What's Stopping Us? Using GnRH Analogs With Stable Hormone Addback in Treatment-Resistant Premenstrual Dysphoric Disorder:

Practical Guidelines and Risk-Benefit Analysis for Long-term Therapy

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ABSTRACT

Objective: Despite the documented success of gonadotropin-releasing hormone analogs (GnRHa) for the treatment of treatment-resistant premenstrual dysphoric disorder (PMDD), many patients struggle to find providers who have sufficient knowledge of PMDD and its evidence-based treatments and/or who are comfortable treating PMDD after first-line treatment options have failed. Here, we discuss the barriers to initiating GnRHa for treatment-resistant premenstrual dysphoric disorder (PMDD) and offer practical solutions to address these barriers for providers who encounter patients with treatment-resistant PMDD but may not have the necessary expertise or comfort with providing evidence-based treatments (ie, gynecologists, general psychiatrists). We have included supplementary materials including patient and provider handouts, screening tools, and treatment algorithms with the hope that this review may serve as a primer on PMDD and the use of GnRHa with hormonal addback as a treatment, as well as a guideline for clinicians delivering this treatment to patients in need.

Options: In addition to offering practical treatment guidelines for first and second lines of treatment for PMDD, this review offers an in-depth discussion of GnRHa for treatment-resistant PMDD.

Outcomes: The burden of illness in PMDD is estimated to be similar to that of other mood disorders, and those suffering from PMDD are at a high risk for suicide.

Evidence: We present a selective review of relevant clinical trials evidence supporting the use of GnRHa with addback hormones in treatment-resistant PMDD (the most recent evidence cited was published in 2021), highlighting the rationale for addback hormones and presenting the different possible hormonal addback approaches.

Values: The PMDD community has and continues to suffer from debilitating symptoms despite the known interventions. This article provides guidance for implementing GnRHa into practice among a broader scope of clinicians including general psychiatrists.

Benefits, Harms, and Costs: The primary benefit of implementing this guideline is that a broad range of clinicians beyond reproductive psychiatrists who encounter patients with PMDD will have a template for assessing and treating PMDD and implementing GnRHa treatment when first-line treatments fail. Harms are expected to be minimal; however, some patients may have side effects or adverse reactions to the treatment or may not respond as they had hoped. Costs of GnRHa can be high depending on insurance coverage. We provide information within the guideline to help navigate this barrier.

Recommendations: (1) Prospective symptom rating in evaluating for PMDD is necessary for diagnosis and evaluating treatment response. (2) SSRIs and oral contraceptives should be trialed as the first- and second-line treatments for PMDD. (3) When first- and second-line treatments have failed to yield symptom relief, the use of GnRHa with hormone addback should be considered. Risks and benefits of GnRHa should be weighed among clinicians and patients, and potential barriers to access should be discussed.

Validation: This article adds to the available systematic reviews on the effectiveness of GnRHa in the treatment of PMDD and Royal College of Obstetrics and Gynecology's guidelines on the treatment of PMDD.

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Premenstrual dysphoric disorder (PMDD) is a cyclical, hormone-triggered mood disorder with symptoms arising during the luteal phase of the menstrual cycle (the 10–14 days leading up to menses), improving during menstruation, and subsiding by the week following menstruation. It affects an estimated 5.5% of people with menstrual cycles. *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (*DSM-5*) criteria for PMDD require the cyclical "on-off" pattern in 1 or more of the core affective symptoms as well as a total of 5 cycling symptoms overall. The most common symptoms are irritability and mood swings, with symptoms of anxiety being the next most common and symptoms of depression being the least common.[1] Despite follicular phase remission, burden of illness is estimated to be similar to that of other mood disorders,[2] and recent evidence suggests a high risk for suicide in this population[3,4] that is not accounted for by comorbidities.[5]

How Is PMDD Diagnosed?

