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Premenstrual dysphoric disorder: A review for the treating practitioner

■ ABSTRACT

Premenstrual dysphoric disorder (PMDD), a severe form of premenstrual syndrome (PMS), is characterized by physical and behavioral symptoms that cause marked social impairment during the last half of the menstrual cycle. Symptoms are believed to result from the interaction of central neurotransmitters and normal menstrual hormonal changes. Treatment usually begins with lifestyle changes, over-the-counter medications, and if needed, selective serotonin reuptake inhibitors. Physicians should be aware of the risks of many of the alternative therapies commonly touted in the popular press.

■ KEY POINTS

PMDD is diagnosed by prospective recording of symptoms for two menstrual cycles and by laboratory testing to rule out thyroid disorders, anemia, and electrolyte disturbances.

The symptoms of PMDD are likely caused by low levels of serotonin, gamma-aminobutyric acid, and beta-endorphins.

Selective serotonin reuptake inhibitors are the first-line medications. Anxiolytics, ovulation suppressants, and diuretics are recommended for specific symptoms.

Patients should be warned of potential risks of herbal products and of large doses of vitamins and food supplements.

*This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

WHILE MOST WOMEN of reproductive age suffer from some degree of premenstrual syndrome (PMS), usually involving mood changes and somatic symptoms, only a small percentage have the more severe form, known as premenstrual dysphoric disorder (PMDD), which causes marked impairment.

This review will help the clinician recognize, understand, and treat this disorder. We also provide an overview of alternative therapies that patients may be using on their own to treat the condition.

■ CONSTELLATION OF SYMPTOMS DURING LUTEAL PHASE

PMDD was first defined in 1987 in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) and revised in the following edition in 1994.¹ Its constellation of somatic and behavioral symptoms occur only in the 10 to 14 days before menstrual bleeding, corresponding to the luteal phase of the cycle.

Symptoms are similar to those of PMS, a condition that affects as many as 75% of women of menstruating age. Only 3% to 8% of women² have symptoms severe enough to be diagnosed with PMDD (TABLE 1).

■ RISK FACTORS

Some women are more prone to PMDD. Risk factors include:

- **Age**—PMDD is most likely to occur in a woman's late 20s to mid 30s³
- **Psychiatric disorders**—As many as 70% of women with PMDD have a history of mood disorders (including major depression), anxiety disorders, personality disorders, or substance abuse^{4–6}



PATIENT INFORMATION

What is premenstrual dysphoric disorder (PMDD)? page 322

TABLE 1

Differences between premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD)

	PMS	PMDD
Prevalence	75%	3%–8%
Symptoms required	1	5 of 11 (see TABLE 2)
Diagnosis	ICD-10*	DSM-IV†
Social impairment	Not required	Required
Prospective charting	Not required	Required

*International Statistical Classification of Diseases and Related Health Problems, 10th revision.

†Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

Central serotonin levels tend to be low in women with PMDD

- **Genetics**—Twin studies suggest a genetic component is present^{4,7,8}
- **Low parity**—Women with fewer pregnancies have a higher incidence of PMDD. Additional exposure to changing levels of estrogen and progesterone from more menstrual cycles may predispose women to the disorder^{9,10}
- **Psychosocial factors**—Studies suggest that the incidence of PMDD increases after major life events and stressors^{4,9,11}
- **Menstrual cycle length**—Data conflict on the association of menstrual cycle length and symptom severity.^{4,12,13}

■ WHAT CAUSES PMDD?

A number of theories have been proposed to explain PMDD, but the exact cause is unknown.

An abnormal response to normal hormone cycles

The current theory is that premenstrual symptoms are caused by normal cyclic changes in ovarian steroids.⁴ In 1984, Muse et al¹⁴ studied the effects of eliminating the hormonal changes of menstrual cycles in eight patients over a 6-month period using the gonadotropin-releasing hormone (GnRH) agonist leuprolide (Lupron). Symptoms resolved with GnRH treatment, then recurred when the medication was withdrawn.

