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Educational Objectives
After studying the article by Freeman and Sondheimer, the participant will be able to:

- Discuss the epidemiology, clinical presentation, neurobiology, and treatment of premenstrual dysphoric disorder.

This pretest is designed to facilitate your study of the material.

1. **Premenstrual dysphoric disorder is characterized by:**
   a. Physical symptoms
   b. No functional disability
   c. Symptom remission in the follicular phase of the menstrual cycle
   d. The presence of depression

Pretest answer and Posttest on page 39.

Disclosure of Off-Label Usage
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Premenstrual Dysphoric Disorder: Recognition and Treatment

Ellen W. Freeman, Ph.D., and Steven J. Sondheimer, M.D.

Premenstrual dysphoric disorder (PMDD) represents the more severe and disabling end of the spectrum of premenstrual syndrome and occurs in an estimated 2% to 9% of menstruating women. The most frequent PMDD symptoms among women seeking treatment consist of anger/irritability, anxiety/tension, feeling tired or lethargic, mood swings, feeling sad or depressed, and increased interpersonal conflicts. Women who develop PMDD appear to have serotonergic dysregulation that may be triggered by cyclic changes in gonadal steroids. The marked increase in the number of well-designed placebo-controlled studies in the past decade has established several selective serotonin reuptake–inhibiting antidepressants as effective first-line treatments for this disorder. Both continuous dosing and intermittent luteal dosing strategies lead to rapid improvement in symptoms and functioning. The present article provides a brief review of current information on the epidemiology, clinical presentation, neurobiology, and treatment of PMDD.

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The formal medical description of premenstrual syndrome (PMS) and the more severe, related diagnosis of premenstrual dysphoric disorder (PMDD) goes back at least 70 years to a paper presented at the New York Academy of Medicine by Robert T. Frank titled "Hormonal Causes of Premenstrual Tension." The specific term *premenstrual syndrome* appears to date from an article published in 1953 by Dalton and Green in the *British Medical Journal*.[1] Since then, PMS has been a continuous presence in our popular culture, occupying a place that is larger than the research attention accorded it as a medical diagnosis. Nonetheless, a MEDLINE search showed that by 1980, over 500 articles had been published on PMS in the medical literature, and more than 50 treatments had been proposed. Only a very small number of these early studies, though, used standard double-blind, placebo-controlled methodology.

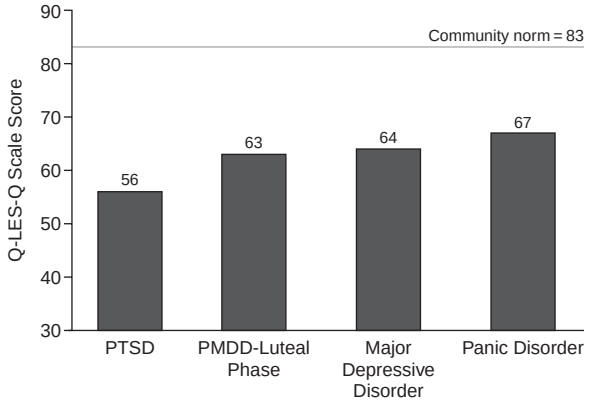
In 1989, the modern era of PMS research began with the appearance in the DSM-III-R of operationally defined diagnostic criteria for PMS (renamed "late luteal phase dysphoric disorder" [LLPDD]). Inclusion of LLPDD was tentative, with the description of the disorder located in the back of the book, in Appendix A, which was reserved for "Proposed Diagnostic Categories Needing Further Study."[2] The introduction of LLPDD as a candidate psychiatric diagnosis was the most controversial of all the revisions in DSM-III-R, with many objecting that its inclusion was an attempt to "pathologize" what was a normal part of a woman's reproductive life. From a scientific standpoint, the operationalized diagnostic criteria were an essential prerequisite for the explosion of descriptive, neurobiological, and treatment research that has followed in the past decade. The result of this research, as highlighted in later sections, is the characterization of a disorder, PMDD, that is more severe and restrictive and requires clear evidence of disability to diagnose.

This article will provide a brief review for clinicians of the prevalence, clinical presentation, pathophysiology, and treatments for PMDD.

EPIDEMIOLOGY

PMDD occurs in 2% to 9% of women of reproductive age and requires clear impairment of functioning.[3–7] Even though the symptoms of PMDD vary from woman to

Figure 1. Premenstrual Dysphoric Disorder Is Associated With Impairment in Quality of Life That Is as Severe as Many Other Psychiatric Disorders[a]



[a]Adapted from Rapaport et al.[102] Quality of life was assessed using the Quality of Life, Enjoyment, and Satisfaction scale (Q-LES-Q).
Abbreviations: PMDD = premenstrual dysphoric disorder, PTSD = posttraumatic stress disorder.

Table 1. Diagnostic Criteria for Premenstrual Dysphoric Disorder[a]

A.	Presence of 5 of 11 depressive, anxiety, cognitive, or physical symptoms, with at least 1 of 4 specific symptoms* experienced in most of the menstrual cycles for the past year. The symptoms may begin a week before menses and must completely remit within a few days after the onset of menses.
	Depressive, anxiety, cognitive, and physical symptoms
	*Markedly depressed mood, feelings of hopelessness, self-deprecation
	*Suddenly feeling sad or tearful, with increased sensitivity to personal rejection
	Decreased interest in usual activities
	Lethargy, fatigue, marked lack of energy
	Marked changes in appetite and cravings for certain foods
	Insomnia or hypersomnia
	*Marked anxiety, tension, feeling of being "keyed up" or "on edge"
	*Persistent or marked irritability, anger, increased interpersonal conflicts
	Feeling overwhelmed or out of control
	Subjective sense of having difficulty concentrating
	Breast tenderness or swelling
	Headaches
	Joint or muscle pain
	Weight gain
	"Bloated" feeling
B.	Symptoms interfere with social, occupational, sexual, or school functioning.
C.	Symptoms are discretely related to menstrual cycle and are not merely worsening of preexisting depression, anxiety, or personality disorder.
D.	Criteria A, B, and C must be confirmed prospectively by daily ratings for at least 2 consecutive menstrual cycles.

