

Treating premenstrual dysphoric disorder

Options include drugs targeting serotonin and various types of hormone therapy.

Most women experience some degree of emotional or physical discomfort a few days before and just after their menstrual period begins each month. About 5% of women of childbearing age, however, experience premenstrual symptoms that are so severe they cause significant mental distress and interfere with work, school, or relationships—thereby meeting the criteria for premenstrual dysphoric disorder, or PMDD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV;* see box, page 5). Another 18% to 35% of women suffer from less severe, but nevertheless bothersome, premenstrual symptoms.

Although sometimes dismissed as trivial, PMDD can disrupt a woman's life and relationships so completely, she may despair that life itself is not worth living. About 15% of women with PMDD attempt suicide. Fortunately, treatment options exist for PMDD—but the most effective are not always prescribed.

Risk factors and diagnosis

Brain areas that regulate emotion and behavior are studded with receptors for estrogen, progesterone, and other sex hormones. These hormones affect the functioning of neurotransmitter systems that influence mood and thinking—and in this way may trigger PMDD. But it's not clear why some women are more sensitive than others. Genetic vulnerability likely contributes. Other risk factors for developing PMDD include stress, being overweight or obese, and a past history of trauma or sexual abuse.

A key challenge in diagnosis is differentiating between mild premenstrual symptoms, which may be annoying but are not disabling, and those severe enough to interfere with daily life.

Partly for this reason, the *DSM-IV* includes PMDD in an appendix of conditions needing further study.

Two other common diagnostic schemes list different criteria and use different terminology. The World Health Organization's *International Classification of Diseases, Tenth Edition* describes a disorder called premenstrual tension syndrome, while criteria from the American College of Obstetricians and Gynecologists help to distinguish premenstrual symptoms severe enough to cause impairment.

Regardless of which criteria clinicians use, it's important to rule out other conditions that cause symptoms similar to PMDD, such as depression, dysthymia, anxiety, and hypothyroidism.

Serotonin reuptake inhibitors

Antidepressants that slow the reuptake of serotonin are effective for many women with PMDD. Options include selective serotonin reuptake inhibitors (SSRIs) such as citalopram (Celexa) and fluoxetine (Prozac); the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine (Effexor); and a tricyclic antidepressant that has a strong effect on serotonin, called clomipramine (Anafranil). Studies report that 60% to 90% of women with PMDD respond to treatment with drugs that block reuptake of serotonin, compared with 30% to 40% of those who take a placebo.

Other types of antidepressants, which target neurotransmitters other than serotonin, have not proven effective in treating PMDD. This suggests that serotonin reuptake inhibitors work in some way independent of their antidepressant effect—but their mechanism of action in PMDD remains unclear.

These drugs also alleviate symptoms of PMDD more quickly than depression, which means that women don't necessarily have to take the drugs ev-

KEY POINTS

- Antidepressants that slow the reuptake of serotonin provide effective treatment for premenstrual dysphoric disorder (PMDD).
- These drugs alleviate PMDD more quickly than depression, which means that women don't necessarily have to take the drugs every day.
- Hormone therapies provide additional options, but are generally considered second-line treatments.
- Some dietary and lifestyle changes may also help relieve symptoms.

ery day. Instead, women can take them on an intermittent basis, also known as luteal-phase dosing because it coincides with the roughly 14-day span that begins just after ovulation and ends when menstruation starts.

The decision about whether to take a serotonin reuptake inhibitor every day or on an intermittent basis depends on the type of symptoms a particular woman experiences and if the symptoms of PMDD are superimposed on a more persistent depression. Intermittent dosing is sufficient for treating irritability or mood, but daily medication may be necessary to control somatic symptoms such as fatigue and physical discomfort.

Side effects of serotonin reuptake inhibitors are usually relatively mild and transient. Nausea, for example, typically subsides after several days of taking a drug for the first time—and the problem tends not to recur even when the drug is taken intermittently.

