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Recognizing and Treating Premenstrual Dysphoric Disorder

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DR. LIANG:

During their menstrual cycles, many women of reproductive age experience adverse physical, emotional, and cognitive symptoms that often recur, usually during the luteal phase of their cycle. These symptoms have great potential to interfere with personal, social, and occupational functions. A constellation of severe symptoms may be indicative of premenstrual dysphoric disorder (PMDD), a severe form of premenstrual syndrome (PMS).¹

Significant changes associated with menstruation are common in women. Up to 80% of women of reproductive age report physical changes associated with menstruation, with 20% to 40% of these women reporting symptoms of PMS, and 2% to up to 10% reporting that their activities of daily life are severely disrupted.² It is these latter women who are of particular concern regarding PMDD, although women who experience less severe symptoms also may be affected.

As noted in this case study, there is no well-assigned or agreed-upon etiology of PMDD, and wide variations are reported.³ It appears that there are multifactorial variables that contribute to the symptomatology, including social, environmental, physiologic, and psychologic factors. Of particular interest, there may be a genetic component; it has been reported that 70% of women whose mothers were affected by PMS have PMS themselves, compared with only 37% of women who are afflicted with the syndrome without maternal involvement.⁴ Further evidence of a strong genetic component includes the finding that there is a 93% concordance rate for PMDD in monozygotic twins, in contrast with only a 44% concordance rate for dizygotic twins.⁴

Depression also appears to be highly linked with PMDD. There is a significant overlap in symptoms experienced by patients with atypical depression and those with PMDD. For example, depressed mood, interpersonal rejection hypersensitivity, carbohydrate

craving, and hypersomnia occur in both disorders, and between 30% and 76% of women that are diagnosed with PMDD have a history of depression.⁵ Further, a family history of depression is associated with women diagnosed with moderate to severe menstrual cycle symptoms.⁶ However, it should be noted that some patients with PMDD do not have symptoms of depression, and absence of depressive symptoms should not lead the primary care provider to assume that the dysphoric disorder diagnosis is excluded.⁷

The presence of the disorder in women of reproductive age and its concurrence with the reproductive cycle point toward at least some contribution of female gonadal hormones. Some studies have provided interesting clues as to some of these contributions. For example, chemical ablation of ovarian gonadal hormones with gonadotropin-releasing hormone agonist relieved PMDD symptoms.⁸ In another study, patients whose symptoms were relieved by administration of a gonadotropin-releasing hormone agonist had these symptoms return when estrogen and progesterone were added.⁹ Control subjects without previous PMS symptoms who received the same regimen did not incur any premenstrual symptoms.⁹

Overall, primary care providers should be alert to female patients of reproductive age who experience severe, disconcerting symptoms associated with their menstrual cycles. Attention to potential mental health issues as well as environmental factors should be emphasized in order to diagnose PMDD and initiate effective treatment.

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Premenstrual symptoms are extremely common among women of reproductive age. As many as 75% of women report minor or isolated premenstrual symptoms, up to 50% of women are estimated to have PMS, and 3% to 5% of women are considered to have severe PMS or PMDD.^{10,11}

PMDD has been defined as a psychophysiological disorder in which both somatic and emotional disturbances are present.¹⁰ These disturbances occur during the luteal phase of the ovulatory cycle and tend to persist for 10 to 14 days. Cessation of symptoms typically occurs 1 to 2 days before onset of menstruation, with a subsequent symptom-free period lasting 2 weeks on average. Although the exact cause of PMDD is not understood, it is thought that normal ovarian functioning triggers biochemical phenomena in the brains and the bodies of susceptible women, which in turn precipitate premenstrual symptomatology. Symptoms are prominent and patterned and cause significant distress.

Controversy surrounds the diagnosis of PMDD, with health care professionals and others continuing to debate whether PMDD is a real condition. Premenstrual symptoms first appeared in the appendix of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM)* in 1987 as "late luteal-phase dysphoric disorder." Clinical entities listed in the appendix are said to have insufficient information to warrant inclusion as an official category and require further study. When the *DSM-IV* was published in 1994, the disorder was renamed PMDD but remained in the appendix; the *DSM-IV* recommended that patients with the symptoms receive the diagnosis "depressive disorder not otherwise specified." In 1998, a round table convened by the Society for Women's Health Research reviewed the literature and concluded that PMDD was a distinct clinical entity, a position supported by the Food and Drug Administration (FDA) Neuropharmacology Advisory Committee.¹² Some critics, however, hold that the diagnosis is harmful because it is used to label women with real, external problems (eg, battering, mistreatment) as mentally disordered.¹³ Controversy also has surrounded the marketing of the first pharmacologic agent approved for the treatment of PMDD, Sarafem, which is fluoxetine with a new name and packaging.

