Premenstrual Dysphoric Disorder

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Introduction

Premenstrual disorders affect women of reproductive age during the late luteal phase of the menstrual cycle. They largely consist of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), both of which are recurrent chronic conditions that cause significant impairment in occupational or social functioning. Symptoms experienced by women with premenstrual disorders follow a cyclical and predictable pattern corresponding to the phases of their menstrual cycle. Specifically, several affective and physical symptoms emerge sometime in the 2 weeks leading up to menstruation, which then remit or become minimal within a few days of menses onset and are absent following menses. Women with PMDD experience a severe form, with more symptoms emerging in the luteal phase than those with PMS. The aetiology of these disorders is unclear, but research suggests involvement of altered neurotransmitter systems and increased sensitivity to gonadal hormone fluctuations. Due to the complexity of the disorder, there is no single treatment that is successful for all women; however, various treatments aimed at regulating neurotransmitter systems and suppressing gonadal steroids have been efficacious. This chapter will provide an up-to-date overview on the diagnosis, epidemiology, course and risk factors, aetiology, and evidence for effective treatments of PMDD.

Definition and Diagnostic Criteria

Premenstrual dysphoric disorder (PMDD), which replaced what was previously termed late luteal phase dysphoric disorder, first appeared in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) under the Appendix as a set of criteria that required further research [1]. Women meeting the suggested criteria were subsequently classified under "depressive disorder not otherwise specified", which failed to recognize its unique clinical presentation and provided no specificity towards risk factors, prevalence, and course of the proposed disorder. Following the ensuing research on the epidemiology, pathology, and treatment,

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it was concluded that PMDD was distinct from other disorders, and it became an official diagnosis under the Depression and Depressive Disorders chapter in the fifth edition of the DSM (DSM-5) [2].

To meet DSM-5 diagnostic criteria for PMDD, at least five symptoms from a list of eleven must be present in the week prior to menstruation and improve within a few days of menses onset and are negligible or absent in the week after menses [2]. Of the five required symptoms, at least one must be affective, including mood swings, anger or irritability, depressed mood, and anxiety or tension. Women must also present with one or more of the following specified symptoms: decreased interest in surroundings, difficulties in concentration, lethargy or fatigue, change in appetite, sleep difficulties, feelings of being overwhelmed or not in control, and physical symptoms (e.g. breast tenderness, joint or muscle pain, swelling of extremities, bloating, or weight gain).

The symptoms presented must have occurred during the majority of menstrual cycles of the previous year and are to be confirmed using a prospective daily ratings of at least two symptomatic menstrual cycles. A key component to diagnosing a premenstrual disorder is determining the timing of symptoms during a women's menstrual cycle. Symptoms must emerge in the luteal phase, improve within a few days of menstruation, and remit until negligible or absent following menses. Retrospective reports are often biased as patients tend to overestimate the cyclical timing of their symptoms leading to overdiagnosis [3]. When prospective ratings are not available, a provisional PMDD diagnosis may be given. In addition to their presence, the symptoms must significantly interfere with the individual's work, school, social life, and/or interpersonal relationships.

Symptoms cannot be related to the effects of a medication, other substance use, or a medical condition. Some physical conditions share overlapping symptoms with premenstrual disorders, such as migraines, anaemia, diabetes, asthma, seizure disorders, endometriosis, uterine fibroids, and hypothyroidism [4]. As a result, these conditions should be considered and assessed in order to exclude them as causal factors for the presenting symptoms.

PMS and PMDD share the same type and cyclical pattern of symptoms, but differ based on the number of symptoms required to meet criteria. Unlike PMDD, PMS does not require a minimum of five symptoms and the presence of an affective symptom is not necessary. Both diagnoses require that women present with physical and behavioural symptoms that impair functioning to a significant degree.

In addition to PMS and PMDD, several other classifications of premenstrual disorders exist and were characterized by the International Society for Premenstrual Disorders (ISPMD) [5]. These include premenstrual exacerbation, premenstrual disorder due to ovarian activity not related to ovulation, progestogen-induced premenstrual disorder following progestogen administration, and premenstrual disorder with absent menstruation following suppression of menses. PMS or PMDD may not be classified if symptoms exist exclusively as an exacerbation of another underlying psychiatric disorder, such as depressive, bipolar, or anxiety disorders. Often women may experience a worsening of symptoms of a pre-existing medical condition or other psychiatric disorder in the luteal phase of menstruation; however, this presentation does not reflect PMS or PMDD if symptoms persist throughout the entirety of the menstrual cycle with no symptom-free period. It is important to also distinguish dysmenorrhea, i.e., menstrual-related pain or cramps in the abdominal region or back that lasts several days and has an onset during menstruation [6], as a distinct condition that is not reflective of PMS or PMDD.

The inclusion of PMDD as a psychiatric disorder in the most recent DSM has been met with debate. One argument against its classification views PMS and PMDD as a culturally bound, social construct that pathologizes women's natural experience based on their reproductive state [7]. Others have criticized that a female-specific diagnosis perpetuates the notion that a woman's

distress may only be taken seriously upon being labelled as a disorder. However, such claims fail to acknowledge the prevalence of PMS/PMDD worldwide and the benefits associated with a formal diagnosis, such as the recognition, research, and treatment needed to ensure full support is given to women [8].

Self-Report Diagnostic Tools

Several rating scales were developed to assess and quantify premenstrual symptoms prospectively to identify women meeting criteria for PMS or PMDD. Of importance is the ability for these assessment tools to collect clinically relevant information in a time-efficient and straightforward manner.

