

## Premenstrual dysphoric disorder: How to alleviate her suffering



© IMAGES.COM/CORBIS

### **Laura Wakil, MD**

Third-Year Psychiatry Resident

### **Samantha Meltzer-Brody, MD, MPH**

Director, Perinatal Psychiatry Program  
University of North Carolina Center for Women's  
Mood Disorders

### **Susan Girdler, PhD**

Director, UNC Stress and Health Research Program  
Menstrually Related Mood Disorders Program  
University of North Carolina Center for Women's  
Mood Disorders

••••

Department of Psychiatry  
University of North Carolina at Chapel Hill  
Chapel Hill, NC

### Accurate diagnosis, tailored treatments can greatly improve women's quality of life

Approximately 75% of women experience a premenstrual change in emotional or physical symptoms commonly referred to as premenstrual syndrome (PMS). These symptoms—including increased irritability, tension, depressed mood, and somatic complaints such as breast tenderness and bloating—often are mild to moderate and cause minimal distress.<sup>1</sup> However, approximately 3% to 9% of women experience moderate to severe premenstrual mood symptoms that meet criteria for premenstrual dysphoric disorder (PMDD).<sup>2</sup>

PMDD includes depressed or labile mood, anxiety, irritability, anger, insomnia, difficulty concentrating, and other symptoms that occur exclusively during the 2 weeks before menses and cause significant deterioration in daily functioning. Women with PMDD use general and mental health services more often than women without the condition.<sup>3</sup> They may experience impairment in marital and parental relationships as severe as that experienced by women with recurrent or chronic major depression.<sup>2</sup>

PMDD often responds to treatment. Unfortunately, many women with PMDD do not seek treatment, and up to 90% may go undiagnosed.<sup>4</sup> In this article, we review the prevalence, etiology, diagnosis, and treatment of PMDD.

### **A complex disorder**

A distinguishing characteristic of PMDD is the timing of symptom onset. In women with PMDD, mood symptoms occur only during the luteal phase of the menstrual cycle (ovulation until onset of menses) and resolve after menstruation onset. Women with PMDD report normal mood and function-

## DSM-IV-TR research criteria for PMDD

- A. In most menstrual cycles of the past year,  $\geq 5$  of the following symptoms must be present for most of the time during the last week of the luteal phase, begin to remit within a few days after the onset of the follicular phase, and are absent in the week postmenses, with  $\geq 1$  of the symptoms being either 1, 2, 3, or 4:
1. Markedly depressed mood, feelings of hopeless, or self-deprecating thoughts
  2. Marked anxiety, tension, feelings of being “keyed up” or “on edge”
  3. Marked affectivity lability
  4. Persistent and marked anger or irritability or increased interpersonal conflicts
  5. Decreased interest in usual activities
  6. Subjective sense of difficulty concentrating
  7. Lethargy, easy fatigability, or marked lack of energy
  8. Marked changes in appetite, overeating, or specific food cravings
  9. Hypersomnia or insomnia
  10. A subjective sense of being overwhelmed or out of control
  11. Physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of “bloating,” weight gain
- B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (eg, avoidance of social activities, decreased productivity and efficiency at work or school)
- C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders)
- D. Criteria A, B, and C must be confirmed by prospective daily ratings during  $\geq 2$  consecutive symptomatic cycles (The diagnosis may be made provisionally prior to this confirmation)

Source: Reference 6

ing during the follicular phase of the menstrual cycle (first day of the menstrual cycle until ovulation).

Although PMS and PMDD criteria share affective and somatic symptoms, more symptoms are required for a PMDD diagnosis, and symptoms often are more severe.<sup>5</sup> As defined in DSM-IV-TR (Table),<sup>6</sup> PMDD has a broader range of symptoms than PMS and includes symptoms not included in the American College of Obstetrics and Gynecology criteria for PMS,<sup>7</sup> such as impaired concentration, appetite, and sleep (hypersomnia or insomnia); and mood lability. PMDD symptoms must occur only during the 2 weeks preceding menses, although on average symptoms last 6 days and severity usually peaks in the 2 days before menses.<sup>1</sup> The prevalence of subthreshold PMDD is fairly common; approximately 19% of women will meet some—but not all—DSM-IV-TR criteria for PMDD.<sup>3</sup>

In a revision proposed for DSM-5, PMDD would be included as a mood disorder,

which represents a significant change from DSM-IV-TR, where it is listed in the appendix as “research criteria.”<sup>8</sup> In addition, in oral contraceptive users, a PMDD diagnosis should not be made unless the premenstrual symptoms are reported to be present and as severe when the woman is not taking the oral contraceptive.<sup>8</sup>

### Comorbidity with other axis I disorders

such as major depressive disorder (MDD), bipolar disorder (BD), and anxiety disorders is high.<sup>9-11</sup> Women with an MDD history have the highest correlation with PMDD,<sup>9</sup> and worsening premenstrual mood symptoms are more common in women with BD.<sup>12</sup> Payne et al<sup>11</sup> found that premenstrual symptoms were reported by twice as many women diagnosed with mood disorders (68%) than women without a psychiatric diagnosis (34%). Moreover, 38% to 46% of women with PMDD have comorbid seasonal affective disorder, and 11% to 38% report a comorbid anxiety disorder.<sup>12</sup> Women with

