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PREMENSTRUAL DYSPHORIC DISORDER (PMDD): CURRENT PHARMACOTHERAPY AND EMERGING TREATMENT APPROACHES

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ABSTRACT

Premenstrual dysphoric disorder (PMDD) is a cyclic mood disorder affecting a subset of women in the late luteal phase, marked by severe affective and physical symptoms that resolve with menses. It is distinguished from milder premenstrual syndrome (PMS) by symptom severity and functional impairment. PMDD causes substantial distress: women with PMDD have functional impairments comparable to other depressive disorders and increased work absences, and PMDD is associated with higher rates of suicidal ideation and attempts. First-line pharmacotherapy consists of selective serotonin reuptake inhibitors (SSRIs) and hormone-based treatments. SSRIs (e.g. sertraline, fluoxetine, paroxetine, escitalopram) are effective when dosed continuously or in the luteal phase, often producing rapid symptom relief at low doses. Hormonal therapies (e.g. combined oral contraceptives with drospirenone/ethinyl estradiol, GnRH agonists with add-back) can mitigate symptoms by suppressing cyclic ovarian hormone fluctuations. Emerging treatments target PMDD's neuroendocrine underpinnings: for example, sepranolone (an allopregnanolone antagonist) has shown promising early results. Novel approaches under investigation include neurosteroid modulators, anti-inflammatory strategies, and personalized interventions (genetic or biomarker-driven therapy). This review summarizes current evidence-based pharmacotherapies for PMDD and discusses emerging treatment avenues based on advances in PMDD neurobiology and psychoneuroendocrinology.

KEYWORDS

Premenstrual Dysphoric Disorder; Premenstrual Syndrome; Selective Serotonin Reuptake Inhibitors; Hormonal Therapy; Women's Mental Health

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1. Introduction

PMDD is a severe, cyclic, hormone-related mood disorder that occurs during the luteal phase of the menstrual cycle and resolves shortly after the onset of menstruation (Halbreich et al., 2003; Hantsoo & Epperson, 2015; Yonkers et al., 2008). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), PMDD is diagnosed when at least five affective, behavioral, cognitive, or somatic symptoms are present during the final week before menses, begin to improve within a few days after menstruation starts, and become minimal or absent in the postmenstrual week. (*Diagnostic and Statistical Manual of Mental Disorders | Psychiatry Online*, n.d.) At least one of the core symptoms must be affective, such as marked mood lability, irritability or anger, depressed mood, hopelessness, anxiety, or tension (*Diagnostic and Statistical Manual of Mental Disorders | Psychiatry Online*, n.d.; Hantsoo & Epperson, 2015). These symptoms may be accompanied by additional manifestations, including decreased interest in usual activities, difficulty concentrating, fatigue, changes in appetite, sleep disturbances, breast tenderness, bloating, headaches, joint or muscle pain, and a subjective sense of being overwhelmed or out of control (*Diagnostic and Statistical Manual of Mental Disorders | Psychiatry Online*, n.d.; Yonkers et al., 2008). Importantly, the symptoms must cause clinically significant distress or impairment in social, occupational, academic, or interpersonal functioning and cannot merely represent an exacerbation of another psychiatric disorder (*Diagnostic and Statistical Manual of Mental Disorders | Psychiatry Online*, n.d.; Halbreich et al., 2003; Hantsoo & Epperson, 2015).

A key diagnostic feature of PMDD is its strict temporal relationship with the menstrual cycle. Symptoms typically emerge in the late luteal phase, intensify in the days immediately preceding menstruation, and remit rapidly after the onset of menstrual bleeding (*Diagnostic and Statistical Manual of Mental Disorders | Psychiatry Online*, n.d.; Hantsoo & Epperson, 2015; Yonkers et al., 2008). Therefore, prospective daily symptom monitoring over at least two symptomatic cycles is recommended to confirm the diagnosis and distinguish PMDD from premenstrual exacerbation of underlying mood or anxiety disorders. Instruments such

as the Daily Record of Severity of Problems (DRSP) are commonly used for this purpose, as they allow clinicians and researchers to document both symptom severity and cyclicity (Endicott et al., 2006). This distinction is clinically important because PMDD is not simply a more intense form of common premenstrual discomfort, but a distinct disorder characterized by recurrent affective destabilization and substantial functional impairment (Halbreich et al., 2003; Hantsoo & Epperson, 2015).

Epidemiological studies indicate that PMDD affects approximately 1.8–5.8% of menstruating women, although estimates vary depending on diagnostic criteria, study population, and whether prospective symptom ratings are required. A broader group of women, estimated at approximately 13–18%, experience clinically significant premenstrual symptoms that do not meet the full diagnostic criteria for PMDD (*Diagnostic and Statistical Manual of Mental Disorders | Psychiatry Online*, n.d.; Halbreich et al., 2003; Reilly et al., 2024; Wittchen et al., 2002). While PMS and PMDD share some overlapping somatic and emotional symptoms, PMDD is distinguished by the predominance of severe affective symptoms, greater functional impairment, and stricter diagnostic requirements. In contrast to milder PMS, PMDD can interfere profoundly with daily life and may require specialized pharmacological or psychotherapeutic intervention (*Diagnostic and Statistical Manual of Mental Disorders | Psychiatry Online*, n.d.; Halbreich et al., 2003; Hantsoo & Epperson, 2015; Yonkers et al., 2008).

The clinical significance of PMDD extends beyond cyclical discomfort. Women affected by PMDD frequently report marked deterioration in quality of life, interpersonal relationships, occupational performance, academic functioning, and social participation during the symptomatic phase of the cycle (Halbreich et al., 2003; Pearlstein & Steiner, 2008; Yonkers et al., 2008). The level of impairment associated with PMDD has been described as comparable to that observed in major depressive disorder, particularly with respect to work productivity, social functioning, and emotional well-being (Cary & Simpson, 2024; Halbreich et al., 2003; Pearlstein & Steiner, 2008). Patients may experience recurrent absenteeism, reduced efficiency at work or school, interpersonal conflicts, and difficulty maintaining stable daily routines. Because symptoms recur monthly over many years of reproductive life, the cumulative burden of PMDD may be substantial (Halbreich et al., 2003; Loukzadeh et al., 2024; Pearlstein & Steiner, 2008).

PMDD is also associated with an increased psychiatric burden. Affected individuals more frequently report comorbid depressive and anxiety symptoms, and recent meta-analyses have linked PMDD with an elevated risk of suicidal ideation, suicide plans, and suicide attempts (Cary & Simpson, 2024; Hantsoo & Epperson, 2015; Prasad et al., 2021; Wittchen et al., 2002; Yonkers et al., 2008). This highlights the importance of careful clinical assessment, particularly in patients presenting with severe mood symptoms, irritability, hopelessness, or functional deterioration in the premenstrual phase (*Diagnostic and Statistical Manual of Mental Disorders | Psychiatry Online*, n.d.; Hantsoo & Epperson, 2015; Prasad et al., 2021). Despite its significant impact, PMDD remains under-recognized and under-treated in many clinical settings. Symptoms are often normalized as part of menstruation, misclassified as nonspecific PMS, or interpreted as an exacerbation of another mood disorder without adequate prospective cycle-based assessment. Improved awareness among gynecologists, psychiatrists, and primary care physicians is therefore essential for timely diagnosis and appropriate treatment planning (Cary & Simpson, 2024; *Diagnostic and Statistical Manual of Mental Disorders | Psychiatry Online*, n.d.; Endicott et al., 2006; Hantsoo & Epperson, 2015).

2. Methodology

A structured literature search was conducted to identify relevant publications on the pharmacological management and emerging treatment strategies for premenstrual dysphoric disorder. The search was performed using major biomedical databases, including PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library. Search terms and combinations of keywords included “Premenstrual Dysphoric Disorder,” “PMDD,” “Premenstrual Dysphoric Disorder treatment,” “selective serotonin reuptake inhibitor,” “SSRI,” “hormonal therapy,” “gonadotropin-releasing hormone agonist,” “GnRH agonist,” “neurosteroid,” “allopregnanolone,” “sepranolone,” “premenstrual syndrome,” “pharmacotherapy,” “antidepressant,” “cognitive behavioral therapy,” and “neuroinflammation.” To ensure comprehensive coverage of the available evidence, the reference lists of relevant reviews, systematic reviews, meta-analyses, and original research articles were also manually screened for additional eligible publications.

Studies were selected according to predefined inclusion and exclusion criteria. Eligible publications included peer-reviewed clinical studies, randomized controlled trials, systematic reviews, meta-analyses, and narrative reviews published in English between 2015 and 2026. Particular emphasis was placed on studies involving adult women with prospectively confirmed PMDD diagnosed according to established diagnostic

criteria, including prospective symptom monitoring. Priority was given to high-quality evidence, especially randomized controlled trials and systematic reviews evaluating treatment efficacy, dosing strategies, safety profiles, and adverse effects. Studies focusing exclusively on PMS without clear differentiation from PMDD were considered only when relevant data on severe premenstrual disorders were available.

