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Educational Objectives
After studying the article by Freeman and Sondheimer, the participant will be able to:

- Discuss the epidemiology, clinical presentation, neurobiology, and treatment of premenstrual dysphoric disorder.

This pretest is designed to facilitate your study of the material.

1. Premenstrual dysphoric disorder is characterized by:
   a. Physical symptoms
   b. No functional disability
   c. Symptom remission in the follicular phase of the menstrual cycle
   d. The presence of depression

   Pretest answer and Posttest on page 39.

Disclosure of Off-Label Usage
The authors of this article have determined that, to the best of their knowledge, alprazolam, bromocriptine, buserelin, busipronine, citalopram, clomipramine, danazol, fluvoxamine, goserelin, leuprolide, mefenamic acid, nafarelin, naproxen, nefazodone, paroxetine, spironolactone, tibolone, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of premenstrual dysphoric disorder.
Premenstrual Dysphoric Disorder: Recognition and Treatment

Ellen W. Freeman, Ph.D., and Steven J. Sondheimer, M.D.

Premenstrual dysphoric disorder (PMDD) represents the more severe and disabling end of the spectrum of premenstrual syndrome and occurs in an estimated 2% to 9% of menstruating women. The most frequent PMDD symptoms among women seeking treatment consist of anger/irritability, anxiety/tension, feeling tired or lethargic, mood swings, feeling sad or depressed, and increased interpersonal conflicts. Women who develop PMDD appear to have serotonergic dysregulation that may be triggered by cyclic changes in gonadal steroids. The marked increase in the number of well-designed placebo-controlled studies in the past decade has established several selective serotonin reuptake–inhibiting antidepressants as effective first-line treatments for this disorder. Both continuous dosing and intermittent luteal dosing strategies lead to rapid improvement in symptoms and functioning. The present article provides a brief review of current information on the epidemiology, clinical presentation, neurobiology, and treatment of PMDD.

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The formal medical description of premenstrual syndrome (PMS) and the more severe, related diagnosis of premenstrual dysphoric disorder (PMDD) goes back at least 70 years to a paper presented at the New York Academy of Medicine by Robert T. Frank titled “Hormonal Causes of Premenstrual Tension.” The specific term premenstrual syndrome appears to date from an article published in 1953 by Dalton and Green in the British Medical Journal.1 Since then, PMS has been a continuous presence in our popular culture, occupying a place that is larger than the research attention accorded it as a medical diagnosis. Nonetheless, a MEDLINE search showed that by 1980, over 500 articles had been published on PMS in the medical literature, and more than 50 treatments had been proposed. Only a very small number of these early studies, though, used standard double-blind, placebo-controlled methodology.

In 1989, the modern era of PMS research began with the appearance in the DSM-III-R of operationally defined diagnostic criteria for PMS (renamed “late luteal phase dysphoric disorder” [LLPDD]). Inclusion of LLPDD was tentative, with the description of the disorder located in the back of the book, in Appendix A, which was reserved for “Proposed Diagnostic Categories Needing Further Study.”2 The introduction of LLPDD as a candidate psychiatric diagnosis was the most controversial of all the revisions in DSM-III-R, with many objecting that its inclusion was an attempt to “pathologize” what was a normal part of a woman’s reproductive life. From a scientific standpoint, the operationalized diagnostic criteria were an essential prerequisite for the explosion of descriptive, neurobiological, and treatment research that has followed in the past decade. The result of this research, as highlighted in later sections, is the characterization of a disorder, PMDD, that is more severe and restrictive and requires clear evidence of disability to diagnose.

This article will provide a brief review for clinicians of the prevalence, clinical presentation, pathophysiology, and treatments for PMDD.