### Clinical Point

PMS and PMDD share symptoms, but more symptoms are required for a PMDD diagnosis, and symptoms often are more severe



Discuss this article at  
[www.facebook.com/CurrentPsychiatry](http://www.facebook.com/CurrentPsychiatry)



## Premenstrual dysphoric disorder

### Clinical Point

To help distinguish PMDD from PMS, patients need to keep a daily diary of symptoms for  $\geq 2$  months

See this article at

[CurrentPsychiatry.com](#)

for a discussion of the etiology of PMDD

### Box 1

## PMS or PMDD? Charting symptoms over menstrual cycles

To distinguish premenstrual syndrome (PMS) from premenstrual dysphoric disorder (PMDD), premenstrual exacerbation of an underlying psychiatric disorder, general medical conditions, or other disorders with no association to the menstrual cycle, it is necessary to have patients conduct daily symptom charting over 2 menstrual cycles. This charting should include documentation of emotional, behavioral, and physical symptoms. PMDD can be differentiated from PMS by the severity and number of symptoms. In PMDD, 1 of the symptoms must be a mood disturbance (depressed, anxious, labile, and/or irritable). For a sample form used for PMDD charting, the Daily Record of Severity of Problems, see [http://pmdd.factsforhealth.org/drsp/drsp\\_month.pdf](http://pmdd.factsforhealth.org/drsp/drsp_month.pdf).

PMDD and a history of MDD have lower cortisol concentrations than non-PMDD women.<sup>10</sup> Although interventions for PMDD and a comorbid axis I disorder may be similar, it is important to consider both when planning treatment.

**Abuse, trauma, and PMDD.** An association between PMS/PMDD and a history of sexual and physical abuse is well-documented.<sup>13</sup> Studies have reported abuse histories among almost 60% of women with PMDD,<sup>14</sup> although studies comparing abuse and trauma in PMDD vs non-PMDD women have been small. A recent study found that trauma and posttraumatic stress disorder are independently associated with PMDD and premenstrual symptoms.<sup>15</sup>

Evidence suggests that a history of abuse is associated with specific biological sequelae in PMDD women, particularly with respect to hypothalamic-pituitary-thyroid axis measures and noradrenergic activity.<sup>16-18</sup> Women with PMDD and a history of sexual abuse show:

- markedly elevated triiodothyronine (T3) concentrations (the more biologically potent thyroid hormone) that appear to result from increased conversion of thyroxine (T4) to T3<sup>16</sup>
- lower circulating plasma norepinephrine concentrations<sup>17</sup>

- greater resting and stress-induced heart rates and systolic blood pressure compared with non-abused PMDD women, an effect that is eliminated by clonidine (an  $\alpha$ -2 adrenergic receptor agonist).<sup>18</sup>

One study showed that PMDD women with abuse histories had higher blood pressure measurements at rest and during stress and exhibited greater vascular tone than non-abused women; these effects were not seen in non-PMDD women with similar abuse histories.<sup>14</sup> This body of evidence is consistent with the concept that PMDD is a stress-related disorder,<sup>19</sup> and that a history of abuse is prevalent and may identify a clinically distinct subgroup of PMDD women with respect to thyroid axis and adrenergic physiology. Screening PMDD patients for abuse histories may help manage the disorder.

For a discussion of the etiology of PMDD, see this article at [CurrentPsychiatry.com](#).

## Mood charting aids diagnosis

A PMDD diagnosis requires prospective daily monitoring of symptoms for  $\geq 2$  consecutive months. Because only 25% to 35% of women who present with PMDD meet diagnostic criteria when prospective daily monitoring is used,<sup>20</sup> it is important for patients to keep a daily diary of PMDD symptoms to distinguish the disorder from PMS (**Box 1**). The Prospective Record of the Impact and Severity of Premenstrual Symptoms calendar and the Daily Record of Severity of Problems (DRSPP)<sup>21</sup> may help make the diagnosis.

The widely used DRSPP allows clinicians to quantify the severity of physical, emotional, and behavioral symptoms and may be the easiest to use in clinical practice because it creates a graphic representation of cyclical symptom changes. The DRSPP includes all PMDD symptoms and severity ratings<sup>21</sup> and is recognized as a valid instrument for diagnosing PMDD. Another option is a revised visual analogue scale. Lastly, a new revised Premenstrual Tension Syndrome (PMTS) rating scale, which combines the PMTS Observer rating scale plus multiple visual analogue scales, shows promise as a tool to assess PMDD symptoms.



