Anxiety Symptoms and Anxiety Disorders: How Are They Related to Premenstrual Disorders?

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Premenstrual symptoms are common among young menstruating women, but the psychiatric disorder premenstrual dysphoric disorder (PMDD) is seen only in approximately 3% of this group. The symptom profile of PMDD has been empirically derived from a number of investigations including a large data base from five university centers. The most commonly reported symptoms are depression and mood swings, but a substantial number of women report tension and anxiety. Lifetime psychiatric illness is also common in women with PMDD, and although mood disorders predominate, past histories of anxiety disorders are also common, further suggesting an association between PMDD and anxiety disorders. The strongest data supporting such an association lie with challenge studies that have been used to provoke panic in panic patients and are effective in precipitating panic attacks in women with PMDD. Finally, treatments that are effective for anxiety disorders are also useful in the treatment of PMDD. In this paper, the above outlined relationship between anxiety disorders and PMDD is reviewed.

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Premenstrual disorders are common in women and share features with a number of psychiatric disorders, such as a continuum of severity and a high degree of comorbidity. In general, disturbances associated with the premenstruum can take several forms: (1) They may be annoying but mild and not associated with functional impairment. (2) Physical symptoms may predominate with relatively milder mood complaints, either of which lead to some degree of functional impairment. These two patterns are consistent with a diagnosis of premenstrual syndrome (PMS). (3) On the other hand, women may experience severe emotional symptoms during the premenstruum, which take a substantial toll on interpersonal relationships and/or work efficiency. Many women in this group will have the psychiatric disorder that in DSM-III-R[1] was named late luteal phase dysphoric disorder but has been renamed premenstrual dysphoric disorder (PMDD) in DSM-IV.[2] (4) Finally, premenstrual symptoms may be experienced by women who have concurrent psychiatric or general medical illnesses. In this article, the term *premenstrual exacerbation* (PME) is used to refer to the worsening of a psychiatric illness experienced at other times of the menstrual cycle. This definition has been questioned by some[3] who suggest that PME represents two conditions or processes.

In the DSM-IV,[2] PMDD was included under the category of "depressive disorders not otherwise specified." This follows from the work of several researchers who find a relationship between mood disorders and either PMS, PMDD, or PME.[4,5] However, symptoms of anxiety and concurrent or lifetime histories of anxiety disorders are also common among women with severe premenstrual disorders. In this paper, the relationship between premenstrual disorders and anxiety symptoms and anxiety disorders is explored.

SYMPTOM CONSTELLATIONS

A number of premenstrual symptoms have been reported. One nonclinical, epidemiologic study[6] finds that 31% of women retrospectively endorse irritability, 19% note depressed mood, 18% report tension or nervousness, and 3% suffer from anxiety, which illustrates the prominence of anxiety and related symptoms among premenstrual complaints. Negative premenstrual affect, including anxiety, irritability, mood swings, depression, and tension, is noted by another group who evaluated retrospective complaints in a nontreatment seeking population.[7] Similar rates are found in an epidemiologic sample of 179 women.[8] In that study, past reports of severe or disabling

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premenstrual anxiety is endorsed by 3.4% of women. Even more common are reports of severe premenstrual tension (7.6%) and irritability (12.2%). Even in a clinical study of women with varying premenstrual severity levels, Clare[9] finds that women commonly complain of depression, anxiety, sleep problems, fatigue, irritability, somatic symptoms, and decreased concentration.

Given the variety of symptoms detected, yet the need to construct a representative set of criteria for patients suffering from severe symptoms, the DSM-IV workgroup evaluated the symptoms of 670 women with premenstrual complaints and prospectively confirmed symptomatology. These were gathered from five academic centers in the United States. Commonly seen symptoms in this group are not very different from those found in retrospective reports and in the less severely afflicted groups.[10] According to the frequency endorsed, these symptoms include depressed mood, mood swings, anxiety/tension, anger/irritability, decreased interest, diminished concentration, low energy, changes in sleep and appetite, and physical symptoms.[10] Thus, one can see that symptoms of anxiety, tension and nervousness are common among women in the community who have milder premenstrual syndromes as well as among women with severe premenstrual disorders.

COMORBIDITY OF SEVERE PREMENSTRUAL DISORDERS WITH ANXIETY DISORDERS

Retrospective reports of premenstrual symptomatology (PMS, PME, or PMDD) are frequently not substantiated by prospectively maintained symptom charts.[11,12] While there are many reasons a patient fails to confirm premenstrual complaints, the lack of confirmation occurs because patients will either have behavioral or somatic symptoms not associated with the premenstruum or have marginal changes in luteal phase symptomatology. Given these limitations, it is instructive to clarify which lifetime and concurrent illnesses are found by researchers who evaluated women only on the basis of retrospective reports of premenstrual symptomatology and in women with prospectively confirmed premenstrual symptoms.

