Management of Premenstrual Dysphoric Disorder: A Scoping Review

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Abstract: Premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS) refer to physical, cognitive, or affective symptoms that arise in the late luteal phase and remit with menses. The present work is a clinically focused scoping review of the last twenty years of research on treatment for these disorders. A search of key terms using the PubMed/Medline, the Cochrane Library, Embase, and Web of Science databases was performed, and 194 studies of adult women met initial inclusion criteria for review. Research studies concerning medications, pharmacological and non-pharmacological complementary and alternative medicine treatments, and surgical interventions with the most available evidence were appraised and summarized. The most high-quality evidence can be found for the use of selective serotonin reuptake inhibitors (SSRIs) and combined oral contraceptives (COCs), with gonadotropin releasing hormone (GnRH) agonists and surgical interventions showing efficacy for refractory cases. While there is some evidence of the efficacy of alternative and complementary medicine treatments such as nutraceuticals, acupuncture, and yoga, variability in quality and methods of studies must be taken into account.

Keywords: premenstrual syndrome, syndrome, dysphoria, dysphoric disorder, disorder, disorders, treatment, scoping, review

Introduction

A subset of women experience physical, cognitive, or affective symptoms in the luteal phase of the menstrual cycle that range from mild to severe and disabling. Initially described as “premenstrual tension” in the 1930s, further observation of common symptoms led to changes in the accepted clinical definition and the use of the new term “premenstrual syndrome” in the 1950s. Premenstrual syndrome (PMS) was initially argued to be culturally bound, however, epidemiological data have demonstrated that the experience of clinically significant premenstrual symptoms is a phenomenon affecting girls and women globally and in various cultural settings. In the past several decades, efforts to establish more rigorous and clearly defined standards of severe premenstrual symptoms have given rise to the additional term premenstrual dysphoric disorder (PMDD), first established by the Diagnostic and Statistical Manual of Mental Disorders 4th edition.

Diagnosis

There has been considerable debate as well as heterogeneity in guidelines across disciplines regarding the appropriate diagnostic criteria for syndromes of clinically significant premenstrual symptoms. The International Society for the Study of Premenstrual Disorders (ISPMD) is an international consensus group that undertook the task of consolidating expert opinion into operational diagnostic, research, and management guidelines. The ISPMD describes a spectrum of premenstrual disorders (PMDs) including core and variant PMDs. Variant PMDs include premenstrual exacerbations of underlying psychiatric disorders, symptoms occurring in response to exogenous progesterone administration, symptoms arising from ovarian activity other than ovulation, and symptoms arising from ovarian activity although...
menstruation has been suppressed. Core PMDs, the topic of the present paper, are defined as the psychological or somatic symptoms that: 1) arise in the 14 day luteal phase; 2) affect normal daily functioning, affect school, work, or interpersonal relationships, or cause significant distress; and 3) and resolve with the onset of menstruation (Table 1). Both PMS and PMDD are considered core PMDs.

In contrast to the common clinical definition of PMS, which focuses on impairment and does not specify number or type of required symptoms, PMDD is strictly defined by the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM5) as requiring a minimum of 5 symptoms that must be present across affective and physical-behavioral symptom categories (Table 1). The affective symptom category includes affective lability, irritability, depressed mood, and anxiety, while the physical-behavioral symptom category includes anhedonia, difficulty concentrating, anergia, change in appetite or cravings, hypersomnia or insomnia, sense of being overwhelmed or out of control, and physical symptoms such as breast tenderness or swelling, weight gain, bloating, and joint and muscle pain. In order to meet criteria for a diagnosis of PMDD, these symptoms must be present in the luteal phase of most menstrual cycles in the prior year and must result in clinically significant distress or interference in daily life.

### Table 1 Diagnosis of Premenstrual Dysphoric Disorder

<table>
<thead>
<tr>
<th>Criterion A</th>
<th>In the majority of menstrual cycles, at least five symptoms must be present in the final week before onset of menses, start to improve within few days after onset of menses, and become minimal or absent in week postmenses.</th>
</tr>
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<tbody>
<tr>
<td>Criterion B</td>
<td>One (or more) of the following symptoms must be present: 1. Marked affective lability (eg, mood swings; feeling suddenly sad or tearful or increased sensitivity to rejection). 2. Marked irritability or anger or increased interpersonal conflicts. 3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts. 4. Marked anxiety, tension, and/or feelings of being “keyed up”, or “on edge”.</td>
</tr>
<tr>
<td>Criterion C</td>
<td>One (or more) of the following symptoms must additionally be present, to reach a total of five symptoms when combined with symptoms from Criterion B above: 1. Decreased interest in usual activities (eg, work, school, friends, hobbies). 2. Subjective difficulty in concentration. 3. Lethargy, easy fatigability, or marked lack of energy. 4. Marked change in appetite, overeating, or specific food cravings. 5. Hypersomnia or insomnia. 6. A sense of being overwhelmed or out of control. 7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, sensation of “bloating”, weight gain.</td>
</tr>
<tr>
<td>Note: The symptoms in Criteria A–C must have been met for most menstrual cycles that occurred in the preceding year.</td>
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<tr>
<td>Criterion D</td>
<td>The symptoms are associated with clinically significant distress or interferences with work, school, usual social activities, or relationships with others (eg, avoidance of social activities, decreased productivity and efficiency at work, school or home).</td>
</tr>
<tr>
<td>Criterion E</td>
<td>The disturbance is not merely an exacerbation of the symptoms of another disorder such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).</td>
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<tr>
<td>Criterion F</td>
<td>Criterion A should be confirmed by prospective daily ratings during at least 2 symptomatic cycles. (Note: The diagnosis may be made provisionally prior to this confirmation.)</td>
</tr>
<tr>
<td>Criterion G</td>
<td>The symptoms are not attributable to the direct physiological effects of a substance (eg, a drug of abuse, a medication other treatment) or another medical condition (eg, hyperthyroidism).</td>
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</tbody>
</table>