[a]Adapted with permission from the American Psychiatric Association.[21]

woman, the symptoms experienced by each individual have been shown to be relatively consistent from cycle to cycle.[8,9]

PMDD typically starts in the early-to-mid 20s, though it may begin at any time after menarche.[3,10,11] Though little information is available from prospective, longitudinal studies, clinical evidence suggests that PMDD tends to be a chronic illness that continues until menopause, frequently showing gradual, though episodic, worsening over time. The symptoms of PMDD tend to remit during pregnancy.[12]

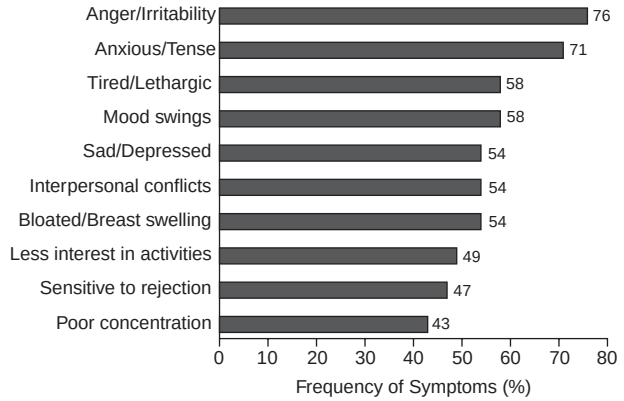
The degree of variability in the incidence of PMS/PMDD from culture to culture and in its cross-cultural clinical presentation has not been systematically studied at this point. Available data suggest that PMS/PMDD occurs across cultures at approximately comparable rates.[13–20] Cultural and psychosocial factors appear to influence the proportion and intensity of physical versus behavioral symptoms, as well as the degree of illness behavior and medical help-seeking associated with the PMS-type symptoms.

CLINICAL PRESENTATION AND RECOGNITION

PMS refers to the milder emotional and physical symptoms that occur in more than half of all women during the week or two before menstruation. Although these symptoms may cause significant distress and even some degree of functional impairment, by definition, they are not severe enough to result in significant disability.[2] PMDD, however, represents the more severe end of the diagnostic spectrum of premenstrual syndromes and is characterized by mood symptoms that are sufficiently severe that they result in significant disruption of a woman's normal level of functioning across family, social, and occupational domains. The degree of disability and impairment in quality of life reported by women with PMDD is very similar to what is reported by patients with other depressive or anxiety disorders (see Figure 1, which shows impairment in quality of life on the Quality of Life, Enjoyment, and Satisfaction scale). The DSM-IV diagnostic criteria for PMDD (Table 1) require a minimum of 5 symptoms that occur during the premenstrual phase of the cycle and stop at the onset of menses, or shortly thereafter. It should be emphasized that premenstrual worsening of an underlying depressive or anxiety disorder, which is common, does not qualify as a diagnosis of PMDD.

The requirement that the premenstrual symptoms significantly interfere with functioning is the most effective way to diagnostically determine that PMDD is present. In addition, it is helpful to obtain a quantitative index of the most common presenting symptoms. These data are summarized in Figure 2 and come from women diagnosed with PMDD who were entering a treatment study.[22] As can be seen, irritable, tense, tired, sad, and hypersensitive feelings are common and are associated with mood

Figure 2. Top 10 Luteal Phase Symptoms Reported by Women Diagnosed With Premenstrual Dysphoric Disorder[a]



[a]Adapted from Halbreich et al.[22] and data on file, Pfizer Inc, New York, N.Y. Proportion with moderate-to-severe symptom intensity on at least 3 of the 6 days leading to onset of menses.

Table 2. Screening Test for Premenstrual Dysphoric Disorder (PMDD): Patient Version

FIRST: Check all the symptoms from both the A-List and the B-List that you have on a daily basis during the week before your period starts:

A-List symptoms (during week leading up to my period)
- ❑ I feel much more depressed and down in my mood
- ❑ I feel anxious, tense, "keyed up," or "on edge"
- ❑ I feel hypersensitive (to rejection or criticism), or I feel very unstable and unpredictable in my emotions
- ❑ I feel much more irritable or I get angry easily

Number of A-List symptoms I checked = _____

B-List symptoms (during week leading up to my period)
- ❑ I am much less interested than usual in my hobbies and daily activities
- ❑ I find it much harder to concentrate on things
- ❑ I feel much more tired and low in energy
- ❑ I have had a tendency to crave carbohydrates or go on eating binges
- ❑ I find myself oversleeping or taking naps, or I'm not sleeping well at night
- ❑ I have been feeling very overwhelmed or out of control
- ❑ During the week leading up to my period, I am very bothered by at least 2 of the following physical symptoms:
  - ❑ Breast tenderness or swelling
  - ❑ Increased headaches
  - ❑ Joint or muscle pain
  - ❑ Feeling "bloated"
  - ❑ Weight gain

Number of B-List symptoms I checked = _____

SECOND: Answer these 4 questions (circle the correct answer):

1. Does the number of A-List symptoms PLUS the number of B-List symptoms add up to 5 or more?	Yes	No
2. Is at least 1 of the symptoms you checked on the A-List?	Yes	No
3. Do most of the symptoms you checked disappear within 3 days of the start of your period?	Yes	No
4. When you are having these symptoms, do they interfere with your ability to function normally and do your daily activities?	Yes	No

If the answer to ALL 4 questions is YES, then you may have PMDD.

Speak with your doctor about what the next step is to get help with your problem.

swings and high levels of interpersonal conflict. A cardinal diagnostic feature of PMDD is the marked difference in the frequency of moderate-to-severe symptoms during the follicular versus luteal phases. In fact, the frequency of each of the symptoms shown in Figure 2 was below 2% in the follicular phase (reference 22 and data on file, Pfizer Inc, New York, N.Y.).

Because of the large number of symptoms that occur in the diagnosis of PMDD, it is helpful to have women complete, prospectively, a daily record of the frequency and severity of PMDD symptoms throughout their menstrual cycle. However, a 1-time screening test is typically more feasible in clinical practice and can be followed by daily symptom ratings when the woman indicates a positive screen for PMDD. Table 2 shows an example of a 1-time screening form that may be self-administered by the patient. The diagnostic and treatment steps that may be taken if a patient has a positive score on this screening form are discussed in a later section.

