The Association Between Premenstrual Dysphoric Disorder and Other Mood Disorders

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Premenstrual dysphoric disorder (PMDD) is a premenstrual mood disorder that cyclically recurs during the majority of menstrual cycles. It is included under the category of "depressive disorders not otherwise specified" in DSM-IV. Given the placement of PMDD with other mood disorders in DSM-IV, the evidence suggesting an association between PMDD and other mood disorders is examined. Primary reports on the epidemiology, phenomenology, family history, psychobiology, and treatment of PMDD were examined for features that are commonly found in other mood disorders. There is an overlap in the symptoms experienced by women with PMDD and patients with other mood disorders. As in patients with other mood disorders, past episodes of mood disorder and family history of mood disorder are common in women with PMDD. Selected biological markers differentiate women with PMDD from controls, and some but not all antidepressants are effective in the treatment of PMDD. Many features of PMDD support its inclusion in the DSM-IV category of mood disorders. However, a number of factors (biological and cognitive studies, treatment response) differentiate PMDD from other mood disorders.
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A constellation of severe premenstrual symptoms is experienced by approximately 3% to 9% of women.[1–5] Although the existence of a cyclically recurring syndrome widely known as premenstrual syndrome (PMS) has been recognized for decades, an attempt to define severe premenstrual conditions has been relatively recent. In the revised third edition of the *Diagnostic and Statistical Manual of Mental Disorders*,[6] the category of late luteal phase dysphoric disorder (LLPDD) was introduced in an attempt to describe a severe form of PMS that is characterized predominantly by mood symptoms. Initially, this category was placed in the appendix as a condition in need of further study, but in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV),[7] the diagnosis was placed under mood disorders in the group of "depressive disorders not otherwise specified." The name of the disorder was simplified to premenstrual dysphoric disorder (PMDD), and the clinical criteria were modified slightly from the LLPDD criteria (Table 1). PMDD was placed in the same category as other mood disorders because it was felt that PMDD had much in common with them.

In this paper, the association between PMDD and other mood disorders is examined in terms of symptom profile, patterns of comorbidity with other psychiatric disorders, results from selected biological and psychological investigations, and outcome in various treatment studies. This review focuses on data regarding PMDD and includes studies that explicitly used PMDD or LLPDD criteria or employed prospective ratings of patients who in all likelihood would have met criteria for PMDD or LLPDD. References related to work on PMS, which may not include an evaluation of daily ratings or stipulate severe symptomatology, explicitly state that the population included women with premenstrual symptoms or PMS. The reader is referred to the work of others that either primarily or comprehensively reviews PMS, PMDD, or a combination of the two.[8–10]

SYMPTOM PROFILE

Up to 150 different premenstrual complaints have been reported in patients with PMS,[10] although only a handful of these symptoms are consistently identified in epidemiologic studies. In an earlier community study, Woods and colleagues found that the most common severe premenstrual symptoms were irritability, tension, painful breasts, headache, and depression.[11] Similar emo-

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Table 1. Premenstrual Dysphoric Disorder

Minimum of five symptoms: low mood, tension, mood swings, irritability, decreased interest, difficulty concentrating, fatigue, change in appetite/sleep, sense of being overwhelmed,[a] physical symptoms
Symptoms begin 1–2 weeks before menstrual flow
Symptoms absent in postmenstrual week[a]
At least one symptom is a mood symptom
Symptoms cause functional impairment at work or with interpersonal relationships

[a]New to DSM-IV.