Studies suggest that PMS symptomatology exacts an emotional as well as economic toll, accounting for much school absenteeism and sick leave for working women.^{14,15} More than 150 symptoms of PMDD have

been described; primary care physicians need to be able to parse through such symptoms and make an accurate diagnosis so that appropriate treatment can be initiated.

CASE STUDY

Initial Presentation

A 35-year-old woman presents to her primary care physician requesting a drug she saw advertised on television to treat her "severe moodiness."

History

The patient states that during the 2 weeks before her period she is extremely moody and irritable and experiences intermittent bouts of tearfulness. Her concentration often wanders at work and she frequently cancels plans with friends because she feels overwhelmed. She says that the symptoms are a significant cause of distress and are interfering with her personal and professional relationships. She reports that she has suffered from the symptoms for approximately 2 years but has recently noticed a worsening in their overall intensity. She admits that there is a significant amount of stress in her life, but she does not feel this is novel for her. The patient has tried over-the-counter PMS preparations and herbal remedies without success. Her primary coping response during these episodes is to "try to get enough sleep."

The patient is divorced, lives with her 2 sons, aged 10 and 6 years, and works full-time as an attorney. She states that she tries to follow a healthy diet but rarely has time to exercise. The patient does not smoke and has approximately 8 drinks per week. She asserts that "having a few drinks" tends to initiate temporary relief of her PMS symptoms. The patient engaged in psychotherapy while undergoing her divorce 4 years ago. She is unaware of having received a formal psychiatric diagnosis at that time. The patient reports a family history of depression and also notes that "many years ago" a paternal uncle committed suicide.

Physical Examination

The physical examination is unremarkable.

- **What are diagnostic criteria for PMDD?**
- **What clinical instruments may aid in the process of diagnosis?**

The *DSM-IV* diagnostic research criteria for PMDD are listed in **Table 1**.¹⁰ In order to meet these criteria, a woman must suffer from a host of luteal phase symptoms and then experience a symptom-free period

Table 1. Diagnostic Research Criteria for Premenstrual Dysphoric Disorder

- A. In most menstrual cycles in the past year, 5 or more of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after onset of the follicular phase, and were absent during the post-menses week, with at least 1 of the symptoms being either 1, 2, 3, or 4:
1. Markedly depressed mood, hopelessness, or self-deprecating thoughts
 2. Marked anxiety, tension, feelings of being “keyed up” or “on edge”
 3. Marked affective lability
 4. Persistent and marked anger or irritability or increased interpersonal conflicts
 5. Decreased interest in usual activities (eg, work, school, friends, hobbies)
 6. Subjective sense of difficulty in concentrating
 7. Lethargy, easy fatigability, or marked lack of energy
 8. Marked change in appetite, overeating, or specific food cravings
 9. Hypersomnia or insomnia
 10. A subjective sense of being overwhelmed or out of control
 11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of “bloating,” weight gain
- B. Marked impairment in social or occupational function (eg, avoidance of social activities, decreased productivity at work)
- C. The disturbance is not an exacerbation of other symptoms of another disorder
- D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least 2 consecutive symptomatic cycles

Adapted with permission from American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed., text revision. Washington (DC): The Association; 1994:774.

during the follicular phase. Some of the symptoms reported by PMDD sufferers are listed in **Table 2**. Symptoms need to be tracked for at least 2 consecutive menstrual cycles before the diagnosis can be made. Women should be asked to keep written track of their symptoms with a prospective symptom calendar or diary (such as the Penn Daily Symptom Report [**Figure 1**]¹⁶) because subjective reports lead to overdiagnosis of PMDD.¹⁷ In a study of 72 subjects, 22% of women who believed they had PMS did not meet the DSM-IV criteria for the disorder.¹⁸ In another study, only 44% of women previous-