The first published tool that was developed to measure premenstrual symptoms was the Moos' Menstrual Distress Questionnaires (MDQ), which is a self-report instrument that assesses 47 symptoms on a 6-point scale [9]. Its use has been criticized as some items measure symptoms not related to the menstrual cycle [10]. Less than a decade later, the first visual analogue scale (VAS) was used, which enabled individual premenstrual symptom ratings to fall on a continuous scale [11]. The VAS is an appealing measure due to its simplistic design which has participants mark a 100 mm horizontal line to display the severity of premenstrual symptoms they experience. The lines are marked at either end to represent the absence (0) and the most severe presence (100) of premenstrual symptoms. Several advantages to the VAS include its simplicity, increased compliance, and its validity and reliability for measuring change in premenstrual symptoms over time [12]. One disadvantage with paper VAS versions is the time-consuming process associated with measuring each marking by hand. Development of electronic devices that are capable of providing these results quickly from markings created on a touchscreen has eliminated that challenge [13].

In 1990, the Daily Record of Severity of Problems (DRSP) was developed and published by Endicott and Harrison [14] to collect information on the severity of symptoms and daily impairment experienced across various phases of the menstrual cycle. The DRSP includes 21 items that cover mood and behavioural and physical symptoms, as well as 3 impairment-related questions that measure impairment of work, social activities, and interpersonal relationships. The individual items are then rated from 0 to 6 (0, not at all severe, to 6, extreme severity) to allow for proper prospective diagnosing of PMS or PMDD that correspond to DSM criteria. This tool highlights the timing and nature of the problems experienced across the menstrual cycle and should be completed for at least two symptomatic cycles to confirm a PMDD diagnosis. Another prospective rating calendar that may be used is the Prospective Record of the Impact and Severity of Menstrual symptoms (PRISM), which is freely available online [15].

Another tool that was developed to help identify women with possible PMDD who are likely to benefit from treatment is the Premenstrual Symptom Screening Tool (PSST) [16]. The PSST assesses premenstrual symptoms retrospectively, thereby making it a less time-consuming tool as compared to the DRSP. A total of 14 symptoms based on the DSM-IV criteria are included that primarily focus on premenstrual mood and behaviours, with one item corresponding to physical symptoms. The participant identifies which symptoms are experienced and the degree of interference of these symptoms on various aspects of daily life using a 0–3 frequency scale ("not at all", "mild", "moderate", "severe"). A recent study on the validation of the PSST against the DRSP reported that there is high sensitivity and low specificity of the PSST for diagnosing PMS/PMDD [17], which may be due to inaccurate recall of the timing and severity of symptoms. Despite the lack of agreement between the two rating scales [17], the PSST is highly beneficial as a time-saving screening tool, and women positively identified by the PSST should be further evaluated using prospective symptom charting, such as the DRSP, to confirm a PMDD diagnosis.

Epidemiology

Approximately 80% of women will report having experienced at least one mild premenstrual symptom during the luteal phase of a menstrual cycle [18, 19]. Twelve-month prevalence rates for PMS are approximately 20–30% [20]. A recent meta-analysis reviewing epidemiological studies reported a pooled prevalence rate of 47.8% for PMS worldwide, with prevalence rates ranging from 12% to 98%, in France and Iran, respectively [21].

Due to differences in severity, PMDD is less common than PMS. Epidemiological studies over the last few decades have provided mixed results for the prevalence of PMDD, which is largely due to different diagnostic criteria used in classifying its diagnosis and different methodologies used in sampling [22, 23]. The estimated prevalence for PMDD is around 5% in menstruating women, with rates ranging between 1.1% and 6.4% observed worldwide [19, 24–30]. Due to strict PMDD criteria of a minimum of 5 symptoms, prevalence rates fail to consider the number of women experiencing severe premenstrual symptom impairment that do not meet the number of required symptoms [23]. Up to 20% of menstruating women are thought to experience clinically significant premenstrual symptoms that warrant treatment [19].

When examining symptom type, the predominant premenstrual symptom experienced globally by reproductive aged women is physical [31], whereas, for women with severe PMDD, depressed mood and irritability is often reported as the most prevalent symptom in the luteal phase [19].

Course, Morbidity, and Quality of Life

Women can develop PMS or PMDD at any time point between menarche and menopause. PMDD is well recognized as a stable disorder in which spontaneous recovery or remission is unlikely. Severity of symptoms tends to worsen over time, with peak symptoms experienced by women in their twenties to thirties, and symptoms tend to subside as ovarian activity declines and ovulation ceases with menopause [32]. Even though remission of premenstrual symptoms can be achieved through various medical treatments, symptoms often re-emerge once treatment is stopped [33]. Likewise, menopausal women can experience premenstrual symptoms when taking cyclical hormone replacement therapy [34].

Women with PMDD are estimated to suffer 3.8 years of disability adjusted life years over their reproductive lifetime [23]. The severity and chronicity of these symptoms results in impairment that extends to all aspects of daily life, with the greatest impact observed on interpersonal relationships and work productivity [32]. Indirect economic costs of burden from decreased work productivity and increased absenteeism due to PMS or PMDD are estimated around $4333 USD per patient per year [35]. Additionally, women with PMDD report increased use of healthcare services including increased number of visits to a healthcare provider and use of prescription medications [35].

Quality of life for women with PMDD in the luteal phase is comparable to those with depressive disorders [36]. Women considered at risk for PMDD based on retrospective reports experienced significantly lower quality of life on physical and mental health-related domains as compared to a US female population average, with greatest impairment observed for bodily pain and mental health [37].

Comorbidities with Other Psychiatric Disorders

Lifetime history of another psychiatric disorder is common in women with moderate to severe premenstrual symptom complaints with a previous major depressive episode most often reported as the most prevalent, followed by anxiety disorders [38, 39]. In a sample of women with prospectively confirmed PMDD, lifetime comorbidity rates were highest for major depression disorder (31.2%), followed by sub-

stance abuse (18.6%) and anxiety disorders (15.3%) [40]. Roughly 30–70% of women with prospectively diagnosed PMS or PMDD have experienced a past major depressive episode, whereas concurrent rates of PMDD comorbid with depressive disorders are between 12% and 25% [41]. Past premenstrual distress may also predict future episodes of depression, as women with a history of depressive premenstrual symptoms are more likely to experience a future depressive episode [42].

