

**GURJIT KAUR, DO**

Department of General Internal Medicine,
Women's Health Center at The Gault Women's
Health and Breast Pavilion, The Cleveland
Clinic Foundation

LILIAN GONSALVES, MD

Department of Psychiatry and Psychology,
Women's Health Center at The Gault Women's
Health and Breast Pavilion, The Cleveland
Clinic Foundation

HOLLY L. THACKER, MD

Department of General Internal Medicine,
Department of Obstetrics and Gynecology,
Women's Health Center at The Gault Women's
Health and Breast Pavilion, The Cleveland
Clinic Foundation

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 abuse⁴⁻⁶

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

MODIFIED WITH PERMISSION FROM THE *DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS*, 4TH ED. TEXT REVISION. COPYRIGHT 2000, AMERICAN PSYCHIATRIC ASSOCIATION.

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.

Spirolactone (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
 Spirolactone (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.

REFERENCES

- Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC, American Psychiatric Association; 1994.
- Rivera-Tovar AD, Frank E. Late luteal phase dysphoric disorder in young women. *Am J Psychiatry* 1990; 147:1634–1636.
- Freeman EW, Rickels K, Schweizer E, Ting T. Relationships between age and symptom severity among women seeking medical treatment for premenstrual symptoms. *Psychol Med* 1995; 25:309–315.
- Steiner M, Born L. Diagnosis and treatment of premenstrual dysphoric disorder: an update. *Int Clin Psychopharmacol* 2000; 15(suppl 3):S5–S17.
- Pearlstein T, Stone AB. Premenstrual syndrome. *Psychiatr Clin North Am* 1998; 21:577–590.
- Praschak-Rieder N, Willeit M, Neumeister A, et al. Prevalence of premenstrual dysphoric disorder in female patients with seasonal affective disorder. *J Affect Disord* 2001; 63:239–242.
- Condon JT. The premenstrual syndrome: a twin study. *Br J Psychiatry* 1993; 162:481–486.
- Kendler KS, Karkowski LM, Corey LA, Neale MC. Longitudinal population-based twin study of retrospectively reported premenstrual symptoms and lifetime major depression. *Am J Psychiatry* 1998; 155:1234–1240.
- Frackiewicz EJ, Shiovitz TM. Evaluation and management of premenstrual syndrome and premenstrual dysphoric disorder. *J Am Pharm Assoc (Wash)* 2001; 41:437–447.
- Merikangas KR, Foeldenyi M, Angst J. The Zurich Study. XIX. Patterns of menstrual disturbances in the community: results of the Zurich Cohort Study. *Eur Arch Psychiatry Clin Neurosci* 1993; 243:23–32.
- Severino SK, Moline ML. *Premenstrual Syndrome: A Clinician's Guide*. New York: Guilford Press; 1989.
- Deuster PA, Adera T, South-Paul J. Biological, social, and behavioral factors associated with premenstrual syndrome. *Arch Fam Med* 1999;8:122–128.
- Hargrove JT, Abraham GE. The incidence of premenstrual tension in a gynecologic clinic. *J Reprod Med* 1982; 27:721–724.
- Muse KN, Cetel NS, Futterman LA, Yen SC. The premenstrual syndrome. Effects of "medical ovariectomy." *N Engl J Med* 1984; 311:1345–1349.
- Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. *N Engl J Med* 1998; 338:209–216.
- Rapkin AJ, Edelmuth E, Chang LC, Reading AE, McGuire MT, Su TP. Whole-blood serotonin in premenstrual syndrome. *Obstet Gynecol* 1987; 70:533–537.
- Taylor DL, Mathew RJ, Ho BT, Weinman ML. Serotonin levels and platelet uptake during premenstrual tension. *Neuropsychobiology* 1984; 12:16–18.