International Society for Premenstrual Disorders: Core Premenstrual Disorder

<table>
<thead>
<tr>
<th>Criterion 1</th>
<th>Symptoms occur in ovulatory cycles.</th>
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</thead>
<tbody>
<tr>
<td>Criterion 2</td>
<td>Symptoms are not specified – they may be somatic and/or psychological.</td>
</tr>
<tr>
<td>Criterion 3</td>
<td>The number of symptoms is not specified.</td>
</tr>
<tr>
<td>Criterion 4</td>
<td>Symptoms are absent after menstruation and before ovulation.</td>
</tr>
<tr>
<td>Criterion 5</td>
<td>They must recur in luteal phase.</td>
</tr>
<tr>
<td>Criterion 6</td>
<td>They must be prospectively rated (two cycles minimum).</td>
</tr>
<tr>
<td>Criterion 7</td>
<td>Symptoms must cause significant impairment.</td>
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</table>
Per the ISPMD as well as the DSM5, the diagnosis of PMDD is properly established by two months of prospective daily symptom monitoring prior to the initiation of any treatment using a validated tool such as the Daily Record of Severity of Problems (DRSP). While screening tools, structured clinical interviews, and self-report scales are available and in use clinically, such retrospective assessments are determined to have limited value due to their subjectivity as well as concerns for recall bias. Biochemical testing, including hormonal testing, and tracking of physical parameters, such as breast size and total body water, has not been shown to be diagnostically useful. As such, prospective symptom monitoring remains the gold standard of diagnosis.

**Epidemiology and Morbidity**

The DSM5 reports a 1.8% to 5.8% 12-month prevalence of PMDD among menstruating women in the United States. PMS with clinically significant distress has been shown to have significantly higher prevalence rates, estimated at 13% to 18%. Globally, prevalence rates of PMDD demonstrate some regional differences. Estimates of PMDD across Europe vary, with a 1.1% prevalence reported among a cohort of Spanish women, a 2.1% prevalence reported among a cohort of Polish women, and a 3.1% prevalence reported among a cohort of Swiss women. In India, prevalence has been reported as 8% for PMDD and 43% for PMS per a recent meta-analysis. The rate of PMDD in East Asia including Japan, Korea, China, Taiwan, Hong Kong, and Macau per a recent literature review was 1.3% to 2.8%. Rates are estimated to be somewhat higher in Latin America, with one cohort of Brazilian women demonstrating a prevalence of 17.6% for PMDD.

Morbidity of severe PMS is significant, with functional impairment similar to other depressive disorders. An international study of the impact of severe PMS found an increase in reported work absenteeism and work impairment compared to those reporting only mild symptoms. Recent meta-analyses have also shown that PMDD is associated with suicidal ideation, plans to suicide, and suicide attempts globally.

**Pathophysiology**

The menstrual cycle consists of a series of reoccurring biological events that produces a uterine environment in which conception may occur. The cycle is an average of 28 days and begins with the first day of menstruation, or the shedding of the endometrial lining in the absence of fertilization. The follicular phase, which is generally the first 14 days of the menstrual cycle, is dominated by rising 17-β estradiol, an ovarian steroid hormone and an estrogen, produced by the action of follicle stimulating hormone (FSH) and luteinizing hormone (LH) on the hormone-producing cells of ovarian follicles. FSH and LH are released by the anterior pituitary in response to pulses of gonadotropin-releasing hormone (GnRH) from the hypothalamus. 17-β estradiol produces changes in the endometrial and cervical environment in preparation for potential fertilization and acts on the anterior pituitary to decrease the secretion of FSH in a negative feedback cycle. The decrease in FSH halts the development of ovarian follicles except for the dominant, FSH-receptor rich follicle, which will continue to produce 17-β estradiol. This production from the now mature ovarian follicle results in positive feedback at the anterior pituitary that ultimately leads to the surge in FSH and LH responsible for ovulation, or the release of the oocyte from the mature follicle.

Following ovulation, the cycle enters the luteal phase, the remaining 14 days of the menstrual cycle. The remaining ovarian follicle becomes the corpus luteum, which continues to secrete diminishing levels of 17-β estradiol but also responds to the low levels of LH by facilitating production of progesterone, the ovarian steroid hormone that dominates the luteal phase. Progesterone produces further changes in the uterine environment to facilitate implantation of a fertilized ovum. If no implantation occurs in the optimal window, the corpus luteum undergoes degeneration to become the corpus albicans, incapable of producing further ovarian hormones, leading to the fall of both progesterone and estrogen. Without hormonal support, the uterine environment degenerates and is shed in a menstrual period, beginning the cycle again.