In a sample of women with prospectively confirmed premenstrual disorders, 59% reported concurrent anxiety disorders, with generalized anxiety (38%), panic disorder (25%), and social phobia (19%) described as the most common [43]. In a longitudinal study assessing obsessive-compulsive symptom change in women with obsessive-compulsive disorder (OCD) across the menstrual cycle, approximately 13% met criteria for PMDD and a greater proportion of women (48%) commonly reported premenstrual exacerbation of symptoms [44].

Large-scale studies utilize retrospective reports of PMDD in general populations worldwide to provide estimates for PMDD comorbidity prevalence. A sample examining PMDD in Korean women across all reproductive ages from the Korean Epidemiologic Catchment Area study reported that 59.3% of women with PMDD had a lifetime history of another psychiatric disorder [27]. Highest associations were reported for social phobia, post-traumatic stress disorder, somatoform disorder, major depressive disorder, specific phobia, and alcohol abuse/dependence. In this sample, PMDD was also associated with insomnia and suicidality, and women who were underweight or had a physical illness were at increased risk of PMDD [27]. In a German sample, young women with PMDD were found more likely to have at least one comorbid psychiatric disorder compared to those without PMDD [19]. Twelve-month comorbidity prevalence rates were 47.4% for anxiety disorders (mostly attributed by high prevalence rates of social phobia and specific phobia of blood or injury), followed by 29.8% for mood disorders [19].

Although comorbid PMDD and bipolar is less studied, a large-scale cohort of 1099 women who met criteria for bipolar disorder type I or II found that 45% of women had retrospectively confirmed PMDD [45]. Additional findings from this study show that women with bipolar disorder comorbid with PMDD are more likely to have additional psychiatric comorbidities (including anxiety disorders, bulimia, adult attention deficit and hyperactivity disorder, and lifetime alcohol or drug abuse) and present with a more severe illness course [45].

The experience of psychotic symptoms limited to the luteal phase of the menstrual cycle is rare but has been described in several case studies [46]. A challenge in determining PMDD comorbidity frequencies with schizophrenia is due to the difficulty in distinguishing PMDD and premenstrual exacerbation in this population. In a Chinese population of 50 women with schizophrenia, 52% met criteria for PMS, with 20% experiencing premenstrual exacerbation [47]. In a study prospectively following schizophrenia patients across one menstrual cycle, no change in psychotic symptoms were experienced across the menstrual cycle, whereas exacerbation of affective and behavioural symptoms were prominent in the premenstrual phase [48].

Large-scale study estimates of comorbidities commonly experienced with PMS or PMDD are challenging due to prospective charting needed to establish a diagnosis. As a result, many studies rely on the use of retrospective reports to assess premenstrual worsening of symptoms, which are subject to bias. Additional challenges remain in the ability to detect cyclical symptom changes in women experiencing severe symptomatic mood or anxiety disorders, which may have overlapping symptoms with PMS/PMDD.

Collectively, these results highlight a need to assess possible PMDD in women presenting with various mood and affective disorders, as morbidity and treatment can be affected. Women with psychiatric and premenstrual disorder comorbidities tend to exhibit a more severe illness course and identification of concurrent PMDD may better inform treatment considerations.

Risk Factors

Several population-based studies have been conducted examining potential risk factors for the development of premenstrual disorders.

Race Varying prevalence rates for PMDD have been reported across different racial groups. Prevalence rates for PMDD appear higher for Caucasian women than African American women in the United States [49], whereas rates in East Asia are lower than those seen in North America (1.3–2.8%) [50]. These findings may be due to cultural differences in awareness of premenstrual disorders and with attitudes regarding premenstrual mood disturbance. This possibility highlights the importance of education, especially for healthcare givers and women who may be unfamiliar with premenstrual disorder terminology and available treatments.

Age Age does not reliably predict risk; however, there seems to be an association of age with premenstrual symptom severity. Older women with PMDD who seek treatment tend to have longer duration of symptoms and are more likely to seek treatment, yet they report lower symptom severity compared to younger women [51, 23]. PMDD symptom severity appears to peak for women in their late twenties to mid-thirties [51].

Lifestyle/Diet Several lifestyle risk factors for the development of PMS have been ascertained through results of a subset of women aged 27–44 who participated in the longitudinal Nurses' Health Study II. Women who smoke cigarettes, especially those who started smoking before the age of 15, were more than 2 times likely to develop PMS [52]. After adjusting for several lifestyle factors such as smoking and physical activity, women with a body mass index (BMI) greater than 27.5 kg/m^2 were at greater risk of developing PMS [53]. Women with PMDD tend to have greater caloric intake and sweet cravings in the late luteal phase compared to the follicular phase and to control women, but no significant differences in BMI were found between PMDD and control groups [54]. Ingesting higher quantities of calcium, vitamin D, thiamine, riboflavin, and non-heme iron was associated with decreased risk for developing PMS, whereas increased potassium intake was associated with a higher risk [55–57].

Stress/Trauma Women with PMDD report a greater worsening of symptoms when accompanied by stressful life events or greater perceived levels of stress [58, 59]. A longitudinal study observing a cohort of young women found that those exposed to traumatic events were four times more likely to have PMDD compared to those experiencing no trauma [59]. Early life emotional and physical abuse increases the risk for PMS development, with an odds ratio of 2.6 and 2.1 for women reporting severe emotional and physical abuse, respectively [60]. Several studies investigating the prevalence of past sexual or physical abuse in women with PMS or PMDD have found significantly higher rates in this clinical population than women in the general population. In 174 women with PMS, 40% reported a history of sexual abuse [61]. In comparison, childhood sexual abuse rates in women in the general population have been found to be around 12.4% and 16% [62, 63]. Scores on the Childhood Trauma Questionnaire (CTQ), which measures emotional, physical, and sexual childhood abuse, were significantly greater in a sample of women from Turkey with PMDD compared to healthy controls [64]. Also noteworthy, a large majority of women (83%) who experienced sexual abuse did not disclose the abuse to any healthcare practitioner, suggesting that abuse history be screened in women presenting with premenstrual disorder symptoms [65].