Table 2. Symptoms of Premenstrual Dysphoric Disorder and Major Depressive Disorder

Found in MDD	Not Found in MDD
Depressed mood	Anxiety and tension
Decreased interest	Affective lability
Difficulty concentrating	Marked anger/irritability
Fatigue	Sense of being overwhelmed
Changes in appetite	Physical symptoms: breast pain, bloating, headache
Changes in sleep	

tional symptoms of irritability, tension, and depression were found in a large Scandinavian survey,[4] while a Canadian epidemiologic study found that women reported symptoms of water retention, behavioral change, negative affect, arousal, and decreased concentration.[5]

The symptoms identified by clinical populations are analogous to those found in community studies. Clare reports that women with premenstrual complaints mention symptoms including depression, anxiety, sleep difficulties, fatigue, irritability, and physical symptoms.[12] The largest database of women with severe premenstrual complaints is derived from the DSM-IV mood disorders work group. This database reports on the symptoms found in 670 women who had severe symptoms and kept prospective longitudinal symptom ratings[13]; these women were recruited from five academic centers in the United States. Several definitions were applied in order to determine which criteria most accurately described the group and thus were reflective of women with severe, mood-predominant premenstrual symptoms. In order of frequency, the most commonly identified symptoms were depressed mood, mood swings, anxiety/tension, anger/irritability, low interest, decreased concentration, poor energy, changes in sleep and appetite, and physical symptoms.[13] This illustrates that the most common and severe symptoms associated with the premenstruum from clinical studies are remarkably similar to what is found in community studies. For many women, the mood symptoms are paramount, and, as Halbreich and Endicott claim, many women will experience a premenstrual depressive syndrome that cross-sectionally mimics an atypical form of major depressive disorder (MDD) (Table 2).[14]

Table 3. Lifetime Histories of MDD Among PMDD Patients

Study	N[a]	% MDD
Fava et al, 1992[18]	32	34
Freeman et al, 1994[22]	26	58
Freeman et al, 1995[67]	170	38
Harrison et al, 1989[23]	56	70
Harrison et al, 1990[15]	30	30
Pearlstein and Stone, 1994[74]	78	46
Rickels et al, 1990[19]	10	40
Steinberg et al, 1994[16]	13	31
Stone et al, 1991[20]	20	45
Yonkers et al, 1996[78]	243	33

[a]N = number of patients.

COMORBIDITY

A number of investigators have reported the lifetime comorbidity rate in their patients with PMDD, and a history of mood disorders predominated with rates ranging from 30% to 70% (Table 3).[15–23,67,74,78] Compared to women with premenstrual symptoms who do not have a history of MDD, women with PMDD and a prior episode of MDD experience premenstrual symptoms that are similar to those of MDD.[24,25] Similarly, the risk of a nonpremenstrual mood disorder may not be equal among all women with PMS, as is suggested by Warner and colleagues.[26] In a group of patients with PMS, women whose luteal phase mood symptoms had a longer duration were more likely to have received treatment for MDD.

Not only is history of mood disorder common among many women with PMDD or PMS, but these women are also at high risk for eventually developing an episode of MDD. This was first shown in a study of college students who complained of PMS and were reevaluated for the presence of a mood disorder 1 year later.[27] A subsequent study found that women with PMDD who had the highest scores on the depression subscale of the Premenstrual Assessment Form were the most likely to eventually develop an episode of MDD.[14,28]

DSM-IV specifies that the diagnosis of PMDD applies only to women who have luteal phase symptoms and are symptom free for at least 1 week after menses. However, some women experience mild follicular phase mood symptoms coupled with more severe premenstrual symptoms. Likewise, some women with MDD may experience severe premenstrual worsening of their symptoms. These patterns, which may only be detected after a woman completes longitudinal symptom ratings, are commonly referred to as "premenstrual exacerbation." Women with mild follicular phase symptoms often suffer from ongoing dysthymic disorder or minor depression and comprise one of the largest groups of patients presenting to PMS clinics for treatment.[29]

Similar issues come up for women with bipolar disorder, particularly those with rapid cycling illness. The differential diagnosis is complicated because PMDD and bi-

polar disorder are characterized by intermittent episodes of mood disturbance such as depression and irritability. Neurovegetative changes in sleep, energy, and appetite also occur in both illnesses. One study that relied on retrospective reports of menstrual cycle symptomatology found that women with rapid cycling bipolar disorder are more likely to have severe premenstrual symptoms than a control group of women; the subgroup of women with severe premenstrual symptoms were also more likely to cycle frequently.[30] As suggested above, prospective ratings can help establish entrainment of mood disturbances to menstrual cycle phase, and it is hoped that studies employing prospective ratings will be conducted to confirm or refute these findings. If the illness does worsen during the premenstrual phase of the cycle, the woman would be designated as having premenstrual exacerbation of her illness.