EPIDEMIOLOGY

PMDD occurs in 2% to 9% of women of reproductive age and requires clear impairment of functioning.3–7 Even though the symptoms of PMDD vary from woman to
woman, the symptoms experienced by each individual have been shown to be relatively consistent from cycle to cycle.8,9

PMDD typically starts in the early-to-mid 20s, though it may begin at any time after menarche.3,10,11 Though little information is available from prospective, longitudinal studies, clinical evidence suggests that PMDD tends to be a chronic illness that continues until menopause, frequently showing gradual, though episodic, worsening over time. The symptoms of PMDD tend to remit during pregnancy.12

The degree of variability in the incidence of PMS/PMDD from culture to culture and in its cross-cultural clinical presentation has not been systematically studied at this point. Available data suggest that PMS/PMDD occurs across cultures at approximately comparable rates.13–20 Cultural and psychosocial factors appear to influence the proportion and intensity of physical versus behavioral symptoms, as well as the degree of illness behavior and medical help-seeking associated with the PMS-type symptoms.

**CLINICAL PRESENTATION AND RECOGNITION**

PMS refers to the milder emotional and physical symptoms that occur in more than half of all women during the week or two before menstruation. Although these symptoms may cause significant distress and even some degree of functional impairment, by definition, they are not severe enough to result in significant disability.3 PMDD, however, represents the more severe end of the diagnostic spectrum of premenstrual syndromes and is characterized by mood symptoms that are sufficiently severe that they result in significant disruption of a woman’s normal level of functioning across family, social, and occupational domains. The degree of disability and impairment in quality of life reported by women with PMDD is very similar to what is reported by patients with other depressive or anxiety disorders (see Figure 1, which shows impairment in quality of life on the Quality of Life, Enjoyment, and Satisfaction scale). The DSM-IV diagnostic criteria for PMDD (Table 1) require a minimum of 5 symptoms that occur during the premenstrual phase of the cycle and stop at the onset of menses, or shortly thereafter. It should be emphasized that premenstrual worsening of an underlying depressive or anxiety disorder, which is common, does not qualify as a diagnosis of PMDD.

The requirement that the premenstrual symptoms significantly interfere with functioning is the most effective way to diagnostically determine that PMDD is present. In addition, it is helpful to obtain a quantitative index of the most common presenting symptoms. These data are summarized in Figure 2 and come from women diagnosed with PMDD who were entering a treatment study.22 As can be seen, irritable, tense, tired, sad, and hypersensitive feelings are common and are associated with mood

---

**Table 1. Diagnostic Criteria for Premenstrual Dysphoric Disorder**

<table>
<thead>
<tr>
<th>A. Presence of 5 of 11 depressive, anxiety, cognitive, or physical symptoms, with at least 1 of 4 specific symptoms* experienced in most of the menstrual cycles for the past year. The symptoms may begin a week before menses and must completely remit within a few days after the onset of menses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive, anxiety, cognitive, and physical symptoms</td>
</tr>
<tr>
<td>*Markedly depressed mood, feelings of hopelessness, self-deprecation</td>
</tr>
<tr>
<td>*Suddently feeling sad or tearful, with increased sensitivity to personal rejection</td>
</tr>
<tr>
<td>Decreased interest in usual activities</td>
</tr>
<tr>
<td>Lethargy, fatigue, marked lack of energy</td>
</tr>
<tr>
<td>Marked changes in appetite and cravings for certain foods</td>
</tr>
<tr>
<td>Insomnia or hypersomnia</td>
</tr>
<tr>
<td>*Marked anxiety, tension, feeling of being “keyed up” or “on edge”</td>
</tr>
<tr>
<td>*Persistent or marked irritability, anger, increased interpersonal conflicts</td>
</tr>
<tr>
<td>Feeling overwhelmed or out of control</td>
</tr>
<tr>
<td>Subjective sense of having difficulty concentrating</td>
</tr>
<tr>
<td>Breast tenderness or swelling</td>
</tr>
<tr>
<td>Headaches</td>
</tr>
<tr>
<td>Joint or muscle pain</td>
</tr>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>“Bloated” feeling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Symptoms interfere with social, occupational, sexual, or school functioning.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. Symptoms are discretely related to menstrual cycle and are not merely worsening of preexisting depression, anxiety, or personality disorder.</td>
</tr>
<tr>
<td>D. Criteria A, B, and C must be confirmed prospectively by daily ratings for at least 2 consecutive menstrual cycles.</td>
</tr>
</tbody>
</table>

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*Adapted from Rapaport et al.¹⁰² Quality of life was assessed using the Quality of Life, Enjoyment, and Satisfaction scale (Q-LES-Q). Abbreviations: PMDD = premenstrual dysphoric disorder, PTSD = posttraumatic stress disorder.