3. Current Pharmacotherapy of PMDD

Pharmacological treatment of premenstrual dysphoric disorder is primarily aimed at reducing the severity of cyclic affective, behavioral, cognitive, and somatic symptoms, improving functional capacity, and preventing recurrent impairment during the luteal phase of the menstrual cycle (Appleton, 2018; Carlini & Deligiannidis, 2020; Hantsoo & Epperson, 2015). Because PMDD is considered a disorder of abnormal sensitivity to physiological fluctuations in ovarian hormones rather than a condition caused by abnormal hormone levels themselves, current pharmacotherapy targets both central neurotransmitter systems and suppression or stabilization of cyclic hormonal changes (Bäckström et al., 2021; Carlini & Deligiannidis, 2020; Schmidt et al., 2017). Treatment selection should therefore be individualized according to symptom severity, predominant clinical presentation, reproductive plans, comorbid psychiatric or gynecological conditions, contraindications, and patient preference (Appleton, 2018; Carlini & Deligiannidis, 2020).

The best-established pharmacological options include selective serotonin reuptake inhibitors (SSRIs) and selected hormonal therapies. SSRIs are widely regarded as first-line agents, particularly in patients with prominent mood symptoms such as irritability, affective lability, anxiety, and depressed mood. (Appleton, 2018; Carlini & Deligiannidis, 2020; Dimmock et al., 2000). Their efficacy, rapid onset of action, and ability to be used either continuously or intermittently make them especially suitable for the cyclical nature of PMDD (Carlini & Deligiannidis, 2020; Dimmock et al., 2000; Reilly et al., 2023). Hormonal therapies, including combined oral contraceptives and gonadotropin-releasing hormone (GnRH) agonists, are mainly used to suppress ovulation and reduce cyclical ovarian steroid fluctuations. These approaches may be particularly useful in patients who require contraception, have prominent somatic symptoms, or do not respond adequately to serotonergic therapy (Appleton, 2018; Carlini & Deligiannidis, 2020).

3.1. Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are currently considered the first-line pharmacological treatment for PMDD, particularly in patients with predominant affective symptoms such as irritability, mood lability, anxiety, depressed mood, or emotional tension (Appleton, 2018; Carlini & Deligiannidis, 2020; Dimmock et al., 2000). This therapeutic role is supported by multiple randomized controlled trials demonstrating that SSRIs significantly reduce both emotional and physical symptoms occurring during the luteal phase of the menstrual cycle (Dimmock et al., 2000; Jespersen et al., 2024; Reilly et al., 2023). The most commonly studied agents include sertraline, fluoxetine, paroxetine, and escitalopram, all of which have shown clinical efficacy in PMDD (Carlini & Deligiannidis, 2020; Reilly et al., 2023). The primary mechanism of action of SSRIs involves inhibition of serotonin reuptake, leading to increased synaptic serotonin availability (Carlini & Deligiannidis, 2020; Jespersen et al., 2024).

In contrast to major depressive disorder, where the therapeutic effect of SSRIs usually develops over several weeks, improvement in PMDD may occur rapidly, often within the first treatment cycle and sometimes within only a few days of initiation. This rapid onset of action suggests that the mechanism of SSRI efficacy in PMDD may differ, at least partly, from their antidepressant effect in depressive disorders (Carlini & Deligiannidis, 2020; Reilly et al., 2023). It is thought that SSRIs may help normalize serotonin-mediated mood regulation during luteal-phase hormonal fluctuations, thereby reducing sensitivity to cyclical changes in ovarian steroids (Bäckström et al., 2021; Carlini & Deligiannidis, 2020; Schmidt et al., 2017). In addition, SSRIs may influence neurosteroid pathways, including the metabolism of progesterone-derived allopregnanolone (ALLO), which acts on GABA-A receptors and has been implicated in the pathophysiology of PMDD (Bäckström et al., 2021; Bixo et al., 2017). Through these serotonergic and neurosteroid-related mechanisms, SSRIs may reduce the abnormal emotional response to otherwise physiological hormonal changes (Bäckström et al., 2021; Carlini & Deligiannidis, 2020; Schmidt et al., 2017).

Several SSRIs have been evaluated in clinical trials for PMDD (Carlini & Deligiannidis, 2020; Dimmock et al., 2000; Jespersen et al., 2024). Sertraline, fluoxetine, paroxetine, and escitalopram have consistently demonstrated efficacy compared with placebo (Carlini & Deligiannidis, 2020; Jespersen et al., 2024). Sertraline has been studied at doses of 50–100 mg daily, while fluoxetine is commonly used at a dose of 20 mg daily. Paroxetine, particularly in its controlled-release formulation, and escitalopram have also shown

beneficial effects on premenstrual mood symptoms (Carlini & Deligiannidis, 2020; Freeman et al., 2004; Pearlstein & Steiner, 2008). These agents reduce core affective symptoms such as irritability, depressed mood, anxiety, and affective lability, and may also improve associated somatic complaints (Carlini & Deligiannidis, 2020; Dimmock et al., 2000; Jespersen et al., 2024). Sertraline is particularly important from a regulatory perspective, as it is specifically approved for the treatment of PMDD and may be administered either continuously or during the luteal phase (Freeman et al., 2004; Yonkers, Pearlstein, et al., 2005; *ZOLOFT (Sertraline Hydrochloride) Label*, n.d.). Although fluoxetine and other SSRIs are also supported by clinical evidence, their regulatory status may vary depending on the country and formulation (Carlini & Deligiannidis, 2020).

An important advantage of SSRIs in PMDD is the flexibility of dosing strategies. Unlike in major depressive disorder, where continuous daily treatment is usually required, PMDD can be treated with either continuous or intermittent SSRI administration (Carlini & Deligiannidis, 2020; Jespersen et al., 2024; Reilly et al., 2023). Continuous dosing involves daily use throughout the menstrual cycle and may be preferred in patients with severe symptoms, comorbid depressive or anxiety disorders, or symptoms that extend beyond the luteal phase (Appleton, 2018). Luteal-phase dosing, in contrast, involves starting the SSRI approximately 14 days before the expected onset of menstruation and discontinuing it shortly after menses begins (Carlini & Deligiannidis, 2020; Reilly et al., 2023). This strategy is based on the cyclical nature of PMDD symptoms and has been shown to be effective in randomized trials (Dimmock et al., 2000; Jespersen et al., 2024; Reilly et al., 2023). Some studies suggest that continuous dosing may provide slightly greater symptom control, whereas others report comparable efficacy between continuous and luteal-phase regimens (Jespersen et al., 2024; Reilly et al., 2023). Therefore, the choice of dosing strategy should be individualized according to symptom pattern, treatment response, patient preference, tolerability, and the presence of psychiatric comorbidities (Appleton, 2018; Carlini & Deligiannidis, 2020).

A further intermittent approach is symptom-onset dosing, in which the medication is started only when premenstrual symptoms begin and stopped after the onset of menstruation. This strategy may be attractive to patients who prefer minimal medication exposure; however, the evidence supporting symptom-onset dosing is less robust than for continuous or luteal-phase treatment (Carlini & Deligiannidis, 2020; Marais-Thomas et al., 2024; Yonkers et al., 2015). Some smaller studies have reported clinical benefit, but larger trials, including studies of symptom-onset sertraline, have shown mixed results, with improvements in some secondary symptom measures but not always in the primary outcome (Marais-Thomas et al., 2024; Yonkers et al., 2015). For this reason, continuous and luteal-phase dosing remain the most evidence-based approaches in routine clinical practice (Carlini & Deligiannidis, 2020; Jespersen et al., 2024; Reilly et al., 2023).

Despite their efficacy, SSRIs are associated with adverse effects that should be discussed with patients before treatment initiation. Common side effects include nausea, headache, insomnia, somnolence, fatigue, gastrointestinal discomfort, decreased libido, and other forms of sexual dysfunction. Weight change may also occur in some patients, particularly during longer-term use (Carlini & Deligiannidis, 2020; Jespersen et al., 2024; *ZOLOFT (Sertraline Hydrochloride) Label*, n.d.). However, intermittent luteal-phase dosing may reduce cumulative drug exposure and therefore may improve tolerability compared with continuous treatment. Clinical studies suggest that cyclic discontinuation of SSRIs during intermittent regimens is generally well tolerated and is not usually associated with significant withdrawal or discontinuation symptoms (Carlini & Deligiannidis, 2020; Reilly et al., 2023). This makes luteal-phase dosing a practical option for many patients, especially those without symptoms during the follicular phase (Appleton, 2018; Carlini & Deligiannidis, 2020; Reilly et al., 2023).

