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Premenstrual Dysphoric Disorder: Epidemiology and Treatment

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Abstract Recently designated as a disorder in the *DSM-5*, premenstrual dysphoric disorder (PMDD) presents an array of avenues for further research. PMDD's profile, characterized by cognitive–affective symptoms during the premenstruum, is unique from that of other affective disorders in its symptoms and cyclicity. Neurosteroids may be a key contributor to PMDD's clinical presentation and etiology, and represent a potential avenue for drug development. This review will present recent literature on potential contributors to PMDD's pathophysiology, including neurosteroids and stress, and explore potential treatment targets.

Keywords Premenstrual · Menstrual cycle · PMS · PMDD · GABA

Introduction—Developments in Defining PMDD

Premenstrual dysphoric disorder (PMDD), a severe mood disorder, is characterized by cognitive–affective and physical symptoms in the week before menses and affects millions of women worldwide [1, 2]. A significant recent development is the recognition of PMDD as a distinct disorder in the DSM-5 [3]. In 2012, a committee of international experts on the pathophysiology and treatment of PMDD submitted to the American Psychiatric Association DSM-5 Executive Committee a review of the current science regarding PMDD and gave their recommendation for PMDD's inclusion in the DSM-5 as a full diagnostic category [2].

In defining PMDD, mood symptoms are key. Both the DSM-IV and DSM-5 diagnoses are based upon a perimenstrual pattern of at least five physical, affective, and/or behavioral symptoms, with a requirement of at least one of the key affective symptoms of affective lability (mood swings, tearfulness, sensitivity to rejection); irritability or anger that is often characterized by increased interpersonal conflicts; marked depressed mood, hopelessness, or self-deprecating thoughts; or anxiety, tension or feeling on edge [3]. The woman may also experience difficulty concentrating or a sense of feeling overwhelmed or out of control. These cognitive–affective symptoms can be accompanied by behavioral and somatic symptoms such as loss of interest in usual activities, lack of energy, changes in appetite or food cravings, changes in sleep, and physical symptoms unique to the premenstruum such as breast tenderness, breast swelling or bloating [3]. Per DSM-5 criteria, these symptoms must have occurred during most menstrual cycles in the past year to meet criteria for PMDD diagnosis. Data from community and clinical samples of women with a prospectively confirmed diagnosis of PMDD report the greatest severity of symptoms from 3–4 days prior to onset of menses to up to 3 days post-menses onset [4]. Symptoms must be absent in the post-menstrual week.

While it may seem a minor difference between the DSM-IV and -5, mood lability and irritability are listed first in the latter version due to findings that these symptoms are considerably more common among women with PMDD than depressed mood which had been listed first in the DSM-IV [2, 5]. Another subtle difference between the DSM-IV and -5 criteria is that the latter included the concept of distress in addition to impairment due to PMDD symptoms. Distress

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and/or impairment must be present in the area of work, school, social activities, or relationships with others.

Of particular importance, the symptoms should be confirmed by prospective daily ratings for at least two symptomatic cycles; this may be accomplished via tools such as the Daily Record of Severity of Problems [6], the Calendar of Premenstrual Experiences [7], or the Premenstrual Assessment Form [8]. Although a presumptive diagnosis of PMDD can be made based upon history alone, prospective daily ratings are invaluable in ruling out premenstrual exacerbation of other psychiatric disorders that are present to some extent throughout the menstrual cycle.

Relative to PMDD, a larger proportion of women experience milder premenstrual symptoms. Recently, attempts have been made to distinguish between mild premenstrual symptoms experienced by many women versus the more severe symptoms present in PMDD [2, 9]. Bodies including the American College of Obstetricians and Gynecologists (ACOG) and the World Health Organization [10, 11] have published descriptions of premenstrual mood changes. While lay language often refers to any unpleasant or undesirable physical, emotional, or behavioral symptom occurring prior to or during menses as premenstrual syndrome or "PMS," the ACOG provides specific criteria for its diagnosis, including one physical or psychological symptom in the 5 days prior to menses [10]. The symptoms must occur in three consecutive menstrual cycles and must subside within 4 days of menses onset. As in PMDD, the symptom(s) must cause significant impairment and must be verified by prospective rating for diagnosis. Given this continuum of severity, future research may focus on the etiology of symptoms shared between PMDD and PMS. The primary focus of the current article is PMDD, however, some studies cited have included women with severe PMS that may include mood symptoms. If the authors have not distinguished between PMDD or severe PMS, we will herein use the term utilized in their article.