Table 2. Symptoms Reported by Premenstrual Dysphoric Disorder Sufferers

Somatic symptoms	Affective symptoms
Fluid retention	Irritability
Generalized swelling	Tension
Breast tenderness	Anxiety/nervousness
Abdominal bloating	Mood lability
Weight gain	Depression
Change in bowel habits	Aggression
Hot flashes	Anger
Acne	Fatigue
Libido change	Inability to concentrate
Backache	Lethargy
Increased appetite/cravings	Sadness
Dizziness	Indecision
Headache	Paranoia
Thirst	Sensitivity
Nausea	Decreased motivation
Clumsiness	Poor impulse control

Adapted from Chuong CJ, Pearsall-Otey LR, Rosenfeld BL. A practical guide to relieving PMS. *Contemp Nurse Pract* May/June:31–7; and Tiller CM, Davidhizar R, Bechtel GA, Stewart J. Premenstrual syndrome. Self-care measures are part of the solution. *Adv Nurse Pract* 2000;8:85–8.

ly given a diagnosis of PMS were found to have PMS when more accurate diagnostic methods were implemented.¹⁹ Other instruments for documenting symptoms have been described in the medical literature (**Table 3**).^{20–25}

- **What are the important historical points to cover in a patient presenting with severe premenstrual symptoms?**

First and foremost, it is essential to clarify how often symptoms arise and to confirm that a symptom-free period actually exists each month. As mentioned, this should be based on a symptom calendar kept by the patient for 2 months. It is also necessary to determine whether the symptoms are indicative of a premenstrual exacerbation of a current mental disorder. It should be noted that the presence of a psychiatric disorder does not automatically rule out the presence of PMDD.

The physician should inquire about symptoms suggestive of other mental disorders. It has been documented in the literature that a significant number of women who meet the criteria for PMDD also suffer

DAILY SYMPTOM RATING		UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER—PMS PROGRAM													NAME _____			
Date (mo/d/yr)																		
Check if menstruating																		
Study medication: no. pills taken																		
Check if other medication taken (list on reverse)																		
0 = not present at all	1 = mild: only slightly apparent to you	2 = moderate: aware of symptoms, but doesn't affect daily activity at all	3 = severe: continuously bothered by symptoms	4 = very severe: symptom is overwhelming and/or interferes with daily activity														
Fatigue, lack of energy																		
Poor coordination																		
Feeling out of control, overwhelmed																		
Feeling hopeless, worthless, or guilty																		
Headache																		
Anxiety, tension, "on edge"																		
Aches																		
Irritability, persistent anger																		
Mood swings																		
Swelling, bloating, weight gain																		
Craving foods, increased appetite, overeating																		
Decreased interest in usual activities																		
Cramps																		
Depression, feeling sad, down, or blue																		
Breast tenderness																		
Insomnia or hypersomnia																		
Difficulty concentrating																		

Figure 1. Penn Daily Symptom Report. Courtesy of the PMS Program for Research and Treatment, Dept. of Ob/Gyn, Hospital of the University of Pennsylvania, 3400 Spruce St., Phila., PA 19104. (Adapted with permission from Freeman EW, DeRubeis RJ, Rickels K. Reliability and validity of a daily diary for premenstrual syndrome. *Psychiatry Res* 1996;65:97–106.)

from comorbid psychiatric conditions. Lifetime prevalence rates of depression are much higher in women with PMDD than in controls. One study²⁶ of 206 women diagnosed with PMDD revealed that 39% also met criteria for an Axis I disorder (primarily mood disorders) and 25% were currently receiving mental health care. Furthermore, 17% of the women who did not have a current comorbid Axis I disorder were receiving mental health care, suggesting that they may have had a psychiatric diagnosis at some point or were suffering from significant psychosocial stress. In their review of 6 studies that examined whether women with PMDD have a higher percentage of past psychiatric disorders than women without PMDD, Breaux and colleagues²⁷ found that women with PMDD did not have higher incidence rates of previous major depressive disorder or anxiety disorder but were more likely to develop major depression in the future than were women not suffering from PMDD.

In distinguishing between PMDD and major depressive disorder, the primary focus of investigation should be duration of the symptoms. PMDD symptoms occur in a monthly and cyclical fashion, and there is a symptom-free interval; this is not the case for major depressive disorder. In addition, the physical symptoms associated with PMDD (eg, breast swelling, fluid retention) do not occur in major depressive disorder. Response to treatment also can help in differentiating between the two conditions: PMDD is generally more improved by selective serotonin reuptake inhibitors (SSRIs) than by other antidepressant drugs, and PMDD sufferers have a much faster response to treatment with SSRIs compared with patients with major depressive disorder. The efficacy of SSRI drugs with PMDD should not be taken as evidence that PMDD is simply a variant of major depressive disorder. The mechanism of action of SSRIs has been found to be different in the two conditions.²⁸ Additionally, suppression of gonadal hormones relieves PMDD symptoms but not major depressive disorder symptoms.