Overall, SSRIs represent the best-established pharmacological option for PMDD (Appleton, 2018; Carlini & Deligiannidis, 2020; Jespersen et al., 2024). Their rapid onset of action, efficacy across multiple affective symptoms, and flexible dosing schedules make them particularly useful in clinical practice (Lanza di Scalea & Pearlstein, 2019; Marais-Thomas et al., 2024; Reilly et al., 2023). Nevertheless, treatment should be individualized, taking into account symptom severity, patient preference, adverse-effect profile, reproductive plans, comorbid psychiatric conditions, and previous response to antidepressant therapy. Proper counseling is essential to improve adherence, minimize concerns about side effects, and ensure realistic expectations regarding treatment outcomes (Appleton, 2018; Carlini & Deligiannidis, 2020).

3.2 Hormonal Therapies

Hormonal therapies represent an important pharmacological approach in the management of PMDD, particularly in patients who do not respond adequately to selective serotonin reuptake inhibitors (SSRIs), require contraception, or present with prominent somatic symptoms (Appleton, 2018; Ma & Song, 2023). The rationale for hormonal treatment is based on the observation that PMDD symptoms are closely linked to cyclic fluctuations in ovarian steroids rather than to abnormal absolute hormone concentrations (Dubey et al., 2017; Schmidt et al., 2017). Therefore, therapies that suppress ovulation, stabilize sex steroid levels, or eliminate luteal-phase hormonal variability may reduce symptom severity in susceptible individuals. However, hormonal treatments differ substantially in efficacy, tolerability, safety profile, and clinical indications, and their use should be individualized according to symptom pattern, reproductive plans, contraindications, and patient preference (Appleton, 2018; Ma & Song, 2023; Schmidt et al., 2017).

Combined oral contraceptives (COCs) may improve PMDD symptoms by suppressing ovulation and reducing cyclical fluctuations in estradiol and progesterone (Ma & Song, 2023; Schmidt et al., 2017). Among COCs, the strongest evidence supports formulations containing drospirenone and ethinyl estradiol, particularly the 24/4-day regimen consisting of 24 active pills followed by 4 placebo pills Drospirenone is a progestin with anti-mineralocorticoid and anti-androgenic properties, which may contribute to improvement in both affective and somatic premenstrual symptoms, including bloating, breast tenderness, fluid retention, and mood-related complaints. Randomized controlled trials have shown that a 24-day active/4-day placebo regimen of drospirenone 3 mg combined with ethinyl estradiol 20 µg significantly reduces total premenstrual symptom scores, commonly assessed using the Daily Record of Severity of Problems (DRSP), compared with placebo. This regimen has therefore become the best-supported oral contraceptive option for women with PMDD (Ma & Song, 2023; Yonkers, Brown, et al., 2005).

In contrast, traditional 21/7 COC regimens, in which 21 days of active pills are followed by a 7-day hormone-free interval, have generally shown less consistent efficacy for PMDD, particularly for core mood symptoms (Appleton, 2018; Ma & Song, 2023). One study evaluating a 21/7 drospirenone/ethinyl estradiol regimen reported only modest improvements, mainly in appetite and food cravings, without a significant benefit for affective symptoms (Freeman, Kroll, et al., 2001). This difference may be related to the longer hormone-free interval in the 21/7 regimen, which may allow greater hormonal withdrawal and symptom recurrence in sensitive patients. For this reason, shorter hormone-free intervals or continuous regimens are often considered more biologically plausible in PMDD, as they provide more stable hormonal exposure (Halbreich et al., 2012; Ma & Song, 2023; Schmidt et al., 2017).

Continuous COC use, in which the hormone-free interval is omitted, has also been investigated as a potential strategy for PMDD management (Eisenlohr-Moul et al., 2017; Halbreich et al., 2012). Theoretically, continuous administration may provide greater suppression of ovarian activity and prevent the hormonal withdrawal that can trigger symptoms (Halbreich et al., 2012; Schmidt et al., 2017). Some studies have suggested that continuous COC use may reduce premenstrual symptoms; however, the available evidence remains mixed (Eisenlohr-Moul et al., 2017; Halbreich et al., 2012; Ma & Song, 2023). A placebo-controlled study of continuous levonorgestrel/ethinyl estradiol demonstrated improvement in PMDD symptoms, but did not directly compare this strategy with standard intermittent dosing (Halbreich et al., 2012). Another smaller trial comparing continuous and cyclic drospirenone/ethinyl estradiol regimens found no clear superiority of continuous treatment, partly due to a strong placebo response (Eisenlohr-Moul et al., 2017). COCs containing other progestins, such as levonorgestrel or desogestrel, have produced inconsistent results. Overall, meta-analytic data suggest that COCs may be more effective for physical symptoms than for depressive or affective symptoms, and no formulation has consistently demonstrated superiority over drospirenone-containing 24/4 regimens (Halbreich et al., 2012; Ma & Song, 2023).

Despite these limitations, COCs remain a clinically useful option, especially for patients who desire contraception and prefer a hormonal approach (Ma & Song, 2023; *Management of Premenstrual Disorders*, 2023). The 24/4 drospirenone/ethinyl estradiol formulation is generally regarded as the preferred COC option when pharmacological treatment of PMDD is considered (Ma & Song, 2023; *Management of Premenstrual Disorders*, 2023; Yonkers, Brown, et al., 2005). However, clinicians should carefully evaluate contraindications to estrogen-containing contraception, including a history of thromboembolism, migraine with aura, uncontrolled hypertension, smoking in women over 35 years of age, and other cardiovascular risk factors (A. T. Nguyen, 2024). Patients should also be counseled that the expected benefit may be moderate and that mood symptoms may not respond as strongly as somatic symptoms (Ma & Song, 2023). Close follow-

up is recommended, particularly during the first months of therapy, to assess efficacy, tolerability, and potential mood worsening (*Management of Premenstrual Disorders*, 2023).

For patients with severe, disabling, or treatment-refractory PMDD, gonadotropin-releasing hormone (GnRH) agonists represent a more potent hormonal intervention. GnRH agonists, such as leuprolide, suppress pituitary gonadotropin secretion after an initial stimulation phase, leading to profound ovarian suppression and a reversible hypoestrogenic state often described as a "medical menopause" (*Management of Premenstrual Disorders*, 2023; Naheed et al., 2025). By eliminating ovulation and luteal-phase ovarian steroid fluctuations, GnRH agonists can markedly reduce or even abolish PMDD symptoms in many patients (Naheed et al., 2025; Schmidt et al., 2017). Monthly depot injections of leuprolide, commonly at a dose of 3.75 mg, have demonstrated efficacy in randomized controlled trials compared with placebo (Freeman et al., 1997).

However, the clinical use of GnRH agonists is limited by their significant adverse-effect profile. Because they induce a hypoestrogenic state, patients may experience vasomotor symptoms such as hot flashes and night sweats, vaginal dryness, sleep disturbance, mood changes, decreased libido, and progressive bone mineral density loss with prolonged use. For this reason, GnRH agonists are not considered first-line therapy and are usually reserved for severe cases that are refractory to SSRIs and COCs or for patients in whom diagnostic confirmation of hormone sensitivity is clinically important. Their use requires careful monitoring, particularly when treatment is extended beyond a short period (*Management of Premenstrual Disorders*, 2023; Naheed et al., 2025).

To reduce hypoestrogenic adverse effects, add-back hormone therapy is commonly used together with GnRH agonists. Add-back therapy typically includes low-dose estrogen, with or without a progestogen, to protect bone health and improve tolerability while maintaining suppression of cyclical ovarian activity. Importantly, available evidence suggests that appropriately selected add-back therapy does not necessarily eliminate the therapeutic effect of GnRH agonist treatment in PMDD (*Management of Premenstrual Disorders*, 2023; Naheed et al., 2025; A. T. Nguyen, 2024). Nevertheless, add-back regimens require careful individualization, because some patients with PMDD are particularly sensitive to progesterone or progestins. In such cases, reintroduction of progesterone may trigger recurrence of mood symptoms. Therefore, low-dose, intermittent, or carefully monitored progestogen exposure may be preferable in progesterone-sensitive individuals (*Management of Premenstrual Disorders*, 2023; A. T. Nguyen, 2024; Schmidt et al., 2017).

More targeted strategies involving estrogen and progesterone modulation have also been considered (T. V. Nguyen et al., 2017; Schmidt et al., 2017). Estrogen stabilization, for example through transdermal estradiol or as part of add-back therapy after GnRH agonist treatment, may theoretically reduce symptom-provoking hormonal variability (*Management of Premenstrual Disorders*, 2023; Schmidt et al., 2017). However, low-dose estrogen therapy has not been sufficiently studied as an isolated treatment for PMDD, and its clinical use is generally limited to specific contexts, such as add-back regimens or management after surgical ovarian suppression (*Management of Premenstrual Disorders*, 2023; Naheed et al., 2025). In women with an intact uterus, estrogen therapy cannot be used without endometrial protection, which means that some form of progestogen is required to prevent endometrial hyperplasia. This creates a therapeutic challenge in PMDD, as progesterone or progestin exposure may provoke symptoms in susceptible patients (*Management of Premenstrual Disorders*, 2023; T. V. Nguyen et al., 2017; Schmidt et al., 2017).

