Duloxetine treatment for women with premenstrual dysphoric disorder: a single-blind trial

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Abstract
Premenstrual dysphoric disorder (PMDD) affects 3–8% of women of reproductive age and is characterized by severe mood symptoms that cause important functional impairment. Serotonergic antidepressants appear to be an effective treatment for this disorder. The purpose of this study was to collect evidence on the efficacy and tolerability of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine, in the treatment of PMDD. We conducted a pilot, single-blind, non-controlled, fixed-dose trial. After two cycles for diagnosis confirmation, including a single-blind placebo cycle, 20 women with PMDD were treated continuously for three menstrual cycles with 60 mg/d duloxetine. The primary measure of the efficacy of treatment with duloxetine was the significant reduction in premenstrual symptoms demonstrated by the comparison between the mean Daily Record of Severity of Problems (DRSP) scores at baseline to endpoint (p = 0.0002). Statistically significant symptom reduction was observed in the first treatment cycle and throughout all the treatment phase. Clinical response, defined as a reduction ≥ 50% of baseline premenstrual symptoms, occurred in 65% of subjects (intention-to-treat population). Significant improvements were demonstrated by secondary measures, including reduction in self-rated functional impairment (p = 0.01) and improvement in quality of life (p = 0.04). The main side-effects associated with duloxetine were dry mouth, nausea, drowsiness, insomnia, decreased appetite, decreased libido, and sweating. Duloxetine was effective and generally well tolerated in the treatment of PMDD. Further large-scale, double-blind, placebo-controlled studies are needed to evaluate duloxetine as an additional treatment strategy for the management of PMDD.

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Key words: Clinical trial, duloxetine, premenstrual dysphoric disorder, premenstrual syndrome, treatment.

Introduction
Premenstrual dysphoric disorder (PMDD) is characterized by cyclic recurring mood, behavioural and somatic symptoms that typically occur during the luteal phase of the menstrual cycle and begin to remit within a few days of the onset of menses. Its main features are irritability, tension, affective lability, anxiety, depressed mood, and decreased interest in activities (APA, 2000; Freeman, 2003). PMDD affects 3–8% of women of reproductive age and is associated with significant functional impairment (Halbreich et al., 2003; Pearlstein et al., 2000; Wittchen et al., 2002).

The aetiology of PMDD remains uncertain. One of the leading theories for its pathogenesis is a dysregulation of central serotonergic activities, induced by normal fluctuations in gonadal hormones into menstrual cycles. Based on this theory, several antidepressant agents have been investigated as therapeutic interventions for PMDD (Parry, 2001; Steiner & Pearlstein, 2000). Twenty-nine double-blind, placebo-controlled trials (RCTs) have provided consistent positive results for various antidepressants including selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, fluoxetine, paroxetine,
sertraline) (Dimmock et al. 2000; Pearlstein, 2002; Shah, 2008) and non-selective serotonergic antidepressants [clomipramine (Sundblad et al. 1992) and venlafaxine (Cohen et al. 2004)]. Rapid onset of action and response rates of 42–83%, compared to 15–47% with placebos, have been reported with serotonergic antidepressants in the treatment of PMDD. Current studies indicate that both continuous and luteal-phase dose administration of these drugs are effective for PMDD (Dimmock et al. 2000; Freeman, 2004; Shah, 2008).

Duloxetine is a dual reuptake inhibitor of serotonin and norepinephrine that has been shown to be effective and well tolerated in the treatment of major depressive disorder (Brannan et al. 2005; Detke et al. 2002; Kirwin & Gören, 2005). Because of its serotonergic properties duloxetine might also significantly alleviate premenstrual dysphoric symptoms, as shown by the preliminary data of Mazza et al. (2008) and Ramos et al. (2008).

The purpose of the present study was to investigate the efficacy and tolerability of duloxetine for the treatment of PMDD.

Materials and methods

This study was a pilot, single-blind, uncontrolled, fixed-dose design to assess the efficacy and safety of duloxetine (60 mg/d) in outpatient women with PMDD. Advertisements within the public medical service of Instituto de Previdência dos Servidores do Estado de Minas Gerais (IPSEMG) and the community were used as recruiting strategies. Participants were enrolled from November 2006 to November 2007, and data collection was completed in February 2008. All patients provided signed informed consent after being informed about the objectives and procedures of this trial. The study protocol was reviewed and approved by the local Institutional Review Boards and was conducted in accordance with the Declaration of Helsinki and under the principles of Good Clinical Practice.