It has been recommended that the assessment of PMDD include the patient's nutritional patterns and lifestyle habits. PMS symptoms appear to be most troubling in women who smoke, lead stressful lives, rarely exercise, sleep too little, or follow a poor diet. Women who perceive their lives as stressful are more likely to have PMS.²⁹ A history of familial psychiatric disturbance should be obtained.

Medical conditions that could account for the patient's symptoms also must be considered. These conditions include hypothyroidism, endometriosis, diabetes mellitus, hypertension, anemia, autoimmune disorders, chronic fatigue, collagen vascular disease, irrita-

Table 3. Instruments Commonly Used for Diagnosing Premenstrual Dysphoric Disorder

- Calendar of Premenstrual Experiences (COPE)²⁰—22-item scale that measures 4 domains (emotional symptoms, physical symptoms, acne/appetite/cravings, and symptoms of water retention). High test-retest reliability has been established. It has been recommended that this instrument be paired with the Bipolar Mood Diary if there are concerns about making a differential diagnosis between bipolar disorder and PMDD.
- Moos' Menstrual Distress Questionnaire²¹—47 items that measure 8 scales (pain, water retention, autonomic reactions, negative affect, impaired concentration, behavior change, control, and arousal). This scale has established reliability.
- Premenstrual Tension Syndrome Observer (PMTS-O) and Self-Rating Scales (PMTS-SR)²²
- Self-Rating Scale for Premenstrual Assessment Form²³—A 95-item test that has been found to have high sensitivity but low specificity. The sheer length of the instrument makes it a less desirable aid.
- Prospective Record of the Impact and Severity of Systems of Menstruation (PRISM)²⁴
- The Daily Rating Form²⁵—21 items, wherein all DSM-IV criteria are included. Assesses affective, behavioral, and somatic symptoms. A reliable instrument.

ble bowel syndrome, perimenopause, adrenal disorders, and seizure disorders.^{30,31}

• **What demographic variables may impact the PMDD symptom presentation?**

According to a study conducted in Virginia,²⁹ women between 25 and 34 years of age are more than twice as likely to experience PMS than those between 35 and 44 years of age. Also, some evidence exists that PMS may be slightly more prevalent among black women (affecting 1 in 10) than among white women (1 in 13) or women of other races (1 in 25). Another study found similar rates of PMDD in black and white women.³²

Prevalence rates in India (6.4%)³³ appear to be consistent with US rates. A study from China³⁴ suggests cultural variation in PMDD symptomatology. Chinese women reported that pain and fatigue were their most significant PMS symptoms; this is in contrast to Western samples, who report depression as the most troubling. The difference in symptom manifestation may very well relate to how women perceive the socially appropriate and sanctioned means of expressing their discomfort.

Further study within the domain of cultural variation in PMDD symptomatology is needed.

- **What are the etiologic predispositions to PMDD?**

Many hypotheses about the etiologic causes of PMDD have been put forth and, as of yet, none have been definitively accepted as preeminent. For example, women with PMDD have been found to be more sensitive to normal fluctuations in gonadal hormones (estrogen and progesterone) than are women who do not suffer from the condition.⁹ Eriksson and his colleagues²⁸ report that many premenstrual symptoms may be triggered by high mid-cycle peaks of progesterone and/or estradiol. Others have suggested that low levels of progesterone in the central nervous system may contribute to PMDD symptomatology.³⁵ Evidence is largely lacking, however, that gonadal steroids or gonadotropins are the etiologic causes behind PMDD.³⁶

Neurotransmitter dysfunction has been implicated as an etiologic factor in PMDD. The two most implicated neurotransmitters are GABA and serotonin. Dysregulation in GABA/benzodiazepine receptor functioning was found in a small-scale study³⁷ that compared the reactions of women injected with a benzodiazepine antagonist, and later, with a placebo. Women with PMDD had significantly greater panic responses than those without the disorder. It has been well established that GABA neurotransmission is affected by progesterone metabolites and that levels of such metabolites drop significantly during the late luteal phase. Furthermore, it has been established that endogenous opiate levels (as largely regulated by GABA plasma levels) drop during the late luteal phase and subsequently correlate with premenstrual feelings of irritability, anxiety, and tension.³⁸

