

Recognizing and Treating Premenstrual Dysphoric Disorder in the Obstetric, Gynecologic, and Primary Care Practices

Frank W. Ling, M.D.

The author's aim is to aid primary care physicians and obstetrician-gynecologists in correctly diagnosing and treating premenstrual dysphoric disorder (PMDD). The symptoms fluctuate markedly, but their timing is key. PMDD patients experience symptoms only during the luteal phase and will have a symptom-free interval after the menstrual flow and before ovulation. The author discusses self-report instruments, which are valuable tools for diagnosis when combined with the ICD-10 criteria for premenstrual syndrome (PMS) or the DSM-IV criteria for PMDD and the ruling out of medical and psychiatric conditions, such as diabetes, hypothyroidism, major depression, and dysthymia, that cause similar symptoms. Treatment strategies ranging from nonpharmacologic approaches such as dietary modification and aerobic exercise to pharmacologic interventions such as antidepressants, anxiolytics, and agents to suppress ovulation are examined. *J Clin Psychiatry (2000;61[suppl 12]:9-16)*

In the sometimes hectic daily practice of a primary care physician, identifying and treating premenstrual dysphoric disorder (PMDD) becomes a challenge even for the most dedicated health care provider. Obstetrician-gynecologists, family physicians, and many general internists are frequently called upon to correctly differentiate PMDD from the myriad of other conditions that might present with a similar constellation of symptoms. The purpose of this article is to help identify PMDD in a logical and efficient fashion in order that appropriate therapy can be instituted in a timely manner.

HOW PATIENTS PRESENT

Often, the presenting complaints for patients with PMDD will depend on what health care provider they seek out for care and what their respective interpretation of symptoms might be. Because patients are typically unaware of scientific definitions of clinical syndromes, they may have an inaccurate perception of what their primary problem is. This self-diagnosis will, in turn, determine where they turn for treatment. In some cases, a patient may be convinced that she has premenstrual syndrome (PMS).

This is the most commonly used term in the lay press and is referred to in the nonpsychiatric literature. Similarly, the patient might be convinced that she suffers from PMDD if she is cognizant of the newer terminology within the mental health arena. Formerly referred to as late luteal phase dysphoric disorder, PMDD is looked upon as a version of PMS in which the mood component is the most striking and debilitating aspect of a woman's symptom complex.

Just as a patient might have preconceptions that she has PMS or PMDD, she might be totally unaware of these diagnoses. Such patients have not intellectually tied their symptoms to their menstrual cycle. In some cases, patients with other mood disorders may have been diagnosed incorrectly as suffering from PMS/PMDD with a resultant lack of therapeutic efficacy of whatever treatments were instituted. In other cases, the diagnosis may have been correct, but the treatment may not have adequately addressed the symptoms. These are some of the typical ways in which patients present to a primary care provider, resulting in a sometimes confusing clinical scenario. Often the correct diagnosis will be dependent upon extensive patient education and, in some situations, replacing previously received misinformation.

MAKING THE DIAGNOSIS

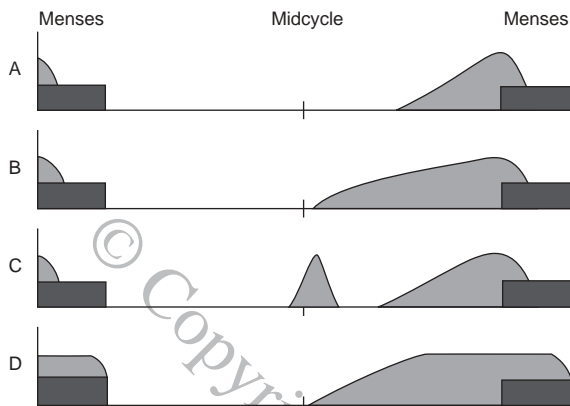
The fundamental key to diagnosing PMS/PMDD is determining the pattern of symptoms that the patient describes. Whereas the primary care provider might be more attuned to behavioral or physical changes, the mental health provider and psychiatrist will be more sensitive in many cases to the mood changes that the patient might

From the Department of Obstetrics and Gynecology, University of Tennessee, Memphis.

Presented at the planning roundtable "New Trends in Treating Premenstrual Dysphoric Disorder," which was held September 13-14, 1999, in Naples, Fla., and supported by an unrestricted educational grant from Eli Lilly and Company.