The pathophysiology of PMS and PMDD is the subject of active research. Neuroactive metabolites of progesterone, which rise sharply in the late luteal phase, have been heavily implicated. Most evidence implicates the specific metabolite allopregnanolone: its interaction with GABA-A receptors in the brain has been hypothesized to provoke the affective symptoms of PMS and PMDD in a subset of women. In studies of women with PMDD, altered sensitivity to allopregnanolone has been found compared to controls. Despite these findings, the specific mechanism by which
allopregnanolone contributes to negative mood symptoms in susceptible women remains elusive, partly due to the variability of responses observed.26

**Rationale and Objectives**
While distressing and even disabling premenstrual symptoms have been described across time and cultures, clinical consensus on diagnostic guidelines is just beginning to coalesce, allowing for increased rigor in studies of potential treatments. The aims of the present scoping review are to explore the recent literature assessing treatment of adult women with PMS or PMDD in order to provide a clinically relevant synthesis of the most studied interventions to assist healthcare providers who are caring for such patients.

**Methods**
A scoping review was performed using PubMed/Medline, the Cochrane Library, Embase, and Web of Science databases on 3/16/2022. The search terms included “Premenstrual Dysphoric Disorder” OR premenstrual syndrome OR premenstrual dysphoric disorder OR premenstrual syndrome AND “drug therapy” or medication* or drug* or pharmacol* or “non-pharmacological”. Results were limited to papers published between 2000 and 2022, published in peer-reviewed journals, written in the English language, assessing adult women (no younger than age 18), and assessing a treatment modality of premenstrual symptoms. Research studies, meta-analyses, and review articles were included. Case reports and conference proceedings were excluded. Grey literature was excluded as it is not peer-reviewed.

The search was performed by a research librarian, and review of the resulting data was conducted by the lead author. Of 2505 articles identified per the search, 1331 were immediately removed as duplicates, 941 were excluded upon screen of the title and abstract due to failure to meet inclusion criteria listed above, and an additional 39 were excluded upon full text review for failure to meet inclusion criteria (Figure 1). A total of 194 articles were thus selected by the lead author for further review by individual authors. Individual authors reviewed the articles relevant to their area of expertise. Articles were additionally excluded by authors due to: 1) low quality of evidence compared to other available studies (for example, open-label design, lack of placebo control, etc.) for a given treatment modality; 2) outcome measures that did not address premenstrual symptom reduction; or 3) very scarce evidence available for the treatment modality. Two articles were identified for device-based treatment modalities (bright light therapy27 and vestibular stimulation28); these were excluded from review given a lack of available studies for comparison. Twenty-nine articles identified were

![Figure 1 PRISMA flow diagram.](https://doi.org/10.2147/IJWH.S297062)
systematic or narrative reviews; such articles are included only as per their relevance. Some articles otherwise included in meta-analyses or systematic reviews were not individually reviewed for the purposes of the present work. An additional 81 articles were thus excluded from the pool, leaving 113 articles selected for this scoping review (Appendix 1). Seminal articles published before 2000 were identified by reviewing references from selected studies and included where appropriate.

Treatment Review

Medication

SSRIs

Evidence from multiple randomized controlled trials (RCTs) has established that selective serotonin reuptake inhibitors (SSRIs), dosed continuously or only in the luteal phase of the menstrual cycle, are the gold standard of treatment for PMDD as per expert guidelines. The mechanism by which SSRIs treat PMDD is hypothesized to be distinct from the mechanism by which they are thought to treat other depressive and anxiety disorders, as the effect on symptoms is rapid and achieved at relatively low doses. One hypothesis is that SSRIs may modulate the synthesis of allopregnanolone, and one open-label trial of sertraline for PMDD demonstrated changes in total peripheral allopregnanolone levels, although these changes varied based on the subjects’ baseline levels.

Sertraline, escitalopram, paroxetine, and fluoxetine, dosed continuously or only in the luteal phase of the menstrual cycle have all been shown to be efficacious in the treatment of PMDD (Table 2). Luteal phase dosing of fluoxetine has also been shown to be efficacious as a dose of 90 mg given 14 days prior to menses and then again 7 days prior to menses. Sertraline dosed continuously, in the luteal phase, or at symptom-onset and fluoxetine dosed continuously have additionally been shown to be efficacious in the treatment of severe PMS.

Luteal phase dosing of SSRIs has been shown to improve symptoms that persist into the follicular phase even when medication is discontinued with the onset of menses. Studies comparing both continuous and luteal phase dosing strategies have shown mixed results, with most studies concluding that continuous and luteal phase dosing are comparable, but with one meta-analysis demonstrating increased efficacy of the continuous dosing strategy compared to luteal phase dosing only. Symptom-onset dosing, in which medication is started only with the onset of premenstrual symptoms, has shown promise with this strategy demonstrated to be more effective than placebo in trials of sertraline for severe PMS and escitalopram for PMDD (Table 2). One large recent trial of symptom-onset dosing of sertraline for PMDD demonstrated a lack of a significant difference for the primary study outcome of Premenstrual Tension Scale total score compared to placebo, however the symptom-onset group did show significant improvements in secondary outcome measures including total DRSP score. Notably, the same study demonstrated no significant discontinuation symptoms in intermittent dosing strategies for sertraline.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Range</th>
<th>Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>50 mg to 100 mg daily</td>
<td>Luteal phase</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10 mg to 20 mg daily</td>
<td>Luteal phase</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10 mg to 20 mg daily</td>
<td>Luteal phase</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10 mg to 20 mg daily</td>
<td>Luteal phase</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75 mg to 112.5 mg daily</td>
<td>Luteal phase</td>
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Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)
The evidence base for the use of serotonin–norepinephrine reuptake inhibitors (SNRIs) for PMDD is small but promising. Venlafaxine has shown efficacy for the treatment of PMDD in one open-label trial using a continuous dosing strategy and one trial of placebo non-responders using a luteal phase dosing strategy (Table 2). Duloxetine has shown efficacy for the treatment of PMDD in one small single-blind trial and one open-label study, both using a continuous dosing strategy. Placebo-controlled trials are warranted for further investigation of these agents for the treatment of PMDD, but it is reasonable to use them as a second-line agent if tolerability limits use of SSRIs.