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*Adapted with permission from the American Psychiatric Association.²¹
swings and high levels of interpersonal conflict. A cardinal diagnostic feature of PMDD is the marked difference in the frequency of moderate-to-severe symptoms during the follicular versus luteal phases. In fact, the frequency of each of the symptoms shown in Figure 2 was below 2% in the follicular phase (reference 22 and data on file, Pfizer Inc, New York, N.Y.).

Because of the large number of symptoms that occur in the diagnosis of PMDD, it is helpful to have women complete, prospectively, a daily record of the frequency and severity of PMDD symptoms throughout their menstrual cycle. However, a 1-time screening test is typically more feasible in clinical practice and can be followed by daily symptom ratings when the woman indicates a positive score on this screening form that may be self-administered by the patient. Table 2 shows an example of a 1-time screening form that may be self-administered by the patient. The diagnostic and treatment steps that may be taken if a patient has a positive score on this screening form are discussed in a later section.

DIFFERENTIAL DIAGNOSIS OF PMDD

Establishing the diagnosis of PMDD can be difficult because the disorder has such a wide and variable range of symptoms (see Table 1 for the DSM-IV criteria) and because there are no confirmatory laboratory tests or signs on physical examination. There is no consensus agreement on how comprehensive the medical and laboratory screening should be before the diagnosis can be made. It should be noted that women with PMDD almost always have normal levels of ovarian hormones.

There is little available research that empirically establishes clinical features that might increase the likelihood that a PMDD diagnosis is present, though some studies suggest that PMDD is more likely to occur in patients with a family history that is positive for either PMDD or major depression.

Perhaps the most crucial factor in establishing the diagnosis of PMDD is making sure that the patient is not presenting with another underlying medical or psychiatric diagnosis that is simply showing a premenstrual exacerbation in symptoms. For example, more than 50% of patients suffering from major depression report a clear-cut premenstrual exacerbation in their depressive symptoms. However, the presence of another medical or psychiatric disorder does not preclude the diagnosis of PMDD if the PMDD symptoms are distinct from the other disorder.

Table 3 summarizes the medical and psychiatric conditions that most frequently present with premenstrual exacerbation, or whose symptoms mimic some of the typical symptoms of PMDD. As a rule, these disorders should be

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Table 2. Screening Test for Premenstrual Dysphoric Disorder (PMDD): Patient Version

<table>
<thead>
<tr>
<th>Symptom Description</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anger/Irritability</td>
<td>76</td>
</tr>
<tr>
<td>Anxious/Tense</td>
<td>71</td>
</tr>
<tr>
<td>Tired/Lethargic</td>
<td>58</td>
</tr>
<tr>
<td>Mood swings</td>
<td>58</td>
</tr>
<tr>
<td>Sad/Depressed</td>
<td>54</td>
</tr>
<tr>
<td>Interpersonal conflicts</td>
<td>54</td>
</tr>
<tr>
<td>Bloating/Breast swelling</td>
<td>49</td>
</tr>
<tr>
<td>Less interest in activities</td>
<td>47</td>
</tr>
<tr>
<td>Sensitive to rejection</td>
<td>43</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>43</td>
</tr>
</tbody>
</table>

---

Table 2. Top 10 Luteal Phase Symptoms Reported by Women Diagnosed With Premenstrual Dysphoric Disorder

- Weight gain
- Feeling “bloating”
- Mood swings
- Sensitive to rejection
- Increased headaches
- Mood swings
- Anxious/Tense
- Poor concentration
- Mood swings
- Anxious/Tense
Changes in gonadal steroids that occur during the luteal phase appear to amplify underlying serotonergic dysregulation. The underlying PMDD vulnerability appears to have a strong genetic component. It should be noted that, while major depression and PMDD share environmental and genetic risk factors, the correlation between the 2 diagnoses appears (based on current evidence) to be surprisingly weak. Many of the typical symptoms of PMDD, most notably irritability and impulse dyscontrol, depressed mood, and carbohydrate craving, have been linked to serotonergic dysfunction. As will be discussed in a subsequent section, serotonergic antidepressants have shown significant efficacy in the treatment of PMDD, while antidepressants that act primarily by noradrenergic mechanisms have not shown efficacy. This is persuasive evidence that improvement in PMDD is not simply due to a nonspecific antidepressant effect, but rather to potent activity targeting the serotonergic system.