## Premenstrual dysphoric disorder

### Clinical Point

Several hormonal interventions may effectively treat PMDD, but none are considered practical

### Treatment options

**Hormonal interventions.** Attempts to treat PMS with progesterone during the luteal phase have been largely unsuccessful, although progesterone is approved to treat PMS in the United Kingdom. Long-acting gonadotropin-releasing hormone (GnRH) agonists are effective but result in medical menopause with its accompanying symptoms, which puts women at risk for osteoporosis.<sup>22</sup> Approximately 60% to 70% of women with PMDD respond to leuprolide (a GnRH agonist), but it is difficult to predict who will respond; daily mood self-ratings of sadness, anxiety, and irritability predict a positive response to leuprolide with high probability.<sup>23</sup> Side effects of GnRH agonists (hot flashes, night sweats, vaginal dryness, etc.) can be tempered by “adding back” some estrogen with a hormonal agent with progestational activity to reduce the risks of unopposed estrogen (ie, endometrial hyperplasia).<sup>24</sup>

Surgical bilateral oophorectomy is effective but extremely invasive, especially in younger women in whom removal of ovaries generally is inadvisable. Patients should receive a trial of a GnRH agonist before a surgical intervention, because oophorectomy may not reduce symptoms and is irreversible. Oophorectomy also would require hormone replacement therapy.

High-dose estrogen as transdermal patches or subcutaneous implants to inhibit ovulation is effective, but because of the risks of unopposed estrogen, a progestin would be needed. Risks of estrogen therapy (alone and in combination with progestins) include increased risk of endometrial cancer, coronary heart disease, breast cancer, stroke, and pulmonary embolism.<sup>25</sup> Danazol, a synthetic androgen and gonadotropin inhibitor, effectively blocks ovulation, but side effects include hirsutism and possible teratogenicity.<sup>26</sup> Although these hormonal manipulations may effectively treat PMDD, none are considered practical.

The use of combined oral contraceptives (estrogen and progestin) is common. Although continuous cycle oral contraceptives often are recommended for PMDD, limited evidence supports their use; studies have been mostly negative.<sup>27,28</sup> A recent

review of 4 studies of a continuous oral contraceptive (levonorgestrel 90 mcg/ethinyl estradiol 20 mcg) for PMDD and PMS had more promising results, although the results were highly variable among studies and a large placebo effect was observed.<sup>29</sup>

A combination oral contraceptive, drospirenone/ethinyl estradiol, is FDA-approved for treating PMDD in women seeking hormonal contraception because it has shown efficacy compared with placebo, with reported improvements in perceived productivity, social activities, and interpersonal relationships.<sup>30</sup> The nature of hormone delivery (ie, a reduction in the pill-free interval from 7 to 4 days) in drospirenone/ethinyl estradiol may contribute to its efficacy because a reduced pill-free interval minimizes the degree of follicular recruitment and subsequent estrogen production and cyclicity seen with standard oral contraceptive.<sup>31</sup>

**Antidepressants** have been shown to effectively ameliorate affective and physical symptoms and improve quality of life and psychosocial function in patients with PMS and PMDD. The response rates for selective serotonin reuptake inhibitors (SSRIs) in PMDD treatment vary from 60% to 90%, vs 30% to 40% for placebo.<sup>32</sup> A 2009 Cochrane review found SSRIs reduced premenstrual symptoms compared with placebo.<sup>33</sup> However, a literature review suggested that the percentage of women with PMDD who respond to SSRIs or continuous oral contraceptives is lower than the percentage of women who do not respond at all, once the placebo effect is taken into account, and that approximately 40% of women with PMDD do not respond to SSRIs.<sup>34</sup> A small study found that citalopram may be effective for women with PMDD who did not respond to a prior SSRI.<sup>35</sup>

However, only antidepressants that affect serotonergic—not noradrenergic—transmission are effective in PMDD.<sup>22</sup> These include:

- the tricyclic antidepressant clomipramine
- the SSRIs citalopram, escitalopram, fluoxetine, paroxetine, and sertraline
- the serotonin-noradrenergic reuptake inhibitor venlafaxine.

See this article at

[CurrentPsychiatry.com](http://CurrentPsychiatry.com)

for a bibliography of studies that support using antidepressants to treat PMDD

Box 2

## Beyond hormones and antidepressants: Other treatments for PMDD

Two reviews of 10 randomized controlled trials (RCTs) that evaluated 62 herbs, vitamins, and mineral treatments for premenstrual symptoms found efficacy for chasteberry (*Vitex agnus-castus*), calcium, and vitamin B6 but not for primrose oil, magnesium oxide, or St. John's wort.<sup>a,b</sup> A study comparing fluoxetine with chasteberry found a similar percentage of patients responded to either agent (68% vs 58%, respectively).<sup>c</sup> Another study showed calcium resulted in a 48% reduction in premenstrual symptoms from baseline, compared with a 30% reduction with placebo.<sup>d</sup> Bright light treatment significantly reduced depression

ratings in women with premenstrual dysphoric disorder (PMDD).<sup>e</sup> Compared with placebo, the aldosterone antagonist spironolactone improved irritability, depression, feelings of swelling, breast tenderness, and food craving in women with premenstrual syndrome (PMS).<sup>f</sup>

A recent systematic review of 7 trials of cognitive-behavioral therapy (CBT) for PMDD, including 3 RCTs, showed a lack of a statistically significant effect.<sup>g</sup> However, a separate review of RCTs of alternative treatments for PMDD—5 of which included CBT—suggested that CBT may be beneficial in reducing premenstrual symptoms, but the evidence was low quality.<sup>h</sup>

Source: For reference citations, see this article at CurrentPsychiatry.com

For a bibliography of studies that support using antidepressants to treat PMDD, see this article at CurrentPsychiatry.com.