Combined Oral Contraceptives (COCs)
There are ample data that combined oral contraceptives (COCs) are effective treatment for somatic symptoms of the menstrual cycle, including but not limited to dysmenorrhea, gastrointestinal changes, and menorrhagia. However, data concerning the effect of COCs on affective premenstrual symptoms have been inconsistent. The data are further complicated by the availability of different combinations of hormones as well as different doses, usage, and timing.

Drospirenone, a progesterone derivative, combined with ethinyl estradiol (EE) is the only current United States Food and Drug Administration (FDA) approved COC for the treatment of PMDD. An early RCT of EE 30 µg and drospirenone 3 mg in a 21 active/7 placebo day pattern versus 28 days of placebo for women with PMDD found significant improvement in the active treatment arm only for acne, appetite, and food craving; although results trended toward improvement in affective symptoms, they did not reach significance. A Phase III multicenter study assessing an altered regimen of EE 20 µg and drospirenone 3 mg in a 24 active/4 day placebo pattern versus placebo did find significant improvement in PMDD symptoms as measures by total DRSP score, with maximum reduction in symptoms occurring after 3 months of use. Post-hoc analyses of the same trial found significant improvement in functional impairment and symptom clusters of negative emotions, food cravings, and water retention over placebo. A smaller study of the same EE/drospirenone 24/4 regimen similarly demonstrated significant improvement in DRSP score for active treatment compared to placebo. A more recent randomized open-label trial performed for women with PMS comparing EE 20 µg and drospirenone 3 mg to EE 20 µg and desogestrel 150 µg in a 24 active/4 placebo day pattern given over six cycles showed significant reduction in PMS symptoms in both treatment groups, although the drospirenone arm demonstrated superior efficacy and faster improvement in symptoms. A study that set out to assess continuously dosed EE/drospirenone against a 21 active/7 placebo day pattern found no difference in efficacy between these arms, however a strong placebo response was also observed in this study, and neither arm ultimately separated from placebo.

Levonorgestrel-containing COCs have also been studied for treatment of PMS and PMDD. Studies assessing continuous dosing without placebo days of levonorgestrel 90 µg with EE 20 µg on PMDD and PMS showed mixed results, with two studies, one placebo controlled and one open-label, demonstrating significant efficacy of the active treatment for premenstrual symptoms and two studies demonstrating a failure of active treatment to separate from placebo. A recent meta-analysis of COCs for PMDD or PMS concluded that while COCs were shown to be effective for symptom reduction overall, they were not effective for depressive symptoms specifically, and no specific formulation has shown superiority over the others to date.

Progesterone
To date, progesterone-only interventions have not consistently demonstrated reduction of PMS and PMDD symptoms. One open-label study of 37 women given 100 mg of sublingual micronized progesterone on day 11 to day 25 of their cycles across three cycles reported significant efficacy of treatment over placebo, with authors hypothesizing that increased bioavailability of sublingual dosing may be responsible for the observed results. One RCT assessing progesterone receptor modulator ulipristal dosed as 5 mg daily over 28 days showed significant increase in remission of PMDD in the treatment arm, a promising result warranting further study.

Estrogen
There is weak evidence concerning the efficacy of unopposed estrogen to suppress ovulation as a treatment PMS, and it may actually worsen symptoms in some women. Estrogen given as either a patch or implant to suppress ovulation with
progestogen for endometrial protection shows some efficacy for premenstrual symptoms, although the evidence was judged to be low quality per a recent systematic review.\textsuperscript{70} Patch dosing tested has ranged from 100 to 200 µg twice weekly in the luteal phase.\textsuperscript{70} Lower doses appear to be better tolerated than higher doses, but long-term adverse effects have not been adequately assessed.\textsuperscript{70}

**Androgens**

Dutasteride is a synthetic 4-azasteroid that selectively inhibits 5α-reductase, thereby preventing metabolism of progesterone to allopregnanolone. A small double-blind placebo-controlled study evaluating daily doses of 0.5 mg and 2.5 mg throughout the menstrual cycle for symptoms of PMDD demonstrated significant efficacy for the 2.5 mg dose in ameliorating anxiety, sadness, bloating, irritability, and food cravings.\textsuperscript{71} Although promising, as dutasteride can negatively impact the development of male fetuses due to its inhibition of testosterone metabolism, caution would need to be exercised in its use for women who may become pregnant.\textsuperscript{71}

**Gonadotropin Releasing Hormone (GnRH) Receptor Agonists**

Ovulation triggers the hormonal cascade linked to PMDD, and continuous exposure to GnRH receptor agonists acts to suppress ovulation through downregulation of GnRH receptors, ultimately leading to falling levels of gonadal steroids. Suppression of ovulation has been shown to treat PMS, presumably by eliminating the hormonal flux that provokes its symptoms.\textsuperscript{72} Leuprolide (Lupron) is a GnRH agonist dosed as a monthly intramuscular 3.75 mg injection that treats PMS via ovulatory suppression.\textsuperscript{72,73} Danazol, an anti-gonadotropic derivative of ethisterone capable of suppressing ovulatory cycles, has also shown some efficacy in treatment of PMS,\textsuperscript{74,75} but significant negative somatic and mood side effects secondary to its anti-androgenic properties preclude long-term use.\textsuperscript{29} Overall, prolonged use of GnRH agonists has significant negative side effects related to the induction of a menopausal state, including vasomotor symptoms and bone demineralization.\textsuperscript{29} The re-introduction of estrogen and progesterone decreases this side effect burden. Such add-back therapy has been shown to not diminish the overall efficacy of GnRH agonists for treatment of PMS,\textsuperscript{73} despite the potential for induction of PMS symptoms with re-introduction of progesterone in some women.\textsuperscript{76} Add-back regimens must be personalized for each woman given these individual variations in response; intermittent progesterone add-back may be preferable for progesterone-sensitive women.\textsuperscript{77,78}