In sum, lifetime comorbidity is quite common among women who have PMDD, but the most frequently seen past psychiatric diagnoses are mood disorders. This strong association, as well as the common occurrence of premenstrual worsening in women with dysthymic disorder, further supports an association of PMDD with mood disorders.

PATHOPHYSIOLOGY

Despite the predictability of luteal phase symptom expression, the etiology of this disorder has not been established. Theories regarding hormonal and vitamin deficiencies have been associated with PMS and may or may not be relevant to PMDD. Nonetheless, neither absolute nor relative deficits of progesterone, estrogen, prostaglandins, insulin, vitamin B_6, or thyroid hormone[9,10,31] have been established in patient groups with either PMS or PMDD. Similarly, functional hormonal tests such as the thyroid-releasing hormone response to thyroid-stimulating hormone and the results of glucose tolerance testing are not abnormal in patients with PMDD.[32–35]

Invoking a hypothesis that premenstrual symptoms are induced by withdrawal of endogenous opiates, several groups have evaluated β-endorphin levels in symptomatic women and controls. In a study that included women who retrospectively reported premenstrual symptoms, Giannini and colleagues found a decline in β-endorphin during the luteal phase of the cycle[36]; however, there was no control group in this study. Nonetheless, four other studies have found lower luteal phase β-endorphin levels in symptomatic patients compared with controls.[37–40] One of the aforementioned studies found lower levels in follicular phase as well as luteal phase,[37] and, in an additional study, β-endorphin levels were lower in symptomatic women during the periovulatory phase.[41] Notably, only two of the investigations previously mentioned included a population in which symptoms were prospectively determined that may or may not have met severity criteria for a diagnosis of PMDD. Differences in patient populations, a small sample size, or a combination of the two may be the basis for different conclusions in a recent study that failed to find differences between PMDD patients and controls during either phase of the cycle.[42] In this study, however, β-endorphin levels decreased during the premenstrual period in both groups. Changes in portal blood levels of β-endorphin during the menstrual cycle have also been found in primates, although the difference was most notable during the periovulatory phase.[43]

Fluctuations of β-endorphins that decline precipitously during the menstrual cycle can increase adrenergic activity in women with PMDD and may explain the results of an investigation into adrenergic receptor binding. Halbreich and colleagues[44] found increased α_2 and imidazoline receptor binding in premenstrually symptomatic women during the luteal phase of the cycle. As reviewed by Grunhaus and colleagues,[45] alterations in adrenergic receptor binding are also associated with MDD and panic disorder, although the direction of the change (increased vs. decreased affinity) is dependent on the platelet preparation and the ligand used in the assay.

Halbreich and colleagues found decreases in plasma gamma-aminobutyric acid (GABA) levels during the luteal phase in women with dysphoric premenstrual symptoms.[46] Low plasma GABA levels have also been found in patients with MDD,[47] although how this may be related to the above findings is not known.

The bulk of biological investigation in PMDD involves another neurotransmitter system implicated in depressive illnesses, serotonin, or 5-hydroxytryptamine (5-HT).[48] A number of different approaches have been used to evaluate this system in women with both PMS and PMDD, including measurements of serotonin in whole blood, platelet 5-HT uptake, and neuroendocrine challenge. On the basis of primate and other evidence that low serotonin is associated with changes in sleep, appetite, and irritability, Rapkin[49] investigated whole-blood serotonin in women with severe premenstrual dysphoria and found that compared with asymptomatic controls, symptomatic women have lower levels of serotonin. Some investigators[50–52] but not all groups[53,54] find that luteal phase platelet 5-HT uptake is decreased in women with PMS or PMDD compared with controls. Imipramine binding sites have also been shown to be reduced in women specifically evaluated for PMDD compared with controls during either the early luteal phase[54] or both phases of the cycle.[55] In the latter study, statistical significance was attained only during the follicular phase.

