

Premenstrual Dysphoria and the Serotonin System: Pathophysiology and Treatment

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The inclusion of research diagnostic criteria for premenstrual dysphoric disorder (PMDD) in the DSM-IV recognizes the fact that some women have extremely distressing emotional and behavioral symptoms premenstrually. PMDD can be differentiated from premenstrual syndrome (PMS), which presents with milder physical symptoms, headache, and more minor mood changes. In addition, PMDD can be differentiated from premenstrual magnification of physical and/or psychological symptoms of a concurrent psychiatric and/or medical disorder. As many as 75% of women with regular menstrual cycles experience some symptoms of PMS, according to epidemiologic surveys. PMDD is much less common; it affects only 3% to 8% of women in this group. The etiology of PMDD is largely unknown, but the current consensus is that normal ovarian function (rather than hormone imbalance) is the cyclical trigger for PMDD-related biochemical events within the central nervous system and other target organs. The serotonergic system is in close reciprocal relationship with the gonadal hormones and has been identified as the most plausible target for interventions. Thus, beyond the conservative treatment options such as lifestyle and stress management, other nonantidepressant treatments, or the more extreme interventions that eliminate ovulation altogether, the serotonin reuptake inhibitors (SRIs) are emerging as the most effective treatment option for this population. Results from several randomized, placebo-controlled trials in women with PMDD have clearly demonstrated that the SRIs have excellent efficacy and minimal side effects. More recently, several preliminary studies indicate that intermittent (premenstrual only) treatment with selective SRIs is equally effective in these women and, thus, may offer an attractive treatment option for a disorder that is itself intermittent.

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The etiology of premenstrual syndrome (PMS)¹ and that of the more severe form known as premenstrual dysphoric disorder (PMDD)² are still uncertain. Nevertheless, clinicians and researchers are now more in agreement that PMS and PMDD are physiologic phenomena, biologically determined and only partially influenced by psychosocial events. This is underscored by recent convincing evidence of the heritability of premenstrual symptoms^{3,4} and by the fact that suppression of ovulation⁵ or surgical menopause^{6,7} will eliminate premenstrual complaints.

There also seems to be a consensus now that PMDD is distinct from other mood disorders. The dysphoria associ-

ated with PMDD is cyclical, and the most common physical symptoms such as breast tenderness and bloating are unique, all tightly linked and entrained to the late luteal phase of the menstrual cycle with a predictable "on-off" pattern.⁸⁻¹¹ This regular reoccurrence of symptoms disappears during pregnancy and after menopause, and not only can it be prevented by suppression of the cyclicity of gonadal hormones, but hormone replacement therapy can provoke the reappearance of symptoms in menopausal women with a history of PMDD.¹² The genetic and environmental risk factors for PMDD are different from those for other mood disorders, and the hypothalamic-pituitary-adrenal axis function is usually normal in PMDD, unlike the overactivity of this axis in patients with major depression. Finally, the response to treatment in women with PMDD is almost immediate compared with the extended time gap usually observed in patients with other mood and anxiety disorders, and the reemergence of premenstrual symptoms is also rapid and almost predictable when treatment is stopped.¹¹⁻¹³

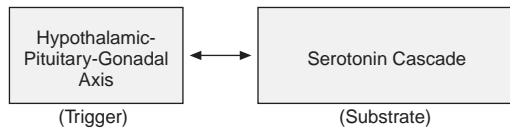
Severe PMS or PMDD affects approximately 3% to 8% of women of reproductive age worldwide, with an enormous burden of illness on themselves, their families, and society. Valid screening and diagnostic tools are now available, which should assist the clinician in identifying

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Figure 1. Pathophysiology of Premenstrual Dysphoric Disorder



women with PMDD, with special emphasis on prospective daily charting (to confirm both the severity and on-offness of the symptoms).^{10,14}

A long list of treatment options has been suggested over the years, including somatic and psychosocial therapies. The nonantidepressant treatment options are reviewed elsewhere in this supplement (see Pearlstein¹⁵). Here, after a brief review of the evidence for the involvement of the serotonergic system in the pathophysiology of PMDD, we will summarize the data that support the effectiveness and tolerability of treatments with serotonin reuptake inhibitors (SRIs) in this condition.

PATHOPHYSIOLOGY

The pathophysiology of severe PMS and PMDD is closely linked to an active hypothalamic-pituitary-gonadal (HPG) axis. The menstrual cyclicity of the ovarian hormones is most likely the trigger for the psychological as well as the somatic premenstrual symptoms. What has become clearer over the years is that no demonstrable hormonal imbalance exists in women with severe PMS or PMDD.¹² Normal ovarian function triggers biochemical events both in the brain and peripherally, which in turn unleash the premenstrual symptoms in vulnerable or predisposed women.