Etiology Update

The etiology of PMDD is an active area of investigation. Potential biological contributors include central nervous system (CNS) sensitivity to reproductive hormones, genetic factors, and psychosocial factors such as stress. The timing of symptom onset and offset in PMDD suggests that hormonal fluctuation is a key component in PMDD's pathogenesis. Paradoxically, women with PMDD cannot be distinguished from asymptomatic women in terms of peripheral ovarian hormone levels. Instead, recent research suggests that women with PMDD have altered sensitivity to normal hormonal fluctuations, particularly estrogen and progesterone, neuroactive steroids that influence CNS function. Here, we discuss several possible mechanisms for affective symptoms in the premenstruum.

Progesterone, Allopregnanolone

Progesterone levels are low during menses and the follicular phase and are mirrored by progesterone's main metabolite, allopregnanolone (ALLO), also a neuroactive steroid. Progesterone and ALLO increase in the luteal phase and decrease quickly around menses. This chronic exposure followed by rapid withdrawal from ovarian hormones may be a key factor in the etiology of PMDD [12]. In a recently developed animal model of PMDD based on progesterone withdrawal, rats in withdrawal from physiological doses of progesterone exhibited social withdrawal and anhedonia, symptoms characteristic of PMDD [13]. Indeed, preclinical research demonstrates that chronic progesterone exposure followed by rapid withdrawal is associated with increased anxiety behavior and alterations in γ-aminobutyric acid $(GABA)_A$ receptor function [12–14]. Recent work suggests that this effect may not be due to progesterone itself, but progesterone's main metabolite ALLO, as blocking progesterone conversion to ALLO blocks the aforementioned effects of progesterone [15].

ALLO is a potent positive allosteric modulator of the $GABA_A$ receptor, similar to alcohol or benzodiazepines, with anxiolytic, anesthetic, and sedative properties [16••]. It is possible that women with PMDD have developed tolerance to the arousal-reducing and GABA-enhancing effects of ALLO. While suboptimal luteal phase $GABA_A$ receptor sensitivity to neuroactive steroids is a potential mechanism for PMDD pathogenesis, another potential mechanism is through direct effects on ALLO biosynthesis. In preclinical studies, manipulations that produce depressive and anxiety-like symptoms in mice are associated with diminished ALLO levels in the amygdala, hippocampus, and medial prefrontal cortex [17]. Modifying formation of neuroactive steroids such as ALLO that impact GABAergic tone may be an important avenue for treatment development for PMDD [16••].

Estrogen

Estradiol exerts potent effects on multiple neurotransmitter systems involved in the regulation of mood, cognition, sleep, eating, and other aspects of behavior [18]. With selective serotonin reuptake inhibitors (SSRIs) as the gold-standard treatment for PMDD, the overall enhancing effects of estradiol on serotonergic function in specific are important to consider in the pathophysiology of PMDD. Clinically, women with PMDD exhibit low mood, craving of specific foods, and impaired cognitive performance during the luteal phase, all cognitive–affective features that may be influenced by serotonin. Earlier work established that ovarian steroids alter expression of the $5\text{-}HT_{2A}$ receptor [19] and serotonin transporter (SERT)

genes [20], and the vesicular monoamine transporter [21], that estrogen administration increases serotonin transporter (SERT) mRNA particularly in brain areas involved with emotion and behavior [22], and low estrogen states were associated with decreased SERT gene expression [23]. Estradiol also decreases monoamine oxidase A (MAOA) and catechol-O-methyltransferase (COMT) expression [24, 25] and may impact brain-derived neurotrophic factor (BDNF) [26, 27].

