

# Premenstrual Symptoms

NEW STRATEGIES  
FOR PATIENT  
MANAGEMENT

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CME/CE Audio Program  
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**NEEDS STATEMENT:**

Most American women experience at least some symptoms during the late luteal phase of their cycle. As many as 25 million US women may experience symptoms bothersome enough to qualify as premenstrual syndrome (PMS), while an estimated 2-5 million meet the criteria for premenstrual dysphoric disorder (PMDD), the most severe type of premenstrual disorder. Although many approaches have been used to ease premenstrual symptoms, three selective serotonin reuptake inhibitors are currently the only agents with a Food and Drug Administration (FDA) indication for PMDD. There is growing interest in finding other treatment options for women who do not want to take antidepressant medications or do not find them effective. Recent research has shown that a new low-dose oral contraceptive formulation containing the novel progestin drospirenone administered over 24 days in a 28-day cycle is effective in reducing the symptoms of PMDD. Clinicians and other healthcare professionals who counsel women need to be familiar with the research supporting the benefits of this formulation for women with PMDD who also need contraception.

**INTENDED AUDIENCE:**

This program has been developed for gynecologists, nurse practitioners, and other physicians treating women with premenstrual symptoms and for other health professionals counseling these patients.

**PROGRAM GOAL:**

This program provides information about the treatment of PMDD, including research showing the benefits of a new oral contraceptive formulation for women with these symptoms.

**LEARNING OBJECTIVES:**

Upon completion of this program, the participants should be able to:

- Discuss the prevalence of premenstrual symptoms and their impact on a woman's life.
- Describe the different treatment options available for premenstrual symptoms, including benefits and risks.
- Explain the rationale for using oral contraceptives to reduce premenstrual symptoms.
- Discuss the rationale for using an extended oral contraceptive regimen in women experiencing symptoms during the late luteal phase of the cycle.
- Describe the design and discuss the outcome of the parallel study that assessed the use of an extended regimen of drospirenone 3 mg plus ethinyl estradiol 20 mcg in women with PMDD.

**ACCREDITATION STATEMENT:**

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Dannemiller Memorial Educational Foundation and MedPro Communications, Inc. The Dannemiller Memorial Educational Foundation is accredited by the ACCME to provide continuing medical education for physicians.

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This program has been approved for 1.0 contact hour of continuing education (which includes 0.7 hour of pharmacology) by the American Academy of Nurse Practitioners. Program ID 0510446.

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**Dr. Kimberly A. Yonkers** discloses that she receives research funding from GlaxoSmithKline Pharmaceuticals and Wyeth-Ayerst Laboratories. She also serves as an advisor and/or consultant for Wyeth-Ayerst Laboratories.

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# Premenstrual Symptoms: New Strategies for Patient Management

Premenstrual disorders affect millions of American women during their reproductive years. The term “premenstrual disorders” refers to mood, somatic, and behavioral symptoms that occur during the late luteal phase of the cycle and disappear soon after the onset of menses. Premenstrual syndrome (PMS) refers to premenstrual symptoms that are bothersome and negatively impact a woman’s quality of life. Premenstrual dysphoric disorder (PMDD) is the severest form of premenstrual disorder, which results in significant impairment. It is estimated that from 20–40% of reproductive-age US women have PMS, and an estimated 3–8% meet the criteria for PMDD.<sup>1</sup>

## **Etiology of Premenstrual Symptoms**

Premenstrual symptoms are multifactorial. These symptoms appear to be due to problems in the interaction between processes of the central nervous system (CNS), gonadal hormones, and other modulators, including neurotransmitters, in ovulatory women. Women with a genetic vulnerability may experience symptoms when the brain and pituitary respond abnormally to normal cyclic fluctuations of gonadal hormones.<sup>2</sup> For example, the opposing effects of estrogen and progesterone on the renin-angiotensin-aldosterone system (RAAS) affect fluid balance. The bothersome fluid retention, bloating, and breast tenderness that can occur in the late luteal phase of women with a premenstrual disorder are the result of an altered response to normal fluctuations in these hormones.<sup>3</sup>