Retrospective self-report of a cyclical symptom pattern is not an accurate method of diagnosis, as it is strongly prone to false-positive reporting.[6] Therefore, a clinical interview alone cannot be used to make a valid diagnosis of PMDD, and the *DSM-5* requires daily ratings of symptoms across 2 cycles to establish the pattern of symptoms.[7,8] Two months of daily severity ratings for each *DSM-5* symptom should be evaluated to determine the presence of distressing or impairing symptoms in the premenstrual week that become minimal or absent by the week after menses. We recommend the use of either a pencil-and-paper rating form or a smartphone app that incorporates the *DSM-5* criteria and dimensional symptom severity (eg, PreMentricS); costs and benefits

Clinical Points

- Despite substantial evidence for the safety and efficacy of gonadotropin-releasing hormone analogs (GnRHa) in treating treatment-resistant premenstrual dysphoric disorder (PMDD), GnRHa are infrequently prescribed by psychiatrists. As a result, patients for whom first-line treatments have failed are often left without treatment options.
- This guideline provides screening tools, patient and provider handouts, and in-depth analysis of GnRHa and hormonal addback paradigms in PMDD, with hopes of increasing provider comfort with prescribing GnRHa for treatment-resistant PMDD where appropriate.

associated with any privacy concerns can be discussed between patients and providers. Pencil-and-paper rating forms for the gold- standard Daily Record of Severity of Problems (DRSP)[9] are available (https://iapmd.org/provider-resources#:~:text=Daily%20Record%20of%20Severity%20of,to%20meet%20DSM%2DIV%20criteria) and can be evaluated using the diagnostic scoring system provided in the original DRSP validation paper.[4]

While the *DSM-5* diagnosis requires that 5 cycling symptoms be present to make the diagnosis of PMDD, most clinical experts agree that evaluating the overall cyclicity of distress and impairment is central for determining the need for treatment. The arbitrary 5-symptom threshold in the *DSM-5* was selected in part to prevent the overdiagnosis of healthy females in response to various academics voicing concern about the "overmedicalization" of the female experience.[5] However, there is evidence that this threshold may be too high; one study found that the optimal cutpoint for prediction of cyclical impairment among patients seeking a diagnosis of PMDD was 4 symptoms.[6] Therefore, in clinical settings, we encourage providers to use daily ratings to evaluate for the presence of clinically significant cyclical distress or impairment.

Comorbidities and Exacerbations of Underlying Illness

There is a widely held misconception that PMDD must not be comorbid with other psychiatric conditions (eg, major depressive disorder, borderline personality disorder); in reality, these diagnostic categories typically intersect, with patients showing some PMDD-pattern symptoms (present only premenstrually), some chronic symptoms that show premenstrual exacerbation (PME; present all the time but worsening premenstrually), and some stable symptoms.[7] We have found that psychiatric comorbidity is the rule rather than the exception, even among patients who have received a prospective diagnosis of PMDD from a medical professional, and that comorbidities do not fully account for adverse outcomes such as suicidality in PMDD.[8,9] Therefore, differential diagnosis of PMDD and PME from other disorders relies on a symptom-by-symptom approach to diagnosis in which each *DSM-5* symptom is evaluated separately for cyclical change using daily ratings.[7] While identification and treatment of stable psychiatric comorbidities are certainly important, their presence does not preclude diagnosis and treatment of cyclical symptom changes.

First-line Treatments for PMDD

After confirming symptom cyclicity with daily ratings and considering comorbidities and exacerbations of other psychiatric diagnoses, medical providers can start first-line treatment for PMDD. Because symptoms of PMDD are due to a neurobiological sensitivity to normal changes in ovarian hormones and their metabolites across the menstrual cycle, treatment aims typically include reversal of abnormal effects of hormones on serotonin levels[10,11] and/or suppression of ovarian hormone fluctuations.[12]