Progesterone-based treatments alone have not shown consistent benefit in PMDD and are not considered reliable therapeutic options (*Management of Premenstrual Disorders*, 2023; Naheed et al., 2025). In fact, current pathophysiological models suggest that altered sensitivity to progesterone metabolites, particularly allopregnanolone, may contribute to the development of PMDD symptoms (Bäckström et al., 2021; Bixo et al., 2017; Hantsoo & Epperson, 2020). This may explain why progesterone supplementation or certain progestin-containing regimens can worsen mood symptoms in some patients rather than improve them (Bäckström et al., 2021; T. V. Nguyen et al., 2017; Schmidt et al., 2017). Therefore, current evidence supports strategies that stabilize or suppress ovarian hormonal fluctuations, such as selected COCs or GnRH agonists with individualized add-back therapy, rather than standalone progesterone treatment (Dubey et al., 2017; Naheed et al., 2025; Schmidt et al., 2017).

3.3 Anxiolytics and Other Pharmacological Agents

Short-acting anxiolytics, particularly benzodiazepines such as alprazolam, have historically been used during the luteal phase to relieve severe premenstrual anxiety, tension, and irritability. (Maharaj & Trevino, 2015; Management of Premenstrual Disorders, 2023). Earlier studies conducted mainly in the 1980s and 1990s suggested that alprazolam administered daily during the 10 days preceding menstruation could reduce premenstrual tension scores compared with placebo, especially in women without comorbid depressive disorders. (Berger & Presser, 1994) Nevertheless, the clinical relevance of these findings is limited by the age of the studies, small sample sizes, and differences between older diagnostic categories and current DSM-5 criteria for PMDD. Moreover, benzodiazepines are associated with important safety concerns, including sedation, psychomotor impairment, cognitive slowing, tolerance, dependence, and potential withdrawal symptoms. For these reasons, they are not considered first-line treatment for PMDD. Their use may be considered only in carefully selected patients with severe, short-lasting anxiety or agitation during the luteal phase, and preferably for brief periods when other evidence-based therapies have been ineffective or are contraindicated (Maharaj & Trevino, 2015; Management of Premenstrual Disorders, 2023).

Buspirone, a non-benzodiazepine anxiolytic and partial serotonin 5-HT1A receptor agonist, has also been investigated as a potential option for premenstrual anxiety symptoms (Maharaj & Trevino, 2015; Nazari et al., 2013). In one small single-blind study, buspirone at a dose of 10 mg daily appeared to be comparable to fluoxetine 20 mg daily in reducing PMS-related anxiety symptoms (Nazari et al., 2013). However, the absence of a placebo group, the limited sample size, and the focus on PMS rather than strictly diagnosed PMDD substantially limit the interpretation of these findings (Maharaj & Trevino, 2015; Nazari et al., 2013). At present, there is insufficient high-quality randomized controlled evidence to support buspirone as an established treatment for PMDD. Therefore, it remains an experimental or adjunctive option rather than a standard pharmacological approach (Maharaj & Trevino, 2015; *Management of Premenstrual Disorders*, 2023).

Serotonin–norepinephrine reuptake inhibitors (SNRIs), including venlafaxine and duloxetine, have been explored as alternatives for patients who do not tolerate SSRIs or who have an inadequate response to serotonergic therapy. Their theoretical rationale is based on enhancement of both serotonergic and noradrenergic neurotransmission, which may help regulate affective symptoms, anxiety, irritability, and energy-related complaints (Maharaj & Trevino, 2015). Small open-label studies suggest that venlafaxine administered continuously may reduce PMDD symptoms, and one study of luteal-phase venlafaxine in patients who did not respond adequately to SSRIs reported clinical benefit (Cohen et al., 2004; Hsiao & Liu, 2003). Similarly, preliminary studies of duloxetine have indicated possible improvement in PMDD symptoms (Mazza et al., 2008; Ramos et al., 2009). However, the current evidence base remains limited, and large placebo-controlled trials are lacking (Maharaj & Trevino, 2015; Mazza et al., 2008; Ramos et al., 2009). Consequently, SNRIs may be considered second-line or off-label options in selected patients, especially those with comorbid anxiety or depressive symptoms, but they cannot currently be regarded as equivalent to SSRIs in terms of evidence strength (Freeman, Rickels, et al., 2001; Maharaj & Trevino, 2015).

Other pharmacological agents have been evaluated only in small pilot studies or case series (Maharaj & Trevino, 2015). For example, adjunctive quetiapine extended-release, at doses ranging from 25 to 200 mg, has been studied in patients with SSRI-refractory PMDD and was associated with improvement in mood symptoms in a limited sample (Jackson et al., 2015). However, antipsychotic medications carry risks such as sedation, metabolic adverse effects, weight gain, extrapyramidal symptoms, and long-term safety concerns, which restrict their use to highly selected cases, usually when there are comorbid psychiatric indications (Jackson et al., 2015; Maharaj & Trevino, 2015). Acetazolamide, a carbonic anhydrase inhibitor with diuretic properties, has also been reported to induce symptom remission in a very small case series of treatment-resistant PMDD, but the evidence is too preliminary to support routine use (Sani et al., 2014). In contrast, clonidine, an alpha-2 adrenergic agonist, did not demonstrate efficacy in randomized controlled studies and is not recommended as a standard treatment option (Maharaj & Trevino, 2015).

4. Emerging Treatment Approaches

4.1 Neurosteroid-based therapies

Neurosteroid-based therapies represent one of the most promising emerging directions in the treatment of premenstrual dysphoric disorder (Bäckström et al., 2021; Bixo et al., 2017). Their development is closely linked to the current understanding of PMDD as a disorder of abnormal sensitivity to physiological fluctuations in ovarian steroids and their neuroactive metabolites, rather than a disorder caused by abnormal circulating hormone concentrations (Bäckström et al., 2021; Schmidt et al., 2017). Particular attention has been given to allopregnanolone, a progesterone-derived neurosteroid that acts as a potent positive allosteric modulator of GABA-A receptors. In most individuals, allopregnanolone has anxiolytic, sedative, and mood-stabilizing effects (Bäckström et al., 2021; Bixo et al., 2017). However, in women with PMDD, cyclic changes in allopregnanolone during the luteal phase may produce a paradoxical emotional response, contributing to irritability, anxiety, mood lability, and dysphoria. This hypothesis has created a rationale for therapies that directly target the allopregnanolone–GABA-A receptor pathway (Bäckström et al., 2021; Bixo et al., 2017; Schmidt et al., 2017).

Sepranolone, also known as isoallopregnanolone or UC1010, is one of the most important investigational compounds developed within this therapeutic framework. It is considered a functional antagonist of allopregnanolone at GABA-A receptors and is designed to reduce the abnormal behavioral response to luteal-phase neurosteroid fluctuations (Bäckström et al., 2021; Bixo et al., 2017). Unlike SSRIs, which indirectly modulate serotonergic and possibly neurosteroid pathways, sepranolone acts more directly on a mechanism believed to be central to PMDD pathophysiology (Bixo et al., 2017; Griffin & Mellon, 1999; Pinna et al., 2006). By attenuating the effects of allopregnanolone, sepranolone aims to prevent the paradoxical mood response that may occur in susceptible women during the late luteal phase (Bäckström et al., 2021; Bixo et al., 2017).

Clinical studies of sepranolone have provided important preliminary evidence for this mechanism-based approach. In a Phase II placebo-controlled trial, subcutaneous sepranolone administered during the luteal phase significantly reduced total scores on the Daily Record of Severity of Problems (DRSP) compared with placebo over one menstrual cycle. The drug was given as 10 mg or 16 mg injections every other day during the luteal phase, with dosing timed to the period when PMDD symptoms typically emerge. In addition to improvement in total symptom scores, secondary outcomes, including negative mood symptoms and functional impairment, also showed favorable trends. The treatment was generally well tolerated, with adverse effects reported as mild and mainly limited to injection-site reactions. Importantly, the frequency of adverse events did not appear to be higher than in the placebo group. These early findings suggested that sepranolone could provide a targeted, non-serotonergic treatment option for PMDD (Bäckström et al., 2021; Bixo et al., 2017).