## **Diagnosis of Premenstrual Disorders**

In 2000 the American College of Obstetricians and Gynecologists (ACOG) published a practice bulletin addressing PMS.<sup>4</sup> The practice bulletin included diagnostic criteria for PMS, as adapted from Mortola and

colleagues.<sup>5</sup> In order to be diagnosed with PMS, a woman must have experienced one or more of the bothersome symptoms in **Table 1** during the 5 days prior to menses in each of 3 previous menstrual cycles; the symptoms must occur reproducibly during 2 cycles of prospective recording. The symptoms must have been relieved within 4 days of the onset of menses and must not recur until at least cycle day 13. The symptoms must also occur in the absence of any pharmacologic therapy, hormone ingestion, or drug or alcohol use and must result in identifiable dysfunction in social or economic performance.<sup>4</sup>

**Table 1. Symptoms Used in the Diagnosis of PMS**

Affective Symptoms	Somatic Symptoms
<ul style="list-style-type: none"> <li>• Irritability</li> <li>• Depressed Mood</li> <li>• Angry outbursts</li> <li>• Anxiety</li> <li>• Confusion</li> <li>• Social withdrawal</li> </ul>	<ul style="list-style-type: none"> <li>• Breast tenderness</li> <li>• Abdominal bloating</li> <li>• Headache</li> <li>• Swelling of extremities</li> </ul>

PMS = Premenstrual Syndrome.

ACOG Practice Bulletin. *Obstet Gynecol* 2000;95: end of issue 4.<sup>4</sup>

The American Psychiatric Association established the following diagnostic criteria for PMDD. Five or more of the symptoms in **Table 2**, including at least one core symptom, must occur during the last week of the luteal phase in most menstrual cycles in the previous year. The symptoms must be relieved within a few days of starting menses and must not recur during the week following menses.<sup>6</sup>

**Table 2. Symptoms Used in the Diagnosis of PMDD**

<b>Core Symptoms</b>
<ul style="list-style-type: none"><li>• Markedly depressed mood, feelings of hopelessness, or self-depreciating thoughts</li><li>• Marked anxiety, tension, feelings of being “keyed up” or “on edge”</li><li>• Marked affective lability, eg, feeling suddenly sad or tearful, or increased sensitivity to rejection</li><li>• Persistent and marked anger or irritability or increased interpersonal conflicts</li></ul>
<b>Other Symptoms</b>
<ul style="list-style-type: none"><li>• A decreased interest in usual activities, eg, work, school, friends, hobbies</li><li>• A subjective sense of difficulty in concentrating</li><li>• Lethargy, easy fatigability, or a marked lack of energy</li><li>• A marked change in appetite, overeating, or cravings for specific foods</li><li>• Hypersomnia or insomnia</li><li>• A subjective sense of being overwhelmed or out of control</li><li>• Physical symptoms, eg, headaches, breast tenderness and/or swelling, joint and/or muscle pain, a sensation of “bloating,” and weight gain</li></ul>

PMDD = Premenstrual Dysphoric Disorder.

*Premenstrual dysphoric disorder.* In: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Washington, DC: American Psychiatric Association, 2000: 771–774.<sup>6</sup>

In addition, the symptoms need to be severe enough to interfere with work, school, or usual activities and must not represent an exacerbation of another disorder (eg, major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder). For a diagnosis of PMDD, the criteria must

be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles.<sup>5</sup>

Clinicians may wish to design their own daily symptom diaries or develop a diary based on the symptoms most often reported by an individual patient. Some clinically validated diaries commonly used to record premenstrual symptoms are shown in **Table 3**. The Daily Record of Severity of Problems is available on-line at [www.pmdd.factsforhealth.org/have/dailyrecord.html](http://www.pmdd.factsforhealth.org/have/dailyrecord.html).

### **Table 3. Validated Tools for Diagnosing PMS and PMDD**

- Daily Record of Severity of Problems (DRSP)<sup>a</sup>
- Premenstrual Symptoms Screening Tool (PSST)<sup>b</sup>
- Premenstrual Symptom Diary<sup>c</sup>
- Prospective Record of the Impact and Severity of Menstrual Symptomatology (PRISM)<sup>d</sup>
- Calendar of Premenstrual Experiences (COPE)<sup>e,f</sup>
- Visual Analogue Scale (VAS)<sup>g</sup>

PMS = Premenstrual Syndrome; PMDD = Premenstrual Dysphoric Disorder.