PMDD sufferers also have been found to have lower serotonin levels and less serotonin uptake during the premenstrual phases of their menstrual cycles.³⁹ The finding remains enigmatic as peripheral levels may not correspond with receptor levels. Women with PMDD who are given intravenous L-tryptophan—a serotonin precursor—during the luteal phase have a blunted serotonin response in comparison with normal controls.⁴⁰ As mentioned, PMDD cannot be understood as a variant of depression simply because the SSRIs have been shown to have efficacy in its treatment. Eriksson and colleagues²⁸ hypothesize that different synapses and/or different post-synaptic serotonin receptors are mediated by the two disorders. However, they also note that some relationship between the conditions is likely to exist given the fact that lifetime prevalence rates of depression are much higher in women with PMDD than in controls.

Another approach to understanding the physiological changes associated with PMDD is the utilization of neuroimaging techniques. Buchpiguel et al⁴¹ made use of single photon emission computed tomography (SPECT) imaging and found that women with premenstrual symptoms had a marked decrease in cerebral blood flow in the temporal lobes during the luteal period, which was not found to be the case during postmenstrual periods in the cycle or among control subjects at any time in the menstrual cycle.

β-Endorphin levels have been found to be lower in women with PMDD, and these levels decrease during the luteal phase.⁴² There is no evidence that thyroid dysfunction⁴³ or hypoglycemia⁴⁴ are causative factors. Studies conducted among twins have found a genetic component to PMDD.⁷

Further Assessment and Initial Management of Case Patient

When questioned about additional symptoms, the patient says she sometimes feels bloated, has flare-ups of acne, and experiences excessive thirst. She is certain that her symptoms are not present on more days than not. The physician empathizes with the patient and assures her that she is going to do her best to help her obtain relief. She explains that she would like the patient to keep a symptom diary for 2 months to help with making an accurate diagnosis. The physician also orders hemoglobin A_{1c} and thyroid-stimulating hormone levels to rule out diabetes mellitus and a thyroid disorder. The patient is educated about PMS and about lifestyle changes that she can make now that may provide symptom relief. A referral to a behavioral health psychologist with the goal of learning stress management techniques is offered and accepted.

- **What lifestyle changes can be recommended to PMDD sufferers?**
- **Is behavioral therapy helpful for treating PMDD?**

Lifestyle Modifications

Lifestyle changes, such as aerobic exercise, a complex carbohydrate diet, and nutritional supplements such as calcium, magnesium, and vitamin E, are recommended by the American College of Obstetricians and Gynecologists.¹⁷ In a recent crossover study, it was found that women who followed a low-fat vegetarian diet over the course of 2 menstrual cycles had reductions in weight, less menstrual pain, and a shorter duration of premenstrual symptomatology.⁴⁵ Relatedly, women who suffer from cyclical breast swelling, tenderness, and pain were found to have higher fat and

cholesterol contents in their diets as compared with control subjects.⁴⁶ The authors of both of these studies posit that dietary habits contribute to varying levels of estrogen and progesterone. Other dietary modifications that have been advanced include increased intake of fresh fruits and vegetables and decreased intake of salt, fat, refined sugar, alcohol, caffeine, and refined or highly processed foods; however, there is little evidence to support the effectiveness of these dietary habits in relieving PMDD.

Considered a front-line strategy for combating many biopsychosocial conditions, exercise is often recommended to women who suffer from PMDD. Although subjective feelings of well-being may be enhanced after engaging in routine exercise, it is unknown whether this is a result of increased self-esteem, biologic changes, or a combination thereof. Furthermore, exercise allows for the elimination of water, which can alter physical symptom patterns (eg, bloating). Pearlstein and Steiner⁴⁷ have noted that aerobic exercise has not clearly been indicated as more effective than nonaerobic exercise for alleviating PMDD symptomatology. Implementing a well-designed research protocol to study the impact of exercise on PMDD is difficult given drop-out rates and standardization of the proposed treatment condition.⁴⁸ Although some studies have shown a decrease in premenstrual symptoms with exercise, subjects included in the study samples did not necessarily meet criteria for PMDD.⁴⁹ Overall, the relationship between PMDD and exercise is an exciting domain of study and more research is greatly needed.