DIFFERENTIAL DIAGNOSIS OF PMDD

Establishing the diagnosis of PMDD can be difficult because the disorder has such a wide and variable range of symptoms (see Table 1 for the DSM-IV criteria) and because there are no confirmatory laboratory tests or signs on physical examination. There is no consensus agreement on how comprehensive the medical and laboratory screening should be before the diagnosis can be made. It should be noted that women with PMDD almost always have normal levels of ovarian hormones.

There is little available research that empirically establishes clinical features that might increase the likelihood that a PMDD diagnosis is present, though some studies suggest that PMDD is more likely to occur in patients with a family history that is positive for either PMDD or major depression.[23]

Perhaps the most crucial factor in establishing the diagnosis of PMDD is making sure that the patient is not presenting with another underlying medical or psychiatric diagnosis that is simply showing a premenstrual exacerbation in symptoms. For example, more than 50% of patients suffering from major depression report a clear-cut premenstrual exacerbation in their depressive symptoms.[24] However, the presence of another medical or psychiatric disorder does not preclude the diagnosis of PMDD if the PMDD symptoms are distinct from the other disorder.

Table 3 summarizes the medical and psychiatric conditions that most frequently present with premenstrual exacerbation, or whose symptoms mimic some of the typical symptoms of PMDD. As a rule, these disorders should be

Table 3. Differential Diagnosis of Premenstrual Dysphoric Disorder (PMDD)[a]

The following underlying psychiatric or medical disorders may present with a pattern of premenstrual exacerbation that mimics the monthly pattern of PMDD
Psychiatric disorders
Major depression
Dysthymic disorder
Bipolar II
Cyclothymic disorder
Panic disorder or generalized anxiety disorder
Bulimia
Posttraumatic stress disorder
Psychosocial: current victim of physical abuse or history of sexual abuse
Medical disorders
Endocrine disorders such as hypothyroidism or diabetes
Autoimmune or collagen vascular disorders
Anemia
Chronic fatigue syndrome
Endometriosis

[a]From Endicott.[27]

treated first before treatment of PMDD is initiated, unless one drug has proven efficacy in both conditions.

The most well-validated and time-efficient screening instrument for the range of depression- and anxiety-related illnesses commonly seen in the primary care setting is the Patient Health Questionnaire (PHQ),[25,26] a patient-rated form of the Primary Care Evaluation of Mental Disorders (PRIME-MD). If the woman meets screening criteria for PMDD but does not screen positive for other psychiatric illness on the PHQ, then a routine medical history, review of systems, and physical examination should be sufficient to rule out the medical conditions listed in Table 3 whose clinical presentations most frequently overlap with PMDD. The differential diagnostic rule is that PMDD is a common diagnosis and should not be viewed as a "diagnosis of exclusion" arrived at only at the end of a very long decision tree. Key characteristics that help distinguish PMDD are the distinctive premenstrual-postmenstrual "on-off" nature of the symptomatology and the fact that the symptoms are severe enough that they cause clear impairment in functioning.

PATHOPHYSIOLOGY

The precise etiology of PMDD is currently unknown. It is unlikely that the illness is due to a "hormonal imbalance" per se. Despite multiple studies, no consistent alterations in gonadal steroids have been identified in PMDD. Instead, it appears that normal cyclical changes in sex hormones serve as a trigger.

Why are some women vulnerable to this cyclical hormonal trigger and others are not? The current predominant hypothesis is that women who develop PMDD have an underlying vulnerability in central nervous system neurotransmitter systems, most notably the serotonergic system. Changes in gonadal steroids that occur during the luteal phase appear to amplify underlying serotonergic dysregulation.[28–35] The underlying PMDD vulnerability appears to have a strong genetic component.[36–40] It should be noted that, while major depression and PMDD share environmental and genetic risk factors, the correlation between the 2 diagnoses appears (based on current evidence) to be surprisingly weak.[39]

Many of the typical symptoms of PMDD, most notably irritability and impulse dyscontrol, depressed mood, and carbohydrate craving, have been linked to serotonergic dysfunction. As will be discussed in a subsequent section, serotonergic antidepressants have shown significant efficacy in the treatment of PMDD, while antidepressants that act primarily by noradrenergic mechanisms have not shown efficacy.[41,42] This is persuasive evidence that improvement in PMDD is not simply due to a nonspecific antidepressant effect, but rather to potent activity targeting the serotonergic system.

TREATMENT

Current Nonpharmacologic and Over-the-Counter Treatments

Table 4 summarizes commonly used nonpharmacologic strategies for managing PMDD.[43–45] They should generally be suggested for patients with less severe variants of PMS. Few have been evaluated in controlled studies, and scientific evidence of their effectiveness for PMDD is lacking. Cognitive therapy, therapy with bright full-spectrum lights, and relaxation therapy all show promise based on positive pilot studies, but again, definitive studies are not available at this time.

Table 5 briefly summarizes miscellaneous agents that have been studied for the treatment of PMDD, many of them over-the-counter (OTC) treatments.[43,46–48] Again, some treatments such as calcium, magnesium, vitamin E, and nonsteroidal anti-inflammatory drugs show promise based on preliminary studies in PMS.

Should nonpharmacologic or OTC management be the initial recommendation for all women who present with PMDD? This question is controversial, but a reasonable answer is "not usually." A woman who meets the criteria for a diagnosis of PMDD has indicated that her symptoms are severe and persistent enough to cause disability. To recommend OTC or other nonpharmacologic treatment as the primary treatment may be interpreted by the woman with PMDD as minimizing her symptoms, which are not serious enough to warrant "real" treatment. A nonpharmacologic treatment may be offered as an option (properly qualified as lacking scientific evidence of efficacy) with the aim of changing to pharmacologic treatment if there is no significant improvement within 1 or 2 menstrual cycles. Nonpharmacologic treatments such as stress reduction techniques and cognitive therapies may also be

Table 4. Nonpharmacologic Management of Premenstrual Dysphoric Disorder[a]

Reduce consumption of:
Caffeine
Salt
Chocolate and refined sugars
Alcohol (may alter serotonergic function and increase anger/irritability)
Increase consumption of:
Complex carbohydrates (small meals)
Increase exercise:
Daily aerobic (moderate)
Other methods:
Relaxation and stress reduction techniques (massage, reflexology)
Cognitive therapy
Marital counseling
Light therapy (bright, full-spectrum lights)
Biofeedback
Sleep deprivation

[a]From Pearlstein and Steiner,[43] Blake et al.,[44] and Lam et al.[45]

Table 5. Miscellaneous Treatments of Premenstrual Dysphoric Disorder[a]

Treatments	Strength of Evidence
Dietary supplements	
Vitamin B_6: 100–200 mg daily	B
Calcium: 1000–1200 mg daily	B
Magnesium: 200 or 360 mg daily, starting 14 days before next menses	B
Vitamin E: 400–800 IU daily	C
OTC analgesics (naproxen, mefenamic acid, etc)	C

[a]Data from Pearlstein and Steiner,[43] Thys-Jacobs et al.,[46] De Souza et al.,[47] and Facchinetti et al.[48] A = ≥ 2 adequately powered positive randomized controlled trials, B = limited or conflicting data, and C = insufficient data.
Abbreviation: OTC = over-the-counter.

helpful in conjunction with medication, but again, there is no scientific information on adjunctive therapies for PMDD at this time.

