
Premenstrual Dysphoric Disorder

A Guide for the Treating Clinician

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For many years, doctors have recognized the link of menstrual cycle to behavior and mood changes in women. In the 1930s, RT Frank used the term “premenstrual tension syndrome” to describe the premenstrual mood problems that he noted in 15 women; by the 1950s, terminology had evolved into the now-familiar “premenstrual syndrome” or PMS.¹ In 1987, the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) listed criteria for diagnosis of what it called “late luteal phase dysphoric disorder” or LLPDD.² This cumbersome and unfamiliar name never became part of popular jargon, but the diagnostic criteria associated with it are used in research and for clinical treatment. In 1993, DSM-IV changed the name to “premenstrual dysphoric disorder”(PMDD), and modified the diagnostic criteria slightly.

As the name implies, PMDD is a cyclical disorder consisting of distressing mood and behavioral symptoms arising during the late luteal (premenstrual) phase of a woman’s ovulatory cycle. Women with PMDD experience marked irritability as well as dysphoria, mood lability, anxiety, fatigue, change in appetite, and a sense of feeling overwhelmed. Up to 75% of women experience some physical and emotional symptoms before menses, but in only 3-8% are symptoms severe enough to qualify as PMDD.

The exact nature of PMDD continues to be debated, but it is generally agreed that it is a distinct psychiatric and medical syndrome rather than an exacerbation of an underlying psychiatric disorder.³ A hormonal basis of PMDD is suggested by twin studies indicating that PMDD is inherited,⁴ and by the observation that medical or surgical suppression of ovulation eliminates premenstrual symptoms.^{5,6} The predictable, cyclical recurrence and remission of symptoms is further evidence that PMDD is a distinct, biologically driven syndrome.

Diagnosis

Diagnosis of PMDD is based on the presence of at least five of the symptoms listed in Table 1. Essential to diagnosis is the occurrence of symptoms during the post-ovulatory, premenstrual period; symptoms typically begin in the late luteal phase (occasionally at ovulation) and remit by the end of menstrual flow. Because patients can misinterpret or overemphasize the relationship of symptoms to their menstrual cycle, it can be useful to have them chart symptoms throughout the month. A number of instruments (the Daily Rating Form, the Menstrual Distress Questionnaire, the Premenstrual Assessment Form, the Calendar of Premenstrual Experiences, and the Prospective Record of the Impact and Severity of Menstrual Symptoms) are available to help identify and quantify the timing and impact of symptoms during the menstrual cycle. As an alternative to formal rating scales, patients may keep an informal diary of symptoms throughout the month. Charts allow clinicians to differentiate PMDD from other psychiatric or medical disorders, and to distinguish it from mood changes expected during normal menstrual cycles.

Many women report that disorders like depression, bipolar disorder, panic disorder, generalized anxiety disorder, and attention deficit disorder are exacerbated during the late luteal phase of their menstrual cycle. Patients with “pure” PMDD will generally be free of symptoms except in the post-ovulatory period of their cycle. As always, other medical causes of dysphoria should be considered. A good history and physical examination and routine laboratory tests can help exclude conditions like hypothyroidism, autoimmune disorders, diabetes, anemia, parathyroid disorders, seizure disorders, sleep disorders, and endometriosis, which also can produce premenstrual complaints.

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Etiology

Severe PMS and PMDD are closely linked to function of the hypothalamic-pituitary-gonadal (HPG) axis, but, contrary to the intuitive assumption of clinicians and patients, PMDD is not the result of demonstrable hormonal imbalance.⁷ Rather, it appears that PMDD is the result of heightened central

nervous system sensitivity to normal hormonal cycling, which leads to reduced levels of the neurotransmitter serotonin or 5-hydroxy tryptamine (5-HT). As women with PMDD enter the late luteal phase of their menstrual cycle, available 5-HT is reduced, triggering symptoms associated with 5-HT depletion (irritability, dysphoria, impulsivity, and carbohydrate craving). Several studies point to altered 5-HT metabolism in the genesis of PMDD. Blood levels⁸ and platelet uptake of 5-HT⁹ are low in PMDD patients, and acute depletion of tryptophan, the precursor of serotonin, aggravates symptoms of PMS and PMDD.¹⁰