Numerous trials have established selective serotonin reuptake inhibitors (SSRIs) as the first-line evidence-based treatment for PMDD[13] (see Supplementary Appendix 1 for further detail). After several months (1 to 3) of nonresponse to an SSRI, trial of another SSRI is a recommended next step. If SSRI treatment fails, or if the patient is seeking contraception, trial of an ovulation-suppressing agent (eg, combined oral contraceptive [OC] formulations containing the progestin drospirenone) is recommended (see Supplementary Appendixes 1 and 2 for further detail). Note that 1 clinical trial also supports the superiority of combined therapy with drospirenone-containing OCs and SSRI relative to drospirenone-containing OC alone[14]; therefore, if response to monotherapy with either SSRI or OC is partial, addition of the other may be a useful strategy. Moreover, if a patient has partially responded to a first-line agent (SSRI) and/or a second-line agent (drospirenone-containing OCs), augmentation strategies may help achieve a more complete response. Augmentation strategies include medications and behavioral interventions. Psychopharmacologic augmentation strategies with supporting evidence include alprazolam,[15] quetiapine,[16] and buspirone.[17] Finally, although drospirenone-containing OCs are currently FDA approved for PMDD, given the proposed treatment mechanism, other combined OCs may also be efficacious and could be reasonable alternatives to consider despite not having an FDA indication for PMDD. A discussion between the patient and provider regarding choosing a specific combined OC is recommended.

Treatment-Resistant PMDD

Although initial psychiatric treatments of PMDD (ie, SSRIs and OCs) are effective for up to 75% of patients with PMDD,[18] many patients suffer from treatment-resistant PMDD (ie, lack of responsiveness to SSRIs, OCs, and augmentation strategies), for which clear treatment guidelines are unavailable. In these cases, it is incumbent upon the diverse field of medical providers who encounter PMDD (ie, reproductive psychiatrists, gynecologists, and general practitioners) to be aware of the efficacy and evidence base supporting the clinical use of gonadotropin-releasing hormone analogs (GnRHa) with stable hormone addback in patients with severe, treatment-resistant PMDD. To

inform clinical research designs and current clinical decision making in treatment-resistant cases, this article provides a narrative review of the evidence for the use of GnRHa in treatment-resistant PMDD, including mechanism of action, clinical trials in PMDD, and available evidence regarding the risks and side effects associated with long-term use with and without hormone addback. Next, we will offer practical steps for prescribing, administering, and managing patients with PMDD who meet criteria for long-term GnRHa therapy.

GNRHA FOR TREATMENT-RESISTANT PMDD: REVIEW OF THE EVIDENCE

Types of GnRHa

There are 2 primary forms of GnRHa, agonists (eg, leuprolide, nafarelin, goserelin, triptorelin, histrelin, buserelin) and antagonists (eg, degarelix, elagolix). Each results in a stable hypogonadal state and likely represents viable long-term treatment options for PMDD; however, the majority of studies have used the GnRH agonist leuprolide acetate. Based on clinical experience, the intramuscular injection of the GnRH agonist leuprolide acetate (monthly; 3.75 mg) is the most commonly prescribed GnRHa in females of reproductive age; it is FDA approved for the treatment of endometriosis, uterine fibroids, central precocious puberty, and prostate cancer and is available in generic form. None of the GnRHa are FDA approved for treatment-resistant PMDD; however, leuprolide acetate has been used in the majority of studies.[19,20] The practical elements of the remainder of this article will focus on the use of leuprolide acetate, a GnRH agonist; however, the underlying logic of GnRHa therapy for PMDD is not specific to leuprolide or to agonists (relative to antagonists).

GnRH agonists. During the first 10 days of treatment, the GnRH agonist leuprolide acetate (monthly IM; 3.75 mg) binds to the GnRH receptor and stimulates the pituitary to produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which leads to a spike in estradiol. This causes a decrease in pituitary secretion of LH and FSH following down-regulation of GnRH receptors and pituitary desensitization, which results in the suppression of ovarian follicular growth and ovulation, thus leading to stable, hypogonadal levels of ovarian hormones.

GnRH antagonists. GnRH antagonists compete with endogenous GnRH for binding to receptors. When antagonists bind to the GnRH receptor, there is suppression of LH and FSH secretion and there is no downstream increase in estradiol. Administration of higher potency GnRH antagonists have been shown to suppress gonadotropin secretion immediately and thus do not cause an initial increase in estradiol, in contrast to GnRH agonists, which require time for their ultimate effects to manifest and initially cause a spike in estradiol. GnRH antagonists are candidates for use in the treatment of PMDD; however, there is currently a lack of evidence to support their use. Future research with GnRH antagonists for treatment-resistant PMDD is needed and would help those suffering.