Cyclic changes of ovarian steroids may not be the only explanation for symptoms. Estrogen and progesterone levels of women with premenstrual symptoms are about the same as those of control subjects, suggesting that behavioral disturbances in affected women may be due to an abnormal response of central neurotransmitters to normal ovarian function.^{4,15}

Low levels of neurotransmitters

Serotonin is the most widely studied neurotransmitter in women with PMDD: central serotonin levels tend to be low,^{16,17} and symptoms are aggravated by depletion of the serotonin precursor tryptophan.¹⁸ In addition, many patients with PMDD improve with treatment using selective serotonin reuptake inhibitors (SSRIs).^{19–21}

Gamma-aminobutyric acid (GABA) and beta-endorphin probably also play a role. Premenstrual women have reduced GABA receptor sensitivity and abnormal levels of allopregnanolone, a progesterone metabolite.²² Differences in beta-endorphin levels between the periovulatory and premenstrual phases have been suggested but remain unconfirmed.^{23–25}

Vitamin and mineral deficiencies unproven

Attempts to link vitamin and mineral deficiencies with PMDD have been inconclusive. No differences in levels of vitamin A,²⁶ vitamin E,²⁷ or vitamin B₆^{28,29} have been observed. Initial studies suggested that women with PMDD may have lower levels of magnesium,^{30,31} but subsequent studies have not confirmed this finding.^{32,33} Calcium levels may also be low in the premenstrual phase.^{34,35}

■ A DIAGNOSIS OF EXCLUSION

PMDD is diagnosed with a thorough history and physical examination and by excluding other causes. No objective diagnostic tests exist.

Record symptoms daily

Symptoms should be recorded as they occur daily for at least two consecutive symptomatic menstrual cycles. Common tools include the Calendar of Premenstrual Experiences (COPE),³⁶ the Moos Menstrual

**TABLE 2****Criteria for diagnosis of premenstrual dysphoric disorder**

Symptoms occur 1 week before menses and resolve in the first few days after menses begins (over most menstrual cycles during the past year)

Five or more of the following (one must be among the first four):

- Markedly depressed mood with feelings of hopelessness
- Marked anxiety or tension
- Marked affective lability
- Irritability and anger
- Decreased interest in usual activities and social withdrawal
- Lack of energy
- Appetite change (overeating or undereating)
- Change in sleep pattern (hypersomnia or insomnia)
- Feeling out of control or overwhelmed
- Difficulty with concentration
- Somatic symptoms such as abdominal bloating, breast tenderness, headaches, or joint pain

Symptoms are severe enough to interfere with work, school, usual activities, or interpersonal relationships

Symptoms may be superimposed upon an underlying psychiatric disorder but may not be an exacerbation of another condition

These criteria must be confirmed by prospective daily charting for a minimum of two consecutive symptomatic menstrual cycles

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Distress Questionnaire (MDQ),³⁷ the Premenstrual Assessment Form (PAF),³⁸ and the Prospective Record of the Impact and Severity of Menstruation (PRISM).³⁹ These questionnaires are similar, and all have proven useful in gathering objective and quantified data about PMDD symptoms.

Symptoms of PMDD typically include mood disturbances and somatic symptoms, and are severe enough to markedly impair day-to-day functioning (TABLE 2). Symptoms occur during the last half of the menstrual cycle (the luteal phase) and are absent in the follicular phase, which begins from the first day of menstruation and lasts about 14 days until ovulation.

Steiner et al^{40,41} proposed that there must be at least a 30% worsening of symptoms between the follicular and luteal phases within each cycle, regardless of the assessment tool used.

Exclude other problems

Other diagnoses need to be excluded (TABLE 3). Blood should be tested if clinically indicated:

- A chemistry profile to assess electrolyte disturbances
- A complete blood cell count to rule out anemia
- A thyroid-stimulating hormone (TSH) level to rule out thyroid disorders.

Clinicians should be careful to differentiate PMDD from premenstrual exacerbations of chronic psychiatric disorders. A referral to a psychiatrist may be indicated to evaluate for a mood or anxiety disorder if the patient has no symptom-free period.

TREATMENT OPTIONS

No single intervention has proven effective for all patients with PMDD, but many options are available.

Start with lifestyle changes

Treatment should begin with a 2- to 3-month trial of lifestyle changes while the patient records her symptoms.⁹

Reducing intake of salt, sugar, caffeine, dairy products, and alcohol⁹ often helps decrease fluid retention, irritability, and bloat-

Reducing intake of salt, sugar, caffeine, dairy products, and alcohol often helps

TABLE 3

Differential diagnosis of premenstrual dysphoric disorder

Thyroid disorders
Migraine
Chronic fatigue syndrome
Irritable bowel syndrome
Seizures
Anemia
Endometriosis
Psychiatric disorders
(especially bipolar disorder, depression,
or anxiety)
Drug or alcohol abuse

ing. Lactose intolerance commonly causes bloating in women and may be alleviated by lactase enzymes such as Lactaid. Eating frequent and smaller portions of foods high in complex carbohydrates may also improve mood symptoms, possibly by raising levels of tryptophan, a precursor in serotonin biosynthesis.^{9,42,43}

Contemporary women fulfill multiple social roles, including wife, mother, caregiver to the elderly, and wage-earner, and often experience considerable emotional strain. Exercise, yoga, relaxation, and stress management may enhance general well-being. If possible, scheduling more challenging and stressful tasks during the first half of menstrual cycles may also help.