In one investigation, Stout and colleagues[13] administered a structured psychiatric interview, the Diagnostic Interview Schedule (DIS),[14] to women attending a premenstrual syndrome clinic. Results were compared with the rates of women in the community who were administered the same instrument in the course of an epidemiologic study. No prospective confirmation of symptoms was obtained, so it is not possible to say whether women attending the clinic had PMS, PMDD, or PME or were misattributing symptoms of another disorder to the premenstruum. Nonetheless, the most commonly found psychiatric disorders among patients in the PMS clinic were phobia, dysthymic disorder, obsessive-compulsive disorder, alcohol abuse and dependence, and somatization disorder. These disorders were between three and seven times more common in the PMS clinic population than in the community sample, illustrating that women complaining of PMS will often have other psychiatric illnesses, including anxiety disorders.

Table 1. Frequency of Emotional Symptoms Associated With the Premenstrual Period*

Emotional Symptoms	Percentage of Women (N = 218)
Depressed mood	18.8
Irritability	30.7
Tension	18.3
Nervousness	17.9
Increased activity	4.1
Anxiety	3.2
Better mood	2.3

*Reprinted from reference 6, with permission.

Table 2. Lifetime Psychiatric Illness in Women With Premenstrual Complaints (N = 140)*

	PMDD (N = 86)	PMS and Concurrent Illness (N = 54)
Major depression	70	93
Panic disorder	16	26
Alcohol abuse	9	13
Drug abuse	7	7
Suicide attempts	12	32

*Data from reference 34, with permission.

In a different epidemiologic study,[6] the likelihood of either concurrent or lifetime psychiatric illness, including major depressive disorder (MDD), panic disorder, generalized anxiety disorder (GAD), agoraphobia, and simple phobia, was much higher among women who reported premenstrual or menstrual symptoms (Table 1). As seen in Table 1, there was a particularly high lifetime risk of anxiety disorders among the women with premenstrual complaints. Again, premenstrual symptomatology was not confirmed in this sample, and thus, some women may have had only ongoing difficulties with an anxiety disorder rather than PME, PMS, or PMDD.

Several clinical studies document concurrent or lifetime psychiatric illness in women who have prospectively confirmed premenstrual difficulties. In the first study, Harrison and colleagues[15] administered a structured clinical interview, the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L)[16] to 86 women with prospectively confirmed PMDD (Table 2). A past history of psychopathology was common, and 70% endorsed a past episode of MDD. Other past diagnoses found included panic disorder (16%) and alcohol or drug abuse (7% in each). In the control group who were without current psychiatric illness including PMDD, 4% had a prior episode of MDD, 5% had a previous history of panic disorder, while the rates for a past history of alcohol and drug abuse were 8% and 3%, respectively.

Lower rates for past psychiatric illness were found in another study of 58 women who confirmed premenstrual

symptomatology.[17] These researchers found that 38% suffered from a previous depressive or anxiety disorder but did not report the specific rates within these categories. Interestingly, the rate for an ongoing mood or anxiety disorder (PME) was 21%.

Greater detail for past psychiatric illness is provided by Pearlstein and colleagues[18] who also used the SADS-L. In their study of 78 women with PMDD, 14% had a history of GAD, phobic disorder, or panic disorder and 69% had a prior episode of either a minor depressive disorder or MDD. Again, although the rates for past diagnoses of mood disorders were highest, the anxiety disorders were common lifetime diagnoses.

The other investigation into comorbid illness among women who confirmed severe premenstrual symptoms is from Fava and colleagues.[19] This research team compared the results of concurrent diagnoses in three groups: (1) women from a premenstrual syndrome clinic who confirmed premenstrual symptoms (PMDD or PME); (2) women presenting for evaluation of amenorrhea; and (3) controls who had neither of these two complaints. In the PMDD and PME group, 32% had an anxiety disorder and no mood disorder, 6% had a mood disorder and no anxiety disorder, and 28% had both. In the amenorrheic group, the incidence of mood disorders was higher than that of anxiety disorders, arguing for some diagnostic specificity accompanying these various conditions.

In sum, while prior and current comorbidity with mood disorders is common, both clinical and epidemiologic studies indicate that lifetime anxiety disorder diagnoses are frequently seen in women with premenstrual complaints. Comorbid anxiety diagnoses are far more common in women with premenstrual symptomatology than among healthy controls.