Evidence for GnRHa in PMDD

A meta-analysis of 5 clinical trials of GnRHa (with or without hormone addback) for premenstrual syndrome concluded that they were effective for reducing both physical and emotional premenstrual symptoms.[21] Since then, additional studies have demonstrated that GnRHa with and without hormone addback are effective for *DSM-5* PMDD.[12,22] Upwards of 70% of patients with treatment-resistant PMDD respond to this form of treatment.[23]

GnRHa appear to exert therapeutic effects in PMDD by suppressing ovarian activity, eliminating the fluctuations in hormones that otherwise occur. This stable background can be supplemented with continuous estradiol and progesterone therapy to maintain stability of hormones at a higher level, which is equally well tolerated over the long term[12] and likely poses fewer risks (see The Role of Addback in Mitigating Risks and Side Effects) than surgical menopause.

Long-term Use of GnRHa in PMDD

Physicians who prescribe GnRHa have not historically considered them to be long-term treatment options for PMDD (or any condition), for reasons that are apparently 4-fold. First, GnRHa are FDA approved for use in gynecologic disorders such as endometriosis in which estrogen addback would directly exacerbate the underlying disorder due to the pathophysiologic role of estradiol in these diseases. Of course, this concern is not relevant to PMDD, in which there are no known abnormalities of gynecologic or endocrine systems (rather, it is an abnormal brain sensitivity to normal changes that serves as the trigger[12]). Second, short-term GnRHa was originally believed to treat PMDD by reducing hormones to low, hypogonadal levels (discussed in review[21])—however, we now know that they work by creating hormonal stability, regardless of absolute levels.[12] Third, short-term GnRHa use was predicated on the belief that GnRHa could not be feasibly continued long-term due to the provocation of PMDD symptoms during the first month of the ovarian hormone addback required for long-term safety.[22] We now know that this symptom resurgence during addback is *temporary*[12] and that symptoms remit again after roughly 1 month of stable high levels. Finally, GnRHa have been used in the treatment of central precocious puberty (CPP) for many years with minimal difference in health outcomes when comparing children with CPP treated with long-term GnRHa to healthy controls without CPP.[24] In summary, while the reasons for advocating only short-term use of GnRHa are understandable in historical contexts, they no longer appear convincing, particularly when contrasted with the risks of oophorectomy. In contrast to previous belief and current clinical realities, and consistent with current expert guidance,[25–27] we support a practice whereby all clinicians who interact with patients diagnosed with PMDD are aware of the safety of treatment using GnRHa plus addback and clinicians who directly treat patients diagnosed with PMDD learn to safely apply GnRHa plus addback over longer durations (ie, years) for those with treatment-resistant

PMDD, given their patient characteristics and suppression of ovarian activity.

Side Effects and Health Risks of GnRHa Without Addback

Without hormone addback, the use of GnRHa results in a chronic hypoestrogenic state,[28] and both menopausal symptoms and medical risks result.[29] Reported menopausal symptoms during chemical or surgical hypogonadism are similar to those reported during natural menopause, including amenorrhea, vasomotor symptoms, joint and muscle pain, sleep disturbances due to hot flashes, urogenital atrophy, and sexual difficulties.[28] Long-term medical risks arising from these hypoestrogenic states primarily include elevated risk of osteoporosis,[30] cardiovascular disease,[31] and higher rates of dementia.[32] Critically, each of these side effects and long-term risks is likely mitigated by addback of ovarian hormones (see more intensive reviews[33–35]); however, long-term studies with greater numbers of patients are still warranted to confirm this mitigated risk.

The Role of Addback in Mitigating Risks and Side Effects

Steady-state addback of estradiol (to reduce hypoestrogenic risks) and progesterone (to protect against endometrial hyperplasia) can address both the side effects and the medical risks that arise during long-term GnRHa therapy. While there are no long-term trials in PMDD demonstrating the safety and effectiveness of this approach in the context of GnRHa, evidence from individuals in surgical menopause consistently indicates that many of the serious long-term health consequences of bilateral oophorectomy can be ameliorated by taking estrogen therapy until at least 60 years of age.[31,32,36] In addition, 10-year follow-up studies of young patients treated with GnRHa and combined estrogen and progesterone addback therapy for endometriosis support the safety of this treatment approach.[37] Given the known risks of surgical menopause versus the less-known risks of prolonged GnRHa therapy with addback, clinicians should work with their patients in weighing the risks and benefits of medical versus surgical strategies in the long-term management of their PMDD.