Medications

Nonsteroidal anti-inflammatory drugs are effective treatments for dysmenorrhea⁴⁴; ibuprofen and naproxen are available over the counter. Acetaminophen (Tylenol) may also alleviate pain. Prescription medications should be used if lifestyle changes and over-the-counter medications do not adequately alleviate symptoms (TABLE 4).

Selective serotonin reuptake inhibitors (SSRIs)^{45–58} are the first-line drugs for PMDD and have been shown to be effective in more than 60% of treated patients.^{45,46} Treatment only during the luteal phase (10–14 days before menses begins) works as well as full-cycle dosing, with fewer adverse effects.^{47–51}

SSRIs have a faster onset of action (1–2 days) when used for PMDD than for depression and other psychiatric disorders, possibly due to their ability to alter allopregnanolone levels.^{56–58} Examples include fluoxetine (Sarafem), sertraline (Zoloft), paroxetine (Paxil), and citalopram (Celexa).

Common SSRI side effects include sexual dysfunction, insomnia, fatigue, nervousness, headache, and nausea.

Other serotonergic agents used to treat PMDD inhibit the serotonin transporter as well as the uptake of norepinephrine. Examples include venlafaxine (Effexor)⁵⁹ and clomipramine (Anafranil).^{60–62}

Alprazolam (Xanax) is a GABA agonist with anxiolytic properties. It has proven effective in double-blind, placebo-controlled crossover studies against premenstrual symptoms, especially tension, anxiety, irritability, and hostility.^{63,64} The addictive potential of this medication makes it a second-line treatment.

Buspirone (BuSpar), a partial agonist of serotonin receptors, is also effective because of its anxiolytic properties. It is not addictive.^{65,66}

Gonadotropin-releasing hormone (GnRH) agonists down-regulate GnRH receptors, which reduce luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels.⁶⁷ This subsequently inhibits ovulation, thereby decreasing estrogen and progesterone levels, creating a pharmacologic menopause.⁶⁷

GnRH agonists are reserved mainly for patients with severe symptoms that do not respond to other treatments. They are expensive and have menopause-like side effects: hot flashes, headaches, muscle aches, vaginal dryness, and irritability. The low-estrogen state also raises concern about development of osteoporosis,⁶⁸ so treatment should be limited to 6 months. If extended treatment is required, patients should be given supplemental estrogen and progesterone.⁶⁹

Danazol (Danocrine) is a weak synthetic androgen that inhibits FSH and LH secretion, thus suppressing ovarian steroid production.⁷⁰ Its use is limited due to multiple androgenic and antiestrogenic side effects such as amenorrhea, weight gain, acne, fluid retention, hirsutism, hot flashes, vaginal dryness, and emotional lability.

Routinely ask your patients about use of vitamins, herbs, and supplements



Bromocriptine (Parlodel), a dopamine agonist, lowers prolactin levels and is useful in decreasing breast tenderness.^{71,72} Side effects may include dizziness and nausea.

Spironolactone (Aldactone) is the diuretic most studied due to its antimineralocorticoid and antiandrogenic properties. Benefits have not consistently been found.^{73–75} Symptoms most likely to improve include bloating, swelling, breast tenderness, and acne. Side effects of lethargy, headache, and irregular menses are more common during continuous dosing, so administration only during the luteal phase is recommended. Serum potassium levels should be monitored because spironolactone can cause hyperkalemia.

Oral contraceptives. Studies of oral contraceptives have been conflicting.^{76,77} In 2001, Freeman et al⁷⁸ showed that ethinyl estradiol 30 mg plus drospirenone 3 mg (Yasmin) alleviated bloating, breast tenderness, and swelling. The drospirenone component has antiandrogenic properties and may also reduce acne and hirsutism.

Meclofenamate (Meclomen) reduces menstrual flow and cramps.

Progesterone. Some believe that women with premenstrual symptoms have a deficiency of progesterone in the luteal phase of the menstrual cycle.⁷⁹ Dennerstein et al,⁸⁰ in a double-blind, randomized, crossover trial, treated women with micronized progesterone in the luteal phase and found progesterone was more effective than placebo for helping mood and some physical symptoms. However, Wyatt et al⁸¹ conducted a systematic review on the use of progesterone in premenstrual women and found no benefit.