PREMENSTRUAL WORSENING OF ANXIETY DISORDERS

Some authors note that patients with anxiety disorders frequently complain of premenstrual worsening.[20] The best studied anxiety disorder among these is panic disorder; there are several prospective studies of premenstrual changes. One group followed 10 women with panic who retrospectively reported premenstrual symptoms and worsening of panic.[21] After their prospective ratings were evaluated, the women were found to have only modest increases in mood and physical symptoms (loss of interest, physical distress, and muscle tension); full situational panic attacks significantly differed in the follicular compared with the premenstrual phase of the cycle.

In a second study, prospective ratings from 19 panic patients revealed a trend toward an increase in premenstrual anxiety.[22] However, neither the number of panic attacks nor the majority of individual symptoms were significantly higher during the luteal phase.

Finally, Stein and colleagues[23] compared premenstrual anxiety ratings in panic patients, healthy controls, and women with PMDD. Although panic patients had neither a premenstrual increase in anxiety or a greater number of panic attacks, PMDD patients had a large premenstrual increase in anxiety.

Prospective evaluation of premenstrual worsening in women with GAD has been investigated with positive results.[24] When women with prospectively confirmed premenstrual symptoms and GAD were evaluated during the follicular and luteal phase, there was a significant premenstrual increase in reports of somatization, obsessive-compulsive symptoms, anxiety, and phobic anxiety.[24]

CHALLENGE STUDIES

The evidence for an association between PMDD and anxiety disorders is more clearly shown through challenge studies. Several provocation paradigms used to induce panic have been applied to women with PMDD. In the first study, women were given compressed air as a placebo and then 35% CO_2 in each testing session during both phases of the menstrual cycle.[25] Fourteen patients with PMDD and 12 healthy controls were to be tested but five women with PMDD who experienced a panic attack after CO_2 administration in the first session refused the second session. In the first session, 64% of PMDD patients and no controls panicked. Only six PMDD patients were tested during both times—the others either refused or encountered scheduling difficulties. Four of this group panicked during both phases of the cycle, one had a near panic attack during the follicular phase, and one did not experience panic. An additional two patients tested only during the follicular phase and three of six tested during only the luteal phase panicked. Thus, this study shows that women with PMDD are likely to develop panic, and the risk is at least as great during the follicular phase as during the luteal phase.

Another study evaluated the panic response to CO_2 during the mid-follicular and mid-luteal phases of the cycle in ten women with panic disorder and in seven controls.[26] These time points were chosen because the research team felt that the anxiolytic effect of progesterone and its metabolites may be protective during the mid-luteal phase but not during the follicular phase. It is known that selected metabolites of progesterone bind to the GABA-benzodiazepine receptor and have anxiolytic-like properties.[27,28] Thus, menstrual cycle Days 19 to 24 (in a normalized 28-day cycle) would be a time when women would have the greatest amounts of endogenous anxiolytics and would be less likely to panic. Later, during Days 25 to 28 and during the follicular phase, there are lesser amounts of these compounds to protect against panic provocation.[29] This hypothesis was confirmed in that seven women during the follicular phase, but only four in the mid-luteal phase, experienced a panic attack. None of the controls panicked.

Administration of sodium lactate will also induce panic. One study finds that slightly more than 65% of panic patients but less than 15% of controls will panic after lactate infusion.[30] Two studies have investigated the propensity for women with premenstrual symptoms to develop panic when administered sodium lactate. In the first, women with premenstrual symptoms who were either free of a concurrent illness or had premenstrual symptoms and a concurrent mood or anxiety disorder were compared with healthy control women during the mid-to-late-luteal phase of the cycle.[31] Sixty-three percent of the women with premenstrual symptoms but only 13% of controls developed panic attacks after lactate administration. When subgroups who had concurrent panic or an ongoing mood or anxiety disorder in addition to premenstrual symptoms were compared with women with a solo diagnosis of PMDD, the rates of panic were 89% (concurrent panic group), 47% (ongoing mood or anxiety disorder group), and 64% (solo diagnosis of PMDD group).

In a second lactate provocation study, 13 women with PMDD and 7 female controls were compared.[32] Again, the rate of panic after lactate infusion was higher among PMDD patients (58%) than controls (0%). The authors state that 85% of the women with PMDD who responded to provocation and 33% of those who did not respond had experienced at least one previous panic attack at some point in their life. However, the number of panic attacks in these women did not approach what is seen in panic disorder. These studies strengthen the suggestion that biological mechanisms or vulnerabilities are shared in women with panic and women with PMDD.

COURSE

In most studies, the average age of PMDD onset is in the mid-to-late twenties.[10,33,34] While the course of PMDD has not been well studied, there are some reports on the course of PMS. Most authors,[6,35] although not all,[36] find that PMS worsens over time. During that time, luteal symptoms cyclically recur and remit. Given this chronic relapsing course of illness, the closest model among other psychiatric illnesses is either recurrent depression or panic disorder.