Administration of tryptophan to women with PMDD produces a blunted growth hormone and cortisol response during both phases of the menstrual cycle,[56] suggesting trait differences between PMDD patients and controls. However, in the same two groups, the prolactin response to tryptophan is blunted only during the premenstrual phase of the cycle.[56] On the other hand, when the 5-HT_{1A} partial

agonist buspirone is administered to PMDD patients and healthy controls during the follicular phase, it produces a blunted prolactin response.[57] Data regarding blunted prolactin response to fenfluramine administration are mixed with one group finding a blunted response in well-characterized PMDD subjects versus controls[58] and another group finding no differences.[59] Finally, depleting the serotonin precursor tryptophan is significantly more likely to provoke premenstrual symptoms during both luteal and follicular phases in PMDD patients compared with asymptomatic women (reference 60 and Halbreich U, oral communication, May 1996).

While the above biological evidence does not definitively implicate any single neurobiological system, changes in adrenergic receptor binding, GABA levels, and various assays of the 5-HT system suggest neurobiological abnormalities associated with the expression of PMDD. Changes in these markers are also found for unipolar MDD.

COGNITIVE STYLE AND PROCESSING

Mood disorders are associated with a number of cognitive features that can be probed in experimental settings. One cognitive processing trial using tests of selective and incidental recall did not find that women with PMDD had a proclivity to remember negative events or preferentially recall negative words.[61] Results are divergent using another paradigm, a dichotic listening task. This paradigm assesses the number of errors made when the participant is subjected to dysphoric and nondysphoric distractor stimuli. Individuals with negative cognitions, such as those with MDD, should be more easily distracted by the dysphoric words. In one study comparing women with intermittent mild depression, premenstrual dysphoria, and controls, significantly more women with intermittent depression were distracted by the negative stimuli during both phases of the cycle; the error rate in the other groups did not differ.[62] In a second study by this group, women with prospectively confirmed PMDD were compared with controls, and the former group made significantly more errors after exposure to the dysphoric stimuli, but again during both phases of the cycle.[62] These studies suggest that the patients in the second study were more severely afflicted and shared the same cognitive style found in major depression, while those in the first study did not have a negative cognitive style. Another group utilizing a dichotic listening task in mildly symptomatic women failed to find significantly greater errors with presentation of negative words during the luteal phase.[63] Thus, it appears that women with milder premenstrual symptoms do not share the cognitive set found in other depressive illnesses. However, when the illness is more severe, such as found with PMDD, a negative cognitive set is found.

Table 4. Psychotropics That Are Effective in PMDD

Alprazolam
Buspirone
Clomipramine
Fluoxetine
Paroxetine
Sertraline

TREATMENT

The codification of research criteria for LLPDD or PMDD added rigor to an extensive body of literature on treatment[9] and was accompanied by an exploration of psychotropics as treatments for severe premenstrual symptoms (Table 4). The choice of lithium as one of the first psychotropic treatments is reasonable given the similarities between PMDD and bipolar illness (periodic nature of the illness and mood-predominant symptoms). Unfortunately, the results of both lithium trials are disappointing. An older study was placebo-controlled but did not incorporate prospective daily ratings in the design to identify women who have severe symptoms limited to the luteal phase.[64] This study found no benefit of lithium over placebo. A second study used rigorous criteria to characterize the population of study but did not include a control group.[65] In that trial only 3 of 15 women benefited from treatment.