Reprint requests to: Frank W. Ling, M.D., University of Tennessee, Department of Obstetrics & Gynecology, 853 Jefferson Ave., E102, Memphis, TN 38103.

Figure 1. Variations in Onset and Duration of PMS Symptoms^a



^aFrom Reid and Yen,¹ with permission.

have. In either case, the symptoms must have a regular cyclic relationship to the late luteal phase of the menstrual cycle, remitting by the end of the menstrual flow. The pattern of symptoms must always include a symptom-free interval after the menstrual flow and prior to ovulation.

There are variations in the pattern of symptoms, but the common aspects of these various presentations are used to confirm the diagnosis. As seen in Figure 1,¹ in some cases the symptoms might last throughout the menstrual flow while, in others, the patient may become asymptomatic near the beginning of the menstrual flow. In some instances, there might be an exacerbation of symptoms at the mid-cycle, i.e., the time of ovulation. It should be noted that the patterns of symptoms depicted are only a few of many variations. All patterns will, however, have a symptom-free interval, which follows the menstrual flow and precedes ovulation. Although the duration of symptoms may vary, to make a diagnosis of PMS/PMDD, all symptoms are confined to the luteal (post-ovulatory) phase of the cycle.

In order for an accurate diagnosis to be made, the pattern of symptoms must conform to the diagnostic criteria. The timing of onset and resolution of symptoms is critical. In some cases, a patient may have already suspected a menstrual-related pattern and kept a diary of symptoms demonstrating the relationship of symptoms and menstrual flow. When documentation of the symptoms is lacking, or if the repetitive pattern of symptoms is in doubt, a number of instruments are available to aid the physician and the patient in determining the ultimate correct diagnosis. These self-reporting instruments can help avoid misdiagnosis based on a patient mistakenly attributing symptoms to the menstrual cycle or amplifying the severity of the symptoms encountered. Among the instruments used are the Daily Rating Form (DRF),² the Menstrual Distress Questionnaire

(MDQ),³ the Premenstrual Assessment Form (PAF),⁴ and the Calendar of Premenstrual Experiences (COPE).⁵

The COPE is depicted in Figure 2.⁵ The follicular phase score is the sum of points for days 3 through 9 of the cycle, while the luteal phase score is the total points for the last 7 days of the cycle. PMS is diagnosed when the luteal phase score is at least 30% greater than the follicular phase score. It should be noted that instruments such as the COPE not only are helpful in diagnosing PMS/PMDD, but can also raise the suspicion of other clinical conditions. For example, if the follicular phase score is greater than 40, irrespective of the luteal phase score, an underlying affective disorder should be suspected.

Another example of a useful instrument to aid in the diagnosis of PMS/PMDD is the Prospective Record of the Impact and Severity of Menstrual Symptoms (PRISM) calendar.⁶ Irrespective of the specific symptoms listed or the severity of those symptoms, the pattern of documented symptoms might lead to the diagnosis of depression (Figure 3) or PMS (Figure 4). The PRISM calendar of the patient with PMS clearly demonstrates the symptom-free interval preceding ovulation, while the symptoms in the patient with depression persist throughout the month.

As an alternative to these instruments, the clinician may choose simply to ask that the patient provide her own calendar. It is helpful to limit the patient's focus of attention to the 3 or 4 most troublesome symptoms. Each can be assigned a letter (e.g., irritability = "I" or bloating = "B"). Each letter is recorded on each day of the calendar accompanied by a severity rating from 0 (no symptoms) to 4 (severe). In addition, the patient records the days of her menstrual flow. The pattern and severity of symptoms will aid both the patient and the clinician in determining the appropriate diagnosis.

Regardless of what method is used to document symptoms, the active involvement of the patient proves helpful as she is less a victim and more a part of the diagnostic process. The dependence on prospective charting of symptoms also eliminates patient recall as a confounding factor in determining the correct diagnosis.

