EXPANDING CHOICES IN TREATING PREMENSTRUAL DYSPHORIC DISORDER*

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ABSTRACT

Over the past 2 decades, considerable progress has occurred in the understanding, diagnosis, and clinical management of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). PMDD is a severe form of PMS and falls within the parameters of specific clinical definitions and specific diagnostic criteria. PMDD accounts for an estimated 3% to 5% of menstruating women. Nonpharmacologic management of premenstrual symptoms has not been studied as extensively as pharmacologic therapies. However, many nonpharmacologic interventions, such as exercise, calcium supplementation, and relaxation response, afford general health benefits and pose little risk to patients, making them reasonable for women with premenstrual symptoms. Among pharmacologic therapy options for premenstrual symptoms are, the selective serotonin reuptake inhibitors (SSRIs). One such SSRI is fluoxetine, which has become first-line therapy, and is supported by a number of controlled clinical trials. Findings from initial clinical trials of luteal-phase dosing of SSRIs have supported the potential for intermittent dosing in patients with PMS and PMDD.

Premenstrual dysphoric disorder (PMDD) is one of several conditions that revolve around the menstrual cycle. Other menstrual conditions include premenstrual molimina, premenstrual syndrome (PMS), and premenstrual exacerbation. It is important that PMDD be distinguished from the other premenstrual conditions to treat it effectively; this, however, can be difficult. The American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and the American College of Obstetricians and Gynecologists (ACOG) diagnostic criteria for PMDD offer guidelines for proper diagnosis.

An array of nonpharmacologic and pharmacologic strategies exist for PMDD. Some of the nonpharmacologic interventions have minimal data to support their use, but anecdotal evidence and other forms of clinical experience suggest the interventions are helpful for some PMDD patients. The selective serotonin reuptake inhibitors (SSRIs) have emerged as the cornerstone of pharmacologic therapy for PMDD, and new dosing strategies offer the potential for further improvements.

EPIDEMIOLOGY AND DIAGNOSIS

PMDD is relatively uncommon, affecting 3% to 5% of menstruating women. In contrast to PMS, PMDD is associated with more severe cyclic symptoms that cause functional impairment. The average age of onset is 26 years. An accurate diagnosis of PMDD begins with the basics of good medical practice: obtaining a detailed medical history, conducting a thorough physical exam, and ultimately ruling out other psychiatric, physical, and psychosocial disorders.

As previously noted, PMDD is one of several menstrual disorders. Premenstrual molimina comprises...
normal changes that occur in association with the menstrual cycle, and the condition is neither an International Classification of Diseases-9 (ICD-9) or ICD-10 diagnosis, nor a chief complaint in clinical practice. Between 30% and 80% of menstruating women have mild cyclic symptoms that define PMS; these symptoms may include mild psychologic discomfort, bloating and weight gain, breast tenderness, aches and pains, poor concentration, sleep disturbance, and change in appetite. Premenstrual exacerbation refers to premenstrual worsening of a concurrent disease or condition.

The next step in the PMDD diagnostic evaluation requires the use of a PMS calendar to establish the severity and luteal cyclicity prospectively. To confirm the PMDD diagnosis, symptoms must be documented over 2 consecutive menstrual cycles. The DSM-IV is specific about the nature and occurrence of the symptoms. The patient must present with at least 5 symptoms from a specified list. One of the symptoms must be a “core” symptom, and all symptoms must be present in the week prior to menses and remit within days of menses (Table 1). Moreover, the symptoms must markedly interfere with work, school, usual activities, or relationships, and must not represent an exacerbation of another disorder.

The ACOG diagnostic criteria for PMS overlap and complement the DSM-IV criteria for PMDD and provide additional diagnostic guidance. The ACOG criteria are similar to DSM-IV in the requirement for prospective documentation of symptoms, which must cause dysfunction in social or economic performance. The ACOG criteria also stipulate that the symptoms must occur in the absence of hormone ingestion. Monitoring symptoms with a calendar is a simple, yet essential, part of the diagnostic process. Information garnered from the monitoring can prove invaluable in evaluating a woman’s menstrual symptoms and arriving at the correct diagnosis.