The next psychotropic agent to receive considerable attention was alprazolam. To date, five acute-phase placebo-controlled trials have investigated the therapeutics of alprazolam.[15,66–69] All of these investigations included women who prospectively confirmed premenstrual symptoms, and, in all likelihood, most probands would have met criteria for PMDD. Alprazolam was administered during the luteal phase in doses between 0.75 mg/day and 4 mg/day for between two and four cycles. In four of five trials, alprazolam was significantly superior to placebo[15,66–68] and was also more efficacious than progesterone.[67] However, it does not appear to be effective for women who have premenstrual worsening of mood symptoms that exist throughout the cycle.[66]

A number of recent investigations have been conducted on antidepressants, including clomipramine,[70] fluoxetine,[20,71–74] bupropion,[75] paroxetine,[76,77] maprotiline,[76] sertraline,[78] nefazodone,[22] and fenfluramine.[79]

Fluoxetine has been extensively investigated at daily doses of 20 mg and 60 mg with four double-blind placebo-controlled trials[20,71,72,80] and four open studies,[19,73,74,81] all of which support its efficacy in treating PMDD. While the initial studies were three cycles or less,[20,71,80] a recent multicenter trial continued for six cycles.[72] Efficacy appeared to wane after the third cycle of treatment, causing concern since treatment may be required for longer periods of time. Two other studies suggest, however, that benefit is more enduring and may be ongoing for as long as 1 year while treatment is maintained.[74,81]

Less evidence supports the use of paroxetine in PMDD. One small, randomized, double-blind trial of paroxetine, maprotiline, and placebo[76] and an open trial[77] support the acute phase efficacy of paroxetine. In both studies the diagnosis was confirmed by prospective ratings of PMDD. Interestingly, paroxetine was superior to placebo but also more effective than maprotiline.[76] A more thorough evaluation in larger patient populations is needed for what appears to be a promising treatment.

A recent multicenter study used sertraline in 223 patients with PMDD.[78] Treatment was administered daily for three cycles using a flexible dosing design. Significantly more women responded to sertraline, and wellness was maintained throughout the course of the study. Analyses show that the majority of PMDD symptoms improved with this treatment. As with the other serotonin reuptake inhibitor (SRI) trials, this investigation used DSM-IV criteria for PMDD.

In two small studies, clomipramine was shown to be effective.[82,83] It and sertraline[84] have been used as luteal phase treatments.

Daily treatment with the 5-HT_2 antagonist and reuptake inhibitor nefazodone was promising for both women with PMDD and women with PME on an open basis.[22] Finally, the serotonin, norepinephrine, and dopamine reuptake inhibitor venlafaxine is currently undergoing clinical trials.

CONCLUSION

The evidence reviewed above indicates that PMDD shares a number of features with other mood disorders. The most common symptoms are those seen in other mood disorders, and the rate of lifetime comorbidity with other mood disorders is high. The cognitive set is similar to what is found in MDD in women who have severe premenstrual symptoms such as PMDD, but not in women who have less severe illness, such as PMS. Preliminary biological evidence from patients with PMDD finds changes that are not found in asymptomatic women; some of these changes are also found in patients with other mood disorders, such as MDD. Finally, PMDD responds favorably to some antidepressants, although there appears to be greater selectivity for agents that affect serotonin reuptake.

On the other hand, some of the features reviewed differentiate PMDD from other mood disorders. The symptoms of PMDD are not all mood-related and also include changes such as bloating and breast pain. PMDD patients also seem to complain as much about anger and irritability as about low mood. In terms of comorbidity, mood disorders are the most common, but these patients are also likely to have comorbidity with anxiety disorders. Biological markers are similar in PMDD and other mood disorders, but there are inconsistencies in the findings. Finally, not all treatments for MDD or bipolar disorder are effective in PMDD. While the latter findings are not an argument for separating PMDD from other mood disorders, they do suggest that it is an entity that can be differentiated from other mood disorders. Future research, which explores the ways in which PMDD is similar or dissimilar to other mood disorders, should help us understand the pathophysiology of the disorder.

Drug names: alprazolam (Xanax), bupropion (Wellbutrin), buspirone (BuSpar), clomipramine (Anafranil), fenfluramine (Pondimin), fluoxetine (Prozac), maprotiline (Ludiomil), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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