It appears that in PMDD, serotonergic agents play a role other than their antidepressant effect.<sup>36</sup> The effect of these agents is rapid in PMS/PMDD; women with PMDD who take antidepressants often

experience reduced symptoms within the first menstrual cycle, whereas in MDD the onset of action can take weeks or months.<sup>37</sup>

Although why onset of antidepressant action is quick in PMDD is unclear, rapid onset allows for several dosing options. Some women prefer continuous dosing throughout the month because they do not have to keep

### Clinical Point

Approximately 60% to 90% of women with PMDD respond to selective serotonin reuptake inhibitors

NOW AVAILABLE!

## The CURRENT PSYCHIATRY app

Access all of CURRENT PSYCHIATRY's peer-reviewed, practical information via your iPhone or iPad, including:

- Evidence-Based Reviews
- Clinical News
- Multimedia
- Interactive Case Studies
- Digital Editions



Available free from the iTunes App Store!





## Premenstrual dysphoric disorder

### Clinical Point

For treating PMDD, only antidepressants that affect serotonergic transmission are effective

track of ovulation. Dosing antidepressants only in the luteal phase (taking the antidepressant from ovulation onset to the start of menses) is an effective treatment strategy.<sup>38</sup> Many women prefer to take medication for only 2 weeks per month, which can decrease side effects and lower treatment costs. Alternatively, symptom-onset dosing—initiating the antidepressant when PMDD symptoms begin and stopping at menses onset or within 3 days thereafter—has shown promising results.<sup>39,40</sup> Paroxetine, sertraline, and fluoxetine are FDA-approved for PMDD as continuous or intermittent regimens, although using fluoxetine intermittently may not make sense because its biologically active metabolite has an extended half-life.<sup>37</sup>

**Other treatments.** Dietary interventions, psychotherapy, vitamins, bright light treatment, and spironolactone have been assessed for PMS/PMDD, although for many evidence-based findings are lacking (*Box 2, page 31*).

### Treatment selection

To enhance compliance and improve the likelihood of successful treatment, tailor treatment decisions to your patient's needs. Carefully discuss with your patient the evidence-based literature to select the best option for her. Factors to consider when counseling patients include:

- the patient's age, cigarette smoking habits, and body mass index, which may contraindicate oral contraceptives
  - does the patient have regular cycle lengths?
  - can she adhere to an on-off schedule?
- If so, intermittent SSRI dosing may be a good treatment option
- does the patient have irregular cycles?
  - is there evidence that symptoms persist into the follicular phase, albeit at a lower level? If so, continuous SSRI dosing may be the best option.

### References

1. Yonkers KA, O'Brien PM, Eriksson E. Premenstrual syndrome. *Lancet*. 2008;371(9619):1200-1210.
2. Halbreich U, Borenstein J, Pearlstein T, et al. The prevalence, impairment, impact and burden of premenstrual dysphoric disorder (PMS/PMDD). *Psychoneuroendocrinology*. 2008; 28(suppl 3):1-23.

3. Wittchen HU, Becker E, Lieb R, et al. Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. *Psychol Med*. 2002;32(1):119-132.
4. Hylan TR, Sundell K, Judge R. The impact of premenstrual symptomatology on functioning and treatment-seeking behavior: experience from the United States, United Kingdom, and France. *J Womens Health Gen Based Med*. 1999;8(8):1043-1052.
5. Biggs WS, Demuth RH. Premenstrual syndrome and premenstrual dysphoric disorder. *Am Fam Physician*. 2011;84(8):918-924.
6. Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
7. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 15, April 2000. Premenstrual syndrome. *Obstet Gynecol*. 2000;95:1-9.
8. American Psychiatric Association. Proposed draft revisions to DSM disorders and criteria. DSM-5 development. <http://www.dsm5.org/proposedrevision/Pages/Default.aspx>. Accessed February 23, 2012.
9. Yonkers KA. The association between premenstrual dysphoric disorder and other mood disorders. *J Clin Psychiatry*. 1997;58(suppl 15):19-25.
10. Klatzkin RR, Lindgren ME, Forneris CA, et al. Histories of major depression and premenstrual dysphoric disorder: evidence for phenotypic differences. *Biol Psychol*. 2010; 84(2):235-247.
11. Payne JL, Roy PS, Murphy-Eberenz K, et al. Reproductive cycle-associated mood symptoms in women with major depression and bipolar disorder. *J Affect Disord*. 2007;99(1-3):221-229.
12. Kim DR, Gyulai L, Freeman EW, et al. Premenstrual dysphoric disorder and psychiatric co-morbidity. *Arch Womens Ment Health*. 2004;7(1):37-47.
13. Golding JM, Taylor DL, Menard L, et al. Prevalence of sexual abuse history in a sample of women seeking treatment for premenstrual syndrome. *J Psychosom Obstet Gynaecol*. 2000;21(2):69-80.
14. Girdler SS, Leserman J, Bunevicius R, et al. Persistent alterations in biological profiles in women with abuse histories: influence of premenstrual dysphoric disorder. *Health Psychol*. 2007;26(2):201-213.
15. Pilver CE, Levy BR, Libby DJ, et al. Posttraumatic stress disorder and trauma characteristics are correlates of premenstrual dysphoric disorder. *Arch Womens Ment Health*. 2011;14(5):383-393.
16. Girdler SS, Thompson KS, Light KC, et al. Historical sexual abuse and current thyroid axis profiles in women with premenstrual dysphoric disorder. *Psychosom Med*. 2004;66(3):403-410.
17. Girdler SS, Sherwood A, Hinderliter AL, et al. Biological correlates of abuse in women with premenstrual dysphoric disorder and healthy controls. *Psychosom Med*. 2003;65(5):849-856.
18. Bunevicius R, Hinderliter AL, Light KC, et al. Histories of sexual abuse are associated with differential effects of clonidine on autonomic function in women with premenstrual dysphoric disorder. *Biol Psychol*. 2005; 69(3):281-296.
19. Perkonig A, Yonkers KA, Pfister H, et al. Risk factors for premenstrual dysphoric disorder in a community sample of young women: the role of traumatic events and posttraumatic stress disorder. *J Clin Psychiatry*. 2004; 65(10):1314-1322.
20. Girdler SS, Pedersen CA, Stern RA, et al. Menstrual cycle and premenstrual syndrome: modifiers of cardiovascular reactivity in women. *Health Psychol*. 1993;12(3): 180-192.
21. Endicott J, Nee J, Harrison W. Daily Record of Severity of Problems (DRSP): reliability and validity. *Arch Womens Ment Health*. 2006;9(1):41-49.
22. Cunningham J, Yonkers KA, O'Brien S, et al. Update on research and treatment of premenstrual dysphoric disorder. *Harv Rev Psychiatry*. 2009;17(2):120-137.
23. Pincus SM, Alam S, Rubinow DR, et al. Predicting response to leuprolide of women with premenstrual dysphoric disorder by daily mood rating dynamics. *J Psychiatr Res*. 2011;45(3):386-394.