Subject selection

Women responding to advertisements were briefly interviewed by phone and then invited to a screening visit. Selection criteria were age (18–45 yr), regular menstrual cycles (duration between 22 and 35 d, at least in the last 6 months), and general good health as determined by medical evaluation. Premenstrual complaints were required to have been present in at least 9/12 menstrual cycles over the previous year. Exclusion criteria included the presence of any concurrent major psychiatric disorders, as assessed by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al. 1998), including any major depressive episode within the last 6 months; concomitant use of any psychotropic medications during the study; current use of any medications or treatments for PMDD symptoms; pregnancy, intending pregnancy, or breastfeeding; not using medically approved contraception (if using hormonal contraception, this treatment should had been in use for at least 6 previous months); hysterectomy, symptomatic endometrioses; severe or unstable general medical illness; or previous hypersensitivity to duloxetine.

Study design

This study consisted of a first phase for the diagnostic confirmation of PMDD, a second phase for treatment and had a total duration of up to six menstrual cycles (Fig. 1).

All eligible patients were instructed to prospectively rate their symptoms using the Daily Record of Severity of Problems (DRSP) for two or three screening cycles to confirm the diagnosis of PMDD. The short form of DRSP is a 14-item patient-rated scale that incorporates all symptoms listed in the DSM-IV-TR diagnostic criteria for PMDD (APA, 2000; Endicott et al. 2006). The first 11 items rate the following symptoms: depression, anxiety, mood swings, irritability, decreased interest, concentration difficulties, fatigue, increased appetite/food cravings, insomnia/hypersomnia, feeling out of control, and physical symptoms. The final three items access the domains of functioning: reduction of productivity; avoidance or less participation in hobbies or social activities; relationship problems. The severity of each item is recorded on a 6-point scale that ranges from 1 (no symptoms) to 6 (extreme). The mean luteal phase DRSP scores (last 6 d before onset of menses) were compared with mean DRSP scores obtained from the
follicular phase (days 5–10 after menses) and subjects were classified as having PMDD if they met the following criteria: (1) DRSP score of < 3 (mild) on any of the symptoms, during the follicular phase; (2) score of at least 4 (moderate) for at least 2 d during the luteal phase, on one or more of the following key symptoms: depression, anxiety, mood lability, or anger/irritability; (3) score of at least 4 (moderate) for at least 2 d during the luteal phase, on at least 5 of the 11 symptoms listed; (4) a 50% increase in scores of ≥ 5 PMDD symptoms, from follicular to luteal phase; (5) scores of at least 4 (moderate) for at least 2 d on at least one of the functional impairment items.

No medication was administered during the first menstrual screening cycle. Patients who achieved the severity criteria for PMDD diagnosis during the first screening cycle entered a placebo screening cycle. An additional screening cycle was available to patients who met all entry criteria at selection visit but failed to achieve the predefined severity of PMDD symptoms after a first period of symptoms rating using DRSP. A single-blind placebo was administered once daily each morning during the second screening cycle (baseline cycle). All patients performed a urine pregnancy test before beginning the use of study medication. Patients who met the severity diagnostic criteria for PMDD for two consecutive screening cycles, including the placebo run-in cycle, were included in the treatment phase (Fig. 1).

Duloxetine capsules, identical in appearance to the placebo capsules, were administered during the treatment phase. All subjects were informed that they would receive both placebo (for one treatment cycle) and duloxetine during the course of the study. A single-blind condition was maintained throughout the study, in order that patients had no knowledge of the treatment phase in use, i.e. placebo or duloxetine treatment. This strategy allowed a greater refinement in the evaluation of the effects of the placebo and of the active drug.

In the treatment phase 60 mg duloxetine, once daily in the morning, continuously, was administrated for up to three menstrual cycles. During treatment cycles patients continued to record their symptoms using DRSP. Study visits were scheduled per menstrual cycle and near the onset of the next menses. Other efficacy assessments conducted at each scheduled visit included the 17-item Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960), a global assessment of disease severity and improvement [Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I); Guy, 1976], a patient-rated assessment of functional impairment [Sheehan Disability Scale (SDS; Sheehan, 2000)] and a self-rated quality of life scale [Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q; Endicott et al. 1993)]. Vital signs, weight and adverse events were also recorded throughout the study visits.