Menopausal symptoms. Although some patients on GnRHa continue to experience menopausal symptoms after hormone addback, a study in the Netherlands confirmed a significant decrease in symptoms after 24 weeks of treatment when comparing patients with endometriosis who received addback of goserelin (subcutaneous depot, 3.6 mg every 4 weeks) and estradiol-norethisterone (2 mg oral micronized estradiol and 1 mg norethisterone acetate; US equivalent: estradiol/norethindrone) compared to those treated with GnRHa therapy alone.[38] A randomized controlled trial (RCT) assessing the use of leuprolide plus tibolone, a synthetic compound with estrogenic and progestogenic properties, in individuals with severe PMS found that GnRHa plus tibolone yielded significantly lower incidence of hot flushes than did GnRHa plus placebo.[39] Yet another RCT found that GnRHa plus hormone replacement (25 µg transdermal estradiol daily and 5 mg oral medroxyprogesterone acetate daily) significantly reduced the incidence and severity of hot flushes compared to GnRHa alone.[40] Therefore, addback of ovarian hormones (primarily those with estrogenic activity) appears to be sufficient for substantially reducing or eliminating menopausal side effects during GnRHa therapy.

Bone density. The typical loss of bone mineral density that occurs with GnRHa can be prevented by addback of estrogenic compounds. Although bone density significantly decreases in patients receiving GnRHa + calcium alone, bone density remains unchanged in patients treated with a GnRHa plus addback of any compound with estrogenic activity.[28] Moreover, this maintenance of bone mineral density among those receiving estrogenic compounds has been tested and confirmed at follow-up periods up to 10 years.[37,41–43]

Cardiovascular risks. Surgical and early menopause likely increase cardiovascular disease (CVD) risk,[44–46] specifically when estrogenic addback is not utilized. Importantly, use of estrogenic compounds, when initiated during a critical window following the onset of menopause, appears to mitigate CVD risks among surgical menopause patients[44] as well as younger naturally postmenopausal patients.[47]

Dementia risks. Both early surgical menopause (before the age of 50) and premature ovarian insufficiency have been linked to increased risk of dimensional cognitive impairment, dementia diagnoses, and Alzheimer's disease.[32,48] Use of estrogenic addback therapy, particularly when initiated during or soon after the menopausal transition, greatly reduces these risks.[49]

Summary

While long-term trials in PMDD are needed to evaluate the safety of long-term GnRHa + combined hormone addback with respect to bone, heart, and brain health, existing data from early and surgical menopause studies strongly suggest the safety of long-term GnRHa when accompanied by careful screening for individual risk factors, use of estrogenic addback, and appropriate monitoring of ongoing risk markers.

PRACTICAL CONSIDERATIONS IN THE USE OF GNRH AGONISTS FOR TREATMENT-RESISTANT PMDD

Assessing Comorbidities and Relevant Risk Factors

When considering use of GnRH agonists plus hormone addback to treat patients with severe PMDD, we recommend completing a thorough history that includes prospective verification of the PMDD diagnosis as well as a detailed review of treatment history including the duration, dosing, response, and associated side effects of medications to confirm adequate failed trials of first- and second-line therapies (see Supplementary Appendixes 1 and 2, Supplementary Figure 1).

In addition, we recommend assessment of possible comorbidities and risks: personal or family history of clotting disorders, estrogen/progesterone-dependent cancers, and

early cardiovascular disease, as well as personal history of endometriosis, migraines, osteoporosis or low bone mineral density, or illness placing them at greater risk for osteoporosis (see Supplementary Appendix 3). If there is concern about the possibility of an inherited or acquired disorder that increases risk for a complication, a discussion about a referral to the appropriate specialist or a geneticist is prudent prior to starting GnRH agonist treatment.