Anovulatory Treatments and Gonadal Steroids

Symptoms of PMDD may remit if ovulation is suppressed. The various treatments that have been employed to achieve an anovulatory state are summarized in Table 6. The adverse events associated with gonadotropin-releasing hormone (GnRH) agonist therapy, together with the fact that chronically low estrogen levels increase the risk of both cardiovascular illness and osteoporosis, make this a third-line treatment for PMDD. Attempts to reduce the long-term risk of GnRH agonist treatments by estrogen add-back therapy have been reported in several very small studies, but whether the very low doses of add-back therapy abolish the positive therapeutic effect remains unclear.[49–51] The synthetic estrogen danazol achieves the same anovulatory effect as leuprolide, but is associated with the same long-term risks.

Suppression of ovulation has also been achieved by various other methods including oral contraceptives[52–54] and estradiol implants.[55] In general, oral contraceptives (especially new, lower-dose formulations) have not been carefully studied in comparably large, well-designed trials. One novel approach involves use of a spironolactone-like progestin with antiandrogenic and anti-mineralocorticoid activity, which may reduce PMDD symptoms, though confirmatory study is needed.[56] Evidence from a large, placebo-controlled study,[57] as well as a recent meta-analysis,[58] suggests that micronized progesterone has no efficacy in the treatment of PMDD.

Anxiolytics

There is evidence that alprazolam, taken during the luteal phase, may have efficacy in the treatment of PMDD in doses of 0.25 mg b.i.d. up to 0.5 mg t.i.d. (anxiolytics and antidepressants used for the treatment of PMDD are briefly summarized in Table 7). Evidence of efficacy, though, is mixed,[59–63] with some studies showing no beneficial effect on mood, possibly because of differences in dosing and/or patient groups studied. One study provides experimental evidence that alprazolam might increase food cravings and caloric intake in some women.[64] Modest efficacy, coupled with its mild cognitive and memory-impairing effects and its potential for physical dependence and withdrawal, makes this drug a second-line treatment for PMDD. One recent study observed no withdrawal symptoms when intermittent luteal dosing was used.[65]

Buspirone has been proposed as a treatment option for PMDD based on its serotonergic mechanism of action. Pilot studies suggest possible efficacy, but the benefit of buspirone in PMDD remains unconfirmed.[66,67] Buspirone has a more favorable cognitive and psychomotor profile than alprazolam, but the need for b.i.d. or t.i.d. administration makes its use less convenient. Buspirone should be considered a second-line treatment.

Antidepressants

Fluoxetine has shown efficacy in the treatment of PMDD based on 3 large double-blind, placebo-controlled trials and a series of small double-blind pilot studies.[68–73] The first large trial[74] examined the efficacy of 2 doses of fluoxetine (20 mg and 60 mg) administered on a daily basis throughout the menstrual cycle. Both doses were significantly superior to placebo in reducing symptoms of tension, irritability, and dysphoria. However, the 60-mg dose was not tolerated well enough to be a useful treatment. The dose of 20 mg is much better tolerated and is the appropriate therapeutic dose for PMDD. A second large trial[75] evaluated the efficacy of the enteric-coated 90-mg dose of fluoxetine administered either once or twice during the 2 premenstrual weeks. The results of this trial found significant efficacy when 2 doses were administered, but no difference from placebo when treatment consisted of 1 dose. The lack of efficacy of the single

Table 6. Pharmacotherapy of Premenstrual Dysphoric Disorder (PMDD): Gonadal Steroids[a]

Therapy	Proposed Mechanism	Comments
Leuprolide, buserelin, goserelin, nafarelin	Depot injections monthly (or intranasal Rx) lead to down-regulation of GnRH receptors in hypothalamus, which leads to lower FSH and LH, which lowers estrogen and progesterone. GnRH agonist: eg, leuprolide, buserelin, goserelin, nafarelin	Chronic low estrogen levels increase risk of osteoporosis Not effective with comorbid depression
GnRH agonist plus estrogen/progesterone add-back therapy	Estrogen/progesterone added to counter the risks of low estrogen	Lessens hypoestrogenic symptoms
Danazol	Synthetic estrogen with mixed evidence for efficacy. Efficacy appears linked to anovulation	Side effects include weight gain, acne, facial hair, nausea
Progesterone	Hypothesized mechanism is by means of barbiturate-like metabolites such as allopregnanolone Administered as micronized progesterone to increase bioavailability	Efficacy not demonstrated in meta-analysis of 14 placebo-controlled trials[55]
Oral contraceptives	Anovulation; progestin effect on endometrium	No consistent scientific evidence of efficacy for PMDD; may worsen PMDD symptoms. Improves dysmenorrhea; less bleeding. Continuous use of oral contraceptives may reduce some symptoms

[a]From references 49 through 58.
Abbreviations: FSH = follicle-stimulating hormone, GnRH = gonadotropin-releasing hormone, LH = luteinizing hormone.