The pattern of symptoms is one critical aspect of making the diagnosis of PMS or PMDD. There are other specific criteria that further aid in refining the appropriate diagnosis. The diagnosis of PMS is based upon the Tenth Revision of the *International Classification of Diseases* (ICD-10).⁷ Table 1 summarizes the diagnostic criteria for PMS. In contrast, the diagnostic criteria for PMDD are far more rigorous. Table 2 is adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).⁸ The chief complaints must include at least 5 of 11 total symptoms, 1 of which must be a core symptom such as irritability, depressed mood, anxiety or tension, or affective lability. In addition, there are specific criteria for prospective charting of symptoms (at least 2 cycles), level

Figure 2. Calendar of Premenstrual Experiences^a

Name _____ Month/Year _____ Age _____ Unit # _____

Begin our calendar on the *first* day of your menstrual cycle. Enter the calendar date below the cycle day.
 Day 1 is your *first* day of bleeding. Shade the box above the cycle day if you have bleeding (■). Put an X for spotting (⊗).

If more than one symptom is listed in a category, i.e., nausea, diarrhea, constipation, you do not need to experience all of these.
 Rate the most disturbing of the symptoms on the 1–3 scale.

Weight: Weigh yourself before breakfast. Record weight in the box below date.

Symptoms: Indicate the severity of your symptoms by using the scale below.

Rate each symptom at about the same time each evening.

- 0 = None (symptom not present)
- 1 = Mild (noticeable but not troublesome)
- 2 = Moderate (interferes with normal activities)
- 3 = Severe (intolerable, unable to perform normal activities)

Other Symptoms: If there are other symptoms you experience, list and indicate severity.

Medications: List any medications taken. Put an X on the corresponding day(s).

Bleeding	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40							
Cycle Day																																															
Date																																															
Weight																																															
SYMPTOMS																																															
Acne																																															
Bloatedness																																															
Breast tenderness																																															
Dizziness																																															
Fatigue																																															
Headache																																															
Hot flashes																																															
Nausea, diarrhea, constipation																																															
Palpitations																																															
Swellings (hands, ankles, breast)																																															
Angry outbursts, arguments, violent tendencies																																															
Anxiety, tension, nervousness																																															
Confusion, difficulty concentrating																																															
Crying easily																																															
Depression																																															
Food cravings (sweets, salts)																																															
Forgetfulness																																															
Irritability																																															
Increased appetite																																															
Mood swings																																															
Overly sensitive																																															
Wish to be alone																																															
Other symptoms																																															
1. _____																																															
2. _____																																															
Medications																																															
1. _____																																															
2. _____																																															

01643 (10-85) 6

©University of California, San Diego; Department of Reproductive Medicine, H-813; Division of Reproductive Endocrinology.

The COPE Calendar is scored by adding the total number of points from days 3–9 of the menstrual cycle (the follicular phase score) and the total number of points from the last 7 days of the cycle (luteal phase score).

PMS is diagnosed by a follicular phase score less than 40 (and a luteal phase score greater than 42).

Follicular phase scores greater than 40 (regardless of luteal phase scores) suggest the possibility of underlying psychiatric disorder, and such patients should be considered for psychiatric consultation.

Although not strictly required for the diagnosis, almost all patients with PMS will have at least a 30% increase in scores from follicular to luteal phase. If this is not observed, the diagnosis should be reconsidered.

^aReprinted from reference 5, with permission.

Figure 3. Typical PRISM Calendar⁶ Record Indicating Depression

BLEEDING	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	
Menstrual Cycle Date:																																				
SYMPTOMS																																				
Irritable	2	3	1	1	2	2	2	2			2	2	2	1	2	2	2		3	2	2	1	2		1	2	2	1								
Fatigue	2	2	1	2	2		1	2	2		1	2	2	2	2	3	2		1	1	2	2	3	2		1	1	2	1	2						
Inward Anger	2	3	2	2	2	2	2	1		1	2	2	1	2	3	1	1	2	2	1		2	2		2	1	2	2	1	2	2					
Labile Mood (crying)	3	3	1	1	2	2		2		1	2	2	1		2	2	2		2	2	1		2	2	1	2	2		1	2						
Depressed	3	1	1	2	1	2			3	1	2	2			1		2	3	2	1		2	2	3		1	2	2								
Restless	1	1	1	1		1	1	1			1	2	1	1		2	1	1	1				1	1			1	1	1							
Anxious	3	2	3	3	3		2	3	3		2	1	2	2	3		2	1	1		2	2	2	2	2		3	3	2	2						
Insomnia			1								2											1														
Lack of Control	1	2	2						2	2	1	2					1	1	2			2	2	3	2		2	2	3							
Edema or Rings Tight					1									1												1	2	1	1							
Breast Tenderness																							2		1	1	2		1							
Abdominal Bloating																								2	2		1	1	2							
Bowels: const. (c) loose (l)			C						C							C	C	C						C					C	C						
Appetite: up ↑ down ↓	↓	↓		↓	↓				↓			↓	↓	↓	↓								↓	↓		↓		↓								
Drive: up ↑ down ↓	↓	↓							↓	↓					↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		↓	↓									
Chills (C) / Sweats (S)																																				
Headaches	2		1	2	2				1	2	2	2					2	2	2	3	2	2			2	2	2	2								
Crave: sweets, salt																																				
Feel Unattractive	2	2	2	2	2	3	1	2	2		1	1	2	2		1	2	2	2	2	2	2		1	2	2		2	2	2	1					
Guilty	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Unreasonable Behaviour			1						2									2									2	2	2							
Low Self-Image	2	2		2	2		1	2	2				2	2	2	1	2	2	3	3	2	2			2	2	2									
Nausea	1																																		1	
Menstrual Cramps	2	2	2	1	2																													1	2	