<sup>a</sup>Endicott J, et al. *Arch Women Ment Health* 2005, Sept 20 [Epub ahead of print].<sup>7</sup>

<sup>b</sup>Steiner M, et al. *Arch Women Ment Health* 2003;6: 203–209.<sup>8</sup>

<sup>c</sup>Thys-Jacobs S, et al. *Psychopharmacol Bull* 1995;31: 389–396.<sup>9</sup>

<sup>d</sup>Reid RL. *Curr Probl Obstet Gynecol Fertil* 1985;8: 1–57.<sup>10</sup>

<sup>e</sup>Feuerstein M, Shaw WS. *J Reprod Med* 2002;47: 279–289.<sup>11</sup>

<sup>f</sup>Mortola JF, et al. *Obstet Gynecol* 1990;76: 302–307.<sup>12</sup>

<sup>g</sup>Steiner M, et al. *J Affect Disord* 1999;53: 269–273.<sup>13</sup>

### **Treatment of Premenstrual Disorders**

A wide variety of treatments for premenstrual symptoms have been used for a number of years. Currently, the primary approaches to treating premenstrual disorders include lifestyle changes, cognitive-behavioral therapy, and pharmacotherapy.

### ***Lifestyle Changes***

Regular aerobic exercise may ease premenstrual symptoms in many women.<sup>14</sup> One possible explanation is that endorphins normally decline in the late luteal phase of the menstrual cycle, potentially contributing to premenstrual symptoms in some women; aerobic exercise results in the release of endorphins in the CNS.<sup>1</sup> The most recent recommendation is that people perform at least 30 minutes per day of moderate-intensity physical activity on most, preferably all, days of the week.<sup>15</sup> Limited research suggests that calcium supplementation may be effective in reducing premenstrual symptoms in some women.<sup>16</sup> According to the ACOG Practice Bulletin on PMS, vitamin E, vitamin B<sub>6</sub>, and evening primrose oil have not been shown to be effective in treating premenstrual symptoms.<sup>4</sup>

### ***Cognitive-Behavioral Therapy***

Cognitive-behavioral therapy (CBT) is a short-term, structured therapy based on the theory that a person's mood and behavior are largely determined by the way he or she sees the world. An active collaboration between the patient and therapist is established in order to achieve therapeutic goals specifically oriented toward current problems and their solutions. This approach uses behavioral techniques that are designed to change maladaptive and inaccurate cognitions, or thoughts.<sup>17</sup> CBT has been shown to be more effective than no treatment in reducing premenstrual symptoms in several studies.<sup>18,19</sup> Hunter, et al conducted a study in women with PMDD to compare the efficacy of 10 sessions of CBT, fluoxetine 20 mg/day, and a combination of these therapies. Although all of the participants had significant improvement after 6 months of treatment, the women receiving fluoxetine had a more rapid improvement and experienced a greater effect on anxiety symptoms.<sup>20</sup>

## **Pharmacotherapy**

The agents often used to treat premenstrual symptoms include selective serotonin reuptake inhibitors (SSRIs), spironolactone, anxiolytic agents, gonadotropin-releasing hormone (GnRH) agonists, and oral contraceptives (OCs). With the exception of three SSRIs, all of these agents are used off-label for the treatment of PMDD.

### **Selective Serotonin Reuptake Inhibitors**

The only agents that currently have a US Food and Drug Administration (FDA) indication for the treatment of PMDD are fluoxetine hydrochloride (Sarafem®),<sup>21</sup> sertraline hydrochloride (Zoloft®),<sup>22</sup> and paroxetine hydrochloride (Paxil®).<sup>23</sup> Although earlier studies assessed the efficacy of fluoxetine administered daily,<sup>24</sup> later research has indicated that it is also effective when taken intermittently.<sup>25</sup> The recommended dose of fluoxetine in patients with PMDD is 20 mg either administered daily or only during the luteal phase of the cycle (ie, 14 days prior to the expected onset of menses). In addition, Miner, et al found that women with PMDD taking two doses of enteric-coated fluoxetine 90 mg during the luteal phase of the cycle—on days 7 and 14 prior to the expected onset of menses—had significant improvements in their premenstrual symptoms.<sup>26</sup>

Sertraline has also been shown to decrease symptoms of PMDD when taken daily<sup>27</sup> or during the luteal phase of the cycle.<sup>28</sup> Treatment of PMDD should be initiated with a dose of 50 mg of sertraline, either administered daily or only during the luteal phase. The daily dose of sertraline can be increased to 100 mg/day for intermittent treatment and 150 mg/day for continuous use throughout the cycle.<sup>22</sup> The recommended daily dose of paroxetine is either 12.5 mg or 25 mg taken throughout the menstrual cycle or only during the luteal phase.<sup>23</sup> Cohen, et al found that although both doses of paroxetine improved mood symptoms in women with PMDD, the larger dose (ie, 25 mg/day) was required to significantly reduce physical symptoms.<sup>29</sup>

