Approach to Premenstrual Dysphoria for the Mental Health Practitioner

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For many centuries, the menstrual cycle has held negative connotations for women. It has been held as evidence for a generalized sense that women were incompetent or unstable, with their resultant exclusion from opportunities in education, employment, and positions of influence.\textsuperscript{1,2} Such views are no longer in the mainstream.

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There has been clear advancement of knowledge with the advent of understanding that female sex hormones underlie the menstrual cycle and that mood disorders related to menstruation are a significant problem for some women. Women commonly present to health care practitioners complaining of premenstrual mood disturbance, warranting diagnosis and treatment. However, it can be challenging for providers to feel confident about managing these complaints because of the wide array of symptoms that women report, the multiple physical and psychiatric conditions on the differential diagnosis, and the psychosocial connotations of the disorder. This review presents an approach to the diagnosis and management of premenstrual mood disturbance and specifically reviews a biopsychosocial approach to the management of premenstrual dysphoric disorder (PMDD) for the mental health practitioner.

SCOPE OF THE PROBLEM

Prevalence

Varying reports in the literature on the prevalence of premenstrual mood disturbance depend in part on the definitions used. The American Psychiatric Association (APA) explicitly acknowledges in the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) that up to 70% of women are affected by at least mild symptoms of premenstrual syndrome (PMS). The American College of Obstetricians and Gynecologists (ACOG) reports that up to 85% of women experience PMS as defined by at least 1 emotional and 1 physical symptom, present in 3 consecutive menstrual cycles, and severe enough to interfere in daily life. The APA has defined, and ACOG acknowledges, PMDD as a more severe and pervasive form of premenstrual mood disturbance that affects a much smaller, albeit significant, proportion of women.

Studying the prevalence of PMDD in community samples has been challenging because the strict DSM-IV-TR diagnostic criteria for PMDD include prospective symptom measurement, exclusion of other psychiatric and physical disorders, and evaluation of functional impairment. Most community prevalence estimates have been based on retrospective symptom reports and have contained variable definitions of severe symptoms. Prevalence estimates based on DSM-IV-TR diagnostic criteria, but without the requirement for prospective symptom ratings, seem to be in the range of 5% to 6% in samples from North America and Europe. However, there may be cultural variability in prevalence or symptom reporting as shown by a reported prevalence of only 1.2% in a Japanese study of 1152 women aged from 15 to 49 years in a cancer screening clinic. Studies that measure symptoms prospectively reveal slightly lower estimates in some cases, with prevalence estimates ranging from 1.6% to 6.4%. Studies of clinical or volunteered populations tend to report prevalence estimates on the higher end of that range. For example, in older premenopausal women recruited into the Harvard Study for Moods and Cycles (women aged 36–44 years), 6.4% of those who completed 1 menstrual cycle of prospective ratings met criteria for PMDD. Estimates from 2 community-based prospective studies in which participants were sampled with the intent of generalizing the information to the general population revealed slightly lower estimates. Using the National Registry of Iceland, Sveindottir and Backstrom reported a prevalence of PMDD between 2% and 6%. In the United States, Gehlert and colleagues interviewed 1246 women (ages 13–55 years) in their homes, and the participants completed prospective daily symptom checklists over 2 menstrual cycles. In this
study, only 1.6% of the women were diagnosed with PMDD using strict DSM-IV-TR criteria.

**Clinical Correlates**

Discerning correlates of PMS and PMDD can aid practitioners in identifying women at risk for the disorder and in need of treatment. However, although these variables may be associated with premenstrual mood disturbance, and therefore can help with identifying who is at risk, they do not necessarily lie along the causal pathway to PMS or PMDD. Potential etiological variables that may help guide treatment are discussed further in this article.

