were 36 reports of newly observed adverse events. Of them, 20 were from 9 patients in the fluoxetine group and 16 were from 8 patients of the AC group ($p > 0.05$). This necessitated withdrawal from the study in two (9.5%) of the fluoxetine group and in one (5.0%) of the AC group. Most frequently experienced side effects in the fluoxetine group were nausea ($n = 6$), headache ($n = 4$) and insomnia ($n = 3$) whereas in the AC group they were nausea ($n = 5$) and headache ($n = 4$). In the fluoxetine group, two patients experienced sexual dysfunction. One had decreased libido and the other had erectile dysfunction. None of the AC group patients experienced any sexual side effect.

DISCUSSION

This preliminary study demonstrates that patients with PMDD respond well to treatment with both fluoxetine and AC extract. The results were consistent across all outcome measures, including DSR scores, HAM-D, CGI-I and global assessment. However, it seems that while fluoxetine is more effective for the psychological

symptoms of PMDD, AC extract is more effective for the physical symptoms.

The first potent serotonin reuptake inhibitor (SRI) reported to be effective for the treatment of PMDD was the non-selective SRI, clomipramine (Eriksson *et al*., 1990). Subsequently, a large number of placebo-controlled studies have supported the efficacy of the SSRIs, fluoxetine (Su *et al*., 1997), sertraline (Young *et al*., 1998) and citalopram (Wikander *et al.*, 1998). The assumption that the SSRIs reduce the signs of PMDD by inhibiting the serotonin transporter gains strong confirmation from the fact that the different SRIs, in spite of marked differences in molecular structure, have all been found to be effective. Further support for the opinion that the clinical signs of PMDD can be modulated by brain serotonergic neurones is obtained from the trials demonstrating that serotonin releasing agents meta-chlorphenylpiperazine (Su *et al*., 1997) and the serotonin (5-HT_{1A}) agonist buspirone (Rickels *et al*., 1989) may relieve the symptoms of PMDD. Using the clinical criterion for improvement, a vast majority of the patients receiving fluoxetine (68.4%) responded in the present investigation. Despite the fact that comparisons are limited by differences in design and measurement, similar levels of improvement (ranging from 65% to 80%) were reported in the trials in which serotonergic antidepressants were used (Halbreich and Smoller, 1997; Freeman *et al*., 1999a,b). In the present study, it was found that fluoxetine led to a great improvement in both DSR and HAM-D scores and supports its efficacy for the treatment of PMDD.

The AC extract was shown to have good efficacy for the treatment of PMDD in the present study. In earlier studies, the efficacy of the treatment of PMDD with AC was demonstrated, with an improvement rate between 46.5% and 55.5% (Berger *et al.*, 2000; Schellenberg *et al*., 2001). Thus, the improvement rate determined in the present study seems to be comparable with the others. The extract was reported to be active as a dopaminergic agonist, possibly by distinguishable plant constituents that govern prolactin release (Hoberg *et al*., 1999). An exaggerated release of prolactin in response to stimuli or basically increased prolactin levels are thought to be a prominent sign of PMDD and so the dopaminergic effect of the drug could account for its efficacy in the treated patients. However, it should be noted that the improvement in the physical symptoms was obvious compared with the psychological symptoms. The aetiology of PMDD is not well understood, and as a result, the different complaints associated with PMDD are usually symptomatically treated. Therefore, it may be suggested that it may be useful to treat PMDD with multiple therapeutic methods, some of which may be present in the different constituents of AC. On the other hand, it may be speculated that the combination of the agents studied in the present investigation may be more useful for the treatment of patients with PMDD because the extract seems to be more useful for the physical symptoms and fluoxetine for the psychological symptoms of PMDD.

In this paper, with regard to safety, the results showed that both drugs were well tolerated. The incidence of adverse events was low and the severity was mild in both groups. The type of side effects observed were those found in populations using these drugs.

Our preliminary results should be cautiously interpreted owing to some methodological limitations. The main limitation of the study is that it was not a placebo-controlled design. Furthermore, the results are based on acute treatment, with a relatively short duration of two menstrual cycles and do not address questions about long-term continuation of medication or relapse if the medication is discontinued. In conclusion, the findings of the present investigation suggest that both fluoxetine and AC have shown promising results in patients with PMDD, with fluoxetine being more effective for psychological symptoms and the extract for the physical symptoms of PMDD. Further placebo-controlled studies with a larger number of patients are needed.

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