Behavioral Therapy

Cognitive behavioral approaches may be useful in helping patients better understand and cope with PMDD. In cognitive behavioral therapy, a trained mental health professional guides a patient toward understanding the interaction between her thoughts, emotions, behaviors, and physiology. Learning to relabel thoughts of pain and discomfort or to engage in structured distraction techniques have been useful interventions in the management of other conditions (eg, chronic pain⁵⁰ and headache⁵¹). Pearlstein and Steiner⁴⁷ found that engaging in relaxation exercises twice daily was more effective than simply charting symptoms or leisure reading but less effective than coping skills training. Additionally, a small-scale preliminary study found that guided imagery significantly lowered premenstrual distress scores.⁵² Further research in this area is needed.

Case Patient—8 Weeks Later

The patient returns for a follow-up visit 8 weeks later. She reports that she was able to increase her consumption of fresh fruits and vegetables and whole grains and has experienced a slight improvement, but she says her monthly symptoms still cause her significant distress. She has not had time to schedule a behavioral therapy appointment.

The physician reviews the patient's symptom calendar and makes a diagnosis of PMDD. She informs the patient that many women suffer from PMDD and that the condition is highly amenable to treatment. She also tells her that symptoms may persist until menopause but will vary in intensity over time. Given the patient's symptom profile and her desire for fairly rapid results, the physician prescribes a trial of an SSRI.

• What is the role of SSRIs in the treatment of PMDD?

SSRIs

The SSRIs have been found to improve both physical and psychosocial symptoms in PMDD^{53–56} and are considered an effective first-line therapy. Success rates vary based upon degree of symptomatology, adequate drug dosing, duration of the drug therapy, and patient compliance. A meta-analysis of 15 randomized controlled trials by Dimmock et al⁵⁷ showed that an SSRI was approximately 7 times more effective than placebo in the treatment of physical and behavioral symptoms in PMDD. SSRIs are a more effective treatment for PMDD than are the other classes of antidepressant drugs.⁵⁸

Although it is not the only SSRI that has been found to have efficacy, fluoxetine is the only drug that has been FDA-approved for the treatment of PMDD, at a dose of 10 to 20 mg daily.⁵⁵ Effectiveness of use over a duration of 6 months has not been examined. Sertraline^{59,60} and paroxetine⁵⁶ also are effective and under consideration for approval. Intermittent use of an SSRI (eg, during the luteal phase only) appears to be at least as effective as continuous daily dosing^{57,61–64} and is gaining support and popularity. One of the greatest benefits of intermittent dosing is the lower cost. However, adherence to an intermittent dosing schedule may prove confusing to some patients and thereby impact treatment follow-through.

The positive effects of the SSRI drugs typically occur within 1 month. It has been recommended that if results are not seen after 2 to 3 menstrual cycles, new treatment should be initiated. The most common side effects of the SSRIs include gastrointestinal complaints (eg, constipation, diarrhea, nausea), central nervous

system complaints (eg, irritability, anxiety, insomnia), and sexual complaints (eg, decreased libido, sexual dysfunction). Sexual dysfunction occurs in up to 25% of women who take SSRIs.⁶⁵ It has been shown that patients who are forewarned about side effects upon time of prescription are less likely to prematurely discontinue use of the medication. Caution has been recommended when prescribing SSRIs for PMDD in girls under the age of 18 years.⁶⁶ Younger adolescents typically are not included in research samples, nor has sufficient study been conducted regarding the long-term effects of such drugs on young women who are not yet fully developed.

- **Is there a role for other pharmacologic agents?**

Anxiolytics

Anxiolytics have a history of being recommended for treatment of PMDD, but their use has dropped since the advent of SSRIs. Alprazolam has been prescribed for alleviation of general PMDD symptoms. It requires tapering upon termination and can lead to significant weight gain. In a double-blind, placebo-controlled study, alprazolam was found to be significantly better than both placebo and progesterone for overall decrease in premenstrual symptom scores⁶⁷ but was not particularly effective in reducing physical symptoms. The researchers note that prescribing solely during the luteal phase decreases the likelihood of abuse. Another study found alprazolam to be no better than placebo for PMDD.⁶⁸ There is minimal information on the use of buspirone for PMDD.⁶⁹ It must be emphasized that SSRIs have been proven to have more robust effect sizes, fewer side effects, and higher compliance rates as compared with the anxiolytics.⁷⁰ Furthermore, both alprazolam and buspirone have been found to increase premenstrual food intake and thereby make them ineffective for the alleviation of food cravings.^{71,72}

Over-the-Counter Remedies

Women with premenstrual symptoms report frequent use of over-the-counter PMS products.⁷³ These medicines usually combine aspirin or acetaminophen with caffeine, antihistamines, or diuretics. Clinical support for these medications is not substantiated. Prostaglandin inhibitors (eg, ibuprofen, naproxen⁷⁴), which can work quite well for mild or moderate PMS, also are available without a prescription.