However, subsequent clinical evaluation produced more mixed results. A larger, multiple-cycle randomized controlled study failed to demonstrate a statistically significant superiority of sepranolone over placebo on the primary endpoint of change in total DRSP score. One possible explanation for this outcome was a strong placebo response, which was reported to be substantially greater than that observed in the earlier Phase II trial. Nevertheless, some secondary analyses suggested potential clinical benefit, including reductions in patient-reported distress and, in post-hoc analyses, improvement in premenstrual DRSP scores with the 10 mg dose during the final treatment cycle. These findings indicate that sepranolone may still have therapeutic potential, but its efficacy, optimal dose, treatment schedule, and target patient population require further investigation in larger and methodologically rigorous trials (Bäckström et al., 2021; Bixo et al., 2017).

The development of sepranolone is particularly important because it represents a shift from symptom-based treatment toward mechanism-based pharmacotherapy (Bäckström et al., 2021; Bixo et al., 2017). Whereas SSRIs remain the best-established first-line treatment for PMDD, their mechanism is broad and not specific to the hormonal sensitivity that characterizes the disorder (Bäckström et al., 2021; Jespersen et al., 2024; Schmidt et al., 2017). In contrast, sepranolone directly addresses the neurosteroid hypothesis of PMDD by modulating the allopregnanolone–GABA-A receptor axis. This makes it a valuable candidate for patients who do not tolerate SSRIs, do not respond adequately to serotonergic therapy, or prefer a treatment specifically targeting luteal-phase neurosteroid mechanisms (Bäckström et al., 2021; Bixo et al., 2017).

Other forms of GABA-A receptor modulation have also attracted interest, particularly because neuroactive steroids such as brexanolone and zuranolone have demonstrated efficacy in postpartum depression. These agents act as positive allosteric modulators of GABA-A receptors and enhance GABAergic inhibitory signaling. However, their role in PMDD is uncertain and potentially problematic (Bäckström et al., 2021; Hantsoo & Epperson, 2020). Since PMDD may involve an abnormal or paradoxical sensitivity to

allopregnanolone and related GABAergic neurosteroids, further enhancing GABA-A receptor activity during the luteal phase could theoretically worsen symptoms in susceptible individuals rather than improve them (Bäckström et al., 2021; Schmidt et al., 2017). For this reason, current research in PMDD has focused less on positive GABA-A modulation and more on reducing or stabilizing abnormal neurosteroid signaling (Bäckström et al., 2021; Bixo et al., 2017).

4.2 Anti-inflammatory and Immunomodulatory Approaches

Growing evidence suggests that immune and inflammatory mechanisms may contribute to the pathophysiology of PMDD, although their role remains less clearly established than that of serotonergic dysfunction or neurosteroid sensitivity (Bertone-Johnson et al., 2014; Tiranini & Nappi, 2022). The luteal phase of the menstrual cycle is associated with physiological changes in immune activity, including alterations in inflammatory mediators, cytokine signaling, and stress-related immune responses. In women with PMDD, these cyclical immune changes may be exaggerated or dysregulated, potentially contributing to mood instability, fatigue, somatic discomfort, sleep disturbance, and heightened sensitivity to stress (Bertone-Johnson et al., 2014). This has led to increasing interest in anti-inflammatory and immunomodulatory strategies as potential adjunctive or future therapeutic approaches (Bertone-Johnson et al., 2014; Mohammadi et al., 2022).

The biological plausibility of this approach is supported by the close interaction between the immune system, the hypothalamic–pituitary–adrenal axis, ovarian steroid hormones, and central neurotransmitter systems (Bertone-Johnson et al., 2014; Tiranini & Nappi, 2022). Pro-inflammatory cytokines may influence serotonin metabolism, glutamatergic signaling, neuroplasticity, and GABAergic regulation, all of which are relevant to PMDD symptomatology. In addition, inflammation has been implicated in several mood disorders, including major depressive disorder, suggesting that immune activation may contribute to affective symptoms in biologically vulnerable individuals (Tiranini & Nappi, 2022). In PMDD, inflammatory activation may not represent the primary cause of the disorder but may act as a modifying factor that amplifies luteal-phase mood and physical symptoms (Bertone-Johnson et al., 2014; Tiranini & Nappi, 2022).

Several anti-inflammatory strategies have therefore been proposed, although most remain theoretical or insufficiently studied in PMDD-specific populations (Bertone-Johnson et al., 2014; Mohammadi et al., 2022). Omega-3 fatty acids are of particular interest because of their anti-inflammatory properties and their potential effects on neuronal membrane function, neurotransmission, and mood regulation (Mohammadi et al., 2022). Omega-3 supplementation has shown some benefit in depressive disorders and may reduce inflammatory signaling; however, dedicated randomized controlled trials evaluating omega-3 fatty acids specifically in prospectively diagnosed PMDD remain limited or lacking (Behboudi-Gandevani et al., 2018; Mohammadi et al., 2022). Therefore, while omega-3 supplementation may be considered a low-risk adjunct in selected patients, it cannot currently be recommended as an evidence-based primary treatment for PMDD (Mohammadi et al., 2022)).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in gynecological practice for dysmenorrhea, pelvic pain, and other menstrual-related somatic symptoms (*Management of Premenstrual Disorders*, 2023; Marjoribanks et al., 2010). In patients with PMDD, NSAIDs may help relieve physical symptoms such as headache, cramps, breast tenderness, or generalized discomfort, especially when these symptoms overlap with dysmenorrhea or inflammatory pain syndromes. However, NSAIDs have not been adequately tested for the core affective symptoms of PMDD, such as irritability, depressed mood, anxiety, or affective lability (Maharaj & Trevino, 2015; *Management of Premenstrual Disorders*, 2023). As a result, their role should be viewed as symptomatic management of associated physical complaints rather than treatment of the underlying mood disorder (Carlini & Deligiannidis, 2020; Maharaj & Trevino, 2015).

More targeted immunomodulatory interventions, including cyclooxygenase-2 inhibitors, cytokine modulators, or other anti-inflammatory agents, remain experimental in the context of PMDD (Bertone-Johnson et al., 2014; *Management of Premenstrual Disorders*, 2023). At present, no specific anti-inflammatory medication has been validated for PMDD in large randomized controlled trials, and there is insufficient evidence to support routine use of immunomodulatory therapy (Carlini & Deligiannidis, 2020; *Management of Premenstrual Disorders*, 2023). Moreover, the potential risks of long-term anti-inflammatory or immune-targeted treatment must be carefully considered, particularly when the inflammatory contribution to PMDD has not yet been clearly defined (Bertone-Johnson et al., 2014; *Management of Premenstrual Disorders*, 2023).

4.3 Digital and Psychotherapeutic Interventions

Although premenstrual dysphoric disorder is primarily conceptualized as a biologically mediated, cycle-related mood disorder, psychotherapeutic interventions represent an important component of comprehensive management (Kleinstäuber et al., 2012; *Management of Premenstrual Disorders*, 2023). Cognitive behavioral therapy (CBT) has received the greatest attention among non-pharmacological approaches and may be particularly useful as an adjunctive treatment in patients with persistent functional impairment, maladaptive coping strategies, comorbid anxiety or depressive symptoms, or a preference to avoid or minimize pharmacotherapy (Busse et al., 2009; Kleinstäuber et al., 2012). The rationale for CBT in PMDD is based on its ability to modify cognitive, emotional, and behavioral responses to recurrent premenstrual symptoms, improve self-monitoring, reduce symptom-related distress, and strengthen adaptive coping mechanisms (Busse et al., 2009; Hunter et al., 2002; Kleinstäuber et al., 2012).

CBT does not directly suppress ovarian hormonal fluctuations or alter the underlying neuroendocrine sensitivity that is thought to contribute to PMDD (Kleinstäuber et al., 2012; Schmidt et al., 2017). However, it may reduce the psychological and functional burden associated with cyclic symptom recurrence (Busse et al., 2009; Kleinstäuber et al., 2012; Schmidt et al., 2017). Patients with PMDD often experience anticipatory anxiety before the luteal phase, negative interpretations of mood changes, interpersonal conflict, and a sense of loss of control during symptomatic days (Hantsoo & Epperson, 2015; Hunter et al., 2002). CBT can address these factors through psychoeducation, cognitive restructuring, behavioral activation, stress-management techniques, emotion-regulation strategies, sleep and lifestyle planning, and relapse-prevention approaches. In this context, CBT may help patients recognize the cyclical pattern of symptoms, distinguish PMDD-related mood changes from stable self-perceptions or relationship problems, and implement structured coping strategies before symptom escalation (Busse et al., 2009; Hunter et al., 2002; Kleinstäuber et al., 2012).

Evidence from randomized controlled trials and meta-analyses suggests that CBT may reduce anxiety, depressive symptoms, and overall premenstrual symptom severity in women with PMS or PMDD (Busse et al., 2009; Kleinstäuber et al., 2012). Some studies have also evaluated mindfulness-based CBT, which combines traditional cognitive-behavioral techniques with mindfulness, acceptance, and nonjudgmental awareness of emotional and physical symptoms. This approach may be particularly relevant in PMDD because it may reduce reactivity to mood fluctuations and improve tolerance of distress during the luteal phase (Hunter et al., 2002; Kleinstäuber et al., 2012). Although available studies are often limited by small sample sizes, heterogeneity of diagnostic criteria, and inclusion of both PMS and PMDD populations, the overall findings support CBT as a clinically meaningful intervention (Busse et al., 2009; Kleinstäuber et al., 2012).