**Office-Based Treatment Options for PMDD**

**Nonpharmacologic Therapy**

Several nonpharmacologic therapies lack compelling data from randomized clinical trials to support their use; therefore, physicians may be less inclined to initiate such treatments. Keep in mind that some of the interventions, such as calcium supplementation, have been evaluated in controlled studies. Moreover, many nonpharmacologic interventions, such as exercise and relaxation training, will not cause patients harm and may, in fact, be beneficial. The number of studies that have evaluated exercise and PMS is limited; nevertheless, the available data suggest exercise is beneficial for PMS and should be widely recommended.

In the traditional obstetrics and gynecology practice, an underused intervention for menstrual disorders is relaxation training and/or cognitive-behavioral therapy. Careful implementation of such therapies can lead to substantial improvement in symptoms. Such results emphasize the value of allowing patients to explore low-risk interventions that might prove useful in some instances.

Dietary modification is another nonpharmacologic intervention that might help some patients minimize menstrual symptoms. Typical recommendations are to reduce intake of caffeine, chocolate, salt, and alcohol, and increase consumption of complex carbohydrates, which may stimulate increased serotonin synthesis and release. One study showed that a complex carbohydrate-containing beverage improved PMS symptoms.

Calcium supplementation has been evaluated carefully, and the data suggest that supplementation improves PMS symptoms. In a randomized, placebo-controlled trial involving 450 women, patients ran-

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**Table 1. Diagnostic Criteria for PMDD**

Five of the following symptoms (with at least 1 of these*) must occur during the week before menses and remit within days of menses.

<table>
<thead>
<tr>
<th>Symptom</th>
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<tr>
<td>• Irritability*</td>
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<tr>
<td>• Affective lability* (sudden mood swings)</td>
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<tr>
<td>• Decreased interest in activities</td>
</tr>
<tr>
<td>• Difficulty concentrating</td>
</tr>
<tr>
<td>• Lack of energy</td>
</tr>
<tr>
<td>• Change in appetite (eg, food cravings)</td>
</tr>
<tr>
<td>• Depressed mood or hopelessness*</td>
</tr>
<tr>
<td>• Tension or anxiety*</td>
</tr>
<tr>
<td>• Change in sleep</td>
</tr>
<tr>
<td>• Feeling out of control or overwhelmed</td>
</tr>
<tr>
<td>• Other physical symptoms (eg, breast tenderness, bloating)</td>
</tr>
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</table>

PMDD = premenstrual dysphoric disorder.
domized to calcium carbonate had a 60% greater reduction in luteal symptoms compared with the placebo group.\(^8\) 

Although evidence from controlled trials is lacking in some instances, a number of nonpharmacologic interventions have yielded positive results in randomized studies. Physicians also can be reassured that nonpharmacologic therapies reviewed in this section have little potential to cause harm. The interventions should be used in conjunction with prospective calendar monitoring of symptoms.

**Pharmacologic Therapy**

A large body of medical literature shows that PMS symptoms improve or resolve altogether in the absence of menstrual periods. This was initially demonstrated by studies that showed a reduction in PMS symptoms following treatment with gonadotropin-releasing hormone (GnRH) agonists. No longer commonly used in clinical practice, the strategy consists of giving a woman a GnRH analog to cause cessation of menstruation, followed by “add-back” hormone replacement therapy. The treatment can result in significant reductions in luteal-phase symptom score.\(^9\) Suppression with oral contraceptives, however, does not seem to work.