of disability arising from the symptoms, and determination that the symptoms are not an exacerbation of another disorder.

Although both the DSM-IV and the ICD-10 classifications are widely used, the applications of each are determined by the health care provider to whom the patient presents. Table 3 summarizes the distinctions between the 2. Patients may be more familiar with the terminology of one or the other, and the specific details of the criteria should not stand in the way of clinical judgment. The degree of impairment for the patient will ultimately be more important than the categorization or “label” used by the clinician.

DIFFERENTIAL DIAGNOSIS

It is not uncommon for the patient to present with symptoms that are compatible with other medical conditions for which she may already be receiving treatment. As the clinician identifies the pattern and severity of the patient’s problems, knowledge of concomitant medical disorders will prove to be critical in making a final diagnosis of PMS or PMDD. Table 4 summarizes the common categories of

conditions that should be included in the differential diagnosis for PMS and PMDD. Since the practice of the primary care provider and/or obstetrician-gynecologist is the frequent site for management of these other conditions, the consideration of the entire spectrum of conditions is not clinically illogical. Again, the patient may have preconceptions as to whether or not her symptoms are due to other underlying medical conditions.

PROPOSED ETIOLOGY

From the standpoint of patient management, the extensive body of research into the exact etiology of PMS/PMDD provides the background onto which therapy is instituted. It is particularly relevant for a patient to be made aware of the scientific basis supporting recommended therapy. Similarly, if there are data to suggest lack of efficacy, those, too, should be shared with the patient. Currently, without definitive evidence of the exact pathophysiology of this condition, the “best guess” as to what may be triggering the clinical phenomena may prove useful in discussing treatment options with the patient.

Figure 4. Typical PRISM Calendar⁶ Record Indicating PMS

BLEEDING		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	
Menstrual Cycle Date:																																					
SYMPTOMS																																					
Irritable	3	2																			1	1	2	1	1	2	3	2	3	3							
Fatigue	2	2	2	2																1	1	1	1	2	2	2	3	2	2	2							
Inward Anger	1																						1	2		1	2	1									
Labile Mood (crying)	2	2																			2		2	2	3	3		2	2	2							
Depressed	2	1	1																			1		2	1	1	2	2	2	2							
Restless	3	1																				2	2		1	2	2		2								
Anxious	2	1																			2		2	3	2	2	2		3	3							
Insomnia	2	1																	1			3	2			1	1	1									
Lack of Control	1																							2	3	3	3	2	3								
Edema or Rings Tight																				2			1				1										
Breast Tenderness	2	2	1																		1		2		3	3	3	3	3								
Abdominal Bloating	3	2	1																		2		1	2	2	2		2	2	2	2						
Bowels: const. (c) loose (l)	L	L	C																		C	C	C		L	L			C	C							
Appetite: up ↑ down ↓																							↑	↑	↑			↑	↑						↓	↓	
Drive: up ↑ down ↓																								↓	↓			↓						↓	↑	↓	
Chills (C) / Sweats (S)																																					
Headaches	3	2	2	1																				1	2	2	3	1	2	2							
Crave: sweets, salt																																					
Feel Unattractive	2																						2	3	2	1	2	2	3	3	2						
Guilty	1																						1	3			2	2	1								
Unreasonable Behaviour	2	2																			1		2				3	2	2								
Low Self-Image	2																						2		1	2	2										
Nausea	1	2																						1	2	2	2	1									
Menstrual Cramps	1	2	2																									2	2								