Psychiatric Disorders As previously described, PMDD is often comorbid with depressive disorders. What is unclear from the literature is whether these disorders predispose risk for premenstrual disorders, or vice versa. Women with diagnosed PMDD often report past depressive episodes [41], and premenstrual distress may increase likelihood of experiencing a future depressive episode [42]. There may be an association between premen-

strual disorders and postpartum depression, as some studies report that women with PMS/PMDD are more likely to develop postpartum depression [66, 67]; however, a recent study examining women with PMDD reported low rates (11.7% of parous women) of past postpartum depression [40].

Genetic Heritability Results from family and twin studies provide mixed evidence that genetic factors contribute to the development of premenstrual disorders. First-degree female relatives in mother-daughter dyads retrospectively report similar presence or absence of PMS [68], whereas no relationship was found in symptom changes across the menstrual cycle among sisters [69]. Twin studies report retrospective premenstrual symptom heritability estimates of 35.1% [70], which was later found to be moderately stable over time in a follow-up study of the same cohort, with heritability estimates of 56% [71]. PMS concordance rates among twins have been higher for monozygotic twins, with one study reporting 0.81 vs 0.67 concordance rates for monozygotic and dizygotic twins, respectively [72]. However, one twin study determined that retrospective reports of premenstrual symptoms were associated with neuroticism personality traits, which may not reflect genetic contribution [73]. Methodological challenges associated with collecting prospective data from families to confirm PMDD diagnosis may explain why this has yet to be performed.

Menstrual Cycle Physiology

Over a century ago, women were estimated to have fewer than 100 menstrual cycles in their lifetime, owing to recurring interruptions for pregnancy and breastfeeding [74]. In today's society, women are experiencing earlier menarche, later menopause, and fewer pregnancies, leading current estimates for women to have around 400–450 menstrual cycles in their lifetime [74]. Understanding the physiology of the menstrual cycle will provide the context needed for understanding the aetiology of PMDD.

The menstrual cycle can be defined by two phases: the follicular phase (from the first day of menstruation to ovulation) and the luteal phase (from ovulation to the start of menstruation). Both phases are accompanied by the fluctuation of ovarian hormones: estradiol and progesterone. Ovarian activity and steroidogenesis occurs as a result of the hypothalamus releasing gonadotropin-releasing hormone (GnRH), which regulates the production and secretion of the pituitary gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The frequency and amplitude of GnRH pulses changes across the menstrual cycle to favour FSH or LH release and is regulated by feedback from oestrogen and progesterone levels [75].

At the start of the menstrual cycle, which is marked by menses onset, estradiol and progesterone levels are low. During this time, GnRH pulses occur approximately every 90–120 minutes, favouring the release of FSH [74]. Elevated levels of FSH are responsible for stimulating the growth of immature ovarian follicles. As the follicles begin maturating, one follicle will obtain a competitive advantage over the others making it more sensitive to FSH levels [76]. This "selected" follicle will continue to mature and release increasing amounts of oestrogen, which is then converted to estradiol. In the mid-late follicular phase, elevated estradiol levels cause a cascade of events on the hypothalamus-pituitary-gonadotropin (HPG) secretion, which results in GnRH pulses occurring once per 60 minutes, thereby favouring LH secretion and suppressing release of FSH [77]. As LH levels surge and peak, estradiol levels drop dramatically and the dominant follicle ruptures, known as ovulation [77].

Ovulation marks the transition into the luteal phase of the menstrual cycle. After ovulation, a large quantity of progesterone is produced and secreted by the corpus luteum, which is the temporary yellow hormone-secreting structure that is formed at the site of the ruptured follicle. Progesterone secreted from the corpus luteum acts on the hypothalamus to slow GnRH pulses to once every 3–5 hours [74]. The production of estradiol from the corpus luteum suppresses FSH release [77]. In the absence of fertilization, the

corpus luteum degrades, leading to decreased levels of progesterone and estradiol. The onset of menses takes place, marking the start of the next menstrual cycle. Decreased levels of these ovarian hormones release the hypothalamus and pituitary from suppression, allowing FSH secretion and the recruitment of a new cohort of follicles for the maturation process.

Aetiology

The aetiology of premenstrual disorders still remains elusive; however, PMDD is well characterized by the cyclical recurrence of symptoms that relates to fluctuations of gonadal hormones during the menstrual cycle. The temporal nature of the symptoms, which coincides with the late luteal phase of the menstrual cycle, led many to the assumption that altered hormone levels may be responsible for the clinical manifestation. However, failure to reliably detect abnormal levels of circulating ovarian hormones suggests that premenstrual disorders are not primarily caused by a simple hormone alteration [77].

Rather, the current literature supports the hypothesis that symptoms emerge in women who are more sensitive to changes in endogenous levels of hormones. Support for this theory comes from a recent study that investigated the effects of oestrogen and progesterone on women who had achieved symptom remission through ovarian suppression [78]. Ovarian suppression was accomplished with GnRH agonist administration, but due to side effects of this therapy, an add-back therapy is often implemented. The researchers found increased ratings for premenstrual tension (self-reported and rater-administered) in the first month following progesterone and oestrogen add-back therapy, whereas no change in symptoms occurred with single-blind placebo add-back [78]. Subsequent months using ovarian steroid add-back therapy led to lowered premenstrual tension scores, suggesting that the initial change in oestrogen and progesterone levels triggered symptom onset, whereas stable levels did not precipitate premenstrual symptoms. The neuromodulatory actions of oestrogen and progesterone on the central nervous system are of interest and are likely to contribute to the pathogenesis of PMDD as well.

Progesterone There is a well-established temporal association between premenstrual symptoms and ovarian steroid fluctuation with progesterone. Premenstrual symptom onset in the late luteal phase coincides with declining levels of progesterone, leading many to hypothesize that a deficiency of progesterone may be eliciting symptoms. This does not appear to be the case in PMS/PMDD, as different studies have failed to provide evidence that supports the association between low levels of progesterone and premenstrual symptoms. Investigations into plasma levels of progesterone, as well as estradiol and ovulation hormones FSH and LH, found no differences among women with PMS and controls across the menstrual cycle [79]. Additionally, premenstrual symptom severity scores were worse in cycles with higher plasma levels of estradiol and progesterone concentrations [80]. Lastly, treatment studies administering progesterone using a double-blind placebo-controlled design found no significant symptom improvement with progesterone use when compared to placebo [81].