24. Wyatt KM, Dimmock PW, Ismail KM, et al. The effectiveness of GnRHα with and without ‘add-back’ therapy in treating premenstrual syndrome: a meta analysis. *BJOG*. 2004; 111(6):585-593.
25. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.
26. Hahn PM, Van Vugt DA, Reid RL. A randomized, placebo-controlled, crossover trial of danazol for the treatment of premenstrual syndrome. *Psychoneuroendocrinology*. 1995; 20(2):193-209.
27. Bancroft J, Rennie D. The impact of oral contraceptives on the experience of perimenstrual mood, clumsiness, food craving and other symptoms. *J Psychosom Res*. 1993;37(2):195-202.
28. Graham CA, Sherwin BB. A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. *J Psychosom Res*. 1992;36(3):257-266.
29. Freeman EW, Halbreich U, Grubb GS, et al. An overview of four studies of a continuous oral contraceptive (levonorgestrel 90 mcg/ethinyl estradiol 20 mcg) on premenstrual dysphoric disorder and premenstrual syndrome [published online ahead of print December 5, 2011]. *Contraception*. doi: 10.1016/j.contraception.2011.09.010.
30. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. *Cochrane Database Syst Rev*. 2009; (2):CD006586.
31. Sullivan H, Furniss H, Spona J, et al. Effect of 21-day and 24-day oral contraceptive regimens containing gestodene (60 microg) and ethinyl estradiol (15 microg) on ovarian activity. *Fertil Steril*. 1999;72(1):115-120.
32. Yonkers KA, Clark RH, Trivedi MH. The psychopharmacological treatment of nonmajor mood disorders. *Mod Probl Pharmacopsychiatry*. 1997;25:146-166.
33. Brown J, O’Brien PM, Marjoribanks J, et al. Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst Rev*. 2009;(2):CD001396.
34. Halbreich U. Selective serotonin reuptake inhibitors and initial oral contraceptives for the treatment of PMDD: effective but not enough. *CNS Spectr*. 2008;13(7):566-572.
35. Freeman EW, Jabara S, Sondheimer SJ, et al. Citalopram in PMS patients with prior SSRI treatment failure: a preliminary study. *J Womens Health Gend Based Med*. 2002;11(5): 459-464.

## Related Resource

• American Psychiatric Association. DSM-5 development: D 04 Premenstrual dysphoric disorder. [www.dsm5.org/proposedrevision/pages/proposedrevision.aspx?rid=484](http://www.dsm5.org/proposedrevision/pages/proposedrevision.aspx?rid=484).

### Drug Brand Names

Citalopram • Celexa	Leuprolide • Lupron
Clomipramine • Anafranil	Levonorgestrel/ethinyl
Clonidine • Catapres, others	estradiol • Seasonale, others
Danazol • Danocrine	Paroxetine • Paxil
Drospirenone/ethinyl	Progesterone • Prometrium
estradiol • Yaz	Sertraline • Zoloft
Escitalopram • Lexapro	Spironolactone • Aldactone
Fluoxetine • Prozac	Venlafaxine • Effexor

### Disclosures

Drs. Wakil and Girdler report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products

Dr. Meltzer-Brody receives research/grant support from AstraZeneca, The Foundation of Hope, and the National Institutes of Health.