Table 1. Diagnosis of Premenstrual Syndrome (PMS)^a

- A. Does not meet DSM-IV criteria for PMDD but does meet ICD-10 criteria for PMS
- B. Symptoms occur only in the luteal phase, peak shortly before menses, and cease with menstrual flow or soon after
- C. Presence of 1 or more of the following symptoms:
 - Mild psychological discomfort
 - Bloating and weight gain
 - Breast tenderness
 - Swelling of hands and feet
 - Aches and pains
 - Poor concentration
 - Sleep disturbance
 - Change in appetite

^aBased in part on ICD-10.⁷

Table 2. Diagnosis of Premenstrual Dysphoric Disorder (PMDD)^a

- A. At least 5 of the symptoms below, with at least 1 being a core symptom, are present a week before menses and remit a few days after onset of menses:
 - Depressed mood or dysphoria (core symptom)
 - Anxiety or tension (core symptom)
 - Affective lability (core symptom)
 - Irritability (core symptom)
 - Decreased interest in usual activities
 - Concentration difficulties
 - Marked lack of energy
 - Marked change in appetite, overeating, or food cravings
 - Hypersomnia or insomnia
 - Feeling overwhelmed
 - Other physical symptoms (eg, breast tenderness, bloating, headache, joint or muscle pain)
- B. Symptoms must interfere with work, school, usual activities, or relationships
- C. Symptoms must not merely be an exacerbation of another disorder
- D. Criteria A, B, and C must be confirmed by prospective daily ratings for at least 2 cycles

^aAdapted from DSM-IV.⁸

Table 3. Differences Between PMS and PMDD

	PMS	PMDD
Diagnostic criteria	Tenth Revision of the <i>International Classification of Diseases (ICD-10)</i>	<i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)</i>
Providers using these criteria	Obstetrician/gynecologists, primary care physicians	Psychiatrists, other mental health care providers
Number of symptoms required	1	5 of 11
Functional impairment	Not required	Interference with social or role functioning required
Prospective charting of symptoms	Not required	Prospective daily charting of symptoms required for 2 cycles

Table 4. Differential Diagnosis

Psychiatric disorders
• Major depression
• Dysthymia
• Generalized anxiety
• Panic disorder
• Bipolar illness (mood irritability)
• Other
Medical disorders
• Anemia
• Autoimmune disorders
• Chronic fatigue syndrome
• Collagen vascular disease
• Diabetes
• Endometriosis
• Hypothyroidism
• Seizure disorders
Premenstrual exacerbation
• Of psychiatric disorders
• Of seizure disorders
• Of endocrine disorders
• Of cancer
• Of systemic lupus erythematosus
• Of anemia
• Of endometriosis
Psychosocial spectrum
• Past history of sexual abuse
• Past, present, or current domestic violence

A common misconception that a patient often has is that abnormal levels of circulating female hormones are the underlying cause of PMS/PMDD. It appears that actually normal ovarian function, not abnormal fluctuations, is the cyclic trigger for symptoms.⁹ Genetic predisposition and societal expectations are among other factors that may play a role.¹⁰⁻¹⁴ The strongest scientific data implicate serotonin as the primary neurotransmitter whose levels are affected by ovarian steroid levels.¹⁵ In addition, other neurotransmitter systems have been implicated. These include the opioid, adrenergic, and the gamma-aminobutyric acid (GABA) systems.¹⁶ It is known that ovarian steroids affect neurotransmitters in a variety of ways, including synthesis, release and reuptake, enzymatic inactivation, and pre- and postsynaptic receptor sensitivity.

Since serotonin appears to have the greatest impact, the clinical choice of therapeutic options can be made more logically. The 2 primary pharmacologic ways to affect the interaction between ovarian steroids and serotonin would logically fall to manipulation of ovarian steroid production or altering the susceptibility of the neurotransmitter to the fluctuations of ovarian steroids.