**TREATMENT**

### Current Nonpharmacologic and Over-the-Counter Treatments

Table 4 summarizes commonly used nonpharmacologic strategies for managing PMDD. They should generally be suggested for patients with less severe variants of PMS. Few have been evaluated in controlled studies, and scientific evidence of their effectiveness for PMDD is lacking. Cognitive therapy, therapy with bright full-spectrum lights, and relaxation therapy all show promise based on positive pilot studies, but again, definitive studies are not available at this time.

Table 5 briefly summarizes miscellaneous agents that have been studied for the treatment of PMDD, many of them over-the-counter (OTC) treatments. Again, some treatments such as calcium, magnesium, vitamin E, and nonsteroidal anti-inflammatory drugs show promise based on preliminary studies in PMS.

Should nonpharmacologic or OTC management be the initial recommendation for all women who present with PMDD? This question is controversial, but a reasonable answer is “not usually.” A woman who meets the criteria for a diagnosis of PMDD has indicated that her symptoms are severe and persistent enough to cause disability. To recommend OTC or other nonpharmacologic treatment as the primary treatment may be interpreted by the woman with PMDD as minimizing her symptoms, which are not serious enough to warrant “real” treatment. A nonpharmacologic treatment may be offered as an option (properly qualified as lacking scientific evidence of efficacy) with the aim of changing to pharmacologic treatment if there is no significant improvement within 1 or 2 menstrual cycles. Nonpharmacologic treatments such as stress reduction techniques and cognitive therapies may also be

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*Table 3: Differential Diagnosis of Premenstrual Dysphoric Disorder (PMDD)*

The following underlying psychiatric or medical disorders may present with a pattern of premenstrual exacerbation that mimics the monthly pattern of PMDD

**Psychiatric disorders**
- Major depression
- Dysthmic disorder
- Bipolar II
- Cyclothymic disorder
- Panic disorder or generalized anxiety disorder
- Bulimia
- Posttraumatic stress disorder
- Psychosocial: current victim of physical abuse or history of sexual abuse

**Medical disorders**
- Endocrine disorders such as hypothyroidism or diabetes
- Autoimmune or collagen vascular disorders
- Anemia
- Chronic fatigue syndrome
- Endometriosis

From Endicott.27

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PATHOPHYSIOLOGY

The precise etiology of PMDD is currently unknown. It is unlikely that the illness is due to a “hormonal imbalance” per se. Despite multiple studies, no consistent alterations in gonadal steroids have been identified in PMDD. Instead, it appears that normal cyclical changes in sex hormones serve as a trigger.

Why are some women vulnerable to this cyclical hormonal trigger and others are not? The current predominant hypothesis is that women who develop PMDD have an underlying vulnerability in central nervous system neurotransmitter systems, most notably the serotonergic system.
helpful in conjunction with medication, but again, there is no scientific information on adjunctive therapies for PMDD at this time.

**Anovulatory Treatments and Gonadal Steroids**

Symptoms of PMDD may remit if ovulation is suppressed. The various treatments that have been employed to achieve an anovulatory state are summarized in Table 6. The adverse events associated with gonadotropin-releasing hormone (GnRH) agonist therapy, together with the fact that chronically low estrogen levels increase the risk of both cardiovascular illness and osteoporosis, make this a third-line treatment for PMDD. Attempts to reduce the long-term risk of GnRH agonist treatments by estrogen add-back therapy have been reported in several very small studies, but whether the very low doses of add-back therapy abolish the positive therapeutic effect remains unclear. The synthetic estrogen danazol achieves the same anovulatory effect as leuprolide, but is associated with the same long-term risks.