Some treatment risks are associated with the hypogonadal state from GnRH alone while other risks are conferred by hormonal addback therapy. As discussed, it is not advisable to consistently treat with a GnRH agonist alone as, after several months of consistent treatment, known side effects and medical risks outweigh benefits and tolerability. As a whole, risks associated with hormone addback therapies are expected to be lower than with use of hormone replacement therapy (HRT) during menopause due to the younger age of the population and the suppression of underlying ovarian activity via the GnRH agonist. Regarding the latter, the amount of estrogen and progesterone in addback regimens is typically less than the normal hormone levels seen in premenopausal patients and most combined contraceptive therapies currently in use. Despite this, those who are deemed unfit for combined hormonal addback are not likely to be good candidates for long-term GnRH agonist. Below, we review the risk factors that should be considered when considering GnRH agonist + addback therapy for PMDD.

Evaluating Individual Risk Factors Relevant to GnRHa Safety

Low bone mineral density risk. DEXA scans are recommended for females aged 65+ as well as postmenopausal females younger than 65 that have elevated risk factors for osteoporosis[50] to monitor possible loss of bone mineral density. Because GnRH agonists alone produce "chemical menopause," clinicians should consider obtaining a baseline DEXA scan before treatment initiation if the patient possesses risk factors for osteoporosis, including various rheumatic, endocrine, gastrointestinal, hematologic, or eating disorders or other dietary conditions.[51] Completing a baseline DEXA prior to every GnRH agonist trial is not a requirement if a decision regarding prolonged use of GnRH agonist has not been made. Follow-up scans can be obtained every 1–2 years or at the discretion of the provider based on the presence/absence of risk factors and the results of previous scans.[52] In addition to estrogenic addback, which mitigates the risk of bone loss for up to 10 years, we advise counseling patients on preventative measures for maintenance of bone health such as weight-bearing exercises, resistance exercises, and aerobics for spine bone mineral density and walking for hip bone mineral density.[53] Calcium and vitamin D supplementation can also be added to the patient's medication regimen.[54–56]

Cardiovascular disease and electrocardiogram (ECG) abnormalities. When determining appropriateness of long-term GnRHa with addback, physicians should consider risk factors for cardiovascular disease including hypertension, hyperlipidemia, and use of tobacco cigarettes. Since certain GnRH agonists, such as leuprolide, and GnRH antagonists, such as abarelix, have been shown to prolong the QTc interval in men receiving GnRH agonists or antagonists for prostate cancer,[57] clinicians should assess female patients for history of QTc prolongation, congenital long QT syndrome, frequent electrolyte abnormalities, and concomitant use of other medications known to prolong the QT interval.[58] We recommend a baseline ECG and, if it is abnormal, regular ECGs over the duration of treatment to monitor for potentially concerning changes.

Epilepsy. In postmarketing reports of GnRH agonists, convulsions have been observed among some individuals without mention of a history of seizures.[59] It is important to make patients with a history of epilepsy aware that leuprolide may lower their seizure threshold, although this is an uncommon event. The lower seizure threshold may be related to increased circulating FSH and LH levels after leuprolide initiation,[59] in which case stable addback hormones could mitigate this risk.

Diabetes. Diabetes and/or worsening of glycemic control have been reported in males receiving GnRH agonists, but not in females receiving GnRHa plus addback. Clinicians should regularly monitor hemoglobin A_{1c} in patients with preexisting diabetes and those at increased risk of developing diabetes.[60]

Evaluating Patient Risk Factors Relevant to Hormone Addback Safety

Clotting/hypercoagulability. Similar with other hormone treatments such as oral or long-acting reversible hormonal contraceptives, there is concern about elevated risk of blood clots with addback hormones.[61] Providers must discuss a patient's individual risk factors such as history of consistent nicotine use, an inherited clotting disorder, obesity, previous deep vein thrombosis or pulmonary embolism, or other hypercoagulable states. Patients identified with an elevated venous thromboembolism risk may still proceed with a GnRHa trial if both the patient and the provider understand the potential risks and determine that the proposed benefits of treatment outweigh the risk of a venous thromboembolism (VTE) event. **We recommend a clear discussion of the signs and symptoms of deep vein thrombosis and pulmonary embolism prior to initiation of addback hormones to mitigate sequelae from unrecognized clotting events.** If there are concerns about an inherited clotting disorder, a referral to a hematologist and/or medical geneticist may be warranted prior to initiating treatment.