**Study objectives**

The primary objective was to investigate the efficacy of continuous treatment with 60 mg/d duloxetine for PMDD. The secondary objective was to assess the safety of this treatment. The primary efficacy variable was the change in the mean total luteal phase DRSP scores from baseline (placebo screening cycle) to end of treatment cycle 3 using duloxetine (endpoint). Secondary efficacy measures included change from baseline to the end of third treatment cycle for: sub-items of DRSP, HAMD, SDS, Q-LES-Q, the proportion of responders (defined as a ≥50% reduction from baseline DRSP scores), and the proportion of responders defined as a CGI-I item score of 1 (very much improved) or 2 (much improved) at endpoint.

**Statistical methods**

As this study was a single-blind, non-controlled trial, the sample size (n = 20) was based on previous similar published trials on antidepressant drugs in the treatment of PMDD.

For all efficacy measures, primary statistical inferences were made on the intention-to-treat (ITT) principle at treatment cycle 3 by using the last observation carried forward (LOCF) approach to deal with missing data.

The non-parametric Wilcoxon signed-rank test was used for all analyses to compare ordinal data between two time-points for the same sample (baseline cycle vs. endpoint). Statistical significance was established at a risk of 5% for all analyses. Epi-Info version 3.3.2 software was used (Centers for Disease Control and Prevention, USA).

A descriptive analysis of the demographic and clinical characteristics, vital signs, and adverse events were also performed for study patients included in treatment phase.

**Results**

**Study sample**

The proposed sample of this study (n = 20) was achieved as following. From a total of 447 candidates screened by phone, 223 women were invited to a selection visit. After this interview, 98 subjects were
selected for the study screening phase to confirm a PMDD diagnosis. Of those, 65 women did not reach the treatment phase, the main reasons being failure to meet the severity criteria for the diagnosis of PMDD (38.4%) and loss of follow-up (28%). Thirty-three patients completed the placebo screening cycle, and 13 (39.4%) were considered placebo responders because of not meeting the severity criteria for PMDD diagnosis after using placebo. Twenty women were enrolled in the treatment phase with duloxetine. Of those, 15 (75%) completed the three treatment cycles, three patients were withdrawn due to non-serious adverse events and two patients missed their follow-up.

The demographic and clinical characteristics of women included in the study treatment phase are shown in Table 1. Eight patients (40%) stated previous treatment for premenstrual symptoms. For this subgroup seven patients had used at least one antidepressive agent and the previous clinical response had not been sufficiently effective for 62% of them. The majority of patients (75%) did not have a prior history of major depression. The comparison of means between premenstrual and postmenstrual symptoms rated in the baseline cycle confirmed the cyclic nature and the typical worsening of symptoms during premenstrual periods associated with PMDD. An analysis of the baseline characteristics of the subgroups that used and did not use oral contraception (OC) revealed no clinically relevant differences with respect to symptom severity as assessed by means of total premenstrual DRSP scores ($p = 0.1450$).

**Treatment response**

For the primary efficacy variable, change in the mean total premenstrual DRSP score from baseline (302.7 ± 83.2) to treatment cycle 3 (187.6 ± 88.6), a statistically significant reduction of 52.62% was demonstrated ($p = 0.0002$) in premenstrual symptoms.

The same comparison of the mean total premenstrual DRSP scores was performed by stratification of each treatment cycle. These analyses showed significant reduction of premenstrual symptoms beginning in the first treatment cycle (44.3%) and to the end the second treatment cycle (53.9%). The difference from baseline to treatment cycle 1 was 96.9 points ($p = 0.0004$) and from baseline to treatment cycle 2 was 118 points ($p = 0.0001$) (Fig. 2).

The changes in mean premenstrual DRSP subitem ratings, from baseline to endpoint, were significantly lower after treatment cycle 3 for all symptoms, except for insomnia/hypersomnia symptoms (baseline mean 20.0 ± 7.1, endpoint mean 15.4 ± 7.9, $p = 0.054$) (Fig. 3).

It was only for the irritability symptom that maximal improvement was reached in the first treatment cycle. The reduction in all DRSP subitems of functioning also reached statistical significance: reduction of productivity (baseline mean 21.1 ± 9.3, endpoint mean 13.3 ± 8.6, $p = 0.0094$), avoidance or less participation in hobbies or social activities (baseline mean 20.1 ± 9.0, endpoint mean 11.8 ± 6.8, $p = 0.0024$), and relationship problems (baseline mean 20.3 ± 8.5, endpoint mean 12.2 ± 6.4, $p = 0.0014$).

The response rate to treatment (defined as a reduction at endpoint of ≥50% from the pretreatment baseline in total premenstrual DRSP scores) was 65% for the ITT population (13/20). Using the clinical response analysis based on CGI-I scores, 70% (14/20) of the subjects showed ratings of 1 (‘very much improved’) or 2 (‘much improved’) at endpoint.