Table 7. Pharmacotherapy Options for Treatment of Premenstrual Dysphoric Disorder[a]

Therapy	Dosage	Dosing Strategy	Comments
Serotonergic antidepressants			
Fluoxetine	20 mg once daily	Continuous, Luteal	Demonstrated efficacy. Long half-life a consideration if rapid clearance is required
	90 mg enteric-coated	Luteal (day 14 and day 7 only)	Evidence of efficacy found for 2 weekly doses in luteal phase
Sertraline	50–150 mg once daily	Continuous, Luteal	Demonstrated efficacy for continuous and luteal-phase dosing
Paroxetine	20–30 mg once daily	Continuous, Luteal	Demonstrated efficacy
Citalopram	10–20 mg once daily	Continuous	Preliminary evidence of efficacy
Fluvoxamine	25–50 mg once daily	Continuous	Insufficient data
Venlafaxine	50–200 mg twice daily	Continuous	Demonstrated efficacy for continuous dosing
Anxiolytics			
Alprazolam	0.25–1.0 mg tid	Luteal	Conflicting evidence of efficacy. Risk of dependence and withdrawal, which may be reduced by strict luteal-phase dosing
Buspirone	5–10 mg tid	Luteal	Insufficient data
Miscellaneous			
Spironolactone	25 mg qid	Luteal	Conflicting evidence of efficacy
Bromocriptine	1.25–2.5 mg daily or bid	Luteal	High risk of side effects
Tibolone	2.5 mg daily		Synthetic steroid (specific estrogen receptor modulator); limited evidence of efficacy

[a]Data from references 59–86 and references 99–101.

90-mg dose may be attributable to its administration on premenstrual day 7.

Fluoxetine has been studied using an intermittent dosing strategy in 1 pilot study[76] and in a recently published large trial.[77] The intermittent dosing strategy administered fluoxetine in the symptomatic premenstrual phase only, i.e., the luteal phase of the menstrual cycle, starting on day 14 and continuing to the menstrual flow. The appeal of luteal-phase dosing is that women may reduce by 50% or more their monthly exposure to drug. Whether the long elimination half-life of fluoxetine (4–6 days) and its active metabolite (norfluoxetine, 4–16 days) reduces the benefit of premenstrual dosing, compared with selective serotonin reuptake inhibitors (SSRIs) with shorter half-lives, has not been evaluated in controlled trials.

Irrespective of dosing strategy, fluoxetine has shown broad efficacy in the treatment of the full array of PMDD symptoms, including improvement in physical symptoms[78] and in ability to function during the late luteal phase of the cycle. The 20-mg dose of fluoxetine should be considered a first-line treatment for PMDD. Currently, it is marketed under the brand name Sarafem to commercially distinguish it from Prozac.

Another medication that is a first-line treatment of PMDD is sertraline, which has demonstrated efficacy across all the major symptom clusters of PMDD, including depression, anger/irritability, appetite and food cravings, concentration and memory effects, and physical symptoms. Improvement in PMDD symptoms has been shown, within the first cycle, to lead to significant improvement in both psychosocial functioning and quality of life.[79]

The benefit of intermittent luteal-phase (premenstrual) dosing has been shown in several pilot studies,[80–83] and in 1 large placebo-controlled study.[84] Premenstrual dosing is typically initiated approximately 14 days prior to the anticipated onset of menstrual bleeding, though data from 1 controlled study suggest that initiating treatment at the time of symptom onset may be just as effective.[85] Sertraline is a significantly effective treatment of PMDD, using both continuous dosing (with a dosage range of 50–150 mg) and premenstrual dosing (with a dosage range of 50–100 mg). Sertraline is very well tolerated using both dosing strategies. Cross-study comparisons (requiring confirmation in head-to-head comparisons of alternative dosing strategies) suggest that adverse events are notably lower when luteal-phase dosing is employed, with 3 of 4 patients reporting no side effects whatsoever, and the remaining patients reporting side effects that were mostly mild and transient.[84,85] Finally, it should be noted that an analysis of symptoms in the first 3 days after stopping sertraline found that abrupt discontinuation did not result in withdrawal symptoms.[86]

General Principles of Treatment

The effective dosage range for treatment of PMDD with fluoxetine and sertraline appears to be somewhat lower than the doses used in other psychiatric disorders such as major depression or obsessive-compulsive disorder. Many clinicians initiate fluoxetine treatment at 10 mg and sertraline at 25 mg. For sertraline, there is evidence from a large crossover study[85] that the 25-mg dose is as effective in treating the PMS/PMDD spectrum as the 50-mg dose, using either a continuous or a premenstrual dosing strategy. A distinctive feature of PMDD treatment with both drugs is the rapid response, which is within 2 to 3 days in the majority of patients.[81–84] It is this rapid response that makes intermittent premenstrual dosing an effective treatment strategy.

The decision as to which dosing strategy to choose for a patient presenting with PMDD must be individualized. Certainly if PMDD is complicated by another comorbid depressive or anxiety disorder, then continuous dosing is indicated. Similarly, if the duration of PMDD symptoms is highly variable, then continuous dosing may also be indicated. In most patients presenting with only PMDD, intermittent premenstrual dosing is highly effective, very well tolerated, and is likely to be the treatment of choice.

There are insufficient data yet available to guide physicians as to what is the appropriate duration of treatment in women whose PMDD has successfully responded to a course of fluoxetine or sertraline. Preliminary studies of sertraline and fluoxetine[87,88] suggest that treatment response is maintained over the long-term, but relapse prevention studies have not been reported for either continuous or premenstrual dosing. It seems reasonable at this point to recommend occasional 1- or 2-cycle treatment "holidays" to permit reassessment of the ongoing need for treatment. Premenstrual dosing would appear to lend itself particularly well to this empirical approach.

Other SSRIs

Effectiveness for PMS or PMDD is reported for other SSRIs (e.g., citalopram,[89,90] paroxetine,[42,95] fluvoxamine[91]) and serotonergic antidepressants (nefazodone,[67,93,94] clomipramine[92]), although the availability of data from large, placebo-controlled trials is currently limited. To date, fluoxetine and sertraline are the only SSRIs with U.S. Food and Drug Administration (FDA) approval for the treatment of PMDD.

Finally, a recently published report[96] has found venlafaxine to have significant efficacy in the treatment of PMDD, based on a large, placebo-controlled trial. This study was conducted with twice-daily dosing in the range of 50 to 200 mg. An extended-release formulation of venlafaxine is now available, but there are no data on its use for the treatment of PMDD.

SSRIs and Pregnancy

All SSRI antidepressants carry an FDA pregnancy category C rating (systematic studies in pregnant women and/or animals are not available; drugs should be given only if the potential benefits justify the potential risks to the fetus.). No evidence to date suggests that SSRIs are associated with fetal risk, but insufficient prospective, well-controlled data are available to provide more definitive guidelines on this issue.[97] Since approximately 50% of pregnancies are unintended,[98] women beginning treatment should be counseled about possible risks and encouraged to discontinue treatment immediately on discovering that they may be pregnant.