INITIATING TREATMENT

Once the patient is identified as suffering from PMS/PMDD, an individualized treatment scheme should be implemented. The treatment algorithm in Figure 5 illustrates a conceptual framework for the primary care physician or obstetrician-gynecologist. Differentiating urgent from nonurgent cases allows the clinician to stratify levels

Figure 5. Recommended Algorithm for Management of Patients With PMS/PMDD

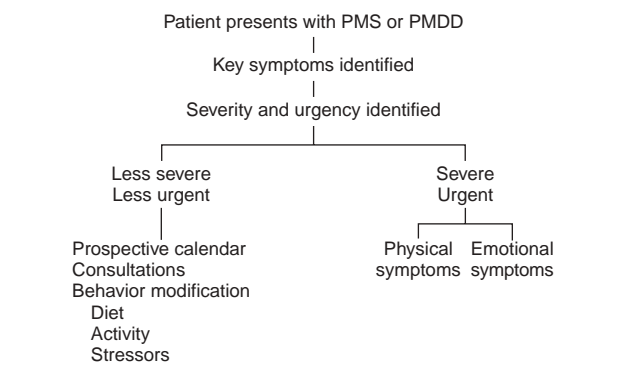


Table 5. Pharmacologic Therapies

Medication	Dose
Antidepressants	
Clomipramine	25–75 mg/d (14 days before menses)
Fluoxetine	20 mg/d
Paroxetine	10–30 mg/d
Sertraline	50–150 mg/d
Anxiolytics	
Alprazolam	1–2 µg/d (6–14 days before menses)
Bupirone	25–60 mg/d (12 days before menses)
Ovulation suppression	
GnRH agonists	
Buserelin ^a	400–900 µg/d (intranasal)
Danazol	200–400 mg/d (at onset of symptoms until onset of menses)
Leuprolide	3.75–7.5 mg/monthly (intramuscular injection)

^aNot available in the United States.

of intervention based on the types of symptoms as well as their severity. A patient-centered approach requires providing adequate time in the office to discuss issues in their entirety. Some offices have dedicated nonphysician staff to address the patient’s concerns as a supplement to the busy clinician’s face-to-face office visit. Determining other background information is useful. If the patient is a “victim” of her condition, she will appear helpless and passive, asking that the physician cure her, without significant active input or effort on her part. These cases are well served by use of the prospective charting of symptoms referred to previously. In this way, the patient is drawn into the active diagnosis of her condition. Similarly, knowledge of the environment, including support of the spouse, will aid in identifying factors that can work counter to the therapeutic plan. Stress in the marriage, a spouse who might not believe the patient’s symptoms, financial pressures, and work-related concerns are examples of deterrents to the simple management of PMS/PMDD symptoms.

Practice-related considerations must be accounted for in the busy primary care practice in which a woman with PMS/PMDD is seen. Appropriate use of the Evaluation and

Management (E and M) codes¹⁷ will allow for billing of services commensurate with the level of care rendered. Both the "Premenstrual Syndrome" code of 625.4 or the "Hormone Imbalance" code of 259.9 should be considered.

The role of laboratory evaluation is limited to screening for medical conditions that are suspected as confounding variables. Obtaining some tests to reassure the patient may also be needed. The patient may also be reassured that there are no differences in serum levels of various hormones for patients with PMS/PMDD in comparison with other patients.

While the patient may be confirming the suspected diagnosis by means of charting of symptoms, other interventions may be attempted. None involve prescription medications and all are attractive treatment steps for a patient who desires more "natural" treatments. Relaxation therapy, particularly in the form of reflexology, has been demonstrated efficacious.^{18,19}

Dietary modification may also prove helpful. The use of pyridoxine, vitamin B₆, has had varying success described in the literature. An initial dose of 50 to 100 mg per day may be beneficial without the risk of peripheral neuropathy, which is associated with higher doses.²⁰ Calcium supplementation during the luteal phase has proven to be beneficial with regard to bloating, pain, mood, and food cravings. The use of 2 Tums-EX tablets twice a day has been described.²¹ Reducing caffeine intake is a common-sense way to minimize the potential ill effects of excess caffeine consumption such as nervousness or jitteriness. Similarly, restriction of sodium might reduce the symptoms of bloating that plague some patients. By reducing refined/processed carbohydrates, and by having 5 or 6 smaller meals during the day instead of 3 large meals, some patients are able to avoid symptoms that simulate hypoglycemia. A commercially available carbohydrate-rich beverage known to increase tryptophan has proven efficacious when taken in the late luteal phase.²²