Gonadotropin-Releasing Hormone Agonists

Gonadotropin-releasing hormone agonists (eg, danazol, leuprolide, buserelin, goserelin) temporarily

inhibit ovarian activity, which is the greatest deterrent to using this intervention. In one study, a low-dose regimen of buserelin caused more than half of the subjects to experience anovulation.⁷⁵ (These women were the older members of the sample.) These drugs have been found to be generally effective in most—but not all—studies. Monthly injection of medroxyprogesterone acetate (Depo-Provera) alleviates symptoms, but the long-term safety and side effects are unknown. Gonadotropin-releasing hormone agonists can cause unpleasant side effects, such as hot flashes, vaginal dryness, reduction in libido, and bone loss.⁷⁶ In response, “add-back” treatment has been used, but this is controversial as well and is not fully supported by research.⁷⁷

Miscellaneous Drugs

Many other drugs have been advanced as treatments for PMDD.

- Spironolactone—A diuretic found to be effective for fluid retention and bloating.⁷⁸ Another study⁷⁹ also found this drug to be clinically significant for decreasing the negative mood changes that accompany PMDD.
- Clomipramine—Effective for premenstrual irritability, sadness, and dysphoria^{80,81} when dosed daily or intermittently.⁸²
- Clonidine—Activates β_2 -adrenergic receptors and may decrease the amount of norepinephrine released at presynaptic sites. Found effective in a small-scale study.⁸³
- Danazol—Effective only for mastalgia; does not impact global PMDD symptoms.⁸⁴ Pregnant women or those trying to get pregnant should not take this drug.
- Oral contraceptives—Though there is little clinical data, combination oral contraceptives are frequently prescribed for PMDD. For women who clearly meet diagnostic criteria for PMDD, oral contraceptives alone are unlikely to provide relief.⁸⁵ Freeman et al⁸⁶ conducted a double-blind, placebo-controlled study of a unique oral contraceptive containing drospirenone and ethinyl estradiol. Between-group differences were statistically significant for changes in appetite, acne, and food cravings. No significant mood findings were established. Further research involving the use of oral contraceptives in PMDD is needed.
- Progesterone/progestogen—Though physicians continue to prescribe progesterone compounds, a meta-analytic review of 14 trials found that they are not effective in the treatment of PMDD.⁸⁷

- Naltrexone—A narcotic antagonist that is not addictive if taken orally. Ovulation is not impacted and general symptoms are alleviated,⁸⁸ but there are a number of side effects (eg, nausea, abdominal pain, headache, skin rash). Support for use of this drug is minimal.
- Dexfenfluramine—Utilized for depression and minimization of food cravings.⁸⁹ Known to have high anti-cholinergic side effects. Given the lack of extensive research and the availability of other viable interventions, use of dexfenfluramine is not recommended.
- Mefenamic acid—A prostaglandin inhibitor. Found to be effective for physical symptoms (most notably fatigue, headache, general pain) and mood (primarily mood swings),⁹⁰ but in another study was found to be no more effective than placebo.⁹¹ Due to potential adverse effects (eg, hematologic, neurologic, renal) and lack of clarity in the literature, this drug is not recommended.
- Bromocriptine—Not effective; also causes a significant proportion of women to terminate usage because of side-effect profile.
- Calcium (1200 mg daily)—Found to reduce overall luteal phase symptoms.⁹⁶ Likely to have only mild effectiveness. Effect sizes lower than those for SSRIs. Women participating in a study who were fed low-calcium diets (during their premenstrual phases) exhibited increased negative affect, greater pain, more water retention, and poorer concentration.⁹⁷
- Magnesium (200–400 mg daily)—Helpful for fluid retention,⁹⁸ breast tenderness, and abdominal bloating, but not useful as an aid for emotional symptoms and not well supported as having efficacy in reducing overall symptoms. An older study⁹⁹ found that while magnesium was no more effective than placebo in reducing pain symptoms, negative mood states were significantly improved. This finding is consistent with the theory that low levels of magnesium impact serotonin action.
- Manganese—Diets low in manganese produce symptoms similar to those seen with low calcium diets.⁹⁷
- Agnus castus fruit extract—A recent double-blind, placebo-controlled study¹⁰⁰ from Germany found this substance to be efficacious for most PMDD symptoms (bloating was not alleviated, but irritability, mood changes, headaches, and mastalgia were impacted) and to have minimal side effects.
- Evening primrose oil—A meta-analysis found this to be an ineffective treatment.¹⁰¹
- Ginger tea (for nausea), Chinese herb dong quai (for cramps), black cohosh, zinc, melatonin, St. John's wort, kava kava, and wild yam—These therapies cannot be recommended, and many have significant side effects.