Few demographic variables are associated with increased risk for PMS or PMDD. Although younger age was associated with increased severity of symptoms in 1 study, clinical experience suggests that older women, particularly those with multiple children, may be more likely to report severe symptoms. It is possible that this observation is confounded by the higher likelihood that younger women (before starting their families) are more likely to be using concomitant hormonal treatments for birth control, thereby reducing the severity of their premenstrual symptoms. The relationship between education level and PMDD has been studied, with conflicting results. Although women with higher levels of education tend to report more premenstrual symptoms in older premenopausal women from the Harvard Study of Moods and Cycles, PMDD was associated with lower levels of education. Additional evidence from the same sample suggests that this effect may have been the result of high comorbidity of PMDD with major depressive disorder.

Another important clinical correlate of premenstrual mood dysphoria is life stress. Several studies have shown an association between PMS/PMDD and stressful life events, including past sexual abuse in up to 40% of women, a substantially higher rate of sexual abuse than has been reported in the female general population. Premenstrual mood disturbance has also been associated with higher levels of day-to-day stress.

Family history of PMDD increases a woman’s risk of having the disorder herself, with twin studies suggesting heritability in the range of 44% to 56%. Personal history of major depressive disorder, particularly when related to other reproductive life stages such as depression in pregnancy or the postpartum period, may also be associated with an increased risk of PMDD.

**Effects**

It has been difficult to specify the distinction between PMS and PMDD regarding the effects of these problems on social and occupational dysfunction. Steiner and colleagues found that preexisting beliefs about work may affect the findings in studies that use self-reports. However, significant evidence of the negative effects of PMDD has been documented. For example, a large study of randomly selected members of a health maintenance organization found that women with PMDD reported decreased work productivity compared with women with milder premenstrual symptoms. More recently, Yang and colleagues attempted to compare the health-related quality of life in women with PMDD with that of women in the general population and women with other chronic health conditions in a community sample based in the United States. They found that the mental health–related quality of life burden for women with PMDD was greater than for women in the general population. It was also greater than for women with chronic back pain, and comparable with women with type II diabetes mellitus, hypertension, osteoporosis, and rheumatoid arthritis.
DIAGNOSTIC CONSIDERATIONS

PMS Versus PMDD

Premenstrual psychiatric symptoms are currently conceptualized and treated as part of the mood disorder spectrum. As outlined earlier, the DSM-IV-TR contains a definition of PMS as a syndrome that may include mild psychological discomfort or physical discomfort such as bloating and breast tenderness. However, these symptoms do not result in significant functional impairment, and PMS symptoms are not considered to be disordered. However, PMDD is listed in DSM-IV-TR as an example of a depressive disorder not otherwise specified and is described as follows:

In most menstrual cycles during the past year, five (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 the onset of the follicular phase, and were absent in the week post-menses .... The disturbance markedly interferes with work or school or with usual social activities and relationships with others (p. 774).

In appendix B, the DSM-IV-TR specifies research criteria for PMDD whereby a diagnosis must include a least 1 of the essential symptoms of marked and persistent anger/irritability, depressed mood, anxiety, or affective lability with a total of 5 (out of a possible 11) symptoms. The other 7 symptoms are anhedonia, lack of energy, change in appetite, change in sleep, sense of feeling overwhelmed or out of control, and other physical symptoms (eg, breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating or weight gain). The diagnosis of PMDD also requires a minimum of 2 consecutive months of prospectively daily symptom ratings. These prospective ratings are considered essential because of concern that retrospective reports of premenstrual symptoms might not be reliable, and because, due to mood and cognitive changes, there may be differential symptom reporting depending on the phase of the menstrual cycle in which women are queried. Prospective daily symptom ratings are usually made using Likert or visual analog scales. Validated tools were described in a recent comprehensive review by Pearlstein and Steiner. Many women do report some premenstrual symptoms during the follicular phase. A change score for symptom severity between the luteal and follicular phases may therefore be a more meaningful outcome, with a change of 30% to 50% having been recommended as an indication that a diagnosis of PMDD is appropriate.

Other Conditions as Differential Diagnoses

Physical disorders that may mimic PMDD can usually be readily differentiated from PMDD by careful history, physical examination, and other relevant investigations. These disorders include systemic diseases such as autoimmune disorders, diabetes mellitus, anemia and hypothyroidism, and gynecologic conditions such as dysmenorrhea and endometriosis in which premenstrual exacerbations are commonly seen.