Premenstrual symptoms may also be lessened if the woman engages in aerobic exercise. This may be of particular use if depressive or fluid-retention symptoms predominate. In addressing the overall health needs of a patient, the benefits of exercise can certainly be justified beyond the scope of PMS/PMDD.^{23,24}

In addition to the nonpharmacologic interventions listed, the primary pharmacologic treatments include antidepressants, anxiolytics, and agents to suppress ovulation. These pharmacologic agents are summarized in Table 5. Because of the data accumulated regarding the role of serotonin, the primary antidepressants found useful for PMS/PMDD are those that would be considered serotonergic, e.g., fluoxetine, paroxetine, sertraline, and clomipramine. Although the latter is not a serotonin reuptake inhibitor as are the others, it is a tricyclic antidepressant with serotonin and norepinephrine reuptake inhibiting properties.²⁵⁻³⁰

Alternatively, anxiolytics such as buspirone and alprazolam have been shown to be efficacious in the treatment of PMS/PMDD. The former is a nonbenzodiazepine that has side effects of headache, nervousness, nausea, and dizziness. It may be administered either throughout the month or during the late luteal phase. Alprazolam, a benzodiazepine, reduces depression, irritability, and anxiety. As with other similar medications, tolerance and dependence are a concern.³¹⁻³³

Hormonal treatments that have been shown to be clinically useful include gonadotropin-releasing hormones (GnRH), oral contraceptives, and danazol. Unlike these 3 medications, progesterone has not proven to be effective despite earlier publications espousing its clinical applicability. The use of GnRH analogues should be considered for only a short period of time since its temporary menopausal hormonal milieu can increase the risk of osteoporosis. Since add-back of hormones to minimize menopausal symptoms can be effective, the patient and clinician may use this medication as a short-term treatment and also to aid in the diagnosis of mood disorders.³⁴

Oral contraceptives have had mixed results. Some of the side effects of oral contraceptives such as bloating, appetite changes, and depressive symptoms might simulate PMS/PMDD, and, as a result, the clinician and patient should recognize the limitations of these treatment options.^{35,36}

Danazol, a synthetic androgen, has demonstrated some efficacy with regard to both mood and physical symptoms. It can be effective with doses that both do and do not suppress ovulation. Side effects such as weight gain, acne, hot flashes, vaginal dryness, and emotional lability may limit the usefulness of this drug.^{37,38}

SUMMARY

In a busy office of a primary care provider or obstetrician-gynecologist, the diagnosis of PMS or PMDD is a likely presenting complaint. It is within the expertise of the clinician to make a timely diagnosis and implement effective treatments.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar), clomipramine (Anafranil and others), danazol (Danocrine), fluoxetine (Sarafem), leuprolide (Lupron), paroxetine (Paxil), sertraline (Zoloft).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, the following agents mentioned in this article are not approved by the U.S. Food and Drug Administration for the treatment of PMS/PMDD: alprazolam, buserelin, buspirone, clomipramine, danazol, leuprolide, paroxetine, pyridoxine, and sertraline.

REFERENCES

1. Reid RL, Yen SSC. Premenstrual syndrome. *Clin Obstet Gynecol* 1983;26: 710-718
2. Endicott J, Schacht S, Halbreich U. Daily Rating Form. New York, NY: Research Assessment and Training Unit; 1982