**Anxiolytics**

Although benzodiazepines have a history of clinical use in the treatment of PMDD, the literature assessing their efficacy is sparse and clinically out-of-date. The two major studies demonstrating efficacy of alprazolam over placebo,\textsuperscript{79,80} for premenstrual symptoms were conducted on women diagnosed with late luteal phase disorder (LLPD), the precursor of PMDD defined in the *Diagnostic and Statistical Manual of Mental Disorders* 3rd edition revised.\textsuperscript{81} Both studies demonstrated efficacy over placebo in cohorts of women without other psychiatric diagnoses or follicular phase symptoms; one study specifically compared women with follicular phase symptoms to those without and concluded that alprazolam only demonstrated efficacy in the group without follicular phase anxiety or depression.\textsuperscript{80} Two studies of women with PMS failed to demonstrate any advantage of alprazolam over placebo.\textsuperscript{82,83} Overall, while benzodiazepines may be useful during the symptomatic phase of PMDD in women without comorbid diagnoses or follicular phase symptoms, the evidence to recommend their use is weak, and they should be considered for adjunctive treatment only in refractory cases.

One single-blind study comparing buspirone 10 mg daily to fluoxetine 20 mg daily for PMS found significant reductions in both groups for self-rated premenstrual symptom scores after one and two months of treatment without significant between-group differences, but the lack of a placebo group limits interpretation of the data.\textsuperscript{48}

**Other Medications**

A small (n = 20) study investigated adjunctive quetiapine SR, a second generation antipsychotic, starting at 25 mg for inadequate therapeutic response for PMDD in patients treated initially with SSRI or SNRI monotherapy and found greater improvements in mood ratings for the treatment group compared to placebo.\textsuperscript{84}
A small open-label case series of 8 women with treatment-resistant PMDD, 6 of whom had additional comorbid psychiatric diagnoses, treated with the carbonic anhydrase inhibitor acetazolamide 125 mg daily in the 7 to 10 days prior to menses reported remission of symptoms in all studied cases.85

One randomized placebo-controlled study of clonidine, an α-2 adrenergic agonist, for PMDD failed to show efficacy over placebo on any collected mood or premenstrual symptom scale.86

**Novel/Investigational Therapeutics**

As the underlying pathophysiology of PMDD is increasingly illuminated, the opportunity for rational drug design grows. As women with PMDD demonstrate paradoxical negative mood symptoms in response to rising allopregnanolone in the luteal phase,87 its antagonism was hypothesized to be a potential treatment for PMDD. Sepranolone is isoallopregnanolone, an isomer and antagonist of allopregnanolone that does not itself interact with GABA-A receptors.88 The compound is delivered as a series of subcutaneous injections of either 10 mg or 16 mg in 0.4 mL given every other day through the luteal phase and beginning at ovulation.88

A Phase 2 study of sepranolone for PMDD, in which participants received 5 injections of either placebo or study drug dosed at 10 mg or 16 mg over the course of one menstrual cycle, demonstrated promising results with significant improvement in total DRSP score for the drug group compared to placebo and no significant between-group differences in frequency of adverse effects.88 Unfortunately, an extension of this study using 5 to 7 injections of placebo or study drug over the course of 3 menstrual cycles failed to demonstrate superiority of drug over placebo at the primary endpoint of change in total DRSP score.89 There was a significant effect of drug on improvement in reported distress, and a post-hoc analysis looking at total DRSP score over 9 premenstrual days in the last treatment cycle only showed significant effect of sepranolone 10 mg over placebo.89 Notably, the placebo response in the study was significant, calculated as 30% greater than the placebo response of the original study, which likely contributed to the failure of study drug to separate from placebo.89 Again, sepranolone was demonstrated to be well-tolerated with only injection-site reactions occurring more frequently in the drug versus the placebo group.89

**Complementary and Alternative Medicine**

The US National Center for Complementary and Alternative Medicine (NCCAM) (currently named the National Center for Complementary and Integrated Health) defines complementary and alternative medicine (CAM) as “approaches that are not typically part of conventional medical care or that may have origins outside of usual Western practice”.90 The WHO utilizes a similar broad definition.91 According to the 2007 National Health Interview Survey, 38.3% of adults in the USA used CAM in the previous year, 33.5% men and 42.8% women.92 CAM use is often in conjunction with conventional medicine and infrequently under the care of a licensed or certified CAM practitioner. In the women’s health and premenstrual disorders’ literature in particular, common use of CAM is reported.93,94