Suppression of ovulation has also been achieved by various other methods including oral contraceptives and estradiol implants. In general, oral contraceptives (especially new, lower-dose formulations) have not been carefully studied in comparably large, well-designed trials. One novel approach involves use of a spironolactone-like progestin with antiandrogenic and anti-mineralocorticoid activity, which may reduce PMDD symptoms, though confirmatory study is needed. Evidence from a large, placebo-controlled study, as well as a recent meta-analysis, suggests that micronized progesterone has no efficacy in the treatment of PMDD.

**Anxiolytics**

There is evidence that alprazolam, taken during the luteal phase, may have efficacy in the treatment of PMDD in doses of 0.25 mg b.i.d. up to 0.5 mg t.i.d. (anxiolytics and antidepressants used for the treatment of PMDD are briefly summarized in Table 7). Evidence of efficacy, though, is mixed, with some studies showing no beneficial effect on mood, possibly because of differences in dosing and/or patient groups studied. One study provides experimental evidence that alprazolam might increase food cravings and caloric intake in some women. Modest efficacy, coupled with its mild cognitive and memory-imparing effects and its potential for physical dependence and withdrawal, makes this drug a second-line treatment for PMDD. One recent study observed no withdrawal symptoms when intermittent luteal dosing was used.

Buspirone has been proposed as a treatment option for PMDD based on its serotonergic mechanism of action. Pilot studies suggest possible efficacy, but the benefit of buspirone in PMDD remains unconfirmed. Buspirone has a more favorable cognitive and psychomotor profile than alprazolam, but the need for b.i.d. or t.i.d. administration makes its use less convenient. Buspirone should be considered a second-line treatment.

**Antidepressants**

Fluoxetine has shown efficacy in the treatment of PMDD based on 3 large double-blind, placebo-controlled trials and a series of small double-blind pilot studies. The first large trial examined the efficacy of 2 doses of fluoxetine (20 mg and 60 mg) administered on a daily basis throughout the menstrual cycle. Both doses were significantly superior to placebo in reducing symptoms of tension, irritability, and dysphoria. However, the 60-mg dose was not tolerated well enough to be a useful treatment. The dose of 20 mg is much better tolerated and is considered a second-line treatment for PMDD. One recent study observed no withdrawal symptoms when intermittent luteal dosing was used.

Buspirone has been proposed as a treatment option for PMDD based on its serotonergic mechanism of action. Pilot studies suggest possible efficacy, but the benefit of buspirone in PMDD remains unconfirmed. Buspirone has a more favorable cognitive and psychomotor profile than alprazolam, but the need for b.i.d. or t.i.d. administration makes its use less convenient. Buspirone should be considered a second-line treatment.

### Table 4. Nonpharmacologic Management of Premenstrual Dysphoric Disorder

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce consumption of:</td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td>A</td>
</tr>
<tr>
<td>Salt</td>
<td>A</td>
</tr>
<tr>
<td>Chocolate and refined sugars</td>
<td>A</td>
</tr>
<tr>
<td>Alcohol (may alter serotonergic function and increase anger/irritability)</td>
<td>A</td>
</tr>
<tr>
<td>Increase consumption of:</td>
<td></td>
</tr>
<tr>
<td>Complex carbohydrates (small meals)</td>
<td>A</td>
</tr>
<tr>
<td>Increase exercise:</td>
<td></td>
</tr>
<tr>
<td>Daily aerobic (moderate)</td>
<td>A</td>
</tr>
<tr>
<td>Other methods:</td>
<td></td>
</tr>
<tr>
<td>Relaxation and stress reduction techniques (massage, reflexology)</td>
<td>A</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>A</td>
</tr>
<tr>
<td>Marital counseling</td>
<td>A</td>
</tr>
<tr>
<td>Light therapy (bright, full-spectrum lights)</td>
<td>A</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>A</td>
</tr>
<tr>
<td>Sleep deprivation</td>
<td>A</td>
</tr>
</tbody>
</table>