■ SURGERY

In severe, refractory cases of PMDD, ovariectomy may be considered if medical treatment fails. Two studies showed complete relief of symptoms.^{82,83} In women of childbearing age, the risk of cardiovascular disease and osteoporosis may increase with the lack of estrogen.

■ INTEGRATIVE THERAPIES

Physicians should routinely ask patients about their use of vitamins, herbs, and supplements.

TABLE 4

Medications for premenstrual dysphoric disorder

Selective serotonin reuptake inhibitors

Fluoxetine (Prozac, Sarafem) 10–20 mg/day⁵² or
90 mg once a week for 2 weeks in the luteal phase^{53*}
Sertraline (Zoloft) 10–150 mg/day^{54*}
Paroxetine (Paxil) 10–30 mg/day^{55*}
Citalopram (Cipramil, Celexa) 5–20 mg/day⁴⁸

Other serotonergic antidepressants

Venlafaxine (Effexor) 50–150 mg/day⁵⁹
Clomipramine (Anafranil) 25–75 mg/day^{60–62}

Other agents

Alprazolam (Xanax) 0.25 mg 3–4 times daily in the luteal phase, taper at the onset of menses
Buspirone (BuSpar) 5–10 mg 3 times daily during luteal phase
Gonadotropin-releasing hormone agonists
(nasal spray, daily or depot injection, and subcutaneous forms available)
Leuprolide (Lupron) depot 3.75 mg IM/month
Danazol (Danocrine) 600–800 mg/day in divided doses.
Bromocriptine (Parlodel) 2.5 mg once daily just before ovulation until the onset of menses⁷²
Spironolactone (Aldactone) 50–100 mg/day for 7–10 days during the luteal phase⁷⁵
Drospirenone (Yasmin)
Meclofenamate (Meclomen) 100 mg twice a day

*Approved by the US Food and Drug Administration for this indication

Although none of these alternative therapies is FDA-approved, they are widely publicized in the popular press, and many patients report relief of symptoms with their use.

Some clinicians may choose to recommend a few of these therapies to certain patients. Most importantly, physicians should be aware of the adverse effects that may occur with self-prescribed supplements and should counsel their patients accordingly.

Vitamins, minerals, and other nutrients

Calcium. Okey et al³⁴ reported that plasma calcium levels are lower before menstruation, and Thys-Jacobs et al³⁵ demonstrated in a large trial that 1,200 mg of elemental calcium daily alleviates tension, anxiety, fluid retention, pain, and food cravings in women with PMS. Calcium is inexpensive, is safe during pregnancy, and helps maintain bone



health. The typical American diet provides less than half of the recommended 1,200 mg of calcium daily. Intake should not exceed 2,000 mg daily.⁸⁴

Magnesium. Women with PMS have lower levels of magnesium in erythrocytes and leukocytes despite normal plasma magnesium levels.^{30–33} Intracellular magnesium is likely a better indicator of true levels, since magnesium is mostly found within cells. Magnesium is a cofactor in many enzymatic reactions, and some believe that supplementation may alleviate some PMS symptoms by correcting any existing deficiency.

Replacing magnesium in doses of 200 mg to 400 mg once daily reduces fluid retention.^{85,86} Magnesium occasionally causes a mild osmotic diarrhea but is usually well tolerated.

Vitamin B₆ is a cofactor in neurotransmitter synthesis, so it may, in theory, play a role in relieving premenstrual mood symptoms. However, studies using vitamin B₆ supplementation have shown inconsistent results.^{28,29} The Institute of Medicine of the National Academy of Sciences recommends that women should limit vitamin B₆ intake to no more than 100 mg daily because of the risk of peripheral neuropathy.⁸⁷

Vitamin E may relieve some mood and physical symptoms, including anxiety and breast tenderness.⁸⁸ It may exert its effect through prostaglandin synthesis or regulation of central neurotransmitters.⁸⁸ Dosage: 400 IU daily.

Manganese levels vary throughout the menstrual cycle. One small study reported that women with low intake of dietary manganese have more premenstrual symptoms of bad mood and pain.⁸⁹ Further studies are warranted. Women should be advised that the recommended dose of 6 mg per day to prevent symptoms is higher than the recommended daily allowance of 1.8 mg.⁹⁰

L-tryptophan is an essential amino acid precursor in the serotonin pathway. It has been shown to reduce hostility and cravings in premenstrual women,⁹¹ but more studies are needed to demonstrate its efficacy. Foods rich in tryptophan include milk and turkey. Treatment in supplement form is not recommended because it has been associated with eosinophilia myalgia syndrome (EMS). It is

believed that EMS was caused by a contaminant, but it was difficult to implicate one specific substance.