Comparative data suggest that CBT may have an effect size broadly comparable to antidepressant treatment in some analyses of premenstrual disorders. However, direct comparisons between CBT and pharmacotherapy remain limited (Hunter et al., 2002; Kleinstäuber et al., 2012). In one study comparing CBT, fluoxetine, and their combination, all treatment groups showed clinical improvement, but the combination of CBT and fluoxetine did not clearly outperform either intervention alone (Hunter et al., 2002). These findings suggest that CBT may be effective as an independent therapeutic option in selected patients, although its additive benefit when combined with SSRIs may depend on individual clinical characteristics, baseline symptom severity, psychiatric comorbidity, treatment adherence, and patient preference (Hunter et al., 2002; Kleinstäuber et al., 2012). Importantly, CBT may offer longer-term benefits by improving coping skills and self-management, even when pharmacological treatment is discontinued (Busse et al., 2009; Hunter et al., 2002).

Digital and internet-delivered CBT (ICBT) has emerged as a promising strategy to improve access to evidence-based psychological interventions for PMDD and severe premenstrual symptoms. This is particularly relevant because many patients experience barriers to traditional face-to-face psychotherapy, including limited availability of trained therapists, financial constraints, geographical distance, stigma, and scheduling difficulties. Internet-based CBT programs may provide structured psychoeducation, symptom tracking, cognitive restructuring exercises, behavioral assignments, relaxation techniques, and modules focused on interpersonal functioning and stress management. Guided ICBT, in which patients receive feedback or support from a therapist or trained professional, may be especially effective because it combines accessibility with clinical supervision (Hoppe et al., 2025; Weise et al., 2019).

Randomized studies of internet-based CBT for premenstrual symptoms have reported superior outcomes compared with control interventions, suggesting that digital psychological programs may reduce symptom severity and improve functioning (Dehnavi et al., 2024; Hoppe et al., 2025). These interventions may be particularly well suited to PMDD because the disorder is cyclical and can be monitored prospectively using

digital tools. Smartphone applications and electronic symptom diaries may support diagnosis by documenting symptom timing across menstrual cycles, while also helping patients identify triggers, anticipate high-risk days, and implement individualized coping strategies. Digital tools may therefore serve both diagnostic and therapeutic purposes (Cho & Na, 2019; Dehnavi et al., 2024; Endicott et al., 2006).

Despite these advantages, digital interventions should not be viewed as a universal replacement for clinical care. The quality of commercially available symptom-tracking applications varies considerably, and many have not been validated in clinical studies (Cho & Na, 2019; Hoppe et al., 2025). Moreover, patients with severe depression, suicidal ideation, complex psychiatric comorbidity, or marked functional impairment require careful clinical assessment and may need more intensive treatment (*Management of Premenstrual Disorders*, 2023; Prasad et al., 2021). Future research should evaluate which patients benefit most from ICBT, whether digital CBT is comparable to face-to-face CBT, and how these interventions can be integrated with pharmacological therapies such as SSRIs or hormonal treatment (Dehnavi et al., 2024; Hoppe et al., 2025).

5. Conclusions

Premenstrual dysphoric disorder is a clinically significant and potentially disabling neuropsychiatric condition characterized by recurrent affective, behavioral, cognitive, and somatic symptoms that occur in close temporal association with the luteal phase of the menstrual cycle. Current evidence indicates that PMDD is not caused by abnormal circulating concentrations of ovarian hormones, but rather by increased sensitivity to physiological fluctuations in estradiol, progesterone, and their neuroactive metabolites. This hormone–brain interaction involves several overlapping mechanisms, including serotonergic dysregulation, altered GABA-A receptor sensitivity, abnormal response to allopregnanolone, stress-system involvement, and possibly immune-inflammatory pathways. These mechanisms explain both the cyclical nature of the disorder and the rationale for current and emerging pharmacological strategies.

Selective serotonin reuptake inhibitors remain the best-established and most evidence-based first-line pharmacological treatment for PMDD. Their rapid onset of action, efficacy in reducing core affective symptoms, and flexibility of administration make them particularly suitable for this disorder. Both continuous dosing and luteal-phase dosing have demonstrated clinical benefit, allowing treatment to be individualized according to symptom severity, patient preference, tolerability, and the presence of comorbid mood or anxiety disorders. Hormonal therapies also play an important role, especially in patients requiring contraception or those with inadequate response to SSRIs. Among combined oral contraceptives, drospirenone-containing formulations with a shortened hormone-free interval have the strongest evidence, although their overall effect appears moderate and may be more pronounced for somatic than affective symptoms.

In severe and treatment-resistant cases, ovarian suppression with gonadotropin-releasing hormone agonists may provide substantial symptom relief by eliminating cyclic ovarian steroid fluctuations. However, this approach is limited by hypoestrogenic adverse effects, including vasomotor symptoms and bone mineral density loss, and therefore requires careful patient selection, monitoring, and individualized add-back hormone therapy. Other pharmacological options, including anxiolytics, SNRIs, and adjunctive psychotropic agents, may be considered in selected cases, but their evidence base remains weaker than that of SSRIs and established hormonal interventions.

Emerging therapeutic approaches increasingly aim to target the specific neurobiological mechanisms underlying PMDD. Neurosteroid-directed treatments, particularly agents modulating the allopregnanolone–GABA-A receptor pathway, represent a promising area of research. Sepranolone, an allopregnanolone antagonist, has provided important proof of concept for mechanism-based treatment, although further trials are required to clarify its efficacy, optimal dosing, and target population. Anti-inflammatory strategies, biomarker-guided treatment, and precision-medicine approaches remain investigational but may become clinically relevant if distinct biological subtypes of PMDD are identified. In parallel, cognitive behavioral therapy, internet-delivered CBT, symptom-tracking tools, and integrative psychosocial interventions may help reduce distress, improve coping, and support long-term self-management.

Overall, effective management of PMDD requires an individualized and multidisciplinary approach. Collaboration between gynecologists, psychiatrists, primary care physicians, psychologists, and other healthcare professionals is essential, particularly in patients with severe symptoms, psychiatric comorbidities, suicidal ideation, or complex reproductive needs. Treatment should address not only symptom reduction but also functional impairment, quality of life, treatment tolerability, reproductive goals, and patient preferences. Future research should focus on large, well-designed randomized controlled trials, long-term safety data, identification of predictive biomarkers, and development of targeted therapies that reflect the underlying neuroendocrine and neurobiological heterogeneity of PMDD. Such advances may enable more precise, effective, and tolerable treatment strategies for affected patients.