Distinguishing PMDD from premenstrual exacerbations or magnification of psychiatric disorders is important because, with successful treatment of the primary condition, premenstrual symptoms will often remit. Women who report premenstrual depressive symptoms should be screened for psychiatric symptoms across all phases of the cycle (and be treated accordingly). Premenstrual exacerbations of depressive disorders are commonly reported. For example, Hartlage and colleagues found that 44% of nondepressed women taking antidepressants reported premenstrual mood symptoms in a community sample in the United States. Results from the National Institutes of Mental Health’s Sequenced Treatment Alternatives to Relieve Depression
STAR-D trial found that, of 433 female participants with major depression, 64% reported a worsening of their depressive symptoms 5 to 10 days before menses. Bipolar disorder must also be considered in the differential diagnosis of PMDD. Women with underlying bipolar disorder may experience premenstrual exacerbations of depressed mood or irritability. Women with personality disorders may also experience increased irritability and interpersonal difficulties in the premenstrual period.

PROPOSED ETIOLOGICAL FACTORS

It has been argued that PMS is a culture-bound syndrome in which women in Western cultures have been socialized to have negative expectations about menstruation. It has been put forward that North American culture and the media further perpetuate the idea that the premenstrual period is associated with negative affect and mood instability, with the result that women negatively interpret normal physiological changes that are essentially neutral in nature. However, there is also clear evidence that sociocultural expectations do not form the complete picture of the cause of PMS, and certainly not of PMDD. As is the case with other psychiatric disorders, evidence is mounting that the cause of PMDD is likely complex, involving multiple biological, psychological, and sociocultural determinants. It is difficult to study how such factors might interact to produce the clinical picture of PMDD. This section highlights factors known to be important in the cause of this disorder, and that may be useful in guiding management and future development of treatment options.

Female Sex Hormones

Although symptoms of PMDD and phases of the menstrual cycle are temporally related, not all women suffer severe premenstrual mood symptoms. It is now being hypothesized that women with PMDD are more vulnerable than women without PMDD to the normal physiological changes associated with the menstrual cycle. This theory has been supported in 2 studies, in which women with and without PMDD responded differently to challenges with physiological levels of estrogen and progesterone. In the first study, women with PMDD responded with more depressive mood than controls, and, in the second study, the 2 groups had differential gonadotropin hormone level responses. The centrally active progesterone metabolite allopregnanolone has also been investigated for its potential role in the pathogenesis of PMDD. In women with PMS and PMDD, there seems to be a relationship between allopregnanolone serum concentrations and the severity of premenstrual symptoms, although some investigators have hypothesized that women with PMDD have differential sensitivity to allopregnanolone, and not to absolute levels of the neurosteroid. Imaging studies show that women with PMDD have differential sensitivity at their \( \gamma \)-aminobutyric acid A (GABA-A) receptors (ie, where allopregnanolone acts in the central nervous system), and that the severity of symptoms in women with PMDD seems to be related to their sensitivity to GABA steroids. In addition, women with PMDD show differential sensitivity to other compounds with GABA-A activity, such as the benzodiazepine antagonist flumazenil and several benzodiazepines compared with controls. Possibly because of drug modulating effects on allopregnanolone levels, via GABA-A receptors, this sensitivity seems to normalize during treatment with serotonin reuptake inhibitors.

Other Hormones and Endocrine Factors

Because of the prominence of irritability as a symptom of PMDD, androgens have also been investigated. Increased testosterone levels have been observed in women who
report severe premenstrual irritability, although one study revealed significantly lower total and free plasma testosterone levels in PMS patients compared with healthy controls. There is little consistent evidence for the involvement of other endocrine factors, including cortisol, thyroid hormone, prolactin, melatonin, aldosterone, and endorphins in the cause of PMS/PMDD.