Given the CNS sensitivity model of PMDD, it is possible that women with PMDD are more sensitive to these effects of estrogens on serotonergic function. Women with PMDD or PMS exhibit specific serotonin (5-HT) abnormalities that are particularly apparent in the late luteal phase when estrogen levels have declined. These include a deficiency in whole blood 5-HT [28], blunted 5-HT production in response to L-tryptophan challenge [29], and aggravated premenstrual symptoms during tryptophan depletion [30].

Recent work has focused on polymorphisms in genes coding for sex steroid hormone receptors, such as estrogen receptor alpha (ESR1), which may confer differential sensitivity to hormones. Single nucleotide polymorphisms in the *ESR1* gene were associated with PMDD in preliminary research [31], and a polymorphism of the $5HT_{1A}$ gene associated with reduced 5-HT neurotransmission and major depression was found to be associated with PMDD [32]. The serotonin transporter gene length polymorphism (*5-HTTLPR*) *s* allele, which is associated with reduced transcriptional efficiency of SERT, was associated with certain psychological features in women with PMDD [33], but was not associated with PMDD itself [34]. Most of the studies exploring genes associated with premenstrual symptoms have utilized small sample sizes, and further epidemiologic studies on the genetics of PMDD are needed.

BDNF

BDNF is a recent avenue in the exploration of PMDD pathophysiology. BDNF, which is expressed in multiple brain regions, particularly those involved in learning and memory and affect regulation, is critical for neurogenesis [35]. Lower BDNF levels and the *Met* allele for the BDNF *Val66Met* polymorphism have been associated, albeit with some inconsistency, with greater risk for depression as well as other neuropsychiatric conditions [36–38]. BDNF levels are upregulated by serotonergic antidepressants, are modified by estradiol, and show cyclicity across the menstrual cycle [39–41]. Women with PMDD who were carriers of BDNF *Val66Met* polymorphism *Met* allele had lower frontocingulate cortex activation during the luteal phase compared to female controls with the *Met* allele [42••]. Women with PMDD had significantly higher serum BDNF in the luteal phase than the control subjects, and within the PMDD group, serum BDNF was significantly higher in the luteal phase compared to the follicular phase [43]. However, the reverse was shown in women with PMS as defined by ACOG criteria [44]. The role of BDNF in PMDD is nascent and requires further investigation.

Stress

History of significant stress exposure has been associated with PMDD. A cross-sectional study of nearly 4000 women found that trauma history was associated with PMDD diagnosis based on the Collaborative Psychiatric Epidemiology Surveys PMDD module [45]. Similarly, a longitudinal case-control study of over 3000 women found that emotional and physical abuse were strongly correlated with moderate to severe PMS, while sexual abuse was less strongly correlated [46••]. However, some studies have not found women with PMDD to experience greater rates of physical, emotional, or sexual abuse than the healthy controls [47].

The next step for researchers will be to determine the mechanisms linking stress history with PMDD. One potential mechanism linking stress exposure and PMDD may be related to ALLO. As described above, ALLO enhances GABAergic transmission and confers sedative effects during times of stress, promoting homeostasis. While ALLO increases in response to acute stress [48, 49], women with PMDD do not exhibit this typical ALLO increase [50]. After repeated or chronic stress, animal models show that serum ALLO levels become blunted [51], but little is known about chronic stress and human ALLO response. Preclinical research indicates that administering exogenous ALLO corrects chronic stress-induced depressive and anxiety-like behaviors and restores normal HPA function [52]. Of key importance as this line of research progresses will be to utilize methods sufficiently sensitive to differentiate ALLO from neurosteroid stereoisomers; gas chromatography–mass spectrometry (GC-MS) is superior to the traditional radioimmunoassay (RIA) in this regard [53].