Duloxetine treatment showed significant reduction of functional impairment associated with premenstrual symptoms as assessed by the total SDS
scores and their subitems: work, social life/leisure activities, and family life/home responsibilities. The mean of premenstrual HAMD scores demonstrated subclinical depressive symptoms before treatment and decreased to normal levels at endpoint. Significant improvement in self-rated quality of life with treatment was noted by an increase in Q-LES-Q scores (Table 2).

The variable use of OC was examined to determine its association with treatment response. The comparison of the mean total premenstrual DRSP scores showed significant reduction of premenstrual symptoms from baseline to treatment endpoint for the OC using subgroup (n = 9, baseline mean 333 ± 97.1, endpoint mean 177.3 ± 55.4, p = 0.0007) and the not using OC subgroup (n = 11, baseline mean 277.9 ± 63.9, endpoint mean 196 ± 110.8, p = 0.0465).

**Adverse events**

Adverse events were reported by the subjects in response to general questioning by a clinician at each visit. Possible side-effects of duloxetine reported for ≥ 10% of patients during the study are shown in Table 3. All patients stated at least two adverse events during treatment cycles, and the mean of side-effects was 5.8 per patient. Common side-effects at the first treatment cycle were gastrointestinal disturbances (dry mouth, nausea, vomiting, constipation) and decreased appetite, and were generally transient. Events such as insomnia, decreased libido, sweating and headaches appeared to persist throughout the treatment cycles. Three of 20 patients were prematurely discontinued due to non-serious adverse events of duloxetine, such as: (1) insomnia and irritability; (2) headache, dizziness, tremors, psychic retardation, concentration difficulties, drowsiness, fatigue, nausea and dry mouth; (3) headache, insomnia, nightmares, drowsiness, increased perspiration, chills, reduced appetite and nausea. Two patients reported mild to moderate, short duration, withdrawal syndrome after abrupt duloxetine interruption at the end of the study. No serious adverse event occurred during this trial.

The analysis of the means of systolic and diastolic blood pressure and of body mass index did not show
any significant change from baseline to endpoint (\(p = 0.72, p = 0.76, p = 0.63\), respectively).

**Discussion**

This study was a pilot, single-blind, uncontrolled, fixed-dose trial to assess the efficacy and safety of duloxetine in treatment of PMDD.

During three treatment cycles, continuous daily doses of 60 mg duloxetine significantly reduced PMDD symptoms and improved functioning. Positive efficacy for all primary and secondary outcome measures were found, as demonstrated in changes from baseline to endpoint analyses for the patients’ daily rating of symptoms (total DRSP score and DRSP sub-item scores), the investigator ratings (HAMD and CGI scales), and the self-rated scales to measure functional impairment related to symptoms (SDS) and assess quality of life (Q-LES-Q). At endpoint, according ITT analysis, a total of 65% (13/20) of the patients had significant response to treatment (defined as a reduction of \(\geq 50\%\) of the global premenstrual symptoms) and 70% (14/20) of the subjects were much improved according to CGI-I scores of \(\leq 2\). These results support the findings of Mazza et al. (2008) that duloxetine is effective for PMDD treatment. In this open trial, 60 mg/d duloxetine provided satisfactory clinical response (defined as a 50% decrease in daily PMDD symptom scores) in 78% (39/50) of the patients who completed two menstrual cycles of treatment. Similar response rates were reported in previous RCTs for PMDD using SSRI antidepressants [fluoxetine 53% (Steiner et al. 1995); sertraline 63% (Freeman et al. 2004); paroxetine 67–76% (Pearlstein et al. 2005); venlafaxine 60% (Freeman et al. 2001)], the latter also being a reuptake inhibitor of serotonin and norepinephrine antidepressant.

Duloxetine was able to reduce functional impairment as a result of direct improvements in premenstrual dysphoric symptoms, which has already been reported by different serotonergic antidepressants for PMDD treatment (Freeman, 2005).