**Serotonin**

Research has revealed that there is a relationship between serotonin function and ovarian hormone secretion, contributing to the plausibility of a complex interaction between hormone secretion and serotonin fluctuation. In support of this hypothesis, a role for serotonin in the pathophysiology of PMDD has been consistently shown in research investigations using several experimental models. During the premenstrual phase, patients with PMDD have lower whole blood serotonin levels and lower platelet serotonin uptake than controls without PMDD, and Melke and colleagues found that women with premenstrual dysphoria had fewer platelet paroxetine binding sites (ie, fewer serotonin transporters) compared with controls. Positron emission technology has revealed differences between women with PMDD and controls in brain serotonergic function across the menstrual cycle. Challenges with serotonergic agents, such as L-tryptophan, fenfluramine, and buspirone, have also provided evidence of serotonin dysfunction in women with PMDD. In addition, serotonergic drugs, and selective serotonin reuptake inhibitors (SSRIs) in particular, can treat PMDD rapidly (see later discussion), strongly supporting the hypothesis that serotonin is involved in the cause of PMDD. Only approximately 60% of patients with PMDD respond to treatment with SSRIs, therefore isolated premenstrual serotonin deficiency is not likely to be the only etiological variable in all PMDD patients.

**Genetic Factors**

As mentioned earlier, there is evidence that PMDD is a heritable disorder. This has led to a search for genes that may be important in the pathophysiology of PMDD. From the evidence outlined earlier, most of the focus on genetic factors has been on genes related to serotonin and estrogen, as these are believed to be of primary importance in PMDD. Praschak-Rieder and colleagues found an association between PMDD and 5HTTLLPR heterozygosity in women with seasonal affective disorder, and Steiner and colleagues identified a relationship between polymorphism in the serotonin transporter gene and severity of PMDD symptoms. More recently, Huo and colleagues identified allelic variation in ESR1, the estrogen- receptor gene in women with PMDD. This work forms an important basis for future research into the pathophysiology of PMDD.

**Psychosocial Factors**

There is little literature investigating how biological and sociocultural variables may interact in the development of severe PMS and PMDD. However, sexual abuse (and childhood sexual abuse in particular) has lasting effects on psychological and physiological responses to stress. It has been hypothesized that past abuse could predispose women to psychiatric disorders, including PMDD through psychological and biological mechanisms. For example, from a psychological perspective, some evidence suggests that women with premenstrual symptoms tend to rely more than other women on less effective strategies for coping with stress, such as avoidance or wishful thinking, than on strategies such as problem-focused coping or direct action. From a biological perspective, preliminary evidence suggests that the high prevalence of sexual abuse among women seeking treatment of premenstrual
symptoms may account for findings of dysregulated cardiovascular and neuroendocrine responses to laboratory stress in PMDD patients.\(^7\text{5}\) In fact, Bunevicius and colleagues\(^7\text{6}\) found that women with PMDD with and without histories of sexual abuse had differential autonomic nervous system responses to a challenge with the \(\alpha\)-adrenergic receptor agonist clonidine. There is potential in this field for further development of the understanding of how biological and psychosocial factors interact to produce psychiatric illness.

**MANAGEMENT**

Although the precise pathophysiology of premenstrual mood dysphoria has yet to be elucidated, treatment strategies for PMDD have been informed by the findings to date. As PMDD has multiple biological and sociocultural etiological determinants, its treatment should involve an integrated approach. Treatment should appropriately reflect the severity and functional impairment associated with the symptoms, with a stepwise approach beginning with the least invasive treatments. An outline of the approach to treatment of PMDD is given in **Box 1**. For all women, treatment of comorbid psychiatric or medical disorders and issues related to any persistent life stressors, or any past or current physical or sexual abuse, is essential.