*From Pearlstein and Steiner,* *Blake et al.*, and *Lam et al.*

### Table 5. Miscellaneous Treatments of Premenstrual Dysphoric Disorder

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary supplements</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₆: 100–200 mg daily</td>
<td>B</td>
</tr>
<tr>
<td>Calcium: 1000–1200 mg daily</td>
<td>B</td>
</tr>
<tr>
<td>Magnesium: 200 or 360 mg daily, starting 14 days before next menses</td>
<td>B</td>
</tr>
<tr>
<td>Vitamin E: 400–800 IU daily</td>
<td>C</td>
</tr>
<tr>
<td>OTC analgesics (naproxen, mefenamic acid, etc)</td>
<td>C</td>
</tr>
</tbody>
</table>

*Data from Pearlstein and Steiner,* *Thys-Jacobs et al.*, *De Souza et al.*, and *Facchinetti et al.* A = ≥ 2 adequately powered positive randomized controlled trials, B = limited or conflicting data, and C = insufficient data.

Abbreviation: OTC = over-the-counter.
90-mg dose may be attributable to its administration on premenstrual day 7.

Fluoxetine has been studied using an intermittent dosing strategy in 1 pilot study \(^{56}\) and in a recently published large trial.\(^ {77}\) The intermittent dosing strategy administered fluoxetine in the symptomatic premenstrual phase only, i.e., the luteal phase of the menstrual cycle, starting on day 14 and continuing to the menstrual flow. The appeal of luteal-phase dosing is that women may reduce by 50% or more their monthly exposure to drug. Whether the long elimination half-life of fluoxetine (4–6 days) and its active metabolite (norfluoxetine, 4–16 days) reduces the benefit of premenstrual dosing, compared with selective serotonin reuptake inhibitors (SSRIs) with shorter half-lives, has not been evaluated in controlled trials.

Irrespective of dosing strategy, fluoxetine has shown broad efficacy in the treatment of the full array of PMDD symptoms, including improvement in physical symptoms\(^ {78}\) and in ability to function during the late luteal phase of the cycle. The 20-mg dose of fluoxetine should be considered a first-line treatment for PMDD. Currently, it is marketed under the brand name Sarafem to commercially distinguish it from Prozac.

### Table 6. Pharmacotherapy Options for Treatment of Premenstrual Dysphoric Disorder (PMDD): Gonadal Steroids

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Proposed Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolide, buserelin, goserelin, nafarelin</td>
<td>Depot injections monthly (or intranasal Rx) lead to down-regulation of GnRH receptors in hypothalamus, which leads to lower FSH and LH, which lowers estrogen and progesterone. GnRH agonist: e.g., leuprolide, buserelin, goserelin, nafarelin</td>
<td>Chronic low estrogen levels increase risk of osteoporosis. Not effective with comorbid depression</td>
</tr>
<tr>
<td>GnRH agonist plus estrogen/progesterone add-back therapy</td>
<td>Estrogen/progesterone added to counter the risks of low estrogen</td>
<td>Lessens hypoestrogenic symptoms</td>
</tr>
<tr>
<td>Danazol</td>
<td>Synthetic estrogen with mixed evidence for efficacy. Efficacy appears linked to anovulation</td>
<td>Side effects include weight gain, acne, facial hair, nausea</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Hypothesized mechanism is by means of barbiturate-like metabolites such as allopregnanolone. Administered as micronized progesterone to increase bioavailability</td>
<td>Efficacy not demonstrated in meta-analysis of 14 placebo-controlled trials.(^ {55})</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Anovulation; progestin effect on endometrium</td>
<td>No consistent scientific evidence of efficacy for PMDD; may worsen PMDD symptoms. Improves dysmenorrhea; less bleeding. Continuous use of oral contraceptives may reduce some symptoms</td>
</tr>
</tbody>
</table>

\( ^{a}\)From references 49 through 58.
Abbreviations: FSH = follicle-stimulating hormone, GnRH = gonadotropin-releasing hormone, LH = luteinizing hormone.