Immune Activation and Inflammation

Depression is strongly associated with dysregulated immune function [54•]. While PMDD is distinct from MDD, inflammatory molecules may have a role in PMDD's pathobiology. The luteal phase is associated with increased production of proinflammatory soluble interleukin 6R (sIL-6R) and tumor necrosis factor alpha (TNF-α) compared to the early follicular phase [55], and proinflammatory IL-6 gene expression was upregulated in the luteal phase compared to the follicular phase [56]. C-reactive protein (CRP) levels vary across the menstrual cycle, and a tenfold increase in progesterone was associated with an increase in CRP of 20 to 23 % [57, 58]. Among healthy women, serum high sensitivity (hs)-CRP was positively associated with elevated menstrual symptom scores, independent of changes in circulating gonadal steroids [59]. Some inflammatory diseases may worsen during the premenstruum, including inflammatory bowel syndrome and

gingivitis [60–62]. Research to date has mainly focused on menstrual changes in inflammatory markers among women without premenstrual mood disorders; however, a recent study among women with premenstrual symptoms does suggest increased proinflammatory markers compared to controls [63].

Research Tools Applied to PMDD

Brain Imaging

Imaging studies suggest differences in brain structure and function between women with PMDD and those without. Regions including the amygdala and prefrontal cortex have been a particular focus. Structurally, women with PMDD had greater gray matter volume in the posterior cerebellum [64•], greater gray matter density in the hippocampal cortex, and lower gray matter density in the parahippocampal cortex compared to healthy controls [65]. More recent work has demonstrated structural plasticity of the amygdala in response to menstrual cycle hormonal fluctuation among non-PMDD women; in specific, researchers showed increased gray matter volume in the dorsal left amygdala during the luteal phase compared with the follicular phase [66••]. The luteal volume increase was positively correlated with stress-induced negative affect, a marker of stress sensitivity; whether this holds true in women with PMDD has yet to be examined.

Functionally, women with PMDD do exhibit increased amygdala response to negative stimuli compared to healthy controls during the luteal phase [67]. Follow-up work showed that amygdala activity in response to negative stimuli was increased during the follicular phase among PMDD women with high trait anxiety, and this correlated with progesterone level [71••]. In an affective modulation task, women with PMDD had increased amygdala reactivity in the follicular phase compared to healthy controls, but this difference did not extend to the luteal phase. This potentiated follicular phase amygdala activity in PMDD women was positively correlated with serum progesterone concentrations [68].

Given the influence of progesterone, and/or its metabolites on these brain regions, proton magnetic resonance spectroscopy (^{1}H-MRS) has been used to study GABA function in women with PMDD. Women with PMDD showed an increase in cortical GABA from the follicular to the luteal phases, while control women showed a decrease in cortical GABA from follicular to luteal, further evidence of altered GABAergic function in PMDD, and perhaps an aberrant interaction between ALLO and GABA in the central nervous system [69]. More recent work showed significantly lower GABA concentrations in the anterior cingulate cortex, medial prefrontal cortex, and left basal ganglia of women with PMDD [70••]. Women with PMDD had lower activation of the pregenual anterior cingulate and ventromedial prefrontal cortex across the menstrual cycle [42••]. In an affective modulation paradigm, PMDD patients also showed enhanced dorsolateral prefrontal cortex reactivity during the anticipation of, but not exposure to, negative stimuli during the luteal phase, and this was positively correlated with progesterone levels [71••]. In a particularly elegant study, researchers sought to differentiate the effects of estrogen versus progesterone on brain function in PMDD patients versus matched controls. They measured positron emission tomography (PET) regional cerebral blood flow and blood oxygen level-dependent (BOLD) functional MRI (fMRI) signal during a working memory task, following a hormone manipulation protocol [72••]. In the hormone manipulation, leuprolide acetate was used to suppress ovarian function; then, some women received estradiol and others received progesterone for 6 months. In both the PET and fMRI studies, PMDD patients showed greater dorsolateral prefrontal cortex activation than control subjects during the working memory task; the authors concluded that prefrontal cortex dysfunction may represent a risk factor for PMDD.