Noted limitations of the CAM literature include studies’ heterogeneity regarding diagnosis, inclusion criteria, dose and duration of treatment, outcome measures, and, importantly, posology, or dose selection, which lead to comparing studies using non-chemically identical products.95 Also, no comprehensive understanding of the mechanism of action of each CAM approach is to date available. Moreover, in the case of non-pharmacological approaches such as exercise or acupuncture, adequate controls are challenging to create.96 Alongside the large placebo response in the PMS literature in general (in some studies as high as 50%), these limitations make interpretation challenging. Although many potential therapeutic CAM candidates have been studied in some form, including anise,97 Echium amoenum,98 ginger,99 Melissa officinalis,100,101 royal jelly,102 curcumin,103 Ginkgo biloba,104 Zataria multiflora,100,105 Nardostachys jatamansi,106 Phaleria macrocarpa,107 oxaloacetate,108 Neptune Krill Oil,109 fennel,110 soy,111 wheat germ,100–112 and lecithin,113 for the purpose of this review we will cover interventions with the most data available for adult women (Table 3). Similarly, CAM approaches with minimal data available and for which dosing cannot be quantified, specifically aromatherapy,114 kinesio taping,115,116 external Qi therapy,117,118 and Chinese herbal medicine practice119 are considered outside the scope of this review.
Chasteberry’s extract (Vitex Agnus-Castus, VAC), obtained from the dried ripe fruit of a plant native to the Mediterranean region and Asia, is the most investigated remedy among pharmacological CAM. Although the exact mechanism of action is not fully known, pathways implicated in the relief of PMS include inhibition of prolactin secretion through dopamine D2 receptor agonism and binding of opioid and estrogen receptors. In addition to positive open-label studies, numerous RCTs and subsequent meta-analyses have been conducted. Following a 2017 meta-analysis of 17 RCTs limited by significant heterogeneity (diagnostic criteria, posology, dosage 8–41 mg/day, luteal phase versus continuous use, outcome measures) showing superiority to placebo, equal efficacy to oral contraceptive or fluoxetine, and superiority to other selected CAM intervention, a 2019 meta-analysis selecting only 3 RCTs with a sufficiently characterized preparation of VAC also demonstrated efficacy, finding that VAC users were 2.57 times more likely to achieve remission than placebo users.

In terms of dosage, comparison of fixed doses of the VAC Ze 440 extract demonstrated that 8 mg daily was not significantly different than placebo while 20 mg and 30 mg were similarly efficacious. Other herbal preparations thought to have anxiolytic, anti-inflammatory, or anti-spasmodic effect, thus theoretically well positioned as a treatment option based on the array of symptoms of PMS, have received interest. Of the eight clinical trials reported on chamomile, only one had placebo as comparison and conclusive results cannot be drawn given the significant studies’ heterogeneity regarding preparations, doses, outcome measures, and follow ups. Conflicting results derive from two small RCTs on curcumin versus placebo. A case series and a small open-label study with positive findings are available for Kami-shoyo-san (TJ-24), a Japanese herbal medicine preparation approved in Japan. Saffron relieved PMS symptoms more than placebo in two RCTs, with one trial additionally demonstrating no significant difference in outcome compared to fluoxetine. One RCT of saffron versus placebo resulted in significant improvement in both groups, with saffron failing to separate from placebo. 

Hypericum perforatum (St John’s wort), a herbal supplement influencing the monoamine system and found helpful in some forms of depression, did not differentiate from placebo in a small RCT but did in another small RCT only for selected symptoms.

### Table 3 Oral Complementary and Alternative Medicine Dosing for Treatment of PMS or PMDD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitex Agnus-Castus</td>
<td>8 mg to 41 mg daily¹⁰⁷-¹⁰⁹</td>
</tr>
<tr>
<td>Kami-shoyo-san</td>
<td>2.5 g three times per day¹¹³</td>
</tr>
<tr>
<td>Saffron</td>
<td>15 mg twice daily¹¹⁴,¹¹⁵</td>
</tr>
<tr>
<td>Hypericum perforatum</td>
<td>600 mg daily¹¹⁷</td>
</tr>
<tr>
<td>Chamomile</td>
<td>100 mg to 400 mg daily¹¹⁰</td>
</tr>
<tr>
<td>Vitamin B6 (pyridoxine)</td>
<td>50 mg to 100 mg daily,¹¹⁸,¹¹⁹</td>
</tr>
<tr>
<td>Vitamin B1 (thiamine)</td>
<td>100 mg daily¹²²,¹²³</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>ab</td>
</tr>
<tr>
<td>Calcium</td>
<td>500 mg to 1200 mg daily¹²⁷-¹³⁰</td>
</tr>
<tr>
<td>Zinc (elemental)</td>
<td>30 mg to 50 mg daily¹³¹,¹³²</td>
</tr>
<tr>
<td>Magnesium</td>
<td>250 mg daily¹³⁴,¹³⁵</td>
</tr>
<tr>
<td>Omega 3 fatty acids</td>
<td>500 mg to 2000 mg daily,¹³⁷</td>
</tr>
<tr>
<td>Myo-inositol</td>
<td>0.6 mg in gel capsule¹³⁸</td>
</tr>
<tr>
<td></td>
<td>2 g in powder¹³⁸</td>
</tr>
</tbody>
</table>

**Notes:** a Higher doses tested, but upper limit of 100 mg/day recommended for adults. b Dose suggestion cannot be determined per available evidence. c Variable DHA and EPA composition.
Vitamins
Vitamin B6 (pyridoxine), a cofactor in the synthesis of monoamines and γ-aminobutyric acid (GABA), is included among the first-line interventions for PMDD in the Royal College of Obstetrician and Gynaecologists (RCOG) guidelines, along with SSRIs, CBT, exercise, and COCs, despite the low level of evidence for its efficacy. A 1999 systematic review including 9 low-quality RCTs (lacking details on randomization and mostly underpowered) concluded that pyridoxine was more than twice as effective as placebo for PMS. Tested doses ranged from 50 mg/day to 150 mg/day in preparation of pyridoxine alone to 600 mg/day in multivitamin preparations; as no change in efficacy with higher doses was observed, lower doses should be prescribed given evidence of adverse effects, such as peripheral neuropathy, of long-term use of high-dose pyridoxine. An upper-limit of 100 mg/day has been suggested for adults using pyridoxine. A 2016 meta-analysis of 12 heterogeneous case–control studies also demonstrates efficacy of pyridoxine over placebo for treatment of PMS.