### Table 7. Pharmacotherapy Options for Treatment of Premenstrual Dysphoric Disorder

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dosage</th>
<th>Dosing Strategy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>20 mg once daily</td>
<td>Continuous, Luteal</td>
<td>Demonstrated efficacy. Long half-life a consideration if rapid clearance is required</td>
</tr>
<tr>
<td></td>
<td>90 mg enteric-coated</td>
<td>Luteal (day 14 and day 7 only)</td>
<td>Evidence of efficacy found for 2 weekly doses in luteal phase</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50–150 mg once daily</td>
<td>Continuous, Luteal</td>
<td>Demonstrated efficacy for continuous and luteal-phase dosing</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20–30 mg once daily</td>
<td>Continuous, Luteal</td>
<td>Demonstrated efficacy</td>
</tr>
<tr>
<td>Citalopram</td>
<td>10–20 mg once daily</td>
<td>Continuous</td>
<td>Preliminary evidence of efficacy</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>25–50 mg once daily</td>
<td>Continuous</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>50–200 mg twice daily</td>
<td>Continuous</td>
<td>Demonstrated efficacy for continuous dosing</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.25–1.0 mg tid</td>
<td>Luteal</td>
<td>Conflicting evidence of efficacy. Risk of dependence and withdrawal, which may be reduced by strict luteal-phase dosing</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5–10 mg tid</td>
<td>Luteal</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>25 mg gid</td>
<td>Luteal</td>
<td>Conflicting evidence of efficacy</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>1.25–2.5 mg daily or bid</td>
<td>Luteal</td>
<td>High risk of side effects</td>
</tr>
<tr>
<td>Tibolone</td>
<td>2.5 mg daily</td>
<td>Luteal</td>
<td>Synthetic steroid (specific estrogen receptor modulator); limited evidence of efficacy</td>
</tr>
</tbody>
</table>

\( ^{a}\)Data from references 59–86 and references 99–101.
Another medication that is a first-line treatment of PMDD is sertraline, which has demonstrated efficacy across all the major symptom clusters of PMDD, including depression, anger/irritability, appetite and food cravings, concentration and memory effects, and physical symptoms. Improvement in PMDD symptoms has been shown, within the first cycle, to lead to significant improvement in both psychosocial functioning and quality of life.79

The benefit of intermittent luteal-phase (premenstrual) dosing has been shown in several pilot studies,80–83 and in 1 large placebo-controlled study.84 Premenstrual dosing is typically initiated approximately 14 days prior to the anticipated onset of menstrual bleeding, though data from 1 controlled study suggest that initiating treatment at the time of symptom onset may be just as effective.85 Sertraline is a significantly effective treatment of PMDD, using both continuous dosing (with a dosage range of 50–150 mg) and premenstrual dosing (with a dosage range of 50–100 mg). Sertraline is very well tolerated using both dosing strategies. Cross-study comparisons (requiring confirmation in head-to-head comparisons of alternative dosing strategies) suggest that adverse events are notably lower when luteal-phase dosing is employed, with 3 of 4 patients reporting no side effects whatsoever, and the remaining patients reporting side effects that were mostly mild and transient.84,85 Finally, it should be noted that an analysis of symptoms in the first 3 days after stopping sertraline found that abrupt discontinuation did not result in withdrawal symptoms.86

General Principles of Treatment

The effective dosage range for treatment of PMDD with fluoxetine and sertraline appears to be somewhat lower than the doses used in other psychiatric disorders such as major depression or obsessive-compulsive disorder. Many clinicians initiate fluoxetine treatment at 10 mg and sertraline at 25 mg. For sertraline, there is evidence from a large crossover study85 that the 25-mg dose is as effective in treating the PMS/PMDD spectrum as the 50-mg dose, using either a continuous or a premenstrual dosing strategy. A distinctive feature of PMDD treatment with both drugs is the rapid response, which is within 2 to 3 days in the majority of patients.81–84 It is this rapid response that makes intermittent premenstrual dosing an effective treatment strategy.

The decision as to which dosing strategy to choose for a patient presenting with PMDD must be individualized. Certainly if PMDD is complicated by another comorbid depressive or anxiety disorder, then continuous dosing is indicated. Similarly, if the duration of PMDD symptoms is highly variable, then continuous dosing may also be indicated. In most patients presenting with only PMDD, intermittent premenstrual dosing is highly effective, very well tolerated, and is likely to be the treatment of choice.