The neurotransmitter serotonin (5-HT) is in a reciprocal relationship with the HPG axis^{16,17} (Figure 1), and increasing evidence suggests that 5-HT is pivotal in the pathogenesis of PMDD.¹⁸⁻²²

PMDD shares many features of other mood and anxiety disorders that are also linked to 5-HT dysfunction.²³⁻²⁶ Reduction in brain 5-HT neurotransmission is believed to be associated with poor impulse control, irritability, dysphoria, and increased carbohydrate craving—all symptoms known to be associated with PMDD. Several studies have in fact demonstrated that 5-HT function is altered in women with PMDD. Whole blood 5-HT levels, platelet uptake of 5-HT, and platelet ³H-imipramine binding have all been reported to be reduced in women with premenstrual syndrome.^{19,27-30} Studies³¹⁻³⁵ using challenge tests including L-tryptophan, fenfluramine, buspirone, and *m*-chlorophenylpiperazine have also suggested abnormal 5-HT function in symptomatic women with PMS or PMDD, but differ in their findings as to whether the response to these 5-HT challenges is

blunted or heightened. Acute tryptophan depletion aggravates premenstrual syndrome,³⁶ whereas drugs facilitating 5-HT transmission are effective in reducing premenstrual symptoms³⁷ (see below).

Other neurotransmitters and neuromodulators, in particular the γ -aminobutyric acid (GABA), adrenergic, and opioid systems, have also been implicated in the pathophysiology of PMS and PMDD. Reduced GABA_A receptor sensitivity as well as reduced plasma GABA levels have been noted in women with PMS and PMDD, respectively, during the luteal phase.^{38,39} Platelet α_2 -adrenergic receptor density correlated positively with symptom severity of PMDD,⁴⁰ possibly linking it to similar findings in other populations of anxious and dysphoric patients. The sharp drop (“withdrawal”) in opiate levels during the late luteal phase has also been suggested as a factor in the etiology of premenstrual irritability, anxiety, and tension.^{41,42}

The current consensus, though, is that premenstrual irritability and dysphoria are probably linked to a difference in the sensitivity of the 5-HT system in predisposed women, rendering them more vulnerable to cyclical hormonal fluctuations.^{22,43-45}

TREATMENT

Over 30 reported studies (and several more ongoing), of which at least 20 are randomized controlled trials, with a total of over 1100 female participants (study completers) discuss treatment with serotonin-enhancing drugs, and all but one (a relatively small study) confirm that these agents are both effective and mostly well tolerated in up to 70% of women with severe PMS or PMDD.^{9,37,46}

The very first studies introducing the notion that SRIs might play a crucial role in helping women with severe PMS were with clomipramine, a tricyclic antidepressant that is predominantly an SRI.⁴⁷⁻⁴⁹ Not only was the response rate very high in these studies, but the doses required were also much lower (10–50 mg/day) than those usually needed to achieve response in depression or obsessive-compulsive disorder.

Among the selective SRIs (SSRIs), both fluoxetine and sertraline have large databases that unequivocally demonstrate that these drugs are effective and well tolerated in women with PMDD. Several open-label studies with fluoxetine^{13,50-53} and with sertraline,^{54,55} as well as randomized controlled trials with these drugs,⁵⁶⁻⁶⁹ all support the efficacy of these drugs in women with severe PMS or PMDD. Two open-label studies^{70,71} and one double-blind, placebo-controlled trial⁷² also confirm the effectiveness of paroxetine. Similarly, a randomized controlled trial⁷³ has proved the efficacy of citalopram. The only relatively small double-blind, placebo-controlled trial⁷⁴ with fluvoxamine has shown the active medication to be no better than placebo. A later open-label study, though, confirmed the efficacy of fluvoxamine for PMDD as well.⁷⁵

In most of the drug trials with SRIs, the dose needed to achieve response was relatively low, although only one dose-response study,⁵⁹ using fluoxetine, was able to establish that there is no advantage in increasing the dose beyond 20 mg/day and that patients taking 60 mg/day had a significantly higher incidence of side effects.

The onset of action/response with SRIs in PMDD is very rapid, sometimes as short as 1 to 2 days, which has prompted several investigators to consider intermittent (luteal phase only) rather than continuous dosing of the medication. To date, the effectiveness and tolerability of the intermittent dosing regimen have been confirmed for sertraline,⁶⁵⁻⁶⁷ fluoxetine,⁷⁶ and citalopram,⁷³ with several additional randomized placebo-controlled trials currently under way. Of note is the recent trial with citalopram⁷³ which showed that not only was the drug more effective than placebo, but intermittent dosing was more effective than continuous dosing.