**Lifestyle Factors**

Education about the condition, supportive counseling, and general healthy lifestyle measures, such as regular exercise and healthy diet, may be sufficient to result in symptom improvement in women with mild symptoms. These recommendations can be made and patients can attempt to follow them during a 2-month trial while the patient completes the prospective daily ratings necessary to confirm the diagnosis of PMDD.\(^7\text{7}\) Increased consumption of fruits, vegetables, legumes, whole grains, and water is recommended, and women can be encouraged to reduce or eliminate intake of salty foods, sugar, caffeine (especially coffee), red meat, and alcohol. Eating smaller, more frequent meals that are high in carbohydrates may specifically improve symptoms of tension and depression.\(^7\text{7}\) Recommendations for regular exercise include 20- to 30-minute periods of aerobic exercise 3 to 4 times per week.\(^7\text{8}\) Reduction of body weight to within 20% of ideal, if possible, is an appropriate goal.\(^3\text{6}\)

Because sleep irregularities are present in many women with PMDD, education about sleep hygiene is important.\(^7\text{9}\) Women can be encouraged to adopt a regular

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**Box 1**

**Step-wise approach to management of PMDD**

1. Psychoeducation
2. Lifestyle modification: healthy eating, regular exercise, good sleep hygiene, limit setting and stress management, moderate alcohol use
3. Dietary supplementation: calcium, vitamin B6
4. Behavioral treatments
5. Psychotherapy
6. Psychopharmacology
7. Hormonal treatments
8. Complementary and alternative therapies (at any time during the course of treatment)
sleep-wake pattern by adhering to consistent bedtimes and waking times throughout their menstrual cycle. Another helpful component of a treatment program is to ensure that women monitor their symptoms and begin to identify triggers of symptom exacerbation. This approach can help women to set appropriate limits and avoid scheduling highly stressful activities during the premenstrual period.

**Dietary Supplementation**

There is some evidence for calcium supplementation in treating PMS/PMDD with one large trial finding that 1200 mg of calcium daily reduced symptoms of PMS, including depression, by the second or third treatment cycle. Calcium is not known to be associated with any adverse effects so long as doses do not exceed 1500 mg daily. Evidence for vitamin B6 (pyridoxine) in the treatment of depressive symptoms in premenopausal women led to investigation into pyridoxine as a treatment of premenstrual mood symptomatology, although no trials have been done in women with strictly diagnosed PMDD. A recent double-blind placebo-controlled trial of 94 women with premenstrual mood and somatic symptoms revealed a greater decrease in psychiatric symptoms with 80 mg of vitamin B6 compared with placebo. Vitamin B6 supplementation does have risks; higher doses have been associated with peripheral neuropathy. With the rationale that increased tryptophan availability might increase serotonin synthesis, the effects of complex carbohydrate supplementation have been studied, and 2 studies have reported positive effects of a carbohydrate-rich beverage on affective symptoms in women with PMS. Although other dietary supplements are recommended in the lay press for treatment of PMS/PMDD symptoms, little scientific evidence is available to support these recommendations.

**Psychoeducation and Behavioral Treatments**

There is some evidence for group psychoeducation and support in treating women with PMS and PMDD. Specifically, women with PMDD who received a psychoeducational group intervention that focused on positive reframing of women’s perceptions of their menstrual cycles had reduced premenstrual symptoms and premenstrual impairment compared with women in a control group. However, the intervention did not result in differences in posttreatment depression or anxiety scores. Relaxation therapy can also be added to the treatment regimen, particularly for women who report high daily stress levels.

**Psychotherapy**

A systematic review by Lustyk and colleagues identified 7 published peer-reviewed studies (3 randomized controlled trials) evaluating the efficacy of cognitive-behavioral therapy (CBT) for PMS and PMDD. The reviewers concluded that, although CBT may provide some benefit, the magnitude of the effect is likely to be smaller than for pharmacotherapy and even relaxation treatments. However, CBT remains an option for women who prefer not to attempt pharmacotherapeutic treatment.

**Psychopharmacology**

Some women will not respond to the nonpharmacological strategies mentioned earlier. Other women will have severe symptoms of PMDD in need of immediate treatment. Serotonergic medications, specifically SSRIs, have become the mainstay of pharmacological treatment with established safety and efficacy. The US Federal Drug Administration (FDA) has approved the use of fluoxetine, sertraline, and paroxetine for PMDD. A Cochrane Database meta-analysis also reveals good evidence of effectiveness for fluvoxamine, citalopram, and the serotonergic tricyclic
antidepressant clomipramine. There is also evidence in randomized controlled trials for efficacy of the selective serotonin and norepinephrine reuptake inhibitor class of medications (ie, venlafaxine and duloxetine).

