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ONLINE EXCLUSIVE

Easing the burden of premenstrual dysphoric disorder

It's much less common than premenstrual syndrome, but it can have a severe impact on your patient's quality of life. Here's how to recognize it and alleviate the symptoms.

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PRACTICE RECOMMENDATIONS

› *Consider low doses of selective serotonin reuptake inhibitors such as fluoxetine, sertraline, or paroxetine as first-line therapy for premenstrual dysphoric disorder.* (A)

› *Consider other treatment options, including diet and lifestyle changes and hormonal therapy.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶ Carol J, 25, comes to your office and tells you that for the past year, she has been suffering from severe discomfort during her menstrual periods. She says that shortly before her period begins, she experiences headaches, breast tenderness, pain in her joints, and a "bloated feeling." She has trouble sleeping and feels irritable and "on edge." She is often too depressed or tired to go to work or go out with her friends. Although the symptoms go away within a few days after her period starts, Ms. J is miserable while they last and worried about the toll they are taking on her job and her relationships. How would you address Ms. J's complaints?

Premenstrual dysphoric disorder (PMDD), the most severe type of premenstrual syndrome (PMS), is a chronic debilitating condition characterized by a constellation of somatic and behavioral symptoms that cause significant functional impairment and greatly diminish quality of life.[1] Although PMDD has a prevalence of only 3% to 8%, compared with a prevalence as high as 75% for PMS, it carries a substantial health and economic burden.[1,2] Diagnosing and managing it can present a clinical challenge.[1]

The diagnostic criteria for PMDD outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), which classifies the condition as a depressive disorder not otherwise specified, help to differentiate PMDD from PMS.[3] The diagnosis requires regular occurrence of at least 5 of 11 mood and physical symptoms during the last week of the luteal phase of the menstrual cycle and remission of symptoms within 4 days of the onset of menses (**TABLE 1**).[3] One of the 5 symptoms must be a mood symptom: depression, anxiety, mood lability, or irritability.[4]

What causes PMDD?

Although the etiology of PMDD is unknown, neuroendocrine

TABLE 1

Research criteria for premenstrual dysphoric disorder

A. In most menstrual cycles during the past year, 5 (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week post-menses, with at least one of the symptoms being either 1, 2, 3, or 4:
1. markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. marked anxiety, tension, feelings of being "keyed up," or "on edge"
3. marked affective lability (eg, feeling suddenly sad or tearful or increased sensitivity to rejection)
4. persistent and marked anger or irritability or increased interpersonal conflicts
5. decreased interest in usual activities (eg, work, school, friends, hobbies)
6. subjective sense of difficulty in concentrating
7. lethargy, easy fatigability, or marked lack of energy
8. marked change in appetite, overeating, or specific food cravings
9. hypersomnia or insomnia
10. a subjective sense of being overwhelmed or out of control
11. other 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 at least 2 consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation).

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*. 4th ed. text revision. 2000.[3]

Symptoms must be severe enough to cause psychological impairment that interferes with relationships and the patient's work life.

and psychological factors have been implicated. Because PMDD is cyclical, the cyclic fluctuations of normal ovarian function, not hormonal imbalance, are thought to trigger PMDD-related biochemical events within the central nervous system and other target tissues.[5,6]

Serotonergic dysregulation. Women with PMDD have increased sensitivity to central nervous system neurotransmitters, including serotonin, which is downregulated by the cyclical change of the ovarian hormones estradiol and progesterone.[7,8] Several clinical studies have shown strong correlation between serotonergic dysfunction and PMDD based on the proven efficacy of selective serotonin reuptake inhibitors (SSRIs) in controlling symptoms. A randomized, double-blind, placebo-controlled trial conducted at 47 outpatient centers in the United States and Canada is one of many studies that implicate serotonergic downregulation by demonstrating that PMDD responds to the SSRI paroxetine.[9]

Gamma aminobutyric acid (GABA), the inhibitory neurotransmitter, also plays a role in PMDD. Low levels of GABA diminish its inhibitory effect, resulting in mood disorders. A small clinical trial comparing plasma GABA levels in healthy women and women with PMDD with and without major depression demonstrated this effect.[10] The study found that plasma GABA levels decreased from the midfollicular to the late luteal phase in women with PMDD, whereas they increased in healthy women; in women with PMDD and depression, GABA levels were low during both phases.