TREATMENT

While many trials evaluate a number of treatments for PMS, only a handful have enrolled women who prospectively confirmed symptomatology and were sufficiently symptomatic during the luteal phase to meet clinical criteria for PMDD. These placebo-controlled trials strongly suggest an association with anxiety disorders because a number of the agents that are efficacious in the treatment of anxiety disorders are also palliative in the treatment of PMDD. These medications include the benzodiazepine alprazolam, the azapirone buspirone, and the class of serotonin reuptake inhibitors clomipramine, paroxetine, fluoxetine, and sertraline.

Table 3. Psychotropic Drug Response in Premenstrual Dysphoric Disorder

Better Than Placebo	Equivalent to Placebo
Fluoxetine (10–60 mg/day)	Lithium
Sertraline (50–200 mg/day)	Maprotiline
Paroxetine (20–40 mg/day)	Bupropion
Clomipramine (25–75 mg/day)	? Fluvoxamine
Alprazolam (.5–1.0 mg, t.i.d.)	
Buspirone (10–20 mg, t.i.d.)	
? Venlafaxine (25–100 mg, b.i.d.)	
? Nefazodone (100–200 mg, b.i.d.)	

Five groups have compared alprazolam with placebo (Table 3).[37–41] All studies administered medication during the luteal phase of the cycle, and all employed a placebo-controlled crossover design. The first study in this area was conducted by Harrison and colleagues[41] who used alprazolam in a dose of 0.25 to 4.0 mg/day. The duration of their study was three cycles. The researchers used categorical measures of global improvement and changes on individual symptoms to show alprazolam more effective than placebo.

An interesting study was conducted by Berger and Presser.[37] They identified two groups: one with dysthymic disorder and premenstrual symptoms (PME) and the other with a solo diagnosis of PMDD. The group with PME did less well on alprazolam therapy than the group who had only PMDD. The latter group had a significantly superior response to alprazolam than to placebo.

Freeman and colleagues[38] recently published a study comparing alprazolam 0.25 mg taken four times daily to oral micronized progesterone, 300 mg administered four times daily, and placebo. Alprazolam was superior to progesterone, whereas progesterone was equivalent to placebo.

Only one trial[39] failed to find statistically significant superiority of alprazolam over placebo. In this crossover study of 20 women, alprazolam was somewhat more effective than placebo, but the only scale that showed statistical superiority was the Beck Depression Inventory, and even on this scale, the improvement was deemed clinically insignificant.

Currently, the most active area of investigation is into the utility of SSRIs, many of which are also palliative in anxiety disorders. Two small open trials, three small placebo-controlled trials, and one large placebo-controlled trial illustrate the effectiveness of fluoxetine for the treatment of PMDD.[42–46] A large multicenter fixed-dose study that included over 300 women evaluated fluoxetine at 20 or 60 mg daily and placebo.[46] The attrition rate was high during the first cycle in the 60-mg group, but evidence for superiority of active treatment over placebo was evident by the second cycle of daily treatment.

Similar results were found for a large multicenter trial using the SSRI sertraline.[47] Again, continuous, daily dosing was used, and in this three-cycle study, substantial benefit was shown by the first cycle of treatment with a modest increment in the number of responders during the second cycle.

The serotonin reuptake inhibitor and agonist nefazodone was evaluated in an open fashion in women with either PMDD or premenstrual worsening of dysthymic disorder.[38] The majority of women in both groups were improved, arguing that this agent should be tested in a double-blind, placebo-controlled fashion.

Two studies included comparators to SSRIs. One study compared paroxetine with maprotiline, and the latter, even though it is effective in trials of depression, was significantly less effective than the SSRI.[48] The efficacy of paroxetine is also supported by an open trial.[49] Another study compared the efficacy of fluoxetine, bupropion, and placebo and found fluoxetine was superior.[50] This suggests that, like in anxiety disorders, there is some specificity of response in PMDD. Agents that block the reuptake of serotonin are more effective than those that primarily work on noradrenergic reuptake (maprotiline) or have other properties that do not involve serotonin agonism, reuptake blockade, or GABA agonism.

No studies have evaluated treatment efficacy for women who have both premenstrual symptoms and an anxiety disorder such as generalized anxiety or panic.

SUMMARY

Severe psychiatric symptoms occurring during the premenstrual phase of the cycle that are consistent with a diagnosis of PMDD or PME are characterized not only by mood symptoms but also by symptoms of anxiety. In addition, lifetime histories of anxiety disorders are common among women who either present for treatment of PMS or have prospectively documented premenstrual symptoms of PMDD. Finally, many treatments found to be efficacious for anxiety disorders are also palliative for those suffering from PMDD. An improved understanding of the shared risk for anxiety disorders and severe premenstrual disorders may inform clinicians about optimal interventions.

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

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