3. Moos R. The development of a menstrual distress questionnaire. *Psychosom Med* 1968;30:853–867
4. Endicott J, Halbreich U. Retrospective report of premenstrual depressive changes: factors affecting confirmation by daily ratings. *Psychopharmacol Bull* 1982;18:109–112
5. Calendar of Premenstrual Experiences. San Diego, Calif: Department of Reproductive Medicine, Division of Reproductive Endocrinology, University of California, San Diego
6. Prospective Record of the Impact and Severity of Menstrual Symptoms (PRISM) Calendar. Hamilton, Ontario, Canada: St. Joseph's Hospital, McMaster University, Women's Health Concerns Clinic
7. World Health Organization. Mental, behavioral and developmental disorders. In: *International Statistical Classification of Diseases and Related Health Problems (ICD-10)*. Geneva, Switzerland: World Health Organization; 1996
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994
9. 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
10. Van den Akker OBA, Stein GS, Neale MC, et al. Genetic and environmental variation in menstrual cycle: histories of 2 British twin samples. *Acta Genet Med Gemellol (Roma)* 1987;36:541–548
11. Condon JT. The premenstrual syndrome: a twin study. *Br J Psychiatry* 1993;162:481–486
12. Kendler KS, Silberg JL, Neale MC, et al. Genetic and environmental factors in the etiology of menstrual, premenstrual and neurotic symptoms: a population-based twin study. *Psychol Med* 1992;22:85–100
13. Logue CM, Moos RH. Perimenstrual symptoms: prevalence and risk factors. *Psychosom Med* 1986;48:388–414
14. Parlee MB. Social factors in the psychology of menstruation, birth and menopause. *Prim Care* 1976;3:477–490
15. Rapkin A. The role of serotonin in premenstrual syndrome. *Clin Obstet Gynecol* 1992;35:629–636
16. Mortola JF. Premenstrual syndrome. *Trends Endocrinol Metab* 1996;7:184–189
17. American Medical Association. *Current Procedural Terminology (CPT)*. Chicago, Ill: American Medical Association; 2000
18. Goodale IL, Domar AD, Benson H. Alleviation of premenstrual syndrome symptoms with the relaxation response. *Obstet Gynecol* 1990;75:649–655
19. Oleson T, Flocco W. Randomized controlled study of premenstrual symptoms treated with ear, hand and foot reflexology. *Obstet Gynecol* 1993;82:906–911
20. Wyatt KM, Dimmock PW, Jones PW, et al. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systemic review. *BMJ* 1999;318:1375–1381
21. Thys-Jacobs S, Starkey P, Bernstein D, et al., and the Premenstrual Syndrome Study Group. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. *Am J Obstet Gynecol* 1998;179:444–452
22. Sayegh R, Schiff I, Wurtman J, et al. The effect of a carbohydrate-rich beverage on mood, appetite, and cognitive function in women with premenstrual syndrome. *Obstet Gynecol* 1995;86:520–528
23. Steege JF, Blumenthal JA. The effects of aerobic exercise on premenstrual symptoms in middle-aged women: a preliminary study. *J Psychosom Res* 1993;37:127–133
24. Prior JC, Vigna Y. Conditioning exercise and premenstrual symptoms. *J Reprod Med* 1987;32:423–428
25. Steiner M, Steinberg S, Stewart D, et al. and the Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group. Fluoxetine in the treatment of premenstrual dysphoria. *N Engl J Med* 1995;332:1529–1534
26. Wood SH, Mortola JF, Chan Y-F, et al. Treatment of premenstrual syndrome with fluoxetine: a double-blind, placebo-controlled, crossover study. *Obstet Gynecol* 1992;80:339–344
27. Pearlstein TB, Stone AB. Long-term fluoxetine treatment of late luteal phase dysphoric disorder. *J Clin Psychiatry* 1994;55:332–335
28. Freeman EW, Rickels K, Sondheimer SJ, et al. Sertraline versus desipramine in the treatment of premenstrual syndrome: an open-label trial. *J Clin Psychiatry* 1996;57:7–11
29. Yonkers KA, Gullion C, Williams A, et al. Paroxetine as a treatment for premenstrual dysphoric disorder. *J Clin Psychopharmacol* 1996;16:3–8
30. 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
31. Harrison WM, Endicott J, Nee J. Treatment of premenstrual dysphoria with alprazolam. *Arch Gen Psychiatry* 1990;47:270–275
32. 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
33. Brown CS, Ling FW, Farmer RG, et al. Buspirone in the treatment of premenstrual syndrome. *Drug Ther Suppl August* 1990:112–121
34. Brown CS, Ling FW, Andersen RN, et al. Efficacy of depot leuprolide in premenstrual syndrome: effect of symptom severity and type in a controlled trial. *Obstet Gynecol* 1994;84:779–786
35. Rubinow DR, Roy-Byrne P. Premenstrual syndromes: overview from a methodologic perspective. *Am J Psychiatry* 1984;141:163–172
36. Graham CA, Sherwin BB. A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. *J Psychosom Res* 1992;36:257–266
37. Bancroft J. The premenstrual syndrome: a reappraisal of the concept and the evidence. *Psychol Med* 1993;(suppl 24):1–47
38. Calton GJ, Bumetti JW. Danazol and migraine [letter]. *N Engl J Med* 1984;310:721–722