The proposed mechanism of action of vitamin B1 (thiamine) as a treatment for PMS remains unclear, although its function as a cofactor in the metabolism of carbohydrates and amino acids has been suggested to be of interest. Thiamine was shown to decrease PMS symptom severity more than placebo in one small RCT of university students, and its efficacy is increased when used concomitantly with calcium at doses of 100 mg/day with 500 mg/day of calcium. A prospective cohort study of nurses found a lower rate of PMS in participants with high dietary intake of thiamine and riboflavin.

Inhibition of cyclooxygenase and nitric oxide synthase, effect on calcium metabolism, and prevention of monoamine depletion are included in the potential rationale for the use of vitamin D in PMS. Vitamin D supplementation has been shown to be effective in improving PMS symptoms in interventional studies per a recent meta-analysis, but no significant association between serum 25-hydroxyvitamin D3 and PMS symptoms was observed, perhaps due to prevalent vitamin D deficiency in the population studied. A subsequent RCT in a similarly vitamin D deficient sample found no effect of vitamin D 2000 IU dosed every other day over placebo. Overall, since available studies are highly heterogeneous in term of dosages, often focused on vitamin D-deficient populations, and also inconsistent regarding the relation between vitamin D serum levels and symptom severity, available evidence is not sufficient to inform recommendations regarding specific dosage range, especially for those without vitamin D deficiency.

Minerals
Variations in calcium homeostasis have been demonstrated to occur over the menstrual cycle in response to hormone fluctuations, with greater variations observed in women with PMS and PMDD compared to controls. Such dysregulation of calcium homeostasis has been implicated in affective disorders. Oral calcium at doses of 500 mg daily and twice per day has been shown to improve symptoms of PMS in RCTs. Calcium in conjunction with pyridoxine and with thiamine has been demonstrated to be more efficacious than either of those vitamins alone. A pilot study comparing calcium 600 mg twice daily compared to fluoxetine found a small effect of calcium and a larger effect of fluoxetine, in line with the overall small effect for calcium on total PMS symptoms compared to placebo (48% vs 30% reduction) observed in the largest RCT of calcium for PMS to date.

Lower serum levels of zinc have been observed in women with PMS compared to controls in some studies, and it has been hypothesized that zinc supplementation may therefore treatment symptoms. Limited evidence supports the use of zinc, dosed as 50 mg of elemental zinc during the luteal phase or up to 30 mg of elemental zinc daily, for PMS. Some observation of low magnesium levels in women with PMS compared to controls has led to the theory that magnesium supplementation may alleviate symptoms. Limited evidence additionally supports use of magnesium supplementation at 250 mg daily, particularly in combination with pyridoxine, for PMS, although to date superiority over placebo has not been demonstrated; overall, improved quality of data is necessary to guide recommendations.

Other Dietary Supplements
Omega-3 polyunsaturated fatty acids (PUFAs), believed to exert various biological functions including monoaminergic pathway enhancement, and control of pain pathways and inflammation, have been the focus of study for use in PMS. In a recent meta-analysis of 8 RCTs, omega-3 fatty acids were shown to be effective for reducing the severity of symptoms of PMS, particularly in older women and with increased length of treatment, but the authors urge caution in interpretation.
of these results due to significant heterogeneity of studies. A meta-analysis of studies on myo-inositol, a sugar-like molecule involved in stress response and the serotonin-signaling system, for depression and anxiety disorders that included two RCTs of PMDD, reported a trend toward efficacy on depressive symptoms over placebo.

**Proprietary Blends**

Femal, a pollen-based herbal medicinal product, and Femi comfort, a blend of pyridoxine, vitamin E, and evening primrose oil, have shown efficacy over placebo for PMS symptoms in RCTs. PMS50, a proprietary blend of primarily B vitamins, magnesium, and chasteberry, improved mood symptoms compared to placebo in an RCT of women with moderate to severe PMS.

**Non-Pharmacological CAM**

A 2019 systematic review of RCTs assessing safety and efficacy of acupuncture or acupressure for PMS or PMDD found greater reductions in physical and psychological symptoms compared to sham treatment without sufficient data to comment on adverse effects of treatment; overall, the evidence was noted to be low quality. Two meta-analyses conducted similarly noted greater efficacy of acupuncture over placebo in pooled data. One recent RCT of auriculotherapy failed to separate from placebo. A meta-analysis and systematic review of reflexology for PMS found an overall effect for the intervention in reduction of severity of symptoms, with increased effect shown with longer duration of reflexology sessions. Small RCTs of yoga for PMS shown positive findings on symptoms as well as dimensions such as sleep quality, but as yoga is a broad intervention compromising multiple techniques, further studies better delineating the specifics of the intervention tested are necessary.