Allopregnanolone, a metabolite of progesterone, produces anxiolytic, antiseizure,

TABLE 2

Premenstrual Symptoms Screening Tool

Please mark an "X" in the appropriate box.

Do you experience some or any of the following premenstrual symptoms which start before your period and stop within a few days of bleeding?

Symptom	Not at all	Mild	Moderate	Severe
1. Anger/irritability				
2. Anxiety/tension				
3. Tearful/increased sensitivity to rejection				
4. Depressed mood/hopelessness				
5. Decreased interest in work activities				
6. Decreased interest in home activities				
7. Decreased interest in social activities				
8. Difficulty concentrating				
9. Fatigue/lack of energy				
10. Overeating/food cravings				
11. Insomnia				
12. Hypersomnia (needing more sleep)				
13. Feeling overwhelmed or out of control				
14. Physical sypmptoms: breast tenderness, headaches, joint/muscle pain, bloating, weight gain				

Have your symptoms, as listed above, interfered with:

	Not at all	Mild	Moderate	Severe
A. Your work efficiency or productivity				
B. Your relationships with co-workers				
C. Your relationships with your family				
D. Your social life activities				
E. Your home responsibilities				

Scoring: The following criteria must be present for a diagnosis of premenstrual dysphoric disorder:

At least 1 of items 1-4 must be severe

At least 4 of items 1-14 must be moderate to severe

At least 1 of items A-E must be severe.

Reproduced with permission from Springer Science+Business Media. Steiner M, Macdougall M, Brown E. The premenstrual symptoms screening tool (PSST) for clinicians. *Arch Womens Ment Health*. 2003;6:203-209, Appendix 1.

It's important to differentiate premenstrual dysphoric disorder from premenstrual exacerbations of chronic psychiatric illness.

anesthetic, sedative, and hypnotic activity by enhancing GABA type A receptor-meditated inhibitory responses.[11,12] Lower levels of allopregnanolone during periods of altered central nervous system excitability, such as stress or ovulation, reduce the inhibitory effect of GABA and lead to irritability, insomnia, tension, and depression. Clinical studies have shown a positive correlation between the severity of PMDD and lower levels of allopregnanolone during the luteal phase.[13]

Hypothalamic-pituitary-adrenal (HPA) axis. PMDD is associated with the dysregulation of the HPA axis, as demonstrated by a comparative study that found a blunted response to adrenocorticotropic hormone and cortisol in the luteal phase after treadmill exercise stress testing in women with PMDD compared with non-PMDD women.[14] The study provides strong evidence for dysregulation of the HPA axis in response to stress in women with PMDD.[14,15]

Psychological factors. Although insufficient data are available to explain the role

Ask patients to record daily symptoms for at least 2 menstrual cycles to provide information about the severity and timing of symptoms.

and impact of psychological stress in the pathogenesis of PMDD, several studies show that stress exacerbates PMDD.[16-18] Girdler and colleagues demonstrated that stressful life events such as sexual and physical abuse may be important determinants of PMDD with their finding that women with PMDD who had a history of abuse scored higher than controls on the Beck Depression Inventory and State-Trait Anxiety Inventory during the luteal phase.[19]

Do the symptoms interfere with relationships and work?