18. **Menkes DB, Coates DC, Fawcett JP.** Acute tryptophan depletion aggravates premenstrual syndrome. *J Affect Disord* 1994; 32:37–44.
19. **Dimmock PW, Wyatt KM, Jones PW, O'Brien PM.** Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review. *Lancet* 2000; 356:1131–1136.
20. **Fingfeld DL.** Selective serotonin reuptake inhibitors and treatment of premenstrual dysphoric disorder. *Perspect Psychiatr Care* 2002; 38:50–60.
21. **Steiner M, Pearlstein T.** Premenstrual dysphoria and the serotonin system: pathophysiology and treatment. *J Clin Psychiatry* 2000; 61(suppl 12):17–21.
22. **Sundstrom I, Backstrom T, Wang M, Olsson T, Seippel L, Bixo M.** Premenstrual syndrome, neuroactive steroids and the brain. *Gynecol Endocrinol* 1999; 13:206–220.
23. **Chuong CJ, Coulam CB, Kao PC, Bergstralh EJ, Go VL.** Neuropeptide levels in premenstrual syndrome. *Fertil Steril* 1985; 44:760–765.
24. **Chuong CJ, Hsi BP, Gibbons WE.** Periovulatory beta-endorphin levels in premenstrual syndrome. *Obstet Gynecol* 1994; 83:755–760.
25. **Giannini AJ, Martin DM, Turner CE.** Beta-endorphin decline in late luteal phase dysphoric disorder. *Int J Psychiatry Med* 1990; 20:279–284.
26. **Chuong CJ, Dawson EB, Smith ER.** Vitamin A levels in premenstrual syndrome. *Fertil Steril* 1990; 54:643–647.
27. **Chuong CJ, Dawson EB, Smith ER.** Vitamin E levels in premenstrual syndrome. *Am J Obstet Gynecol* 1990; 163:1591–1595.
28. **Kleijnen J, Ter Riet G, Knipschild P.** Vitamin B6 in the treatment of the premenstrual syndrome—a review. *Br J Obstet Gynaecol* 1990; 97:847–852.
29. **Wyatt KM, Dimmock PW, Jones PW, Shaughn O'Brien PM.** Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *Br Med J* 1999; 318:1375–1381.
30. **Sherwood RA, Rocks BF, Stewart A, Saxton RS.** Magnesium and the premenstrual syndrome. *Ann Clin Biochem* 1986; 23:667–670.
31. **Facchinetti F, Borella P, Fioroni L, et al.** Reduction of monocyte's magnesium in patients affected by premenstrual syndrome. *J Psychosom Obstet Gynaecol* 1990;11:221.
32. **Rosenstein DL, Elin RJ, Hosseini JM, Grover G, Rubinow DR.** Magnesium measures across the menstrual cycle in premenstrual syndrome. *Biol Psychiatry* 1994; 35:557–561.
33. **Posaci C, Erten O, Uren A, Acar B.** Plasma copper, zinc and magnesium levels in patients with premenstrual tension syndrome. *Acta Obstet Gynecol Scand* 1994; 73:452–455.
34. **Okey R, Stewart J, Greenwood M.** Studies in the metabolism of women. IV. The calcium and inorganic phosphorous in the blood of normal women at the various stages of the monthly cycle. *J Biol Chem* 1930; 87:91–102.
35. **Thys-Jacobs S, Starkey P, Bernstein D, Tian J.** Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. *Premenstrual Syndrome Study Group. Am J Obstet Gynecol* 1998; 179:444–452.
36. **Mortola JF, Girton L, Beck L, Yen SS.** Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: the calendar of premenstrual experiences. *Obstet Gynecol* 1990; 76:302–307.
37. **Moos RH.** The development of a menstrual distress questionnaire. *Psychosom Med* 1968; 30:853–867.
38. **Endicott J, Halbreich U.** Retrospective report of premenstrual depressive changes: factors affecting confirmation by daily ratings. *Psychopharmacol Bull* 1982; 18:109–112.
39. **Reid RL.** Premenstrual syndrome. *Curr Probl Obstet Gynecol Fertil* 1985; 8:1.
40. **Steiner M.** Premenstrual syndrome and premenstrual dysphoric disorder: guidelines for management. *J Psychiatry Neurosci* 2000; 25:459–468.
41. **Steiner M, Streiner DL, Steinberg S, et al.** The measurement of premenstrual mood symptoms. *J Affect Disord* 1999; 53:269–273.