It should be noted that some women with PMDD experience improvement with placebo medication. In one study, 20% of subjects showed sustained improvement with placebo at 3 months, whereas 80% showed no or partial improvement.⁹²

- **What is the role of complementary and alternative therapies?**

Complementary/alternative therapies are popular with women who have PMS.⁹³ Despite their popularity, however, validation of the efficacy of complementary therapies is generally lacking. Stevinson and Ernst⁹³ conducted a systematic review of randomized controlled trials to determine whether use of alternative therapies is supported by compelling evidence and concluded that no alternative therapies could be recommended as viable treatment for PMDD at the present time. For the sake of completeness, some herbs and vitamins that have been discussed in the literature are listed below.

- Vitamin B₆/pyridoxine—The existing evidence of positive effects is weak.⁹⁴ Large doses (more than 100 mg daily) can cause nerve disorders (eg, peripheral neuropathy) if taken long term. Andrews⁹⁵ reports that up to 92% of PMDD sufferers have tried pyridoxine or vitamin B₆ despite the fact that evidence supporting its efficacy is lacking.

- **What about phototherapy?**

Evidence supporting this intervention for PMDD is developing. In a small-scale preliminary study, exposure to 3 different light treatments (bright white morning light, bright white evening light, and placebo dim red evening light) all led to significant decreases in depressive mood associated with premenstrual symptomatology.¹⁰² Another study found that 30 minutes of light therapy daily during the luteal period was effective in reducing PMDD symptoms.¹⁰³ Another study showed evening bright light treatment is more effective than morning treatment.¹⁰⁴ It is believed that phototherapy positively impacts PMDD symptomatology through increased production of melatonin, which subsequently boosts serotonin levels. Relatedly, women

with seasonal affective disorder are more likely to have PMDD than women in the general population.¹⁰⁵

• **What are surgical interventions for PMDD?**

Hysterectomy with bilateral salpingo-oophorectomy is an effective therapy for severe PMS/PMDD. In severe cases, women may wish to discuss this option with their physician.

Case Patient—Follow-up

The patient does well on the SSRI and experiences no side effects after the first week. At the 10-week follow-up visit, substantial improvement is noted based on patient self-report and her symptom diary. The patient reports significantly less irritability and feeling less bothered by her physical symptoms as well. She states that she initially felt anxious after beginning SSRI therapy but notes that this feeling subsided after a week. She is attending a mental health clinic and has begun to employ cognitive behavioral strategies during the luteal phase of her cycle; she says that she finds the technique helpful. The patient and physician agree to meet for a brief 15-minute appointment in 2 months.

CONCLUSION

Significant numbers of women in their reproductive years, across a wide age span, are affected by PMDD. Although PMS and PMDD may have been poorly understood or trivialized in the past, they are now recognized as unique disorders for which effective treatment is available.

Given that women may not even broach the subject of PMDD due to a sense of shame, embarrassment, or fear of stigma, it may be helpful to routinely question patients about PMDD symptomatology during annual physical examinations. It is worth noting that a patient's failure to bring up the subject does not mean she is not suffering from significant levels of distress. As assessed by a mail survey completed by more than 1000 respondents, it was discovered that older age, greater symptom severity, and less negative attitudes toward premenstrual conditions were associated with treatment-seeking behavior.¹⁰⁶ Frequent, nonjudgmental, and normalizing inquiries from health care providers about premenstrual symptoms may assist in breaking down misguided notions about PMDD and attitudinal barriers toward seeking treatment.

HP

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