Psychophysiology

Measures of physiological arousal, such as the acoustic startle response, may be altered in women with PMDD. During the follicular phase when ALLO levels are low, PMDD women did not differ from healthy controls in acoustic startle response, but in the luteal phase, PMDD women showed increased startle response [73]. As startle response, under some conditions, is modulated by ALLO, altered startle response could be reflective of suboptimal ALLO function in PMDD. In a similar study, women with PMDD displayed greater arousal across the menstrual cycle compared to controls, and the PMDD participants' ASR was particularly accentuated in the luteal phase [74]. This suggests increased arousal in women with PMDD during the premenstruum and may translate to increased stress reactivity to environmental cues.

Laboratory Stressors

Women with PMDD show evidence of altered hypothalamic-pituitary-adrenal (HPA) axis function, including lower cortisol levels during mental stress [50, 75] and higher baseline cortisol levels during the luteal phase [29] compared to controls. However, findings have been mixed, with some reports of typical HPA function in women with PMDD [76], or altered HPA indicators only in a subset of PMDD women, e.g., blunted nocturnal cortisol was exhibited only by PMDD women with high serum levels of ALLO [77••]. The observed HPA abnormalities in women with PMDD may arise from the relationships between the HPA and hypothalamic–pituitary–gonadal (HPG) axes. Further work on the HPA–HPG axes'

relationship relative to PMDD is needed and may be probed via laboratory stressors, particularly if PMDD is conceptualized as a hormone by stress interaction involving fluctuations in stress sensitivity [78], or challenge studies involving 5-alpha reductase inhibitors or gonadotropin-releasing hormone (GnRH) antagonists.

PMDD Treatment

Antidepressants

Pharmacotherapy is the recommended first-line treatment for PMDD, according to the American College of Obstetricians and Gynecologists [10]. The SSRIs are the gold-standard treatment for PMDD and severe mood-related PMS. Meta-analyses of randomized clinical trials (RCTs) reveal a moderate to large effect size for continuous and luteal phase (see below) SSRI treatment [79, 80], with no clear difference between the two dosing regimens [81••]. However, some meta-analyses have found small to medium effect sizes for SSRIs [82], with response rates ranging from roughly 12 to 50 % [83]. There are a number of side effects that may occur with SSRI use, the most common being nausea, insomnia, and headache, although these are typically time-limited [79, 81••]. SSRIs can adversely affect sexual function, a side effect that is persistent and can lead to medication discontinuation [81••].

Intermittent Dosing, Symptom Onset Therapy

In contrast to other mood disorders, SSRIs have been shown to have a short onset of therapeutic action in PMDD, taking effect within hours to days, in contrast to the weeks that are often required for response to SSRIs in major depression [84, 85]. This rapid onset of action is likely due to the SSRIs' ability to enhance formation of neuroactive steroids, such as ALLO. SSRIs increase conversion of 5α-dihydroprogesterone (5α-DHP) to ALLO within minutes of exposure, likely via their action on enzymes that catalyze the reactions between progesterone and ALLO [86, 87]. This short onset of action makes intermittent dosing (administering the medication only during the luteal phase, from the time of ovulation until menstruation begins) possible [88–90]. Intermittent treatment may be particularly useful for irritability, affect lability, and mood swings, while having a weaker effect on depressed mood and somatic symptoms [90]. Depressed mood and somatic symptoms may require a longer duration of SSRI treatment to show improvement.

In symptom onset therapy, women take an SSRI as soon as PMDD symptoms initiate, then stop at menstruation. This method has been examined using fluoxetine [85], citalopram [91], paroxetine [92], and the escitalopram [93]. Relatively low doses (e.g., 25 to 50 mg sertraline) were found to reduce symptoms [89], likely due to SSRIs' selective brain steroidogenic stimulant (SBSS) properties [94•].