CONCLUSION

Over the past decade, PMDD has been established as a menstrually related disorder associated with moderate-to-marked disability. The pathophysiology of PMDD, involving cyclical changes in gonadal steroids interacting with underlying serotonergic dysregulation, is beginning to be elucidated. The advent of operationalized criteria for PMDD and the recent completion of several large controlled trials have, for the first time, provided physicians with highly effective treatment options.

Drug names: alprazolam (Xanax and others), bromocriptine (Parlodel and others), buspirone (BuSpar and others), citalopram (Celexa), clomipramine (Anafranil and others), danazol (Danocrine and others), fluoxetine (Sarafem and others), fluvoxamine (Luvox and others), goserelin (Zoladex), leuprolide (Lupron, Eligard, and others), mefenamic acid (Ponstel), nafarelin (Synarel), naproxen (Anaprox, Naprosyn, and others), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), spironolactone (Aldactone and others), venlafaxine (Effexor).

REFERENCES

1. Dalton K, Greene R. The premenstrual syndrome. Br Med J 1953;1:1007
2. Spitzer RL, Severino SK, Williams JB, et al. Late luteal phase dysphoric disorder and DSM-III-R. Am J Psychiatry 1989;146:892–897
3. Logue CM, Moos RH. Perimenstrual symptoms: prevalence and risk factors. Psychosom Med 1986;48:388–414
4. Ramcharan S, Love EJ, Fick GH, et al. The epidemiology of premenstrual symptoms in a population-based sample of 2650 urban women: attributable risk and risk factors. J Clin Epidemiol 1992;45:377–392
5. Woods NF, Most A, Dery GK. Prevalence of perimenstrual symptoms. Am J Public Health 1982;72:1257–1264
6. Johnson SR. The epidemiology and social impact of premenstrual symptoms. Clin Obstet Gynecol 1987;30:369–384
7. Rivera-Tovar AD, Frank E. Late luteal phase dysphoric disorder in young women. Am J Psychiatry 1990;147:1634–1636
8. Mira M, Abraham S, McNeil D, et al. The inter-relationship of premenstrual symptoms. Psychol Med 1995;25:947–955
9. Bloch M, Schmidt PJ, Rubinow DR. Premenstrual syndrome: evidence for symptom stability across cycles. Am J Psychiatry 1997;154: 1741–1746
10. Yonkers KA, Halbreich U, Freeman E, et al, for the Sertraline Premenstrual Dysphoric Collaborative Study Group. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. JAMA 1997;278:983–988
11. Freeman E, Sondheimer S, Rickels K, et al. Ineffectiveness of progesterone suppository treatment for premenstrual syndrome. JAMA 1990;264:349–353
12. Cohen LS. Pharmacologic treatment of depression in women: PMS, pregnancy, and the postpartum period. Depress Anxiety 1998;8(suppl 1):18–26
13. van den Akker OB, Eves FF, Service S, et al. Menstrual cycle symptom reporting in three British ethnic groups. Soc Sci Med 1995;40: 1417–1423
14. Banerjee N, Roy KK, Takkar D. Premenstrual dysphoric disorder: a study from India. Int J Fertil Women Med 2000;45:342–344
15. Khella AK. Epidemiologic study of premenstrual symptoms. J Egypt Public Health Assoc 1992;67:109–118
16. Rupani NP, Lema VM. Premenstrual tension among nurses in Nairobi, Kenya. East Afr Med J 1993;70:310–313
17. Chang AM, Holroyd E, Chau JP. Premenstrual syndrome in employed Chinese women in Hong Kong. Health Care Women Int 1995;16: 551–561
18. Montero P, Bernis C, Loukid M, et al. Characteristics of menstrual cycles in Moroccan girls: prevalence of dysfunctions and associated behaviours. Ann Hum Biol 1999;26:243–249
19. Chau JP, Chang AM, Chang AM. Relationship between premenstrual tension syndrome and anxiety in Chinese adolescents. J Adolesc Health 1998;22:247–249
20. McMaster J, Cormie K, Pitts M. Menstrual and premenstrual experiences of women in a developing country. Health Care Women Int 1997;18:533–541
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
22. Halbreich U, Bergeron R, Yonkers KA, et al. Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder [poster]. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology; Dec 10–14, 2000; San Juan, Puerto Rico
23. Deuster PA, Adera T, South-Paul J. Biological, social, and behavioral factors associated with premenstrual syndrome. Arch Fam Med 1999;8:122–128
24. Endicott J. The menstrual cycle and mood disorders. J Affect Disord 1993;29:193–200
25. Spitzer RL, Williams JB, Kroenke K, et al. Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. Am J Obstet Gynecol 2000;183:759–769
26. Spitzer RL, Kroenke K, Williams JBW, and the Patient Health Questionnaire Primary Care Study Group. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999;282:1737–1744
27. Endicott J. Differential diagnosis and comorbidity. In: Gold JH, Severino SK, eds. Premenstrual Dysphorias: Myths and Realities. Washington, DC: American Psychiatric Press;1994:3–17
28. Rojansky N, Halbreich U, Zander K, et al. Imipramine receptor binding and serotonin uptake in platelets of women with premenstrual changes. Gynecol Obstet Invest 1991;31:146–152
29. Bancroft J, Cook A, Davidson D, et al. Blunting of neuroendocrine responses to infusion of L-tryptophan in women with perimenstrual mood change. Psychol Med 1991;21:305–312
30. Ashby CR, Carr LA, Cook CL, et al. Alteration of platelet serotonergic mechanism and monoamine oxidase activity in premenstrual syndrome. Biol Psychiatry 1988;24:225–233
31. Menkes DB, Coates DC, Fawcett JP. Acute tryptophan depletion aggravates premenstrual syndrome. J Affect Disord 1994;32:37–44
32. Fitzgerald M, Malone K, Li Shuhua, et al. Blunted serotonin response to fenfluramine challenge in premenstrual dysphoric disorder. Am J Psychiatry 1997;154:556–558
33. Steiner M, Yatham LN, Coote M, et al. Serotonergic dysfunction in women with pure premenstrual dysphoric disorder: is the fenfluramine challenge test still relevant? Psychiatry Res 1999;87:107–115
34. Rapkin AJ, Edelmuth E, Chang LC, et al. Whole blood serotonin in premenstrual syndrome. Obstet Gynecol 1987;70:533–537
35. Kouri EM, Halbreich U. State and trait serotonergic abnormalities in women with dysphoric premenstrual syndromes. Psychopharmacol Bull 1997;33:767–770
36. Dalton K, Dalton ME, Guthrie K. Incidence of the premenstrual syndrome in twins. Br Med J (Clin Res Ed) 1987;295:1027–1028
37. van den Akker OB, Stein GS, Neale MC, et al. Genetic and environmental variation in menstrual cycle: histories of two British twin samples. Acta Genet Med Gemellol 1987;36:541–548
38. Kendler KS, Silberg JL, Neale MC, et al. Genetic and environmental factors in the aetiology of menstrual, premenstrual and neurotic symptoms: a population-based twin study. Psychol Med 1992;22:85–100
39. Kendler KS, Karkowski LM, Corey LA, et al. Longitudinal population-based twin study of retrospectively reported premenstrual symptoms and lifetime major depression. Am J Psychiatry 1998;155:1234–1240
40. Condon JT. The premenstrual syndrome: a twin study. Br J Psychiatry 1993;162:481–486
41. Freeman EW, Rickels K, Sondheimer SJ, et al. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: a randomized controlled trial. Arch Gen Psychiatry 1999;56:932–939
42. Eriksson E, Hedberg MA, Andersch B, et al. The serotonin reuptake inhibitor paroxetine is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. Neuropsychopharmacology 1995;12:167–176
43. Pearlstein T, Steiner M. Non-antidepressant treatment of premenstrual syndrome. J Clin Psychiatry 2000;61(suppl 12):22–27
44. Blake F, Salkovskis P, Gath D, et al. Cognitive therapy for premenstrual syndrome: a controlled trial. J Psychosom Res 1998;45:307–318
45. Lam RW, Carter D, Misri S, et al. A controlled study of light therapy in women with late luteal phase dysphoric disorder. Psychiatry Res 1999;86:185–192
46. Thys-Jacobs S, Starkey P, Bernstein D, et al. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. Am J Obstet Gynecol 1998;179:444–452
47. De Souza MC, Walker AF, Robinson PA, et al. A synergistic effect of a daily supplement for 1 month of 200 mg magnesium plus 50 mg vitamin B6 for the relief of anxiety-related premenstrual symptoms: a random-