In the treatment of major depressive disorder, SSRIs generally require at least 2 weeks for onset of therapeutic efficacy. However, used for PMDD, SSRIs have shown efficacy when used continuously or only in the luteal (premenstrual) phases of each cycle. One advantage of luteal-phase dosing is that SSRI discontinuation effects are rarely seen, perhaps because of the lack of sustained use. Regardless of dosing method, symptoms can recur rapidly when treatment is discontinued, and women with the most severe symptoms at baseline are most at risk.

**Hormone Manipulation**

The next step in the treatment algorithm involves manipulating female sex hormones to avoid the periodic fluctuations associated with menstruation (and hence avoid associated mood fluctuations). Although there is a strong theoretical basis to this treatment, few ovulation-suppression treatments have been effective for PMDD, and some come with significant risk for adverse effects. These include deep vein thrombosis and pulmonary embolus from oral contraceptives, androgenization and osteoporosis from gonadotropin-releasing hormone (GnRH) agonists, permanent sterilization from oophorectomy.

Because oral contraceptives do provide a reasonably safe means of inhibiting ovulation (and may be most appropriate if women also desire oral contraceptives as a form of birth control), the efficacy of traditional oral contraceptives in treatment of PMDD has not been well established. However, a recent Cochrane Database systematic review supports the efficacy of a combination of ethinyl estradiol and drospirenone for the treatment of PMDD. The FDA has approved this treatment of PMDD; however, indication has been limited to women who also wish to use the medication for contraception, likely because the potential for adverse effects is greater than for SSRIs.

GnRH agonists, such as leuprolide acetate, have shown efficacy in PMS/PMDD, but the effect seems to be greater for physical than for emotional symptoms. As described, long-term use (ie, greater than 6 months) of GnRH agonists has been associated with several unfavorable side effects such as risk for hypoestrogenism and osteoporosis. The synthetic steroid danazol can reduce emotional and physical symptoms of PMS/PMDD; however, at low doses (200 mg/d), ovulation, and thus conception, are still possible, and danazol can cause virilization of the fetus. Undesirable side effects, including weight gain, mood changes, and acne, have been observed with higher doses sufficient to inhibit ovulation (600–800 mg/d). Suppression of ovulation through bilateral ovariectomy with hysterectomy has been reported to be highly effective in permanently eliminating symptoms of PMS. However, because of the extreme nature of this treatment method, it is not usually recommended, even in severe cases of PMDD.

**Complementary and Alternative Strategies**

Many patients and practitioners are turning to herbal, complementary, and other treatment options for management of PMS and PMDD. Some of these treatments have been supported by research. At present, the strongest evidence seems to be for *Vitex agnus castus* (chasteberry), although it may be more beneficial for physical rather than psychological symptoms of PMDD. Chasteberry may act as a dopamine agonist to reduce follicle-stimulating hormone or prolactin levels. Small randomized controlled trials also support saffron, Qi therapy, massage, reflexology, chiropractic
manipulation, and biofeedback.\textsuperscript{105,106} There is some evidence provided in open trials for the efficacy of yoga, guided imagery, photic stimulation, and acupuncture.\textsuperscript{33} With the rationale that it may induce rapid increase in serotonin (without the side effects of psychotropic medication), bright-light therapy has been studied as a treatment of PMDD, and a systematic review of 4 trials suggests that bright-light therapy may be an effective option for women with PMDD.\textsuperscript{107}

**SUMMARY**

Premenstrual mood symptoms are common and a small but significant proportion of women experience recurrent premenstrual mood symptoms that are severe enough to cause substantial social and occupational dysfunction. There is convincing evidence for important roles for biological and sociocultural variables in the development of premenstrual mood symptoms. There are several effective treatments, used alone or in combination, that have been found to ameliorate psychological symptoms associated with the menstrual cycle. Further interdisciplinary research into risk factors for PMDD, and the interaction between them, will provide a more complete understanding of the cause of this disorder, and ultimately guide future developments in treatment.

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