36. Freeman EW, Rickels K, Sondheimer SJ, et al. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: a randomized controlled trial. *Arch Gen Psychiatry*. 1999;56(10):932-939.
37. Steiner M, Pearlstein T, Cohen LS, et al. Expert guidelines for the treatment of severe PMS, PMDD, and comorbidities: the role of SSRIs. *J Womens Health (Larchmt)*. 2006;15(1):57-69.
38. Freeman EW. Luteal phase administration of agents for the treatment of premenstrual dysphoric disorder. *CNS Drugs*. 2004;18(7):453-468.
39. Yonkers KA, Holthausen GA, Poschman K, et al. Symptom-onset treatment for women with premenstrual dysphoric disorder. *J Clin Psychopharmacol*. 2006;26(2):198-202.
40. Freeman EW, Sondheimer SJ, Sammel MD, et al. A preliminary study of luteal phase versus symptom-onset dosing with escitalopram for premenstrual dysphoric disorder. *J Clin Psychiatry*. 2005;66(6):769-773.

## Clinical Point

**A patient’s age, smoking status, menstrual cycle pattern, and other factors influence PMDD treatment selection**

## Bottom Line

Distinguishing premenstrual dysphoric disorder (PMDD) from premenstrual syndrome requires having patients complete prospective rating scales over ≥2 menstrual cycles. Antidepressants—particularly selective serotonin reuptake inhibitors—are a mainstay of treatment, but up to 50% of women do not respond. Hormonal and surgical interventions are less practical.

## References

- a. Dante G, Facchinetti F. Herbal treatments for alleviating premenstrual symptoms: a systematic review. *J Psychosom Obstet Gynaecol*. 2011;32(1):42-51.
- b. Whelan AM, Jurgens TM, Naylor H. Herbs, vitamins and minerals in the treatment of premenstrual syndrome: a systematic review. *Can J Clin Pharmacol*. 2009;16(3):e407-e429.
- c. Atmaca M, Kumru S, Tezcan E. Fluoxetine versus Vitex agnus castus extract in the treatment of premenstrual dysphoric disorder. *Hum Psychopharmacol*. 2003;18(3):191-195.
- d. Thys-Jacobs S, Starkey P, Bernstein D, et al. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. *Am J Obstet Gynecol*. 1998;179(2):444-452.
- e. Parry BL, Berga SL, Mostofi N, et al. Morning versus evening bright light treatment of late luteal phase dysphoric disorder. *Am J Psychiatry*. 1989;146(9):1215-1217.
- f. Wang M, Hammarbäck S, Lindhe BA, et al. Treatment of premenstrual syndrome by spironolactone: a double-blind, placebo-controlled study. *Acta Obstet Gynecol Scand*. 1995;74(10):803-808.
- g. Lustyk MK, Gerrish WG, Shaver S, et al. Cognitive-behavioral therapy for premenstrual syndrome and premenstrual dysphoric disorder: a systematic review. *Arch Womens Ment Health*. 2009;12(2):85-96.
- h. Busse JW, Montori VM, Krasnik C, et al. Psychological intervention for premenstrual syndrome: a meta-analysis of randomized controlled trials. *Psychother Psychosom*. 2009;78(1):6-15.





## Premenstrual dysphoric disorder

### Box 3

## Reproductive hormones in PMDD etiology

Although questions remain about the pathogenesis of premenstrual dysphoric disorder (PMDD), literature documents the role of gonadal steroids (estrogen and progesterone) in the etiology of premenstrual syndrome (PMS)/PMDD and suggests that women with PMDD are differentially sensitive to the normal physiologic fluctuations of gonadal hormones throughout the menstrual cycle.<sup>a</sup>

The first half of the menstrual cycle—the follicular phase—begins with increasing levels of follicular stimulating hormone (FSH) leading to maturity of the ovarian follicle. Once the follicle is ripe, the luteal phase of the menstrual cycle begins with a surge in luteinizing hormone (LH), which results in ovulation of the mature follicle, followed by increased secretion of progesterone, followed by increased estrogen secretion. The system is regulated via negative feedback, and high levels of progesterone decrease gonadotropin-releasing hormone (GnRH) pulse frequency, which leads to decreased secretion of FSH and LH, and subsequent decline of estrogen and progesterone. If the ovarian follicle is not fertilized, menstruation begins and FSH levels rise again, initiating the follicular phase of the menstrual cycle.

Fluctuations in reproductive steroid levels have been implicated in the etiology of PMDD from studies showing that oophorectomy and ovulation inhibitors (GnRH agonists) relieve symptoms.<sup>b</sup> Some researchers proposed that symptoms are related to the drop of progesterone in the late luteal phase; however, many women have symptoms that start at ovulation or during the early luteal phase before the fall in progesterone concentrations.<sup>c</sup> PMS symptoms may occur independently of the mid-to-late luteal phase.<sup>d</sup> Because production of gonadal steroids does not differ between women with or without PMS or PMDD,<sup>e</sup> it may be that follicular or periovulatory changes in levels of estradiol or progesterone secretion trigger symptoms of PMDD in susceptible women, while women without PMDD appear to be immune to these effects of gonadal steroids. This idea is supported by a study showing that pharmacologic induction of a hypogonadal state eliminates symptoms in most women with severe PMS, while “adding back”

estrogen or progesterone within the context of hypogonadism elicits return of PMS symptoms in those with PMS but not in controls.<sup>a</sup>