Hormonal Treatment

There is limited research evidence for the efficacy of hormonal treatment for PMDD [95]. A meta-analysis of combined oral contraceptives containing the synthetic progestin drospirenone found that drospirenone (3 mg) plus ethinyl estradiol (20 μg) somewhat reduced severe PMDD symptoms, but there was also a large placebo effect [96]. Continuous dosing of oral contraceptives refers to skipping the week of placebo pills, thus avoiding hormonal withdrawal. A series of randomized, double-blind, placebo-controlled trials and one open-label substudy on continuous dosing of levonorgestrel (90 mcg) and ethinyl estradiol (20 mcg) showed some improvement of premenstrual symptoms, but again, a high placebo response rate [97]. Hormone monotherapy may be less effective than combined hormones. A Cochrane review meta-analysis of progesterone for PMS did not find strong evidence for progesterone use alone [98]. Other hormone-based interventions include gonadotropin releasing hormone (GnRH) agonists and inhibitors, which induce postmenopausal levels of estradiol, progesterone, and ALLO. Leuprolide acetate, a GnRH agonist, showed improvement in women with PMDD who had a certain PMDD symptom profile [99, 100]. This strategy is often recommended when women with PMDD have failed trials of SSRI treatment. In addition, this "chemical oophorectomy" serves as a test for how a woman's PMDD symptoms would respond to a surgical menopause [101].

Psychotherapy

Cognitive-behavioral interventions for PMDD might include modifying negative cognitions or improving coping strategies. A systematic review indicated that while SSRI was more beneficial in treating anxiety symptoms of PMDD, cognitive-behavioral therapy (CBT) was associated with increased use of cognitive-behavioral coping strategies and a shift in attribution of premenstrual symptoms [82]. CBT also showed better maintenance of treatment effect at follow-up, compared to the SSRI fluoxetine [82]. CBT interventions produce small to medium effect sizes [82, 102] and are superior to control conditions [103]. However, these meta-analyses included studies in which women did not always meet *DSM* criteria for PMDD, comorbid disorders were not always excluded, and not all studies included prospective rating of premenstrual symptoms. While both pharmacologic and CBT treatment of PMDD show efficacy in symptom reduction, meta-analysis suggests no added benefit from combined treatment [82]. A recent development in mental health treatment is the use of internet-based cognitive-behavioral therapy, which reduces burden on the patient and has shown promising results in other

female lifespan affective conditions such as postpartum depression [104•]. While a computer-assisted or internet-based CBT program has yet to be developed for PMDD, researchers have proposed its development and testing [105•].

Other Therapies

Per ACOG guidelines, alternative nonmedical treatments including yoga, aerobic exercise, or dietary supplementation are more appropriate for PMS than PMDD [10]. In terms of dietary supplementation, calcium may offer some benefit for premenstrual symptoms. In a study that compared calcium carbonate (600 mg twice daily) to fluoxetine (10 mg twice daily) and placebo in treating symptoms in women with at least three moderate to severe premenstrual symptoms, fluoxetine showed therapeutic benefit while the effect of calcium was much smaller [106•]. Other dietary or herbal supplements such as omega-3 fatty acids [107•], gingko biloba, crocus sativus, or evening primrose oil [108] have shown limited benefit in treating premenstrual physical symptoms. Similarly, studies on exercise for premenstrual symptoms have been of limited sample size and low quality [109]; better quality research must be undertaken before clinical recommendations can be made.

Conclusions

Recently designated as a disorder in the *DSM-5*, PMDD is a disorder that presents multiple avenues for further research. As PMDD is clinically unique from major depressive disorder and may have more irritability and anxiety-like features, one potential avenue of research might focus on the unique biological aspects of PMDD and PMS. Neurosteroids and the GABAergic system are particularly intriguing areas of potential study with solid preclinical and clinical literature [13, 16••, 110]. Lifetime exposure to stress may also interact with genetic predisposition for affective disorders, including PMDD. Treatment research is also needed. Given ALLO and GABA's potential role in PMDD pathophysiology, research on neurosteroid modulation of GABAergic function across the menstrual cycle may prove fruitful.

Compliance with Ethics Guidelines

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