In most of these studies, the treatment period was usually for 3 menstrual cycles; only one randomized placebo-controlled trial⁵⁹ with fluoxetine had a treatment period of 6 cycles. Three open-label trials^{13,52,53} with fluoxetine of longer duration (between 12–18 months) and one with paroxetine⁷⁷ suggest that the effect does not decline with time, but to further clarify the issue of tolerance, more longer studies are required.

Given that in most women with severe PMS and PMDD, the cardinal symptoms are irritability and dysphoria, it is perhaps not surprising that the SRIs are so effective in this condition. What is surprising, though, is the observation that these agents are also extremely effective in alleviating the somatic complaints, in particular breast tenderness and bloating.^{48,72,78} Whether this is a primary, direct effect on the somatic symptoms per se or just a perceived secondary benefit (due to the reduction in irritability/dysphoria that renders the somatic symptoms less bothersome) has yet to be determined.

The DSM-IV criteria² for PMDD require the establishment and documentation of premenstrual impairment in psychosocial functioning, but few of the large-scale treatment studies have actually monitored prospectively the impairment in social or role functioning and the effects treatment has on this aspect of the disorder. Three studies have reported improvement in social impairment with fluoxetine using a visual analogue measure for work efficiency and social activity⁷⁹ and a subtotal score of social impairment derived from the Premenstrual Tension Syndrome Scale,⁸⁰ respectively. Only one study⁶⁴ has systematically monitored functioning and quality of life in a large number of women treated with sertraline for PMDD. Psychosocial functioning was measured using the Daily Record of Severity of Problems, the Social Adjustment Scale, and the short form of the Quality of Life Enjoyment and Satisfaction Scale (all self-rating scales). The results clearly indicate that sertraline was superior to placebo in

improving interpersonal and role functioning and quality of life in women with PMDD.⁸¹

CONCLUSION

Overwhelming evidence now supports the effectiveness and tolerability of SRIs in the treatment of severe PMS and PMDD using continuous dosing, and some initial evidence suggests that intermittent (premenstrual only) dosing might be at least as effective if not better than continuous dosing.

The mechanism of action of SRIs in PMDD is believed to be different from the one that underlies their therapeutic effect in major depression or obsessive-compulsive disorder. Thus, the ability of SRIs to enhance 5-HT activity is not the only mechanism responsible for their wide range of clinical efficacy. In the case of PMDD, it has been suggested that the effect of SSRIs on allopregnenolone biosynthesis is independent from 5-HT reuptake inhibition and may be due to a specific action on the enzymes that synthesize allopregnenolone from its precursor progesterone. It is hypothesized that the increase in allopregnenolone synthesized during the action of SSRIs acts on GABA_A receptors, which might explain the rapid alleviation of irritability and dysphoria associated with PMDD.^{82,83}

This hypothesis is further supported by recent animal data suggesting that the changes in expression of GABA_A receptor subunits result from progesterone withdrawal.⁸⁴ Women with PMS have lower levels of allopregnenolone than controls⁸⁵ and have different sensitivity to neuroactive steroids and a decreased GABA_A receptor sensitivity.³⁸ In a preliminary open-label trial,⁸⁶ citalopram has been shown to increase pregnenolone sensitivity.

The uniqueness of the SRIs is further underscored by the observation that most other antidepressants do not seem to be effective in treating PMDD. In a recent study,⁶⁸ sertraline was found again to be effective in treating women with severe PMS, but desipramine was not better than placebo. This finding is in keeping with those of 2 previous studies^{61,72} showing that paroxetine and fluoxetine were effective, whereas the comparison antidepressants, maprotiline and bupropion, respectively, were not.

Finally, all the studies that have demonstrated the effectiveness of SRIs in PMDD have excluded women taking oral contraceptives and those under the age of 18 years. It is noteworthy that many women who are prescribed SSRIs for other approved indications are taking oral contraceptives, and no untoward effects whatsoever have been reported. Similarly, there is a growing acceptance of the appropriateness of the use of SSRIs in children and adolescents, and again, the effectiveness and tolerability profile in younger age groups is not much different from that observed in adults. Nevertheless, it would be prudent to await further studies before prescribing SRIs for PMDD in younger girls.

Drug names: bupropion (Wellbutrin), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Sarafem), fenfluramine (Pondimin), fluvoxamine (Luvox), maprotiline (Ludiomil), paroxetine (Paxil), sertraline (Zoloft).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, the following agents mentioned in this article are not approved by the U.S. Food and Drug Administration for the treatment of PMDD: bupropion, buspirone, citalopram, clomipramine, desipramine, fenfluramine, fluvoxamine, maprotiline, paroxetine, and sertraline.

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