The current consensus holds that dysregulation of serotonin is the primary cause of PMDD symptoms, but there is evidence that other neurotransmitters may play a significant role. Levels of gamma aminobutyric acid (GABA) are low in patients with PMDD and PMS.¹¹ Studies of the opiate antagonists naltrexone and naloxone suggest a possible acute withdrawal of endogenous opioids in the late luteal phase of the menstrual cycle, which would produce the irritability and mood lability characteristic of such withdrawal.^{12,13}

Finally, in PMDD, selective serotonin reuptake inhibitor (SSRI) drugs are effective, and their onset of action is usually much quicker than the two to four weeks needed to treat depression, panic disorder, or obsessive-compulsive disorder. This has led to the theory that SSRIs work by a different mechanism in PMDD than in depressed or anxious patients. One suggestion is that SSRIs work in PMDD by indirectly increasing synthesis of allopregnenolone from progesterone; the binding of allopregnenolone to GABA receptors would account for the rapid relief of PMDD symptoms by SSRIs.¹⁴

Regardless of uncertainty about the exact biochemical mechanism, it appears that the symptoms of PMDD are caused by central sensitivity rather than peripheral hormonal abnormality. Therefore, it makes sense that treatment should focus on correcting or compensating for central sensitivity, or on stopping the cycle altogether, rather than modifying the hormones of the menstrual cycle.

Table 1. Symptoms associated with PMDD

Irritability	Increased or decreased sleep duration
Depressed mood	Feeling of being overwhelmed
Anxiety	Physical symptoms
Labile affect	Breast tenderness
Decreased interest in usual activities	Bloating
Decreased concentration	Headache
Lack of energy	Joint or muscle pain
Increased or decreased appetite	

Treatment

Many regimens for treating PMS and PMDD have been proposed and tried over the years. Currently, the SSRIs have the best record of efficacy and appear to be effective in up to 70% of PMDD patients. Sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil), and citalopram (Celexa) have all been successful in controlled trials of treating PMS and PMDD symptoms. Because women often see improvement in PMS/PMDD symptoms a day or two after beginning an SSRI, several studies have investigated the use of these drugs only in the late luteal phase, and indeed SSRIs appear to be effective when taken just during the week or so prior to menses. In fact, a 1998 study by Wikander et al suggested that intermittent dosing of citalopram might be even better than continuous dosing in relieving PMDD symptoms.¹⁵ A surprising finding has been that SSRIs can decrease physical symptoms of PMS like breast tenderness and bloating. This further suggests that their effectiveness is due to more than just inhibition of central serotonin re-uptake. Intermittent and post-ovulatory dosing may decrease the adverse side effects of SSRIs, including sexual dysfunction and weight gain.

It is noteworthy that non-serotonin enhancing antidepressants like bupropion or the tricyclic antidepressants are not effective in the treatment of PMS/PMDD symptoms. If SSRIs cannot be used or are ineffective, ovulation suppression can be used to halt menstrual cycling. Gonadotropin-releasing hormone (GnRH) agonists act on the hypothalamus to decrease secretion of follicle stimulating and luteinizing hormones. This causes anovulation and decreased estrogen and progesterone synthesis. GnRH agonists can help some women with PMDD, but they do not work well in women who have severe dysphoria or exacerbation of pre-existing major depression in the late luteal phase.¹⁶ Danazol suppression of the HPG axis has been used to treat PMDD/PMS. Results have been mixed, but positive responses appear to be the result of suppressed ovulation.¹⁷ Danazol may cause acne, increased facial hair, weight gain, and