Some primary care physicians and their patients are hesitant about using antidepressant agents for PMDD. Common side effects include nausea, insomnia, decreased libido, sedation, weight gain, and anxiety.<sup>30</sup> In one study of women using either tricyclic antidepressants or SSRIs, almost half had discontinued within 1 year, and more than 60% had discontinued at the end of 2 years.<sup>31</sup>

### ***Spironolactone***

Spironolactone is the only diuretic that has been shown to be effective in treating premenstrual symptoms.<sup>4</sup> In addition to decreasing somatic symptoms, as might be expected, spironolactone has also been shown to decrease negative symptoms and increase positive symptoms.<sup>32</sup> The usual dose of spironolactone ranges from 50 to 100 mg/day.<sup>1</sup>

### ***Anxiolytic Agents and Gonadotropin-Releasing Hormone Agonists***

These agents are seldom used to treat premenstrual disorders unless the symptoms are severe and the woman has not responded to other treatment. Studies of the anxiolytic agent alprazolam have had mixed results. Evans, et al found that alprazolam did not improve negative mood in the luteal phase, but increased food intake in the luteal phase and negative mood in the follicular phase.<sup>33,34</sup> The ACOG practice bulletin noted that GnRH agonists have been shown to be effective in reducing PMS symptoms in most studies; however, this approach is both expensive and results in hypoestrogenic side effects. The possibility of bone loss while using a GnRH agonist necessitates either add-back estrogen therapy, which may lead to the return of symptoms, or other therapy for osteoporosis prevention.<sup>4</sup>

### ***Oral Contraceptives***

Since ovulation is a prerequisite for premenstrual symptoms, it would seem logical to assume that using OCs to suppress ovulation would also

decrease symptoms during the luteal phase. Nevertheless, early studies did not support the efficacy of OCs in reducing premenstrual symptoms.<sup>35,36</sup> In a study of 658 women using OCs, almost three-fourths (71.4%) of the group reported no effect, 16.3% reported deterioration, and only 12.3% reported improvement in premenstrual mood.<sup>37</sup>

One exception has been an OC containing the novel progestin drospirenone 3 mg and ethinyl estradiol 30 mcg (drospirenone/30EE, Yasmin®). Other progestins in US OCs are derived from 19-nortestosterone; however, drospirenone is derived from 17 $\alpha$ -spiro lactone and is an analogue of spironolactone.<sup>38</sup> Drospirenone resembles progesterone in that it has both antimineralocorticoid and antiandrogenic activity. Drospirenone counteracts estrogen's effect on RAAS to increase sodium and water excretion.<sup>39</sup> A number of studies have shown that drospirenone/30EE is effective in reducing premenstrual symptoms.<sup>40-45</sup>

One issue that complicates assessing the efficacy of OCs in treating premenstrual symptoms is that of hormone withdrawal. Strictly speaking, no anovulatory women have premenstrual symptoms. However, women using OCs administered using the standard regimen (ie, 21 days of active treatment followed by 7 hormone-free days, or 21/7) have been shown to have greatly increased symptoms during the hormone-free interval compared with the 21 days of active hormone use.<sup>46</sup> Most patients are unlikely to distinguish between premenstrual symptoms in the week prior to menses and hormone-withdrawal symptoms prior to the monthly bleed while using OCs. Therefore, there is increasing interest in extending the number of active pills taken by women using current low-dose OCs to prevent follicular development and reduce hormone withdrawal symptoms that may occur with the 21/7 regimen.

## **A New Treatment Approach**

A new low-dose formulation has been developed that contains drospirenone 3 mg plus EE 20 mcg and is administered for 24 days, followed by 4 hormone-free days, ie, a 24/4 regimen (drospirenone/20EE-24/4). This investigational formulation is under review at the FDA. Two recent randomized, placebo-controlled studies in women with a diagnosis of PMDD have shown that this formulation is effective in reducing not only somatic symptoms, but also mood and behavioral symptoms.<sup>47,48</sup> In these studies, drospirenone/20EE-24/4 had a response rate (based on a rating of “much improved” or “very much improved” on the Clinical Global Impression-Improvement scale) similar to that for both continuous and intermittent sertraline.<sup>27,28</sup>

## **Conclusion**

Premenstrual disorders affect the quality of life of millions of US women. The recent establishment of diagnostic criteria for PMS and PMDD has allowed controlled research to assess the efficacy of treatment options. Currently, three SSRIs are the only agents with an FDA indication for the treatment of PMDD. The unique pharmacologic profile of drospirenone has led to the use of a product containing this progestin in women with PMS or PMDD. A new low-dose formulation containing drospirenone that is administered using a 24/4 regimen has been shown to be effective in reducing mood, somatic, and behavioral symptoms of PMDD for women who also need contraception.