42. **Wurtman JJ.** Carbohydrate craving. Relationship between carbohydrate intake and disorders of mood. *Drugs* 1990; 39(suppl 3):49–52.
43. **Sayegh R, Schiff I, Wurtman J, Spiers P, McDermott J, Wurtman R.** The effect of a carbohydrate-rich beverage on mood, appetite, and cognitive function in women with premenstrual syndrome. *Obstet Gynecol* 1995; 86:520–528.
44. **Budoff PW.** The use of prostaglandin inhibitors for the premenstrual syndrome. *J Reprod Med* 1983; 28:469–478.
45. **Eriksson E.** Serotonin reuptake inhibitors for the treatment of premenstrual dysphoria. *Int Clin Psychopharmacol* 1999; 14(suppl 2):S27–S33.
46. **Endicott J, Amsterdam J, Eriksson E, et al.** Is premenstrual dysphoric disorder a distinct clinical entity? *J Womens Health Gend Based Med* 1999; 8:663–679.
47. **Young SA, Hurt PH, Benedek DM, Howard RS.** Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: a randomized, double-blind, placebo-controlled crossover trial. *J Clin Psychiatry* 1998; 59:76–80.
48. **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; 18:390–398.
49. **Halbreich U, Smoller JW.** Intermittent luteal phase sertraline treatment of dysphoric premenstrual syndrome. *J Clin Psychiatry* 1997; 58:399–402.
50. **Halbreich U, Bergeron R, Yonkers KA, Freeman E, Stout AL, Cohen L.** Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 2002; 100:1219–1229.
51. **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; 100:435–444.
52. **Steiner M, Steinberg S, Stewart D, et al.** Fluoxetine in the treatment of premenstrual dysphoria. *Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group. N Engl J Med* 1995; 332:1529–1534.
53. **Miner C, Brown E, McCray S, Gonzales J, Wohlreich M.** 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; 24:417–433.
54. **Yonkers KA, Halbreich U, Freeman E, et al.** Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. A randomized controlled trial. *Sertraline Premenstrual Dysphoric Collaborative Study Group. JAMA* 1997; 278:983–988.
55. **Eriksson E, Hedberg MA, Andersch B, Sundblad C.** The serotonin reuptake inhibitor paroxetine is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. *Neuropsychopharmacology* 1995; 12:167–176.
56. **Pearlstein T.** Selective serotonin reuptake inhibitors for premenstrual dysphoric disorder: the emerging gold standard? *Drugs* 2002; 62:1869–1885.
57. **Guidotti A, Costa E.** Can the antidysphoric and anxiolytic profiles of selective serotonin reuptake inhibitors be related to their ability to increase brain 3 alpha, 5 alpha-tetrahydroprogesterone (allopregnanolone) availability? *Biol Psychiatry* 1998; 44:865–873.
58. **Griffin LD, Mellon SH.** Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes. *Proc Natl Acad Sci U S A* 1999; 96:13512–13517.
59. **Freeman EW, Rickels K, Yonkers KA, Kunz NR, McPherson M, Upton GV.** Venlafaxine in the treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 2001; 98:737–744.
60. **Sundblad C, Hedberg MA, Eriksson E.** Clomipramine administered during the luteal phase reduces the symptoms of premenstrual syndrome: a placebo-controlled trial. *Neuropsychopharmacology* 1993; 9:133–145.
61. **Sundblad C, Modigh K, Andersch B, Eriksson E.** Clomipramine effectively reduces premenstrual irritability and dysphoria: a placebo-controlled trial. *Acta Psychiatr Scand* 1992; 85:39–47.
62. **Eriksson E, Lisjo P, Sundblad C, Andersson K, Andersch B, Modigh K.** Effect of clomipramine on premenstrual syndrome. *Acta Psychiatr Scand* 1990; 81:87–88.
63. **Harrison WM, Endicott J, Nee J.** Treatment of premenstrual dysphoria with alprazolam. A controlled study. *Arch Gen Psychiatry* 1990; 47:270–275.