Abnormalities in serotonin levels also may contribute to PMDD.<sup>f</sup> In 1 study, a serotonin receptor antagonist precipitated return of symptoms within 24 hours of administration in women with PMDD but not in controls.<sup>g</sup> PMDD symptoms also can be evoked by depleting the serotonin precursor tryptophan.<sup>h</sup> When women with PMDD received paroxetine at different phases of their menstrual cycle, they showed fluctuations in serotonergic function across their cycles; these fluctuations were not seen in controls.<sup>i</sup> Other neurotransmitters implicated in PMDD include  $\gamma$ -aminobutyric acid (GABA),<sup>j</sup> glutamate,<sup>k</sup> lower levels of cortisol and beta-endorphins,<sup>l</sup> and an abnormal stress response.<sup>m</sup>

Other studies have focused on differing concentrations of luteal phase hormones<sup>n</sup> and gene associations. Two studies suggested that PMDD is heritable<sup>o,p</sup> and other studies have looked at the association between specific psychological traits that are more prominent in PMDD and single nucleotide polymorphisms in the estrogen receptor alpha gene.<sup>q,r</sup>

Thyroid hormones also may play a role in the etiology of PMS/PMDD. Thyroid function tests have shown greater variability in women with PMS vs controls,<sup>s</sup> although this variability appears to be limited to women with a sexual abuse history.<sup>t</sup> Other studies have evaluated hormones regulated across the circadian and sleep-wake cycles, including melatonin, cortisol, thyroid-stimulating hormone, and prolactin, which suggests that although levels of these hormones may not differ between women with PMDD and controls, the timing of their excretion may vary.<sup>u</sup> Additionally, women with PMDD are characterized by prefrontal brain asymmetry on electroencephalography that also is evident in patients with major depressive disorder.<sup>u</sup>

There also may be dysregulation of allopregnanolone (ALLO) in women with PMDD.<sup>v,w</sup> ALLO is a metabolite of progesterone that is a neurosteroid produced in the brain as well as in the ovary and adrenals.<sup>v</sup> It produces anxiolytic effects by acting as a modulator of GABA receptors.<sup>x</sup> In PMDD, ALLO levels may influence the severity of premenstrual symptoms.<sup>w</sup>

## References

- a. Schmidt PJ, Nieman LK, Danaceau MA, et al. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. *N Engl J Med*. 1998;338(4):209-216.
- b. Muse KN, Cetel NS, Futterman LA, et al. The premenstrual syndrome. Effects of "medical ovariectomy." *N Engl J Med*. 1984;311(21):1345-1349.
- c. Yonkers KA, O'Brien PM, Eriksson E. Premenstrual syndrome. *Lancet*. 2008;371(9619):1200-1210.
- d. Schmidt PJ, Nieman LK, Grover GN, et al. Lack of effect of induced menses on symptoms in women with premenstrual syndrome. *N Engl J Med*. 1991;324(17):1174-1179.
- e. Rubinow DR, Schmidt PJ. The neuroendocrinology of menstrual cycle mood disorders. *Ann N Y Acad Sci*. 1995;771:648-659.
- f. Steiner M, Pearlstein T. Premenstrual dysphoria and the serotonin system: pathophysiology and treatment. *J Clin Psychiatry*. 2000;61(suppl 12):17-21.
- g. Roca CA, Schmidt PJ, Smith MJ, et al. Effects of metergoline on symptoms in women with premenstrual dysphoric disorder. *Am J Psychiatry*. 2002;159(11):1876-1881.
- h. Menkes DB, Coates DC, Fawcett JP. Acute tryptophan depletion aggravates premenstrual syndrome. *J Affect Disord*. 1994;32(1):37-44.
- i. Inoue Y, Terao T, Iwata N, et al. Fluctuating serotonergic function in premenstrual dysphoric disorder and premenstrual syndrome: findings from neuroendocrine challenge tests. *Psychopharmacology (Berl)*. 2007;190(2):213-219.
- j. Epperson CN, Haga K, Mason GF, et al. Cortical gamma-aminobutyric acid levels across the menstrual cycle in healthy women and those with premenstrual dysphoric disorder: a proton magnetic resonance spectroscopy study. *Arch Gen Psychiatry*. 2002;59(9):851-858.
- k. Batra NA, Seres-Mailo J, Hanstock C, et al. Proton magnetic resonance spectroscopy measurement of brain glutamate levels in premenstrual dysphoric disorder. *Biol Psychiatry*. 2008;63(12):1178-1184.
- l. Straneva PA, Maixner W, Light KC, et al. Menstrual cycle, beta-endorphins, and pain sensitivity in premenstrual dysphoric disorder. *Health Psychol*. 2002;21(4):358-367.
- m. Epperson CN, Pittman B, Czarkowski KA, et al. Luteal-phase accentuation of acoustic startle response in women with premenstrual dysphoric disorder. *Neuropsychopharmacology*. 2007;32(10):2190-2198.
- n. Thys-Jacobs S, McMahon D, Bilezikian JP. Differences in free estradiol and sex hormone-binding globulin in women with and without premenstrual dysphoric disorder. *J Clin Endocrinol Metab*. 2008;93(1):96-102.
- o. Payne JL, Klein SR, Zamoiski RB, et al. Premenstrual mood symptoms: study of familiarity and personality correlates in mood disorder pedigrees. *Arch Womens Ment Health*. 2009;12(1):27-34.
- p. Kendler KS, Karkowski LM, Corey LA, et al. Longitudinal population-based twin study of retrospectively reported premenstrual symptoms and lifetime major depression. *Am J Psychiatry*. 1998;155(9):1234-1240.
- q. Miller A, Vo H, Huo L, et al. Estrogen receptor alpha (ESR-1) associations with psychological traits in women with PMDD and controls. *J Psychiatr Res*. 2010;44(12):788-794.
- r. Huo L, Straub RE, Roca C, et al. Risk for premenstrual dysphoric disorder is associated with genetic variation in ESR1, the estrogen receptor alpha gene. *Biol Psychiatry*. 2007;62(8):925-933.
- s. Girdler SS, Pedersen CA, Light KC. Thyroid axis function during the menstrual cycle in women with premenstrual syndrome. *Psychoneuroendocrinology*. 1995;20(4):395-403.
- t. Girdler SS, Thompson KS, Light KC, et al. Historical sexual abuse and current thyroid axis profiles in women with premenstrual dysphoric disorder. *Psychosom Med*. 2004;66(3):403-410.
- u. Accortt EE, Stewart JL, Coan JA, et al. Prefrontal brain asymmetry and pre-menstrual dysphoric disorder symptomatology. *J Affect Disord*. 2011;128(1-2):178-183.
- v. Paul SM, Purdy RH. Neuroactive steroids. *FASEB J*. 1992;6(6):2311-2322.
- w. Girdler SS, Straneva PA, Light KC, et al. Allopregnanolone levels and reactivity to mental stress in premenstrual dysphoric disorder. *Biol Psychiatry*. 2001;49(9):788-797.
- x. Brot MD, Akwa Y, Purdy RH, et al. The anxiolytic-like effects of the neurosteroid allopregnanolone: interactions with GABA(A) receptors. *Eur J Pharmacol*. 1997;325(1):1-7.