ized, double-blind, crossover study. J Womens Health Gend Based Med 2000;9:131–139
48. Facchinetti F, Borella P, Sances G, et al. Oral magnesium successfully relieves premenstrual mood changes. Obstet Gynecol 1991;78:177–181
49. Leather AT, Studd JW, Watson NR, et al. The treatment of severe premenstrual syndrome with goserelin with and without 'add-back' estrogen therapy: a placebo-controlled study. Gynecol Endocrinol 1999;13:48–55
50. Schmidt PJ, Nieman LK, Danaceau MA, et al. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N Engl J Med 1998;338:209–216
51. Mezrow G, Shoupe D, Spicer D, et al. Depot leuprolide acetate with estrogen and progestin add-back for long-term treatment of premenstrual syndrome. Fertil Steril 1994;62:932
52. Serfaty D, Vree ML. A comparison of the cycle control and tolerability of two ultra low-dose oral contraceptives containing 20 micrograms ethinylestradiol and either 150 micrograms desogestrel or 75 micrograms gestodene. Eur J Contracept Reprod Health Care 1998;3:179–189
53. Graham CA, Sherwin BB. A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. J Psychosom Res 1992;36:257–266
54. Backstrom T, Hansson-Malmstrom Y, Lindhe BA, et al. Oral contraceptives in premenstrual syndrome: a randomized comparison of triphasic and monophasic preparations. Contraception 1992;46:253–268
55. Magos AL, Brincat M, Studd JW. Treatment of the premenstrual syndrome by subcutaneous estradiol implants and cyclical oral norethisterone: placebo controlled study. Br Med J 1986;292:1629–1633
56. 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
57. Freeman EW, Rickels K, Sondheimer SJ, et al. A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. JAMA 1995;274:51–57
58. Wyatt K, Dimmock P, Jones P, et al. Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. BMJ 2001;323:776–780
59. Berger CP, Presser B. Alprazolam in the treatment of two subsamples of patients with late luteal phase dysphoric disorder: a double-blind, placebo-controlled crossover study. Obstet Gynecol 1994;84:379–385
60. Schmidt PJ, Grover GN, Rubinow DR. Alprazolam in the treatment of premenstrual syndrome: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 1993;50:467–473
61. Harrison WM, Endicott J, Nee J. Treatment of premenstrual dysphoria with alprazolam: a controlled study. Arch Gen Psychiatry 1990;47: 270–275
62. Smith S, Rinehart JS, Ruddock VE, et al. Treatment of premenstrual syndrome with alprazolam: results of a double-blind, placebo-controlled, randomized crossover clinical trial. Obstet Gynecol 1987;70:37–43
63. Diegoli MS, da Fonseca AM, Diegoli CA, et al. A double-blind trial of four medications to treat severe premenstrual syndrome. Int J Gynaecol Obstet 1998;62:63–67
64. Evans SM, Haney M, Levin FR, et al. Mood and performance changes in women with premenstrual dysphoric disorder: acute effects of alprazolam. Neuropsychopharmacology 1998;19:499–516
65. Rickels K, Freeman EW. Prior benzodiazepine exposure and benzodiazepine treatment outcome. J Clin Psychiatry 2000;61:409–413
66. Rickels K, Freeman E, Sondheimer S. Buspirone in treatment of premenstrual syndrome. Lancet 1989;1:777
67. Landen M, Eriksson O, Sundblad C, et al. Compounds with affinity for serotonergic receptors in the treatment of premenstrual dysphoria: a comparison of buspirone, nefazodone and placebo. Psychopharmacology (Berl) 2001;155:292–298
68. Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1991;52:290–293
69. Wood SH, Mortola JF, Chan YF, et al. Treatment of premenstrual syndrome with fluoxetine: a double-blind, placebo-controlled, crossover study. Obstet Gynecol 1992;80(3 pt 1):339–344
70. Menkes DB, Taghavi E, Mason PA, et al. Fluoxetine's spectrum of action in premenstrual syndrome. Int Clin Psychopharmacol 1993;8:95–102
71. Pearlstein TB, Stone AB, Lund SA, et al. Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. J Clin Psychopharmacol 1997;17:261–266
72. Ozeren S, Corakci A, Yucesoy I, et al. Fluoxetine in the treatment of premenstrual syndrome. Eur J Obstet Gynecol Reprod Biol 1997;73:167–170
73. Su TP, Schmidt PJ, Danaceau MA, et al. Fluoxetine in the treatment of premenstrual dysphoria. Neuropsychopharmacology 1997;16:346–356
74. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. N Engl J Med 1995;332:1529–1534
75. Miner C, Brown E, McCray S, et al. 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
76. Steiner M, Korzekwa M, Lamont J, et al. Intermittent fluoxetine dosing in the treatment of women with premenstrual dysphoria. Psychopharmacol Bull 1997;33:771–774
77. Cohen L, Miner C, Brown E, et al. Premenstrual daily fluoxetine for premenstrual dysphoric disorder: a placebo-controlled, clinical trial using computerized diaries. Obstet Gynecol 2002;100:435–444
78. Steiner M, Romano SJ, Babcock S, et al. The efficacy of fluoxetine in improving physical symptoms associated with premenstrual dysphoric disorder. BJOG 2001;108:462–468
79. Pearlstein TB, Halbreich U, Batzar ED, et al. Psychosocial functioning in women with premenstrual dysphoric disorder before and after treatment with sertraline or placebo. J Clin Psychiatry 2000;61:101–109
80. Halbreich U, Smoller JW. Intermittent luteal phase sertraline treatment of dysphoric premenstrual syndrome. J Clin Psychiatry 1997;58:399–402
81. Young SA, Hurt PH, Benedek DM, et al. 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
82. Freeman EW, Rickels K, Arredondo F, et al. Full- or half-cycle treatment of severe premenstrual syndrome with a serotonergic antidepressant. J Clin Psychopharmacol 1999;19:3–8
83. Jermain DM, Preece CK, Sykes RL, et al. Luteal phase sertraline treatment for premenstrual dysphoric disorder: results of a double-blind, placebo-controlled, crossover study. Arch Fam Med 1999;8:328–332
84. Halbreich U, Bergeron R, Yonkers KA, et al. Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. Obstet Gynecol 2002;100:1219–1229
85. Kornstein S, Pearlstein T, Farfel G, et al. Efficacy of sertraline in the treatment of premenstrual syndrome [poster]. Presented at the 41st annual meeting of the New Clinical Drug Evaluation Unit; May 28–31, 2001; Phoenix, Ariz
86. Pearlstein T, Gillespie JA. When should premenstrual dosing in PMDD end? [poster]. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
87. Freeman EW, Sondheimer SJ, Rickels K, et al. A pilot study of extended sertraline treatment for severe PMS [poster]. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
88. Pearlstein TB, Stone AB. Long-term fluoxetine treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1994;55:332–335
89. Freeman EW, Jabara S, Sondheimer SJ, et al. A pilot study of the effectiveness of citalopram in patients with premenstrual syndrome with prior selective serotonin reuptake inhibitor treatment failure [abstract]. Obstet Gynecol 2001;97(4, suppl 1):S18
90. 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
91. Freeman EW, Rickels K, Sondheimer SJ. Fluvoxamine for premenstrual dysphoric disorder: a pilot study. J Clin Psychiatry 1996;57(suppl 8): 56–59
92. 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
93. Freeman EW, Rickels K, Sondheimer SJ, et al. Nefazodone in the treatment of premenstrual syndrome: a preliminary study. J Clin Psychopharmacol 1994;14:180–186
94. Kodesh A, Katz S, Lerner AG, et al. Intermittent, luteal phase nefazodone treatment of premenstrual dysphoric disorder. J Psychopharmacol 2001;15:58–60
95. Yonkers KA, Gullion C, Williams A, et al. Paroxetine as a treatment for premenstrual dysphoric disorder. J Clin Psychopharmacol 1996;16:3–8
96. Freeman EW, Rickels K, Yonkers KA, et al. Venlafaxine in the treatment of premenstrual dysphoric disorder. Obstet Gynecol