Allopregnanolone Researchers. turned their investigations to a neuroactive steroid metabolite of progesterone: allopregnanolone (3alpha-hydroxy-5alpha-pregnan-20-one; ALLO). ALLO is synthesized in the brain and fluctuates in parallel with progesterone in the menstrual cycle [82]. ALLO is a positive modulator of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system. ALLO exerts agonistic effects on the $GABA_A$ receptor, which selectively conducts chloride anions [83]. When ALLO binds to the $GABA_A$ receptor, it enhances the effects of GABA by increasing the frequency and duration of chloride channels opening, thereby reducing neuronal excitability [83]. Typically, high concentrations of positive modulators of $GABA_A$ receptors, such as benzodiazepines and ALLO, exert anxiolytic, sedative, and anti-epileptic effects in women

[84], whereas lower concentrations induce anxiogenic effects and aggressive behaviours in animals [82]. A paradoxical effect is observed in women with PMDD, as endogenous levels of ALLO that are increased in the mid-luteal phase of the menstrual cycle are associated with an increase in negative mood symptoms [85]. An inverted U-shaped relationship between ALLO concentration and negative mood in women has been suggested and supported, with endogenous luteal levels of ALLO showing the greatest increase in negative mood, whereas low and high concentrations of ALLO have less of an effect on mood [82].

One possible mechanism by which ALLO influences $GABA_A$ receptor activity differently in women with PMDD involves increased susceptibility to abrupt changes in progesterone levels, and subsequently ALLO. levels, which triggers the emergence of premenstrual symptoms in the luteal phase. Rodent studies have demonstrated $GABA_A$ receptor subunit conformational change following fluctuations of ALLO, which returns to the usual conformation in the presence of stable hormone levels [86]. This type of conformational change could reflect short-term tolerance to the GABA-enhancing effect of ALLO in the luteal phase [87].

Further evidence supporting the role of ALLO in premenstrual disorders comes from inhibiting the rate-limiting enzyme responsible for the conversion of ALLO from progesterone, 5alpha-reductase, which led to improved mood in women with PMDD [88]. Additionally, selective serotonin reuptake inhibitors (SSRIs), which are an effective treatment option for some women with premenstrual disorders, may influence levels of ALLO. Specific SSRIs have been shown to increase levels of ALLO through influencing the activity of the second-step enzyme, 3alpha-HSD, responsible for its conversion [89]. In a treatment study for women with prospectively defined PMS, those displaying low levels of ALLO at baseline experienced a significant increase of ALLO following treatment with the SSRI sertraline, whereas the opposite was observed for women with higher baseline levels of ALLO, as they experienced a decrease in levels after treatment [90]. Furthermore, women with lower baseline levels of ALLO experienced an improvement in depression-related symptoms (feelings of depression, being out of control, and hopelessness) [90]. Taken together, there is a substantial amount of evidence supporting the involvement of ALLO-mediated $GABA_A$ receptor function. in the occurrence of negative mood symptoms in the late luteal phase.

Serotonin A monoamine neurotransmitter that has gained widespread interest among various mood disorders and is thought to play a significant role in the pathophysiology of premenstrual disorders is serotonin. Serotonergic neurons project from the raphe nucleus in the brainstem to various regions throughout the brain, and serotonergic activity regulates behaviours such emotion, mood, eating, arousal, and sleep and circadian rhythms [91]. Aberrations of the serotonergic system that result in deficiency have been associated with a myriad of mood symptoms including depression, anxiety, panic, obsessions, and compulsions [92].

Results from pharmacological studies utilizing drugs that either enhance or inhibit serotonergic transmission in women with PMS/PMDD provide the strongest implication for its involvement. Treatments that facilitate serotonergic transmission, such as through the actions of SSRIs that block the reuptake of serotonin from the synaptic cleft, reduce the symptoms of PMS [93]. In fact, SSRIs are the current first-line treatment approach for PMS/PMDD, with approximately 60% treatment response [94]. Similar observations of a reduction in premenstrual symptoms following modifications to serotonergic functioning after administering compounds that increase the amount of available or released serotonin are observed with meta-chlorophenylpiperazine (mCPP) [95], d-fenfluramine [96], and the serotonin precursor tryptophan [97], whereas drugs that counteract or decrease serotonin activity are found to worsen premenstrual symptoms, as reported with dietary tryptophan depletion studies [98] and administra-

tion of the serotonin receptor antagonist metergoline in women who achieved remission via SSRI [99]. It is of importance to note that causality cannot be inferred from pharmacological response data, as the mechanism by which each drug operates is unclear.

SSRIs are an effective treatment option for reducing premenstrual symptoms in women with severe PMS/PMDD and are commonly prescribed antidepressants for the treatment of major depression. Despite overlapping symptoms between PMDD and depression, there are marked differences in treatments for these disorders that suggest different underlying serotonergic involvement. SSRIs for the treatment of depression require continuous administration over several weeks in order to observe noticeable changes [100], whereas premenstrual symptoms, such as irritability, are reduced a few days after beginning SSRI treatment [101]. As a result, intermittent dosing of SSRIs administered in the luteal phase is a possible and feasible option for the treatment of PMDD. Further evidence supporting dissimilarities between PMS and depression come from antidepressants that non-specifically target serotonergic activity. Serotonin and norepinephrine reuptake inhibitors (SNRIs) are effective in treating depression [102], but are not as effective in treating PMS [103], which further highlights the importance and specificity of serotonin in premenstrual disorders.