REFERENCES

1. Appleton, S. M. (2018). Premenstrual syndrome: Evidence-based evaluation and treatment. *Clinical Obstetrics and Gynecology, 61*(1), 52–61. https://doi.org/10.1097/GRF.0000000000000339
2. Bäckström, T., Ekberg, K., Hirschberg, A. L., Bixo, M., Epperson, C. N., Briggs, P., Panay, N., & O'Brien, S. (2021). A randomized, double-blind study on efficacy and safety of sepranolone in premenstrual dysphoric disorder. *Psychoneuroendocrinology, 133*, 105426. https://doi.org/10.1016/j.psyneuen.2021.105426
3. Behboudi-Gandevani, S., Hariri, F.-Z., & Moghaddam-Banaem, L. (2018). The effect of omega 3 fatty acid supplementation on premenstrual syndrome and health-related quality of life: A randomized clinical trial. *Journal of Psychosomatic Obstetrics and Gynaecology, 39*(4), 266–272. https://doi.org/10.1080/0167482X.2017.1348496
4. Berger, C. P., & Presser, B. (1994). Alprazolam in the treatment of two subsamples of patients with late luteal phase dysphoric disorder: A double-blind, placebo-controlled crossover study. *Obstetrics and Gynecology, 84*(3), 379–385.
5. Bertone-Johnson, E. R., Ronnenberg, A. G., Houghton, S. C., Nobles, C., Zagarins, S. E., Takashima-Uebelhoer, B. B., Faraj, J. L., & Whitcomb, B. W. (2014). Association of inflammation markers with menstrual symptom severity and premenstrual syndrome in young women. *Human Reproduction, 29*(9), 1987–1994. https://doi.org/10.1093/humrep/deu170
6. Bixo, M., Ekberg, K., Poromaa, I. S., Hirschberg, A. L., Jonasson, A. F., Andréen, L., Timby, E., Wulff, M., Ehrenborg, A., & Bäckström, T. (2017). Treatment of premenstrual dysphoric disorder with the GABA-A receptor modulating steroid antagonist sepranolone (UC1010)—A randomized controlled trial. *Psychoneuroendocrinology, 80*, 46–55. https://doi.org/10.1016/j.psyneuen.2017.02.031
7. Busse, J. W., Montori, V. M., Krasnik, C., Patelis-Siotis, I., & Guyatt, G. H. (2009). Psychological intervention for premenstrual syndrome: A meta-analysis of randomized controlled trials. *Psychotherapy and Psychosomatics, 78*(1), 6–15. https://doi.org/10.1159/000162296
8. Carlini, S. V., & Deligiannidis, K. M. (2020). Evidence-based treatment of premenstrual dysphoric disorder: A concise review. *The Journal of Clinical Psychiatry, 81*(2), 19ac13071. https://doi.org/10.4088/JCP.19ac13071
9. Cary, E., & Simpson, P. (2024). Premenstrual disorders and PMDD—A review. *Best Practice & Research Clinical Endocrinology & Metabolism, 38*(1), 101858. https://doi.org/10.1016/j.beem.2023.101858
10. Cho, S.-E., & Na, K.-S. (2019). Questioning the beneficial effects of internet-based cognitive behavioral therapy on premenstrual dysphoric disorder. *Psychotherapy and Psychosomatics, 88*(4), 236. https://doi.org/10.1159/000499681
11. Cohen, L. S., Soares, C. N., Lyster, A., Cassano, P., Brandes, M., & Leblanc, G. A. (2004). Efficacy and tolerability of premenstrual use of venlafaxine (flexible dose) in the treatment of premenstrual dysphoric disorder. *Journal of Clinical Psychopharmacology, 24*(5), 540–543. https://doi.org/10.1097/01.jcp.0000138767.53976.10
12. Dehnavi, S. I., Mortazavi, S. S., Ramezani, M. A., Gharraee, B., & Ashouri, A. (2024). Emotion-focused therapy for women with premenstrual dysphoric disorder: A randomized clinical controlled trial. *BMC Psychiatry, 24*(1), 501. https://doi.org/10.1186/s12888-024-05681-8
13. *Diagnostic and statistical manual of mental disorders | Psychiatry Online.* (n.d.). DSM Library. Retrieved June 3, 2026, from https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425787
14. Dimmock, P. W., Wyatt, K. M., Jones, P. W., & O'Brien, P. M. (2000). Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: A systematic review. *The Lancet, 356*(9236), 1131–1136. https://doi.org/10.1016/S0140-6736(00)02754-9
15. Dubey, N., Hoffman, J. F., Schuebel, K., Yuan, Q., Martinez, P. E., Nieman, L. K., Rubinow, D. R., Schmidt, P. J., & Goldman, D. (2017). The ESC/E(Z) complex, an effector of response to ovarian steroids, manifests an intrinsic difference in cells from women with premenstrual dysphoric disorder. *Molecular Psychiatry, 22*(8), 1172–1184. https://doi.org/10.1038/mp.2016.229
16. Eisenlohr-Moul, T. A., Girdler, S. S., Johnson, J. L., Schmidt, P. J., & Rubinow, D. R. (2017). Treatment of premenstrual dysphoria with continuous vs. intermittent dosing of oral contraceptives: Results of a three-arm randomized controlled trial. *Depression and Anxiety, 34*(10), 908–917. https://doi.org/10.1002/da.22673
17. Endicott, J., Nee, J., & Harrison, W. (2006). Daily Record of Severity of Problems (DRSP): Reliability and validity. *Archives of Women's Mental Health, 9*(1), 41–49. https://doi.org/10.1007/s00737-005-0103-y
18. Freeman, E. W., Kroll, R., Rapkin, A., Pearlstein, T., Brown, C., Parsey, K., Zhang, P., Patel, H., Foegh, M., & PMS/PMDD Research Group. (2001). Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *Journal of Women's Health & Gender-Based Medicine, 10*(6), 561–569. https://doi.org/10.1089/15246090152543148
19. Freeman, E. W., Rickels, K., Sondheimer, S. J., Polansky, M., & Xiao, S. (2004). Continuous or intermittent dosing with sertraline for patients with severe premenstrual syndrome or premenstrual dysphoric disorder. *The American Journal of Psychiatry, 161*(2), 343–351. https://doi.org/10.1176/appi.ajp.161.2.343

20. Freeman, E. W., Rickels, K., Yonkers, K. A., Kunz, N. R., McPherson, M., & Upton, G. V. (2001). Venlafaxine in the treatment of premenstrual dysphoric disorder. *Obstetrics and Gynecology, 98*(5 Pt 1), 737–744. https://doi.org/10.1016/S0029-7844(01)01530-7
21. Freeman, E. W., Sondheimer, S. J., & Rickels, K. (1997). Gonadotropin-releasing hormone agonist in the treatment of premenstrual symptoms with and without ongoing dysphoria: A controlled study. *Psychopharmacology Bulletin, 33*(2), 303–309.
22. Griffin, L. D., & Mellon, S. H. (1999). Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes. *Proceedings of the National Academy of Sciences of the United States of America, 96*(23), 13512–13517. https://doi.org/10.1073/pnas.96.23.13512
23. Halbreich, U., Borenstein, J., Pearlstein, T., & Kahn, L. S. (2003). The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). *Psychoneuroendocrinology, 28*(Suppl. 3), 1–23. https://doi.org/10.1016/S0306-4530(03)00098-2
24. Halbreich, U., Freeman, E. W., Rapkin, A. J., Cohen, L. S., Grubb, G. S., Bergeron, R., Smith, L., Mirkin, S., & Constantine, G. D. (2012). Continuous oral levonorgestrel/ethinyl estradiol for treating premenstrual dysphoric disorder. *Contraception, 85*(1), 19–27. https://doi.org/10.1016/j.contraception.2011.05.008
25. Hantsoo, L., & Epperson, C. N. (2015). Premenstrual dysphoric disorder: Epidemiology and treatment. *Current Psychiatry Reports, 17*(11), 87. https://doi.org/10.1007/s11920-015-0628-3
26. Hantsoo, L., & Epperson, C. N. (2020). Allopregnanolone in premenstrual dysphoric disorder (PMDD): Evidence for dysregulated sensitivity to GABA-A receptor modulating neuroactive steroids across the menstrual cycle. *Neurobiology of Stress, 12*, 100213. https://doi.org/10.1016/j.ynstr.2020.100213
27. Hoppe, J. M., Weise, C., Kleinstaeuber, M., Skalkidou, A., Vegelius, J., Comasco, E., Gröndal, M., Kaltsouni, E., Sundström, F., Sampaio, F., Andersson, G., & Buhrman, M. (2025). Emotion regulation-based internet-delivered cognitive behavioural therapy for premenstrual dysphoric disorder: Study protocol for a randomised controlled trial in Sweden. *BMJ Open, 15*(1), e091649. https://doi.org/10.1136/bmjopen-2024-091649
28. Hsiao, M.-C., & Liu, C.-Y. (2003). Effective open-label treatment of premenstrual dysphoric disorder with venlafaxine. *Psychiatry and Clinical Neurosciences, 57*(3), 317–321. https://doi.org/10.1046/j.1440-1819.2003.01123.x
29. Hunter, M. S., Ussher, J. M., Browne, S. J., Cariss, M., Jelley, R., & Katz, M. (2002). A randomized comparison of psychological (cognitive behavior therapy), medical (fluoxetine) and combined treatment for women with premenstrual dysphoric disorder. *Journal of Psychosomatic Obstetrics and Gynaecology, 23*(3), 193–199. https://doi.org/10.3109/01674820209074672
30. Jackson, C., Pearson, B., Girdler, S., Johnson, J., Hamer, R. M., Killenberg, S., & Meltzer-Brody, S. (2015). Double-blind, placebo-controlled pilot study of adjunctive quetiapine SR in the treatment of PMS/PMDD. *Human Psychopharmacology, 30*(6), 425–434. https://doi.org/10.1002/hup.2494
31. Jespersen, C., Lauritsen, M. P., Frokjaer, V. G., & Schroll, J. B. (2024). Selective serotonin reuptake inhibitors for premenstrual syndrome and premenstrual dysphoric disorder. *Cochrane Database of Systematic Reviews, 2024*(8), CD001396. https://doi.org/10.1002/14651858.CD001396.pub4
32. Kleinstäuber, M., Witthöft, M., & Hiller, W. (2012). Cognitive-behavioral and pharmacological interventions for premenstrual syndrome or premenstrual dysphoric disorder: A meta-analysis. *Journal of Clinical Psychology in Medical Settings, 19*(3), 308–319. https://doi.org/10.1007/s10880-012-9299-y
33. Lanza di Scalea, T., & Pearlstein, T. (2019). Premenstrual dysphoric disorder. *The Medical Clinics of North America, 103*(4), 613–628. https://doi.org/10.1016/j.mcna.2019.02.007
34. Loukzadeh, Z., Eslamy, N., Dehghan, M., & Houshang Mehrparvar, A. (2024). The impact of premenstrual disorders on work disruptions among working women: A cross-sectional study. *International Journal of Reproductive Biomedicine, 22*(2), 149–156. https://doi.org/10.18502/ijrm.v22i2.15712
35. Ma, S., & Song, S. J. (2023). Oral contraceptives containing drospirenone for premenstrual syndrome. *Cochrane Database of Systematic Reviews, 2023*(6), CD006586. https://doi.org/10.1002/14651858.CD006586.pub5
36. Maharaj, S., & Trevino, K. (2015). A comprehensive review of treatment options for premenstrual syndrome and premenstrual dysphoric disorder. *Journal of Psychiatric Practice, 21*(5), 334–350. https://doi.org/10.1097/PRA.0000000000000099
37. *Management of premenstrual disorders.* (2023). https://www.acog.org/clinical/clinical-guidance/clinical-practice-guideline/articles/2023/12/management-of-premenstrual-disorders
38. Marais-Thomas, H., Chapelle, F., de Vaux-Boitouzet, V., & Bouvet, C. (2024). [Premenstrual dysphoric disorder (PMDD): Drug and psychotherapeutique management, a literature review]. *L'Encephale, 50*(2), 211–232. https://doi.org/10.1016/j.encep.2023.08.007
39. Marjoribanks, J., Proctor, M., Farquhar, C., & Derks, R. S. (2010). Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database of Systematic Reviews, 2010*(1), CD001751. https://doi.org/10.1002/14651858.CD001751.pub2
40. Mazza, M., Harnic, D., Catalano, V., Janiri, L., & Bria, P. (2008). Duloxetine for premenstrual dysphoric disorder: A pilot study. *Expert Opinion on Pharmacotherapy, 9*(4), 517–521. https://doi.org/10.1517/14656566.9.4.517