64. **Smith S, Rinehart JS, Ruddock VE, Schiff I.** Treatment of premenstrual syndrome with alprazolam: results of a double-blind, placebo-controlled, randomized crossover clinical trial. *Obstet Gynecol* 1987; 70:37–43.
65. **Rickels K, Freeman E, Sondheimer S.** Buspirone in treatment of premenstrual syndrome. *Lancet* 1989; 1:777.
66. **Brown CS, Ling FW, Farmer RG, et al.** Buspirone in the treatment of premenstrual syndrome. *Drug Ther* 1990; 20:S112–S121.
67. **Hazum E, Cuatrecasas P, Marian J, Conn PM.** Receptor-mediated internalization of fluorescent gonadotropin-releasing hormone by pituitary gonadotropes. *Proc Natl Acad Sci U S A* 1980; 77:6692–6695.
68. **American College of Obstetricians and Gynecologists.** Premenstrual Syndrome: Clinical Management Guidelines for Obstetrician-Gynecologists. *ACOG Practice Bulletin* 2000; 15:1–9.
69. **Mortola JF, Girton L, Fischer U.** Successful treatment of severe premenstrual syndrome by combined use of gonadotropin-releasing hormone agonist and estrogen/progestin. *J Clin Endocrinol Metab* 1991; 72:252A–252F.
70. **Dmowski WP.** Endocrine properties and clinical application of danazol. *Fertil Steril* 1979; 31:237–251.
71. **Andersch B.** Bromocriptine and premenstrual symptoms: a survey of double blind trials. *Obstet Gynecol Surv* 1983; 38:643–646.
72. **Elsner CW, Buster JE, Schindler RA, Nessim SA, Abraham GE.** Bromocriptine in the treatment of premenstrual tension syndrome. *Obstet Gynecol* 1980; 56:723–726.
73. **Wang M, Hammarback S, Lindhe BA, Backstrom T.** Treatment of premenstrual syndrome by spironolactone: a double-blind, placebo-controlled study. *Acta Obstet Gynecol Scand* 1995; 74:803–808.
74. **Burnet RB, Radden HS, Easterbrook EG, McKinnon RA.** Premenstrual syndrome and spironolactone. *Aust N Z J Obstet Gynaecol* 1991; 31:366–368.
75. **O'Brien PM, Craven D, Selby C, Symonds EM.** Treatment of premenstrual syndrome by spironolactone. *Br J Obstet Gynaecol* 1979; 86:142–147.
76. **Backstrom T, Hansson-Malmstrom Y, Lindhe BA, Cavalli-Bjorkman B, Nordenstrom S.** Oral contraceptives in premenstrual syndrome: a randomized comparison of triphasic and monophasic preparations. *Contraception* 1992; 46:253–268.
77. **Graham CA, Sherwin BB.** A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. *J Psychosom Res* 1992; 36:257–266.
78. **Freeman EW, Kroll R, Rapkin A, et al.** Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *J Womens Health Gend Based Med* 2001; 10:561–569.
79. **Dalton K.** *The Premenstrual Syndrome and Progesterone Therapy*. 2nd ed. Chicago, IL: Year Book Medical Publisher; 1984.
80. **Dennerstein L, Spencer-Gardner C, Gotts G, Brown JB, Smith MA, Burrows GD.** Progesterone and the premenstrual syndrome: a double blind crossover trial. *BMJ* 1985; 290:1617–1621.
81. **Wyatt K, Dimmock P, Jones P, Obhrai M, O'Brien S.** Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. *BMJ* 2001; 323:776–780.
82. **Casper RF, Hearn MT.** The effect of hysterectomy and bilateral oophorectomy in women with severe premenstrual syndrome. *Am J Obstet Gynecol* 1990; 162:105–109.
83. **Casson P, Hahn PM, Van Vugt DA, Reid RL.** Lasting response to ovariectomy in severe intractable premenstrual syndrome. *Am J Obstet Gynecol* 1990; 162:99–105.
84. **Institute of Medicine.** Dietary reference intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, DC: National Academy Press; 1997.
85. **Facchinetti F, Borella P, Sances G, Fioroni L, Nappi RE, Genazzani AR.** Oral magnesium successfully relieves premenstrual mood changes. *Obstet Gynecol* 1991; 78:177–181.
86. **Walker AF, De Souza MC, Vickers MF, Abeyasekera S, Collins ML, Trinca LA.** Magnesium supplementation alleviates premenstrual symptoms of fluid retention. *J Womens Health* 1998; 7:1157–1165.