PMDD is diagnosed using the DSM-IV-TR criteria described previously.[3] The symptoms must be severe enough to cause psychosocial impairment that interferes with relationships and social functioning at work, school, or other activities, and they should not be merely an exacerbation of another disorder.[3]

No objective diagnostic tests are available. Diagnosis depends on a thorough history and physical examination and exclusion of other conditions, including thyroid disorders, migraines, chronic fatigue syndrome, irritable bowel syndrome, seizures, anemia, endometriosis, perimenopause, and drug and alcohol abuse.[2] Laboratory tests should be ordered as clinically indicated and may include chemistry studies to assess electrolyte disturbances, a complete blood count to rule out anemia, and measurement of thyroid-stimulating hormone to rule out thyroid disease.

PMDD may coexist with psychiatric illness, particularly depression and anxiety disorders, and also dysthymia, panic disorders, bipolar disorders, and personality disorders.[4,20] The lifetime incidence of psychiatric conditions in women diagnosed with PMDD is 50% to 75%.[21] Take care to differentiate PMDD from premenstrual exacerbations of chronic psychiatric illness.[20]

Patients must prospectively record daily symptoms for at least 2 menstrual cycles to provide information about the severity and timing of symptoms.[3] Standardized daily symptom calendars, such as the Calendar of Premenstrual Experiences and the Prospective Record of the Impact and Severity of Menstruation, are available to help differentiate luteal from nonluteal phase symptoms.[22,23] The Premenstrual Symptoms Screening Tool, or PSST, a simpler, more user-friendly tool developed by researchers at McMaster University in Canada, has been validated against prospective daily charting in some countries (**TABLE 2**).[24]

What are the treatment options?

Therapy for PMDD is highly individualized and should target well-defined symptoms.[11,25] Treatment should begin with conservative management.[2,26] Conservative measures, such as diet and lifestyle modification, are considered first-line treatment, although supporting evidence is scarce.[11] Carbohydrate-rich foods such as brown rice and pasta and protein-poor diets have been found to alleviate symptoms, as has exercise.[26]

Consider antidepressants and hormonal therapy

SSRIs are the only class of antidepressants approved by the US Food and Drug Administration (FDA) for treatment of PMDD and are considered first-line pharmacologic therapy, although they have only about a 60% response rate.[9,11,27,28] Within this class, fluoxetine, sertraline, and paroxetine are FDA-approved for PMDD.[6,11,21,27]

SSRIs have proven effective at low doses and produce a faster response time in treat-

TABLE 3
SSRIs used to treat PMDD[32-34]

Drug	Daily dose
Fluoxetine*	10-20 mg
Sertraline*	25-50 mg
Paroxetine CR*	12.5-25 mg
Escitalopram	20 mg
Venlafaxine	50-200 mg

PMDD, premenstrual dysphoric disorder; SSRI, selective serotonin reuptake inhibitor.

*FDA-approved for premenstrual dysphoric disorder.

ing PMDD—within 1 or 2 days of onset—than depression (2-4 weeks).[6] Continuous and intermittent treatment are both effective.[29,30] However, continuous dosing yields a higher response rate, with 85% to 90% of patients experiencing improvement.[22,31] The symptoms that respond best to continuous dosing are irritability, mood swings, and affect lability.[22] Lack of response to an SSRI after 2 menstrual cycles constitutes treatment failure.[8]

Another antidepressant that has been found effective compared with placebo is venlafaxine, a serotonin and noradrenaline reuptake inhibitor with a quick response time.[32] **TABLE 3** lists antidepressants used to treat PMDD.[32-34]

The anxiolytic alprazolam, a GABA agonist,[35] is also effective for PMDD but is considered second-line therapy because of its adverse effects (drowsiness and confusion) and potential for dependence.[2,26]

Hormonal therapy. Low-dose progestin oral contraceptives provide some relief of PMDD, although definitive evidence is lacking to support using progesterone to manage the disorder.[36] A combination oral contraceptive pill (OCP) containing 3 mg of the progestin drospirenone and 20 mcg of ethinyl estradiol has proved beneficial in treating the bloating, food cravings, breast tenderness, and mood swings of PMDD because of drospirenone's antimineralocorticoid and antiandrogenic activity.[36-38] The OCP is taken in

TABLE 4

How strong is the evidence for nutritional and herbal supplements for premenstrual dysphoric disorder?