A 2020 meta-analysis of RCTs evaluating the effect of exercise on PMS selected 15 studies of at least eight weeks duration; significant improvement in PMS symptoms was demonstrated compared to controls, but evidence quality was limited, with high heterogeneity of studies. Other studies of swimming, pilates, traditional Chinese exercise Baduanjin, and simple aerobic exercise have had similar positive results, although quality of data is limited. Given the benefit of regular exercise for overall health, complementary use in the treatment of PMS as part of an integrated, holistic approach is likely to be useful.

**Psychotherapies**

Several psychotherapeutic modalities have been shown to be efficacious in the treatment of PMS and PMDD, although the preponderance of evidence favors cognitive behavioral therapy (CBT). One meta-analysis of randomized controlled trials including 5 trials utilizing CBT in women with PMS found significant reductions in symptoms of anxiety and depression, although the quality of the available studies was concluded to be low. Mindfulness-based CBT (MCBT) has additionally been shown to be efficacious for PMS in two small randomized controlled studies. Several controlled studies assessing CBT delivered to a group of subjects have concluded that the intervention remains effective in this format. Two randomized controlled trials of internet-based CBT have demonstrated superiority of this care delivery model over control interventions, a finding that has implications for broadening access to therapy. In terms of comparative efficacy, one meta-analysis concluded that CBT showed the same small to moderate effect size as antidepressants in the treatment of PMS and PMDD and hypothesized that improved outcomes could be achieved with combination treatment. An additional study assessing CBT versus fluoxetine versus combined treatment for women with PMDD also demonstrated similar efficacy between treatment groups, however no additional effect was observed for combination therapy. Psychoeducation alone has been shown to be effective in reducing symptoms of PMS in two randomized control trials.

**Surgery**

**Hysterectomy with Bilateral Salpingectomy/Oophorectomy (BSO)**

Hysterectomy with BSO has been successfully utilized as a definitive treatment option for women with PMDD refractory to other interventions. A retrospective study of 47 women who underwent hysterectomy with BSO reported a 96% satisfaction rate and a 93.6% remission rate, with women reporting an average of nearly 10 years of distressing symptoms prior to the procedure. Seventeen women in the cohort additionally suffered from symptoms such as menorrhagia, uterine
fibroids, and ovarian cysts, providing additional indications for surgery.\textsuperscript{201} As with all therapies resulting in ovulatory suppression, hormonal add-back is required following surgery to prevent the complications of medical menopause.\textsuperscript{201}

**Endometrial Ablation**

Novasure is a procedure to thermally ablate the endometrial lining, usually performed for treatment of menorrhagia. A prospective cohort study of 36 women undergoing the procedure found significant improvement in symptoms of PMS.\textsuperscript{203}

The mechanism of the effect on PMS is not clear, and further research is needed to validate these preliminary findings.

**Discussion**

The PMS/PMDD treatment literature overall suffers from a paucity of high quality data. Consensus on diagnostic criteria has evolved in the last several decades, and rigorous studies assessing prospectively confirmed PMDD are necessary to continue to build the evidence base for treatment. The robust placebo response seen across studies warrant their own study and inquiry. Combinations of treatments may be more effective than a single approach, but studies assessing the superiority of combined approaches are lacking. Finally, the study of CAM approaches to treatment has been classically limited by posology as well as factors contributing to significant heterogeneity. However, clinicians can use existing data to guide decision making according to the unique needs and preferences of their patients.

For mild symptoms or patients who decline pharmacotherapy, evidence supports psychotherapeutic interventions and non-pharmacological complementary and alternative practices such as exercise, yoga, and acupuncture. For more severe symptoms and if patients are agreeable, treatments with the most robust evidence, namely SSRIs and COCs, should be prioritized. Low-risk pharmacological CAM interventions with promising evidence, such as calcium and pyridoxine supplementation, can be used as adjuncts to bolster treatment or as first approaches for patients who prefer nutraceutical treatment with caution and diligent assessment of potential medical contraindications (eg for proposed calcium supplementation, a history of nephrolithiasis or hypercalcemia). Liaison with primary care is recommended to support safe and informed prescribing of complementary agents, and more research is needed overall to clarify the potential benefit of such multimodal approaches to treatment. Finally, GnRH agonists or even surgical measures may be warranted for severe refractory symptoms, although such interventions require ongoing monitoring and hormonal add-back.

**Limitations**

The present study is limited in some ways relating to adjustments made for feasibility and clinical utility. Firstly, as the initial search included only studies published from 2000 onwards, relevant data published prior to this date may be excluded. Secondly, excluding treatment modalities with a scarcity of data narrows the scope of the review.

**Conclusion**

Overall, despite the limitations of the reviewed literature noted above, effective treatments for PMDD and PMS, important and under-recognized disorders, are available and should be utilized. Growing evidence concerning the pathophysiology of PMDD has led to the development of novel investigative compounds, however it remains to be seen as to when and whether such therapies might become available. By assessing the needs of each unique patient and appropriately utilizing an inter-disciplinary approach involving psychiatric and obstetrics–gynecological practitioners as appropriate, individualized treatments can be assembled through careful review of the available evidence.

**Disclosure**

Dr. Deligiannidis receives research funding from the National Institutes of Health (R01MH118269, R01MH120313) which supported her time for this research and manuscript. Dr. Deligiannidis has also received research funding from Sage Therapeutics, Inc. and Vorso Corporation (contracted research) and serves as a consultant to Sage Therapeutics, Inc., Brii Biosciences, GH Research, Ireland LLC and Brainify.AI. Dr. Carlini, Dr. Lanza di Scalea, Dr. McNally, and Ms. Lester have no disclosures to report for this work.
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