REVIEW

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 Adminstration for the use under discussion.

PATIENT INFORMATION
What is premenstrual dysphoric disorder (PMDD)? page 322

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 women[2] 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 30s[3]
- **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]

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.

- **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]

Central serotonin levels tend to be low in women with PMDD

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 al[14] 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 B_6[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

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 alcohol[9] 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]

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

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 dysmenorrhea[44]; 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.

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 al[78] 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 al[81] 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/day[52] 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/day[48]

Other serotonergic antidepressants
- Venlafaxine (Effexor) 50–150 mg/day[59]
- 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 menses[72]
- Spironolactone (Aldactone) 50–100 mg/day for 7–10 days during the luteal phase[75]
- 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 al[34] reported that plasma calcium levels are lower before menstruation, and Thys-Jacobs et al[35] 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 B_6 is a cofactor in neurotransmitter synthesis, so it may, in theory, play a role in relieving premenstrual mood symptoms. However, studies using vitamin B_6 supplementation have shown inconsistent results.[28,29] The Institute of Medicine of the National Academy of Sciences recommends that women should limit vitamin B_6 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 pregnancy[98] 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 study[101] 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 Flocco[108] 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

1. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC, American Psychiatric Association; 1994.
2. **Rivera-Tovar AD, Frank E.** Late luteal phase dysphoric disorder in young women. Am J Psychiatry 1990; 147:1634–1636.
3. **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.
4. **Steiner M, Born L.** Diagnosis and treatment of premenstrual dysphoric disorder: an update. Int Clin Psychopharmacol 2000; 15(suppl 3):S5–S17.
5. **Pearlstein T, Stone AB.** Premenstrual syndrome. Psychiatr Clin North Am 1998; 21:577–590.
6. **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.
7. **Condon JT.** The premenstrual syndrome: a twin study. Br J Psychiatry 1993; 162:481–486.
8. **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.
9. **Frackiewicz EJ, Shiovitz TM.** Evaluation and management of premenstrual syndrome and premenstrual dysphoric disorder. J Am Pharm Assoc (Wash) 2001; 41:437–447.
10. **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.
11. **Severino SK, Moline ML.** Premenstrual Syndrome: A Clinician's Guide. New York: Guilford Press; 1989.
12. **Deuster PA, Adera T, South-Paul J.** Biological, social, and behavioral factors associated with premenstrual syndrome. Arch Fam Med 1999;8:122–128.
13. **Hargrove JT, Abraham GE.** The incidence of premenstrual tension in a gynecologic clinic. J Reprod Med 1982; 27:721–724.
14. **Muse KN, Cetel NS, Futterman LA, Yen SC.** The premenstrual syndrome. Effects of "medical ovariectomy." N Engl J Med 1984; 311:1345–1349.
15. **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.
16. **Rapkin AJ, Edelmuth E, Chang LC, Reading AE, McGuire MT, Su TP.** Whole-blood serotonin in premenstrual syndrome. Obstet Gynecol 1987; 70:533–537.
17. **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. **Finfgeld 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 paroxetin 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. **Sliutz 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.** Homoeopathic 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. **Oprendek 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.*