Duloxetine’s improvement of DRSP scores was reported in the first treatment cycle and continued to be significant until the end of the treatment period. Approximately 84% of the decrease in total premenstrual DRSP scores at endpoint occurred in the

<p>| Table 2. Mean premenstrual total scores of HAMD, CGI-S, SDS (total and subitems) and Q-LES-Q scales at baseline and endpoint study cycles |</p>
<table>
<thead>
<tr>
<th>Scales</th>
<th>Baseline cycle (mean ± S.D.)</th>
<th>Endpoint cycle (mean ± S.D.)</th>
<th>(p) value</th>
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</thead>
<tbody>
<tr>
<td>HAMD</td>
<td>10.7 ± 4.9</td>
<td>6.3 ± 3.9</td>
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<tr>
<td>CGI-S</td>
<td>4.9 ± 0.6</td>
<td>2.5 ± 1.7</td>
<td>0.0000</td>
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<tr>
<td>SDS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>17.6 ± 5.0</td>
<td>11.5 ± 6.8</td>
<td>0.0050</td>
</tr>
<tr>
<td>Work</td>
<td>5.6 ± 2.5</td>
<td>3.5 ± 2.6</td>
<td>0.0121</td>
</tr>
<tr>
<td>Social life/leisure activities</td>
<td>5.7 ± 2.4</td>
<td>4.0 ± 2.0</td>
<td>0.0255</td>
</tr>
<tr>
<td>Family life/home responsibilities</td>
<td>6.3 ± 2.5</td>
<td>4.0 ± 2.8</td>
<td>0.0093</td>
</tr>
<tr>
<td>Q-LES-Q</td>
<td>49.0 ± 11.2</td>
<td>56.6 ± 12.1</td>
<td>0.0273</td>
</tr>
</tbody>
</table>

CGI-S, Clinical Global Impression of Severity; HAMD, Hamilton Rating Scale for Depression; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; SDS, Sheehan Disability Scale.

<p>| Table 3. Side-effects incidence associated with duloxetine (60 mg/d) treatment ((\geq 10%) (n = 20) |</p>
<table>
<thead>
<tr>
<th>Side-effects</th>
<th>(n) (%)</th>
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</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8 (40)</td>
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<tr>
<td>Decreased libido</td>
<td>8 (40)</td>
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<tr>
<td>Dry mouth</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Increased perspiration</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Excessive thirst</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Tremor</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

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first treatment cycle. Maximal improvement was noted in the first treatment cycle for irritability symptom, indicating the rapid onset of irritability-relieving effects of duloxetine. These evidences are similar to previous literature reports that the onset of serotonergic antidepressant is more rapid in PMDD treatment than in treatment of other mood disorders (Cohen et al. 2002; Freeman et al. 1999, 2001; Steiner et al. 1995; Wikander et al. 1998; Yonkers et al. 1997).

Overall, duloxetine was well tolerated. Common adverse events were dry mouth, nausea, drowsiness, insomnia, decreased appetite, decreased libido, and sweating. No significant weight change was shown after three treatment cycles of duloxetine.

The strict inclusion and exclusion criteria of this study ensured that an appropriate population of subjects with severe premenstrual dysphoric symptoms was studied. The number of subjects interviewed, selected, and included in the treatment phase was an 11:5:1 ratio. It demonstrates the stringent requirements used for a diagnosis of PMDD, the complexity of prospective assessments of the cyclical nature of such symptoms, and the high placebo response (39.3%) associated to this disorder (Freeman & Rickels, 1999).

The single-blind, placebo run-in screening cycle used conferred greater consistency to response rates reported in the present study (65%). As this strategy allows the exclusion of placebo responders, it reduces the overall efficacy of the intervention studied. Even after removal of placebo responders the response rate reported in this study is significantly positive (Wyatt et al. 2002).

Duloxetine is an antidepressant that selectively inhibits the reuptake of serotonin and norepinephrine and might be an additional treatment strategy in the management of PMDD (Mazza et al. 2008). Additional corroborative evidence already supports the positive efficacy of other non-selective serotonergic antidepressants in the management of PMDD, such as clomipramine (Sundblad et al. 1992, 1993) and venlafaxine (Cohen et al. 2004; Freeman et al. 2001).

This study presents significant limitations and its results should be interpreted with caution. As a single-blind trial, there is no control for any bias in the assessment of efficacy and safety. In addition, other limitations should be considered such as the small sample size ($n=20$), the number of patients who completed all study evaluations (15/20, 75%), and the relatively brief duration of treatment (three menstrual cycles).

In conclusion, this trial provides preliminary evidence that a continuous daily dose of 60 mg duloxetine is effective in treating symptoms of PMDD in addition to reducing the functional impairment experienced by these patients. Clinical response can be expected within the first treatment cycle, and side-effects are well tolerated. Additional large-scale, double-blind, well-controlled studies are necessary to support the current findings. Duloxetine appears to be a promising treatment strategy for the management of PMDD.

Acknowledgements
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Statement of Interest
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References