Benzodiazepines have been used with some success for a number of years. Low-dose alprazolam, in particular, can reduce baseline symptom scores by 20% to 70%, depending on the specific symptom evaluated.\(^10\)

The emergence of SSRIs has shifted the focus away from benzodiazepines and other medical therapies for PMDD largely because of the landmark study by Steiner and colleagues. Their study showed significant improvement in overall luteal-phase scores with fluoxetine, 20 mg daily; raising the fluoxetine dose to 60 mg daily offered no additional benefits.\(^11\) The trial results played a major role in fluoxetine’s approval for treatment of PMDD. Fluoxetine remains the only SSRI approved for use in PMDD, although others undoubtedly will follow.

Steiner and colleagues’ data showed substantial improvement in bloating and breast tenderness. Initially, such improvement in physical symptoms was surprising because it was not an attribute normally associated with fluoxetine. However, the effects appear to be fairly specific to fluoxetine therapy and have been consistent across clinical trials of the drug.

Following this initial study that demonstrated efficacy of fluoxetine for PM S/PM D D, a number of other psychotropic medications were examined. Interestingly, drug efficacy for PM S appears to be specific to agents that modulate serotonergic activity, including sertraline, citalopram, paroxetine, and even drugs such as venlafaxine, which is not an SSRI, but has significant serotonergic activity.

Fluoxetine by far is the most widely studied SSRI in PM D D and PM S. More than 1000 patients have been treated with fluoxetine in controlled trials, which have consistently shown significant reductions in premenstrual tension, irritability, dysphoria, and somatic symptoms.\(^11,12\) Sertraline and paroxetine also reduce emotional premenstrual symptoms associated with PM S/PM D D, with sertraline also demonstrating improvement in functional impairment in a large multicenter trial.

The most commonly reported side effects of fluoxetine are nervousness, nausea, insomnia, and drowsiness.\(^11-13\) The side effects are usually mild and transient. Sexual dysfunction is a significant side effect reported with all SSRIs.\(^14\)

In early PM S studies, it was noted that symptom improvement occurred in the first menstrual cycle after initiation of fluoxetine.\(^11\) This finding was unexpected, because 6 weeks or even several months of SSRI therapy might be required for a response in patients with clinical depression. The rapid onset of action with the use of SSRIs for PM S/PM D D led to the study of intermittent, luteal-phase administration of these drugs. Fluoxetine, sertraline, and citalopram all demonstrated efficacy in pilot studies of luteal-phase administration for PM D D.

Recently, intermittent dosing with fluoxetine was evaluated in a randomized, placebo-controlled clinical trial.\(^15\) The trial compared 2 different doses of fluoxetine (10 mg and 20 mg) with placebo in patients with PM D D. Fluoxetine or placebo was given only during the luteal phase of the menstrual cycle. The results showed significant improvement in mood, physical symptoms, and in social and functional activities with the 20-mg dose of fluoxetine compared with placebo.

Intermittent dosing of sertraline also has been evaluated, and the results have been positive. Published data from these evaluations are likely to be forthcoming in the near future. All of the SSRIs have a rapid (first cycle) onset of action, and the data accumulated thus far suggests the agents are effective when given in intermittent luteal-phase dosing.
Early in 2002, published data emerged from an evaluation of another alternative dosing schedule for fluoxetine. The trial showed that fluoxetine effectively reduced menstrual symptoms when a once-weekly 90-mg dose was administered 14 days before the onset of menses and a second 90-mg dose was administered 7 days prior to menses. The strategy proved highly effective for reducing PMS symptoms.\textsuperscript{16}

Specialty organizations that have taken a position on the treatment of PMS and PMDD are consistent in supporting SSRIs as first-line therapy and include the ACOG and the Association of Professors of Gynecology and Obstetrics. These organizations have concluded that SSRIs are effective for reducing moderate to severe symptoms, including mood and somatic symptoms. Side effects are typically mild and transient. Loss of libido can emerge with continued treatment.