41. Mohammadi, M. M., Dehghan Nayeri, N., Mashhadi, M., & Varaei, S. (2022). Effect of omega-3 fatty acids on premenstrual syndrome: A systematic review and meta-analysis. *The Journal of Obstetrics and Gynaecology Research, 48*(6), 1293–1305. https://doi.org/10.1111/jog.15217
42. Naheed, B., Kuiper, J. H., O'Mahony, F., & O'Brien, P. M. (2025). Gonadotropin-releasing hormone (GnRH) analogues for premenstrual syndrome (PMS). *Cochrane Database of Systematic Reviews, 2025*(6), CD011330. https://doi.org/10.1002/14651858.CD011330.pub2
43. Nazari, H., Yari, F., Jariani, M., Marzban, A., & Birgandy, M. (2013). Premenstrual syndrome: A single-blind study of treatment with buspirone versus fluoxetine. *Archives of Gynecology and Obstetrics, 287*(3), 469–472. https://doi.org/10.1007/s00404-012-2594-x
44. Nguyen, A. T. (2024). U.S. medical eligibility criteria for contraceptive use, 2024. *MMWR Recommendations and Reports, 73*. https://doi.org/10.15585/mmwr.rr7304a1
45. Nguyen, T. V., Reuter, J. M., Gaikwad, N. W., Rotroff, D. M., Kucera, H. R., Motsinger-Reif, A., Smith, C. P., Nieman, L. K., Rubinow, D. R., Kaddurah-Daouk, R., & Schmidt, P. J. (2017). The steroid metabolome in women with premenstrual dysphoric disorder during GnRH agonist-induced ovarian suppression: Effects of estradiol and progesterone addback. *Translational Psychiatry, 7*(8), e1193. https://doi.org/10.1038/tp.2017.146
46. Pearlstein, T., & Steiner, M. (2008). Premenstrual dysphoric disorder: Burden of illness and treatment update. *Journal of Psychiatry & Neuroscience, 33*(4), 291–301.
47. Pinna, G., Costa, E., & Guidotti, A. (2006). Fluoxetine and norfluoxetine stereospecifically and selectively increase brain neurosteroid content at doses that are inactive on 5-HT reuptake. *Psychopharmacology, 186*(3), 362–372. https://doi.org/10.1007/s00213-005-0213-2
48. Prasad, D., Wollenhaupt-Aguiar, B., Kidd, K. N., de Azevedo Cardoso, T., & Frey, B. N. (2021). Suicidal risk in women with premenstrual syndrome and premenstrual dysphoric disorder: A systematic review and meta-analysis. *Journal of Women's Health, 30*(12), 1693–1707. https://doi.org/10.1089/jwh.2021.0185
49. Ramos, M. G., Hara, C., & Rocha, F. L. (2009). Duloxetine treatment for women with premenstrual dysphoric disorder: A single-blind trial. *The International Journal of Neuropsychopharmacology, 12*(8), 1081–1088. https://doi.org/10.1017/S1461145709000066
50. Reilly, T. J., Patel, S., Unachukwu, I. C., Knox, C.-L., Wilson, C. A., Craig, M. C., Schmalenberger, K. M., Eisenlohr-Moul, T. A., & Cullen, A. E. (2024). The prevalence of premenstrual dysphoric disorder: Systematic review and meta-analysis. *Journal of Affective Disorders, 349*, 534–540. https://doi.org/10.1016/j.jad.2024.01.066
51. Reilly, T. J., Wallman, P., Clark, I., Knox, C.-L., Craig, M. C., & Taylor, D. (2023). Intermittent selective serotonin reuptake inhibitors for premenstrual syndromes: A systematic review and meta-analysis of randomised trials. *Journal of Psychopharmacology, 37*(3), 261–267. https://doi.org/10.1177/02698811221099645
52. Sani, G., Kotzalidis, G. D., Panaccione, I., Simonetti, A., De Chiara, L., Del Casale, A., Ambrosi, E., Napoletano, F., Janiri, D., Danese, E., Girardi, N., Rapinesi, C., Serata, D., Manfredi, G., Koukopoulos, A. E., Angeletti, G., Nicoletti, F., & Girardi, P. (2014). Low-dose acetazolamide in the treatment of premenstrual dysphoric disorder: A case series. *Psychiatry Investigation, 11*(1), 95–101. https://doi.org/10.4306/pi.2014.11.1.95
53. Schmidt, P. J., Martinez, P. E., Nieman, L. K., Koziol, D. E., Thompson, K. D., Schenkel, L., Wakim, P. G., & Rubinow, D. R. (2017). Premenstrual dysphoric disorder symptoms following ovarian suppression: Triggered by change in ovarian steroid levels but not continuous stable levels. *The American Journal of Psychiatry, 174*(10), 980–989. https://doi.org/10.1176/appi.ajp.2017.16101113
54. Tiranini, L., & Nappi, R. E. (2022). Recent advances in understanding/management of premenstrual dysphoric disorder/premenstrual syndrome. *Faculty Reviews, 11*, 11. https://doi.org/10.12703/r/11-11
55. Weise, C., Kaiser, G., Janda, C., Kues, J. N., Andersson, G., Strahler, J., & Kleinstäuber, M. (2019). Internet-based cognitive-behavioural intervention for women with premenstrual dysphoric disorder: A randomized controlled trial. *Psychotherapy and Psychosomatics, 88*(1), 16–29. https://doi.org/10.1159/000496237
56. Wittchen, H.-U., Becker, E., Lieb, R., & Krause, P. (2002). Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. *Psychological Medicine, 32*(1), 119–132. https://doi.org/10.1017/S0033291701004925
57. Yonkers, K. A., Brown, C., Pearlstein, T. B., Foegh, M., Sampson-Landers, C., & Rapkin, A. (2005). Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. *Obstetrics and Gynecology, 106*(3), 492–501. https://doi.org/10.1097/01.AOG.0000175834.77215.2e
58. Yonkers, K. A., Kornstein, S. G., Gueorguieva, R., Merry, B., Van Steenburgh, K., & Altemus, M. (2015). Symptom-onset dosing of sertraline for the treatment of premenstrual dysphoric disorder: A randomized clinical trial. *JAMA Psychiatry, 72*(10), 1037–1044. https://doi.org/10.1001/jamapsychiatry.2015.1472
59. Yonkers, K. A., O'Brien, P. M. S., & Eriksson, E. (2008). Premenstrual syndrome. *The Lancet, 371*(9619), 1200–1210. https://doi.org/10.1016/S0140-6736(08)60527-9
60. Yonkers, K. A., Pearlstein, T., Fayyad, R., & Gillespie, J. A. (2005). Luteal phase treatment of premenstrual dysphoric disorder improves symptoms that continue into the postmenstrual phase. *Journal of Affective Disorders, 85*(3), 317–321. https://doi.org/10.1016/j.jad.2004.10.006
61. *ZOLOFT (sertraline hydrochloride) label.* (n.d.). Retrieved June 4, 2026, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019839s74s86s87_20990s35s44s45lbl.pdf