## Premenstrual dysphoric disorder

### Bibliography

## Evidence supporting antidepressants as treatment for PMDD

Cohen LS, Miner C, Brown EW, et al. Premenstrual daily fluoxetine for premenstrual dysphoric disorder: a placebo-controlled, clinical trial using computerized diaries. *Obstet Gynecol.* 2002;100(3):435-444.

Eriksson E, Ekman A, Sinclair S, et al. Escitalopram administered in the luteal phase exerts a marked and dose-dependent effect in premenstrual dysphoric disorder. *J Clin Psychopharmacol.* 2008;28(2):195-202.

Eriksson E, Hedberg MA, Andersch B, et al. The serotonin reuptake inhibitor paroxetine is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. *Neuropsychopharmacology.* 1995;12(2):167-176.

Menkes DB, Taghavi E, Mason PA, et al. Fluoxetine treatment of severe premenstrual syndrome. *BMJ.* 1992;305(6849):346-347.

Miner C, Brown E, McCray S, et al. Weekly luteal-phase dosing with enteric-coated fluoxetine 90 mg in premenstrual dysphoric disorder: a randomized, double-blind, placebo-controlled clinical trial. *Clin Ther.* 2002;24(3):417-433.

Ozere S, Corakçi A, Yücesoy I, et al. Fluoxetine in the treatment of premenstrual syndrome. *Eur J Obstet Gynecol Reprod Biol.* 1997;73(2):167-170.

Pearlstein TB, Stone AB, Lund SA, et al. Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. *J Clin Psychopharmacol.* 1997;17(4):261-266.

Ravindran LN, Woods SA, Steiner M, et al. Symptom-onset dosing with citalopram in the treatment of premenstrual dysphoric disorder (PMDD): a case series. *Arch Womens Ment Health.* 2007;10(3):125-127.

Steiner M, Brown E, Trzepacz P, et al. Fluoxetine improves functional work capacity in women with premenstrual dysphoric disorder. *Arch Womens Ment Health.* 2003;6(1):71-77.

Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of late luteal phase dysphoric disorder. *J Clin Psychiatry.* 1991;52(7):290-293.

Sundblad C, Hedberg MA, Eriksson E. Clomipramine administered during the luteal phase reduces the symptoms of premenstrual syndrome: a placebo-controlled trial. *Neuropsychopharmacology.* 1993;9(2):133-145.

Sundblad C, Modigh K, Andersch B, et al. Clomipramine effectively reduces premenstrual irritability and dysphoria: a placebo-controlled trial. *Acta Psychiatr Scand.* 1992;85(1):39-47.

Su TP, Schmidt PJ, Danaceau MA, et al. Fluoxetine in the treatment of premenstrual dysphoria. *Neuropsychopharmacology.* 1997;16(5):346-356.

Wikander I, Sundblad C, Andersch B, et al. Citalopram in premenstrual dysphoria: is intermittent treatment during luteal phases more effective than continuous medication throughout the menstrual cycle? *J Clin Psychopharmacol.* 1998;18(5):390-398.