Serotonergic transmission can also be measured outside the central nervous system by examining serotonin activity in blood platelets. Differences in platelet uptake of serotonin, activity of the enzyme that metabolizes serotonin (monoamine oxidase, MAO), and serotonin transporter density have been reported in women with PMS compared to healthy control subjects [104, 105]. Another method for evaluating serotonergic activity is to measure levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid. One study failed to find differences in 5-HIAA mean concentrations across the menstrual cycle and between controls and women with PMS; however, they reported that women with PMS had a lower ratio between 5-HIAA and a dopamine metabolite levels [106]. A small number of positron emission tomography (PET) studies that measure metabolic processes have been conducted to examine serotonergic functioning in vivo in women with PMDD compared to controls. A study examining the change of serotonin 1A receptor binding potential from follicular to luteal phase found that women with PMDD had a much smaller change in the raphe nucleus compared to controls [107]. Although the study was conducted on a small sample size, this pilot suggests altered density of serotonin 1A receptors in those with severe PMDD.

Oestrogen and progesterone modify serotonergic transmission by altering the amount of available serotonin at synapses through its effects on their nuclear receptors that act as gene transcription factors. Several studies examining the effects of oestrogen administration using nonhuman primates have reported increased gene transcription of the enzyme responsible for synthesizing serotonin from tryptophan (tryptophan hydroxylase, TPH) and reduced transcription of the serotonin transporter, MAO-A (subtype which selectively degrades serotonin), and the auto-receptor serotonin 1A [108]. However, the modifying effect of oestrogen on the transcription of serotonin-related genes and proteins appears to depend on several factors that include type of receptor, brain area, and duration of oestrogen treatment [109]. Progesterone also has been shown to influence serotonergic functioning through regulating several of the same serotonin genes mentioned above [108].

Taken together, all of these results suggest that a complex interaction between serotonin, sex steroids, and other neurotransmitters are likely to contribute to the pathophysiology of PMDD, but the exact pathways and mechanisms remain to be found.

Brain-Derived Neurotrophic Factor One of the most important trophic factors that has been investigated in association with PMDD and plays an important role in neuronal growth and survival, as well synaptic signalling and synaptic plasticity, is brain-derived neurotrophic factor (BDNF). BDNF expression can be influenced by

a number of internal and external factors, including neurotransmitters, sex steroids, and stress [110]. Oestrogen has been shown to increase BDNF levels [111] and BDNF may mediate progesterone's effect on cognition and mood [112]. Alterations in BDNF serum levels have been found in various psychiatric and neurodegenerative diseases [113]. In premenopausal women, BDNF serum levels are higher in the luteal phase compared to the follicular phase [114]. In patients with PMDD, higher serum levels of BDNF were reported in the luteal phase compared to the follicular phase and were significantly higher in both phases of the menstrual cycle compared to controls [115, 116].

Genetics Results from twin and family studies have implicated genetic factors in the pathogenesis of PMDD, albeit mixed evidence. Candidate gene studies have largely focused on polymorphisms within several key neurotransmitter pathways, which include genes coding for the serotonin transporter (SERT), catechol-o-methyl transferase (COMT), MAO-A (MAOA), BDNF, and oestrogen receptors alpha and beta (ESR1 and ESR2, respectively). For an in-depth summary on the genetic basis of PMDD, please see McEvoy and colleague's paper [117].

A primary polymorphism within the SERT gene that has been widely investigated among several psychiatric disorders is the serotonin transporter-linked polymorphic region (5-HTTLPR), which is comprised of a 44-bp insertion/deletion polymorphism primarily composed of two alleles: the short (S) allele and long (L) allele. Some studies found no association between 5-HTTLPR and PMDD [105, 118], whereas one study found that the S allele was associated with neuroticism personality traits in women with PMDD [119]. No associations were found for polymorphisms in genes coding for COMT [120], ESR2 [120], or BDNF [121] with PMDD. An association was detected for variations within the ESR1 gene, but only for those with a specific Val/Val genotype from the COMT polymorphism [120]. Due to the limited number of studies that have investigated the genetics underlying PMDD, it remains unclear as to whether these genes contribute increased susceptibility.

Neuroimaging A sophisticated method for observing neural structure and function in vivo is through use of neuroimaging techniques, such as magnetic resonance imaging (MRI), functional MRI (fMRI), PET, and diffusion tensor imaging (DTI), to name a few. For a review of neuroimaging studies conducted across the menstrual cycle and in women with PMDD, see Comasco and Sundström-Poromaa's review [122]. Some studies have shown abnormal grey matter volume of several structures, including the hippocampal gyrus, parahippocampal gyrus, and cerebellum in women with PMDD [123, 124]. Abnormal regional cerebral blood flow was detected in women with PMDD across different hormone conditions, where greater activity was reported in the dorsolateral prefrontal cortex, medial frontal gyrus, and the cerebellum during a working memory task, which was also consistent with activation measured using functional magnetic resonance imaging (fMRI) [125].

Several studies have been conducted analysing emotional reactivity in women with PMDD. A whole brain analysis study assessing response to emotional faces showed that patients with PMDD had reduced activation in the fronto-cingulate cortex and increased frontal and parietal activation compared to healthy women [121]. Another study using the same paradigm but with a region of interest (ROI) approach found mid-follicular increased activity at the bilateral amygdala in PMDD compared to healthy women [126]. When dealing with social stimuli, women with PMDD showed greater activation in the amygdala and insula as compared to non-social stimuli, and bilateral amygdala activity to negative social stimuli was positively correlated with progesterone levels in the luteal phase in women with PMDD [127]. Altered reactivity was also detected in women with PMDD when anticipating negative emotional stimuli such that women recruited prefrontal cortex areas more so than

healthy controls [128]. Currently, there are a limited number of neuroimaging studies that have investigated women with PMDD, which makes drawing conclusions at this stage difficult and emphasizes an area that is desperately in need of future research.