There are insufficient data yet available to guide physicians as to what is the appropriate duration of treatment in women whose PMDD has successfully responded to a course of fluoxetine or sertraline. Preliminary studies of sertraline and fluoxetine87,88 suggest that treatment response is maintained over the long-term, but relapse prevention studies have not been reported for either continuous or premenstrual dosing. It seems reasonable at this point to recommend occasional 1- or 2-cycle treatment “holidays” to permit reassessment of the ongoing need for treatment. Premenstrual dosing would appear to lend itself particularly well to this empirical approach.

Other SSRIs

Effectiveness for PMS or PMDD is reported for other SSRIs (e.g., citalopram,89,90 paroxetine,42,95 fluvoxamine91) and serotonergic antidepressants (nefazodone67,93,94 clozapine85), although the availability of data from large, placebo-controlled trials is currently limited. To date, fluoxetine and sertraline are the only SSRIs with U.S. Food and Drug Administration (FDA) approval for the treatment of PMDD.

Finally, a recently published report96 has found venlafaxine to have significant efficacy in the treatment of PMDD, based on a large, placebo-controlled trial. This study was conducted with twice-daily dosing in the range of 50 to 200 mg. An extended-release formulation of venlafaxine is now available, but there are no data on its use for the treatment of PMDD.

SSRIs and Pregnancy

All SSRI antidepressants carry an FDA pregnancy category C rating (systematic studies in pregnant women and/or animals are not available; drugs should be given only if the potential benefits justify the potential risks to the fetus.). No evidence to date suggests that SSRIs are associated with fetal risk, but insufficient prospective, well-controlled data are available to provide more definitive guidelines on this issue.97 Since approximately 50% of pregnancies are unintended,98 women beginning treatment should be counseled about possible risks and encouraged to discontinue treatment immediately on discovery that they may be pregnant.

CONCLUSION

Over the past decade, PMDD has been established as a menstrual-related disorder associated with moderate-to-marked disability. The pathophysiology of PMDD, involving cyclical changes in gonadal steroids interacting with underlying serotonergic dysregulation, is beginning to be elucidated. The advent of operationalized criteria for PMDD and the recent completion of several large controlled trials have, for the first time, provided physicians with highly effective treatment options.
Drug names: alprazolam (Xanax and others), bromocriptine (Parlodel and others), buspirone (BuSpar and others), citalopram (Celexa), clomipramine (Anafranil and others), danazol (DanoCrine and others), fluoxetine (Sarafem and others), fluvoxamine (Luvox and others), goserelin (Zoladex), leuprolide (Lupron, Eligard, and others), mafenamic acid (Ponstel), nafarelin (Synarel), naproxen (Anaprox, Napsyn, and others), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), sirmipronato (Aldactone and others), venlafaxine (Effexor).

REFERENCES

22. Halbreich U, Bergeron R, Yokners KA, et al. Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder [poster]. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology; Dec 10–14, 2000; San Juan, Puerto Rico
23. Deuster PA, Adera T, South-Paul J. Biological, social, and behavioral factors associated with premenstrual syndrome. Arch Fam Med 1999;8:122–128
86. Pearlstein T, Gillespie JA. When should premenstrual dosing in PMDD end? [poster]. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa

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1. Impairment in quality of life with premenstrual dysphoric disorder (PMDD) is:
   a. Minimal
   b. Seldom a clinical issue
   c. Similar to that of other major physical and emotional disorders
   d. Nonresponsive to treatment

2. The diagnosis of PMDD relies on the patient’s daily symptom reports.
   a. True
   b. False

3. Which of these disorders does not mimic the pattern of PMDD?
   a. Hypothyroidism
   b. Diabetes
   c. Major depression
   d. Heart disease

4. The treatment that is least likely to be effective for PMDD is:
   a. Sertraline
   b. Progesterone
   c. Alprazolam
   d. Leuprolide

5. In studies of luteal phase dosing with selective serotonin reuptake inhibitors (SSRIs) for PMDD, response is generally:
   a. No different than with placebo
   b. Slow, requiring several months of treatment
   c. Significantly better than with continuous dosing
   d. Significantly better than with placebo

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