87. **Institute of Medicine.** Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic acid, Biotin, and Choline. Washington, DC: National Academy Press; 1998.
88. **London RS, Murphy L, Kitlowski KE, Reynolds MA.** Efficacy of alpha-tocopherol in the treatment of the premenstrual syndrome. *J Reprod Med* 1987; 32:400–404.
89. **Penland JG, Johnson PE.** Dietary calcium and manganese effects on menstrual cycle symptoms. *Am J Obstet Gynecol* 1993; 168:1417–1423.
90. **Daugherty JE.** Treatment strategies for premenstrual syndrome. *Am Fam Physician* 1998; 58:183–192, 197–198.
91. **Harrison WM, Endicott J, Rabkin JG, Nee J.** Treatment of premenstrual dysphoric changes: clinical outcome and methodological implications. *Psychopharmacol Bull* 1984; 20:118–122.
92. **Johnson SR.** Premenstrual syndrome therapy. *Clin Obstet Gynecol* 1998; 41:405–421.
93. **Collins A, Cerin A, Coleman G, Landgren BM.** Essential fatty acids in the treatment of premenstrual syndrome. *Obstet Gynecol* 1993; 81:93–98.
94. **Khoo SK, Munro C, Battistutta D.** Evening primrose oil and treatment of premenstrual syndrome. *Med J Aust* 1990; 153:189–192.
95. **Foster S, Tyler V.** *Tyler's Honest Herbal*. 4th ed. New York, NY: Haworth Press; 1999.
96. **Sluizt G, Speiser P, Schultz AM, Spona J, Zeillinger R.** *Agnus castus* extracts inhibit prolactin secretion of rat pituitary cells. *Horm Metab Res* 1993; 25:253–255.
97. **Schellenberg R.** Treatment for the premenstrual syndrome with *Agnus castus* fruit extract: prospective, randomised, placebo controlled study. *BMJ* 2001; 322:134–137.
98. **Blumenthal M, Busse W, Goldberg A, et al.** *The complete German Commission E monographs. Therapeutic Guide to Herbal Medicines*. Austin, TX: American Botanical Council; 1998.
99. **Problems with dietary supplements: kava.** *Med Lett Drugs Ther* 2002; 44:84–86.
100. **Almeida JC, Grimsley EW.** Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med* 1996; 125:940–941.
101. **Stevinson C, Ernst E.** A pilot study of *Hypericum perforatum* for the treatment of premenstrual syndrome. *BJOG* 2000; 107:870–876.
102. **Habek D, Habek JC, Barbir A.** Using acupuncture to treat premenstrual syndrome. *Arch Gynecol Obstet* 2002; 267:23–26.
103. **Van Zak DB.** Biofeedback treatments for premenstrual and premenstrual affective syndromes. *Int J Psychosom* 1994; 41:53–60.
104. **Chapman E, Angelica J, Spitalny G, et al.** Results of a study of the homeopathic treatment of PMS. *J Am Inst Homeopath* 1994; 87:14–21.
105. **Katz T.** Homeopathic treatment of premenstrual symptoms. *Complement Ther Nurs Midwifery* 1995; 1:133–137.
106. **Walsh MJ, Polus BI.** A randomized, placebo-controlled clinical trial on the efficacy of chiropractic therapy on premenstrual syndrome. *J Manipulative Physiol Ther* 1999; 22:582–585.
107. **Hernandez-Reif M, Martinez A, Field T, Quintero O, Hart S, Burman I.** Premenstrual symptoms are relieved by massage therapy. *J Psychosom Obstet Gynaecol* 2000; 21:9–15.
108. **Oleson T, Flocco W.** Randomized controlled study of premenstrual symptoms treated with ear, hand, and foot reflexology. *Obstet Gynecol* 1993; 82:906–911.
109. **Parry BL, Udell C, Elliott JA, et al.** Blunted phase-shift responses to morning bright light in premenstrual dysphoric disorder. *J Biol Rhythms* 1997; 12:443–456.
110. **Lam RW, Carter D, Misri S, Kuan AJ, Yatham LN, Zis AP.** A controlled study of light therapy in women with late luteal phase dysphoric disorder. *Psychiatry Res* 1999; 86:185–192.
111. **Oprendeck T, Parry B, Brown S.** Differential reduction in symptoms of late luteal phase dysphoric disorder as a function of light therapy. *J Womens Health* 1994; 3:115–124.

ADDRESS: Gurjit Kaur, DO, Department of General Internal Medicine, A91, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail kaurg@ccf.org.