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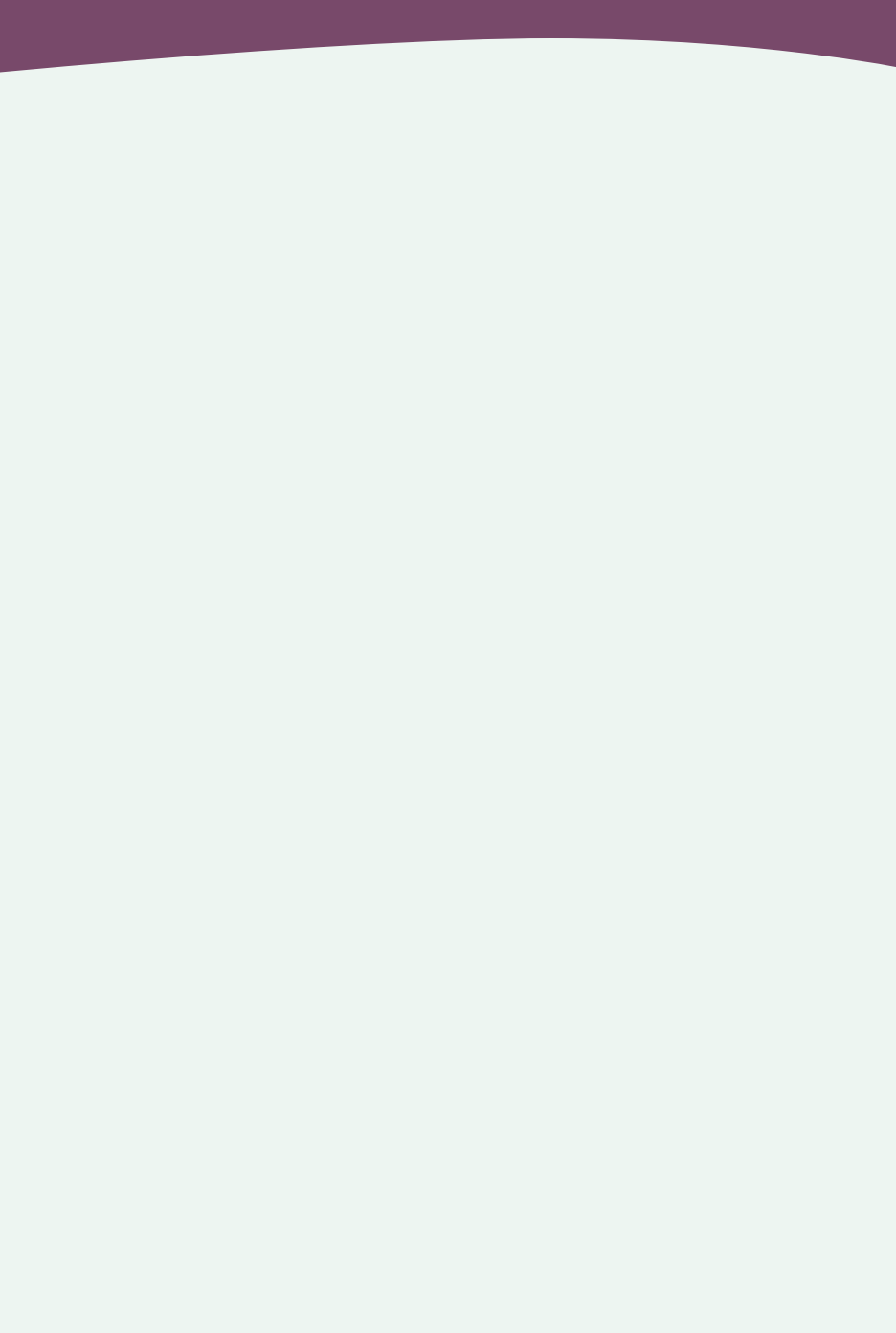
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