2001;98(5 pt 1):737–744
97. Wisner KL, Gelenberg AJ, Leonard H, et al. Pharmacologic treatment of depression during pregnancy. JAMA 1999;282:1264–1269
98. Institute of Medicine. Brown SS, Eisenberg L, eds. The Best Intentions: Unintended Pregnancy and the Well-Being of Children and Families. Washington, DC: National Academy Press; 1995
99. Wang M, Hammarback S, Lindhe BA, et al. Treatment of premenstrual syndrome by spironolactone: a double-blind, placebo-controlled study. Acta Obstet Gynecol Scand 1995;74:803–808
100. Meden-Vrtovec H, Vujic D. Bromocriptine (Bromergon, Lek) in the management of premenstrual syndrome. Clin Exp Obstet Gynecol 1992;19:242–248
101. Taksin O, Gokdeniz R, Yalcinoglu A, et al. Placebo-controlled cross-over study of effects of tibolone on premenstrual symptoms and peripheral beta-endorphin concentrations in premenstrual syndrome. Hum Reprod 1998;13:2402–2405
102. Rapaport MH, Endicott J, Chung H, et al. Quality of life impairment in depressive and anxiety disorders [poster]. Presented at the 15th annual congress of the European College of Neuropsychopharmacology; Oct 5–10, 2002; Barcelona, Spain

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a. Minimal
b. Seldom a clinical issue
c. Similar to that of other major physical and emotional disorders
d. Nonresponsive to treatment

2. The diagnosis of PMDD relies on the patient's daily symptom reports.
a. True
b. False

3. Which of these disorders does *not* mimic the pattern of PMDD?
a. Hypothyroidism
b. Diabetes
c. Major depression
d. Heart disease

4. The treatment that is least likely to be effective for PMDD is:
a. Sertraline
b. Progesterone
c. Alprazolam
d. Leuprolide

5. In studies of luteal phase dosing with selective serotonin reuptake inhibitors (SSRIs) for PMDD, response is generally:
a. No different than with placebo
b. Slow, requiring several months of treatment
c. Significantly better than with continuous dosing
d. Significantly better than with placebo

Answer to Pretest: 1. c

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