Evidence-Based Treatment

Due to the complexity of premenstrual disorders, there is no single treatment that is effective for all women with PMS or PMDD. Current treatment strategies primarily target neurotransmitter function or hormonal fluctuations through inhibiting ovarian activity. For a more detailed review on available treatments, please refer to Yonkers and Simoni's paper [129] or Reid and Soares' paper [130]. This section will provide a current review of evidence-based treatments including those that modify neurotransmitter systems or induce ovarian cycle suppression, as well psychotherapies and alternative therapies.

Selective Serotonin Reuptake Inhibitors Pharmacotherapies, especially SSRIs, are the first-line treatment option for severe PMS and PMDD. Approximately 60% of women with severe PMS or PMDD respond to SSRI treatment [94]. Many randomized controlled trials (RCTs) have been conducted using the SSRIs paroxetine, fluoxetine, sertraline, citalopram, and escitalopram in treating PMS/PMDD and are more effective than placebo in treating symptoms overall [93]. Investigations into SSRI efficacy have often used continuous administration, while some studies investigated effects with intermittent use during the luteal phase only or following symptom onset. Regardless of administration method, SSRIs in general have shown improvement of premenstrual symptoms and overall functioning in women with PMS or PMDD [93]. This cannot be said of all SSRIs, as fluvoxamine has limited evidence supporting its beneficial actions and therefore should not be considered until sufficient evidence arises demonstrating its efficacy [131].

SSRI dosages used to treat PMDD are lower than what is commonly prescribed for depression, suggesting different underlying biological mechanisms between PMDD and depression. Recommended dosages for the SSRIs in treating severe premenstrual disorders are as follows: paroxetine 5–25 mg/day, fluoxetine 10–20 mg daily, sertraline 50–100 mg daily, citalopram 10–20 mg daily, and escitalopram 10–20 mg/day [130]. Other antidepressants that do not target serotonin functioning are less effective than SSRIs, further supporting that serotoninergic dysfunction is involved in PMDD. Guidelines illustrating practical treatment algorithms to follow for administering an SSRI for women with severe PMS or PMDD can be found in Steiner and colleague's paper [132].

Premenstrual symptoms have been reported to re-emerge following SSRI discontinuation [133]; therefore some women may require long-term treatment over reproductive years to ensure premenstrual symptom alleviation. Despite its efficacy, a proportion of women fail to respond to SSRIs, and long-term use may be accompanied by several adverse side effects, including nausea, fatigue, decreased libido, headaches, sweating, and insomnia, which were found to be dose dependent [93].

Serotonin-Norepinephrine Reuptake Inhibitors In addition to SSRIs, SNRIs have also been evaluated as a possible treatment option for women with PMDD. SNRIs are a newer class of medications and block reuptake of both serotonin and norepinephrine. Results from studies of RCTs and open-label trials using SNRIs to treat PMDD have shown that venlafaxine is effective in reducing premenstrual symptoms [134, 135]. Fewer studies have investigated the efficacy of duloxetine; however, results from open-label trials suggest that duloxetine is beneficial for treating PMDD symptoms [136]. Double-blind, placebo-controlled studies are needed to confirm if duloxetine is an effective treatment option. Common side effects reported for both venlafaxine and duloxetine include nausea and insomnia [134, 136]. When directly compared, SNRIs appear to be less effective than SSRIs for the

treatment of PMS [103]. Additionally, norepinephrine-dopamine reuptake inhibitors such as bupropion are not as effective as SSRIs [137], further supporting a greater involvement of serotonergic dysfunction in PMS/PMDD.

Oral Contraceptives Due to the timing of symptoms, it is expected that treatments that regulate the cyclical change in oestrogen and progesterone that naturally occur throughout the menstrual cycle would be effective for women with PMDD. Oral contraceptive pills that are a combination of 3 mg of drospirenone and 20 μg of ethinyl estradiol and are taken for 24 days, followed by 4 days of inactive pills, have been shown to be effective in treating PMDD in clinical trials [138]. However, drospirenone-containing medicines require consideration as they may be linked to higher risk of developing blood clots. Other progestin-containing oral contraceptives or oral contraceptives used continuously show inconclusive findings for treating PMS [129]. Women with premenstrual worsening of depression taking antidepressants found that adjunct use of combination oral contraceptive pills ameliorated premenstrual depression symptoms [139]. Oral contraceptives are beneficial treatment options for women seeking contraception, but its use has also been accompanied by side effects, such as nausea, breast pain, and inter-menstrual bleeding [140].

Gonadotropin-Releasing Hormone Agonists Another form of hormonal therapy to consider for women who do not respond well to SSRI or SNRI is ovulation suppression via GnRH agonists. GnRH agonists stimulate GnRH receptors on the pituitary, which become desensitized with continuous administration and leads to reduced secretion of LH and FSH [141]. GnRH agonists replaced use of danazol, a synthetic steroid that was shown to be successful in treating PMDD at higher dosages but was also associated with adverse androgenic side effects (acne, hair growth, voice deepening) [142]. For the treatment of PMDD, GnRH agonists are 60–75% effective when compared to placebo [143]. It is important to note that GnRH agonist places the body in a state of hypoestrogenism, and long-term use is accompanied by adverse side effects such as hot flashes, bone mineral density loss, and decreased libido [143]. Hormonal add-back therapy is a strategy often used to counteract these adverse side effects and doesn't appear to influence efficacy [144].

Surgical Menopause Hysterectomy or oophorectomy can also be considered in women with severe PMDD that do not respond to other treatments; however this option is the most invasive and should only be used as a last resort. Before consideration of this treatment, confirmation that premenstrual symptoms can be alleviated and tolerated with ovulation suppression via GnRH agonist is highly recommended.

Anxiolytics Several anxiolytic medications have been tested for the treatment of premenstrual symptoms. Alprazolam, when used intermittently in the luteal phase, has been reported as being effective in some [145, 146], but not all studies [147]. Its use requires careful consideration as there is a risk for misuse and dependence. Buspirone has also been found to reduce some premenstrual symptoms, such as irritability [148], and is associated with a lower risk for medication abuse or dependence. These medications are typically considered as an adjunct for women who do not respond to SSRI or hormone regulation treatment [149].