Sexual side effects, such as reduced libido and inability to reach orgasm, can be troubling and persistent, however, even when dosing is intermittent. Of course, PMDD can also lessen sexual desire, so as a practical matter, taking a serotonin reuptake inhibitor on an intermittent basis may still seem

like an acceptable strategy. (For information about how to deal with the sexual side effects of antidepressants, see *Harvard Mental Health Letter*, May 2008.)

If anxiety or insomnia are the prevailing symptoms, a clinician may prescribe a benzodiazepine, such as alprazolam (Xanax), in addition to an SSRI or SNRI. Just keep in mind that benzodiazepines may lead to dependency. This problem can be avoided by monitoring use and—in the case of patients with a history of substance abuse—by discussing risks specific to this subgroup.

Hormone therapy

One of the most common PMDD treatments is progesterone supplementation, but the studies consistently find no evidence that a deficiency of this hormone contributes to the disorder.

The hormone therapies that do seem to work in PMDD act not by countering hormonal abnormalities, but by interrupting aberrant signaling in the hypothalamic-pituitary-gonadal circuit that links brain and ovaries and regulates the reproductive cycle. Largely because of side effects, however, the following strategies are considered second-line treatments for PMDD.

Oral contraceptives. Although frequently prescribed for PMDD because they regulate and stabilize reproductive hormones, oral contraceptives have seldom been studied for this purpose, and it's not clear if they are effective.

The one exception is YAZ, a contraceptive approved by the FDA in 2006 that combines ethinyl estradiol (an estrogen) with drospirenone. Clinical trials have demonstrated that this drug is effective for treating PMDD.

Estrogen. Another option is to inhibit ovulation with estrogen, which can be delivered via a skin patch or via a subcutaneous implant. Doses of es-

Proposed criteria for premenstrual dysphoric disorder (PMDD)

- Five or more of the following symptoms (at least one related to mood) for most menstrual cycles in the past year:
 - Depression
 - Anxiety or tension
 - Sudden mood changes
 - Irritability
 - Loss of interest in daily activities
 - Difficulty concentrating
 - Decreased energy
 - Food cravings and appetite changes
 - Insomnia or sleepiness
 - Physical symptoms, such as breast tenderness or bloating
- Symptoms interfere with activities, work, school, or relationships
- Symptoms are not due to a cyclical exacerbation of another disorder
- Documentation by daily symptom ratings for at least two menstrual cycles

Source: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*

trogen tend to be higher than those prescribed for hormone therapy during menopause, but lower than those used for contraception in childbearing years. If estrogen is prescribed, it should be taken along with a progestogen to reduce risk of uterine cancer—except for women who have had a hysterectomy.

GnRH agonists. Gonadotropin-releasing hormone (GnRH) agonists, which are usually prescribed for endometriosis and infertility, suppress the hormonal cycle—and may be helpful for women whose PMDD symptoms have not responded to other drugs.

Examples of GnRH agonists include buserelin (Suprefact) and goserelin (Zoladex). But these agents can induce a menopausal state, triggering hot flashes and increasing risk of osteoporosis, so they are often supplemented with estrogen and a progestogen—which may trigger PMDD symptoms again in some women.

Under investigation

Lifestyle changes and psychotherapies have not been well studied in PMDD, but a few have shown promise.

Diet. The usual dietary advice given to women with mild or even moderate premenstrual symptoms—such as consuming less caffeine, sugar, or alcohol, and eating smaller, more frequent meals—is unlikely to help women with PMDD.

Preliminary evidence suggests that what *may* help is consuming more high-protein foods or complex carbohydrates to raise levels of tryptophan, a precursor of serotonin and other neurotransmitters.

Aerobic exercise. Although it has not been well studied for PMDD, a wealth of evidence concludes that aerobic physical activity, such as walking, swimming, or biking, tends to improve mood and energy levels.

Supplements. Vitamin B₆, calcium, magnesium supplements, and herbal remedies have all been studied for use in PMDD—but as yet there is no consistent or compelling evidence leading to consensus about their efficacy. ♥

Cunningham J, et al. "Update on Research and Treatment of Premenstrual Dysphoric Disorder," *Harvard Review of Psychiatry* (April 1, 2009): Vol. 17, No. 2, pp. 120–37.*

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For more references, please see www.health.harvard.edu/mentalextra.