Table 2. An approach to caring for patients with PMS/PMDD

1. Establish the diagnosis by having the patient chart her symptoms throughout the course of the menstrual cycle.
2. Rule out other medical or underlying psychiatric disorders with a thorough history, physical and laboratory examinations.
3. Consider noninvasive interventions such as calcium carbonate, multivitamin with magnesium, and pyridoxine; increase intake of complex dietary carbohydrates; increase exercise; decrease caffeine intake.
4. If symptoms persist, consider using an SSRI in the late luteal phase; if intermittent dosing is ineffective or if there are depressive or anxiety symptoms throughout the cycle, use an SSRI on a continuous schedule (increase in dosage in the late luteal phase if needed).
5. Consider referral for cognitive behavioral therapy or relaxation therapy, especially if external stressors exacerbate symptoms.
6. Benzodiazepines can sometimes be useful as adjunctive treatment, but are generally less effective than SSRIs. They should be used with caution in patients with a history of substance abuse or impulse control problems.
7. If symptoms remain refractory to treatment or if the PMDD is so severe as to be life-threatening, psychiatric consultation is indicated.
8. Medical or surgical suppression of ovulation is a last resort because of the risks associated with long-term lack of estrogen.

depression; long-term reduction of estrogen has been linked to an increased incidence of heart disease and decreased bone density.

Other proposed treatments for PMS/PMDD include oral contraceptives or addition of progesterone during the luteal phase. Unfortunately, despite widespread use, there is no real evidence that oral contraceptives alleviate PMS/PMDD symptoms. Estrogen may worsen mood symptoms in women with significant PMS/PMDD, and at least one study found that continuous use of oral contraceptives increased PMDD symptoms.¹⁸ The steroid hormone allopregnenolone, on the other hand, has anxiolytic properties, and so there has been interest in using its precursor, progesterone, during the luteal phase. Unfortunately, several controlled trials have shown progesterone to be no more effective than placebo.

Because benzodiazepines act on GABA receptors, they have been used to treat PMS/PMDD symptoms. The results are mixed. Some studies show mild efficacy compared to placebo and others do not. Several studies have found that low-dose alprazolam improved severe PMS symptoms somewhat, but the improvement rate was less than that of SSRIs. Because of the risk for abuse, benzodiazepines should be used with caution in patients with a history of substance abuse. Also, benzodiazepines can cause disinhibition in some patients, and so should be used with caution in those with impulse control difficulties.

Studies of vitamin and mineral supplementation have also given mixed results. The best evidence suggests that calcium supplementation is helpful. A large 1998 study showed that 48% of women taking calcium carbonate im-

proved compared to 30% of those taking placebo.¹⁹ This rate of response is less than that for SSRIs, but calcium does offer a cheap and non-invasive option for treating PMS/PMDD symptoms. At least one study indicated that PMDD symptoms improved with magnesium supplementation, but a more recent study indicated only a decrease in fluid retention.²⁰ Vitamin B6 (pyridoxine) in doses of 50-100 mg per day may produce a very mild benefit; larger doses should be avoided to minimize the risk of neurotoxicity.

Nonpharmacological treatment—with diet, exercise, and cognitive and relaxation therapy—can be of significant benefit. Increased dietary intake of complex carbohydrate foods, a decrease in caffeine, and frequent meals in the late luteal phase can be helpful; there is speculation that the carbohydrate craving noted during the premenstrual period is a result of a need to increase brain tryptophan, the precursor of serotonin. Exercise can increase endogenous endorphins, alleviating anxiety and dysphoria. Finally, both relaxation and cognitive therapy have been reported to lessen PMS/PMDD symptoms and improve coping with those symptoms.

Summary

Up to 75% of women report some premenstrual symptoms, but less than 10% have symptoms severe enough to qualify for a diagnosis of PMDD. A key to diagnosis is establishing a pattern of typical PMDD symptoms that recur during the late luteal phase of the menstrual cycle and remit after menses. Underlying psychiatric and medical disorders that

might mimic PMDD should be ruled out or addressed. The clinician should recognize that severe PMS and PMDD are most likely caused by sensitivity to hormonal cycling rather than an abnormality of hormone levels.

Current treatment is based on the hypothesis that serotonin depletion is responsible for the premenstrual irritability, dysphoria, and poor impulse control in PMDD. There is

some evidence that GABA, endogenous opiates, allopregenolone, and various vitamins and minerals might play roles in severe PMS and PMDD. Treatment with oral contraceptives or supplementary progesterone or estrogen has not been effective. For the treating clinician, a reasonable approach to the patient with severe PMS or PMDD is shown in Table 2.

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