Cognitive Behavioural Therapy Cognitive behavioural therapy (CBT) has also been tested in the treatment of PMS and PMDD. The beneficial effects of CBT appear to involve modifying negative thoughts and improve coping strategies to better handle premenstrual distress. Symptom severity following CBT was reduced in several studies, but a recent meta-analysis found small to medium effect sizes [150]. One study reported that CBT was equally as effective as the SSRI fluoxetine after 6 months of treatment, with no additive combined effects [151]. Specifically, fluoxetine induced earlier onset of symptom alleviation and had a greater impact on anxiety symptoms, while CBT was associated with the

use of more coping strategies and may be associated with greater long-term efficacy. A major limitation to use of CBT is cost and lack of available resources, as it must be delivered by a trained healthcare practitioner or psychologist.

Diet, Lifestyle Changes, and Alternative Therapies The use of complementary and alternative medicine (CAM) to alleviate premenstrual symptoms has been investigated over several decades. These approaches are non-pharmacological and reflect healthy habits. Women, especially those suffering from PMDD, are more likely to try CAM, and these options may be favoured over other medical treatments [152]. Despite the skepticism that surrounds CAM, many have been scientifically tested using RCTs. Therefore, the following will primarily focus on RCTs and systematic reviews that have investigated herbal medicine, diet, exercise, and other therapies in women with PMS/PMDD.

A systematic review of RCTs for herbal remedies in the treatment of PMS found that *Vitex agnus-castus* (also known as chasteberry) was the most well studied, and it has been consistently reported as effective in alleviating premenstrual symptoms over placebo [153, 154]. The potential mechanism by which chasteberry acts to reduce affect and physical symptoms in premenstrual disorders are unknown, but it may be through effects on the dopaminergic system [155]. *Ginkgo biloba* (also known as maidenhair tree) and *Crocus sativus* (also known as saffron crocus) were also found to be effective over placebo, but these results require replication. No beneficial effect was found for *Oenothera biennis* (also known as evening primrose) and *Hypericum perforatum* (also known as St. John's wort). It is important to note that these trials used relatively small samples, did not include severe cases of PMDD, and were not associated with any major health risks or adverse outcomes [153].

It is hypothesized that serotonin availability can be altered via diet, and a prominent theory postulates that levels of tryptophan increase following ingestion of complex carbohydrates. Two RCTs reported improvements in premenstrual symptoms following the ingestion of a carbohydrate-rich beverage compared to an isocaloric placebo drink [156, 157]. A different study administered L-tryptophan amino acid to women with PMDD found a significant effect on alleviating premenstrual mood symptoms compared to placebo [97].

Supplements, such as vitamin B6 and calcium, have also been widely studied due to their involvement in neurotransmission. Vitamin B6 is a cofactor in the tryptophan-serotonin synthesis pathway and calcium modulates neurotransmission by regulating neurotransmitter release. A systematic review reported beneficial actions of vitamin B6 (up to 100 mg/day) in treating premenstrual symptoms, but the authors cautioned their conclusions due to the low methodological quality of trials included [158]. Calcium supplements were reported effective in treating mood and somatic symptoms in women with PMS in several RCTs [159], with dosages as low as 500 mg/day [160].

From the existing literature, there is evidence that aerobic exercise intervention may help prevent or alleviate premenstrual symptoms in women who experience milder forms of PMS [161]. Exercise is often recommended by general practitioners for alleviating premenstrual symptoms, and its contribution to greater general health and well-being in all individuals is well recognized. In studies surveying treatment practices for premenstrual symptoms, women report exercise as one of the most commonly tried and effective treatments [162]. Women may also be more willing and compliant to this type of intervention over other pharmacotherapy treatments due to adverse side effects that commonly occur with pharmaceuticals; however, this treatment option may only be effective for women with milder forms of PMS.

A systematic review conducted on the effects of acupuncture treatments which contained studies with different techniques, varying number of sessions and administration periods throughout the menstrual cycle found that hand moxibustion, which involves a burning and warming stimulation of specific points on the hand, was associated with the highest improvement in overall premenstrual symptoms [163].

Other therapies that include light or sleep deprivation that are aimed at correcting circadian rhythm abnormalities in women with PMDD have also been investigated [164]. Premenstrual symptom alleviation was observed following exposure to bright white light in the evening compared to red dim light [165].

The evidence supporting use of CAM or other therapies to treat premenstrual disorders is limited. Most of the research conducted to date has focused on milder forms of PMS, lacked controls, and have yet to be tested in women with prospectively defined PMDD. However, some results are promising and demonstrate a need for replication using rigorous methodology to better determine the effectiveness of these therapies in treating PMS or PMDD.

Conclusions and Future Directions

The inclusion and recognition of PMDD in the DSM-5 was a monumental milestone for those researching or suffering from this debilitating disorder. Despite this achievement, there are still many gaps in our understanding and treatment of PMDD that require direct investigation.

SSRIs are currently considered a first-line treatment for PMDD, in addition to those that suppress ovarian hormone function; however, several factors should be considered when choosing an appropriate treatment. These factors include severity of premenstrual symptoms, prior treatment use and response, personal preferences, and future reproductive plans. It may be that different subtypes of PMDD exist based on clinical presentation that respond differently to treatment options or require different administration instructions (i.e. different dosage, longer duration, etc.). If this is the case, then research identifying homogeneous groups within PMDD is warranted and would provide great improvements to current diagnostic and treatment practices.

If ALLO sensitivity or effects on GABA-mediated neural activity play a significant role in the aetiology of PMDD, then novel treatments that target ALLO or GABA neurotransmission should be explored in the future. There is also a need for the discovery or development of other alternative therapies that may better target specific premenstrual symptoms or overall symptom complaints. In addition to finding novel treatments, future studies should aim to determine possible predictors of response to current treatment options to help determine an appropriate first-line treatment that is tailored to the patient.

Lastly, awareness and validation of premenstrual complaints are important for reducing the possible stigma attached to women's symptoms and will more effectively reduce barriers for women seeking treatment for severe premenstrual distress.

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