Nutritional supplements	Daily dose	Symptom(s)	Efficacy (SOR)	Adverse effects
Calcium[27, 41]	1200 mg	Pain, fatigue, depression, insomnia, bloating, food cravings	Yes (A)	Kidney stones with doses >2500 mg[20]
Magnesium[40,42]	200-400 mg	Bloating, mood changes, pain	Possibly yes (B)	Diarrhea
Vitamin B_6[40,43]	50-100 mg	Depression, overall symptoms	Possibly yes (B)	Peripheral neuropathy >100 mg/d
Vitamin E[40]	400 IU	Mastalgia	Possibly yes (B)	Bleeding (hemorrhagic stroke), nausea, fatigue
Herbal supplements				
Chasteberry (*Vitex agnus-castus*)[39,40,44]	20 mg	Overall symptoms	Possibly yes (B)	Mild skin rash, acne, headache, gastrointestinal symptoms[26]
Ginkgo biloba[40,42]	160 mg in 2 80-mg doses	Mastalgia, bloating, mood changes	Possibly yes (B)	Increased risk of bleeding
St. John's wort[40,42]	900 mg in 3 300-mg doses	Mood changes	Possibly yes (B)	Photosensitivity
Evening primrose oil[40]	2-3 g	Overall symptoms	Possibly no (B)	None

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

a 24/4 regimen (24 days of active medication with a 4-day hormone-free interval). It provides adequate blood levels of estrogen and progesterone to suppress gonadotropins at the beginning of the active medication cycle while the shortened hormone-free interval helps reduce symptoms.[36-38]

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide relieve symptoms of PMDD by decreasing secretion of both follicle-stimulating hormone and luteinizing hormone, inducing anovulation and amenorrhea.[27] GnRH agonists also induce menopausal symptoms such as hot flashes, fatigue, irritability, vaginal dryness, osteopenia, and cardiac problems and are not recommended for prolonged use.[27,38]

Like GnRH, danazol, a derivative of the synthetic modified testosterone ethisterone (pregneninolone), relieves PMDD symptoms by suppressing the HPA axis and causing anovulation. Its adverse effects may include acne, increased facial hair, weight gain, and depression, however.[38] GnRH and danazol are usually used as a last resort because of their adverse effects and significant cost.

Acupuncture shows promise for alleviating symptoms of premenstrual dysphoric disorder.

Consider complementary therapy, as well

Nutritional and herbal supplements have been shown to be useful for relieving PMDD, but more evidence is needed to support their benefit.[39] **TABLE 4** describes nutritional and herbal supplements used to treat PMDD.[27, 39-44]

Acupuncture, which is widely used in the United States according to the National Institutes of Health Consensus Conference,[45] also shows promise for alleviating PMDD symptoms. A review article discussing the use of acupuncture in a woman who met 8 of the 11 DMV-IV-TR diagnostic criteria for PMDD reported that during menstrual cycles in which the woman was treated with acupuncture the number of symptoms, as recorded by the patient on the Menstrual Distress Questionnaire, decreased from 8 to between 3 and 5.[46] When treatment was stopped, the number of symptoms returned to 8, then decreased to between 2 and 5 when acupuncture resumed.

CASE ▶ A thorough history and physical examination suggest that Ms. J's symptoms are caused by PMDD uncomplicated by psychiatric illness. You ask her to record her symptoms for 2 menstrual cycles. You also suggest that she walk or engage in other regular exercise and eat more carbohydrates, such as brown rice and pasta, and less meat and other protein because doing these things may help her feel better in the meantime. When these measures fail to provide significant relief, you prescribe fluoxetine, 10 mg per day. Ms. J reports feeling markedly better at her next menstrual period. **JFP**

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