The practice of prescribing oral contraceptives for treatment of PMS and PMDD remains common, regardless of the lack of clinical trials and of data proving its efficacy for this purpose. The one possible exception is drospirenone/ethinyl estradiol, which has some early data to suggest improvement in water retention, appetite, and certain other symptoms. Trials are ongoing to validate these effects.

**PERIMENOPAUSE AND PREGNANCY**

Few studies have assessed the effects of medical therapy on perimenopausal symptoms. However, the evidence that is available suggests unopposed estrogen may have a favorable effect on depressive symptoms in the perimenopausal time period. In addition to estrogen therapy, it is likely that SSRIs would be effective for perimenopausal mood disturbances, although this is based largely on anecdotal experience.

By definition, PMDD patients are of reproductive age and ovulating, so the effects of therapy during pregnancy deserve consideration. All the SSRIs fall into the US Food and Drug Administration pregnancy category C; however, the data on SSRI exposure during pregnancy have been reassuring, particularly for fluoxetine. Fluoxetine is not teratogenic in animal models, and published papers that address fluoxetine exposure in pregnancy have shown no indication of an increase in major malformations (Table 2).

One study of prenatal exposure to fluoxetine revealed after follow-up on 55 preschoolers with documented intrauterine exposure to fluoxetine that no abnormalities related to global intelligence quotient, language and behavioral development, or neurobehavioral dysfunction were reported. The data added to the overall reassurance about the safety of fluoxetine use during pregnancy.\textsuperscript{17}

SSRIs and other psychotropic medications are found in breast milk, and exposure may be an issue for premature infants. However, no controlled studies have evaluated the effects of psychotropic medications taken by breastfeeding women.

**SUMMARY**

PMDD affects 3% to 5% of women of reproductive age. This disorder can be distinguished from depression and anxiety disorders, and the diagnosis is dependent on prospective symptom recording. Nonpharmacologic therapies of potential value include exercise, calcium supplementation, and relaxation response. Effective pharmacologic therapies include GnRH analogs, benzodiazepines, and serotonergically active agents, especially the SSRIs, which several women's health groups recognize as first-line therapy for PMDD and PMS.

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**Table 2. Prospectively Ascertained Pregnancy Outcomes Following Exposure to Fluoxetine**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Design</th>
<th>Number of Pregnancies*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pastuszak et al, 1993\textsuperscript{18}</td>
<td>Cohort-controlled</td>
<td>96</td>
</tr>
<tr>
<td>Brunel et al, 1994\textsuperscript{19}</td>
<td>Survey</td>
<td>7</td>
</tr>
<tr>
<td>Goldstein, 1995\textsuperscript{20}</td>
<td>Survey</td>
<td>112\textsuperscript{1}</td>
</tr>
<tr>
<td>Chambers et al, 1996\textsuperscript{21}</td>
<td>Cohort-controlled</td>
<td>174</td>
</tr>
<tr>
<td>McElhatton et al, 1996\textsuperscript{22}</td>
<td>Survey</td>
<td>67</td>
</tr>
<tr>
<td>Goldstein et al, 1997\textsuperscript{23}</td>
<td>Survey</td>
<td>686\textsuperscript{1}</td>
</tr>
<tr>
<td>Nulman et al, 1997\textsuperscript{17}</td>
<td>Cohort-controlled</td>
<td>55\textsuperscript{1}</td>
</tr>
</tbody>
</table>

\*Number of live-born pregnancies exposed to fluoxetine. \textsuperscript{1}Third-trimester exposures; some overlap with pregnancies reported by Goldstein et al, 1995. \textsuperscript{1}Includes 123 reported by Goldstein in Letter to the Editor, \textit{N Engl J Med}, 1997. \textsuperscript{1}Contains 36 fluoxetine-exposed pregnancies reported by Nulman in \textit{Clin Pharmacol Ther}, 1997. Some (number uncertain) reported by Pastuszak et al, 1993.
REFERENCES