Herbals

Evening primrose oil, derived from the American wildflower *Oenothera biennis*, is a rich source of gamma linolenic acid. This essential omega-6 fatty acid is a prostaglandin precursor. Some believe that women in the premenstrual phase of their cycle are deficient in gamma linolenic acid, leading to symptoms attributable to abnormal prostaglandin synthesis.⁹²

Evening primrose oil 3 to 6 g daily has been used to treat breast tenderness; other putative uses are for irritability and ankle swelling. Studies, however, have shown no advantage of evening primrose oil over placebo.^{93,94}

Black currant oil and **borage seed oil** contain a higher content of gamma linolenic acid; however, borage seed oil may contain toxic alkaloids and is not recommended.⁹⁵

Chaste tree extract is obtained from a shrub (*Vitex agnus-castus*) native to southern Europe and the Mediterranean. Prolactin levels are believed to be high premenstrually; chaste tree extract binds to dopamine receptors, inhibiting prolactin release,^{95,96} and thereby perhaps relieving irritability and breast tenderness.⁹⁷

Chaste tree extract is not safe during pregnancy⁹⁸ on the basis of case reports of uterine stimulation and should not be taken by sexually active women who are not using reliable contraception. The dose is 20 mg to 40 mg per day (aqueous extract). Side effects include gastrointestinal upset, rash, and headache.

Black cohosh stimulates estrogen receptors and is used to treat premenstrual anxiety and breast pain.⁹⁵ Currently, no controlled trials exist to support its efficacy. No toxicity has been reported with its use, but experts do not recommend using it longer than 6 months since the long-term safety is unknown.⁹⁸

Wild yam root contains diosgenin, a compound used in steroid hormone synthesis.⁹⁵ Diosgenin converts to progesterone in vitro,⁹⁵ and some believe that it should therefore alleviate premenstrual symptoms. However, not much is known about its effects in premenstrual women.

Dong quai is a Chinese herb used for PMS

The typical diet provides < half of the recommended 1,200 mg of calcium daily

and other gynecological conditions, but no controlled studies support its efficacy.⁹⁵ Dong quai is not safe in pregnancy and should not be used by sexually active women who are not using contraception.⁹⁵ Since dong quai contains a coumarin derivative, it may increase the prothrombin time and the international normalized ratio, and should not be used by women on warfarin (Coumadin).

Kava kava is used by some women to treat premenstrual anxiety. However, it should not be recommended, as there have been reports of hepatotoxicity.⁹⁹ It also may interact with alprazolam.¹⁰⁰

St. John's wort (*Hypericum perforatum*) is used to treat mild to moderate depression. A pilot study¹⁰¹ over two cycles showed improvement in premenstrual mood symptoms, but long-term effects are unknown. St. John's wort interacts with SSRIs, transplant medications, and anti-HIV drugs.

Other alternative therapies

Acupressure and acupuncture are traditional Chinese forms of medicine thought to restore the body's normal flow of energy.¹⁰²

Vaginal biofeedback. Patients can learn to increase their vaginal temperature, warming the pelvic and vaginal tissue. This emulates the thermogenic effects of progesterone and may relieve symptoms.¹⁰³

Homeopathic remedies may have a role in the treatment of premenstrual symptoms as demonstrated by one study,¹⁰⁴ showing the powerful effects of placebo. More studies are needed. Homeopathy has been used successfully at a London clinic.¹⁰⁵

Chiropractic and massage therapy. Women may benefit from high-velocity, low-amplitude spinal manipulation and soft-tissue kneading two or three times a week premenstrually.¹⁰⁶ Massage therapy has also been shown to decrease anxiety, depressed mood, and pain immediately after massage sessions.¹⁰⁷ Effects over a 5-week period include reduced pain, menstrual distress, and fluid retention.¹⁰⁷

Reflexology involves applying manual pressure to reflex points (ears, hands, and feet) that correspond to specific areas of the body. Oleson and Flocco¹⁰⁸ found a reduction in premenstrual symptoms in patients treated with reflexology compared with a placebo form of the practice.

Light therapy. Three studies^{109–111} found that bright white light used during the luteal phase of the menstrual cycle helps women with PMDD. Women with depressive and physical symptoms are most likely to benefit.

Acknowledgement: The authors would like to thank Diane Crouse for her assistance in preparing this manuscript.

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