Migraine with aura. Individuals with hormone-sensitive conditions such as migraine with aura, especially menstrual migraines, could be impacted by the addition of addback hormones to GnRHa treatments. As with VTE risk, there is no increased risk of menstrual migraines without addback, and, in fact, migraine intensity and frequency may improve. Additionally, stable low dose addback should not significantly impact the frequency and intensity of hormone-sensitive migraines and may improve migraines in patients with estrogen withdrawal–related migraines.

However, in some postmenopausal patients, addition of HRT triggered an increase in migraine frequency and intensity despite the hypoestrogenic state.[62] Therefore, it is prudent to counsel patients to monitor migraine frequency before and after onset of GnRHa and hormone addback to identify any concerning, persistent changes in migraine associated with treatment.

Estrogen-dependent cancer risk. Generally, cancer risks associated with hormone addback are expected to be lower than use of HRT during menopause due to suppression of underlying ovarian activity via the GnRH agonist; nonetheless, individual risks for hormone-dependent cancer should be assessed prior to initiation of addback during GnRH agonist treatment as multiple meta-analyses have highlighted the risks of ever using estrogen, progesterone, oral contraceptives, and levonorgestrel-releasing intrauterine systems (LNG-IUS).[63,64] With the exception of known estrogen or progesterone dependent cancer risk, such as breast cancer gene (*BRCA*) mutations or personal history of estrogen receptor (ER) and/or progesterone receptor (PR) positive breast cancer, GnRHa agonists with addback hormones can be administered without added screenings or surveillance with appropriate counseling. Indeed, GnRH agonists have been used in the treatment of breast cancer for decades and without hormone addback serve as a protective agent against the development of breast cancer.[65]

Endometriosis and uterine fibroids. GnRHa plus addback hormones has regularly been used and shown to be an effective treatment for endometriosis and uterine fibroids.[28,31,36–38,66] The addback hormones manage symptoms related to the decrease in overall hormone levels.

Preauthorization and Insurance Coverage

Insurance providers lack familiarity with the use of GnRHa for severe PMDD and frequently require submission of prior authorizations with supportive evidence from the literature[21] before approving GnRHa prescription coverage. Further, many insurance providers require annual resubmissions of previously approved authorizations and, despite evidence of successful treatment and remission of symptoms, do not always approve continued use for the subsequent year. It is important to educate patients about these potential difficulties and encourage patients to be as proactive as possible in regards to informing the provider and pharmacy about any insurance denials or changes to help minimize interruptions in treatment. This difficulty highlights the importance of continued research in the field to help support the safety and clinical efficacy of prolonged GnRHa treatment with addback hormones for patients who suffer from PMDD.

Acquiring Treatment Consent

After a patient and provider have concluded that GnRHa is a safe treatment option and insurance coverage has been obtained, monthly GnRHa injections can begin. Prior to and on the day of the first injection, it is recommended that the provider reviews, with the patient, the benefits, risks, and side effects of GnRHa treatment both with and without addback hormones (see Supplementary Appendixes 3 and 4). We also recommend discussing that although PMDD is not a listed FDA indication for leuprolide, the scientific evidence has supported this indication for more than 20 years, and this discussion should be documented in the electronic medical record.

Administering GnRHa Injections

To aid in presenting a reasonable course of administration, we have included a GnRHa treatment flowchart in the supplementary materials (see Supplementary Figure 2). With the known sensitivity of this population to rapid hormone changes, it is ideal to time the injection with the onset of menses or within the early follicular phase, which should minimize large hormone level shifts and help with tolerability. It is prudent to discuss the likelihood of experiencing menopausal symptoms while receiving GnRHa without addback and highlight that after addback hormones are added, these menopausal symptoms should decrease or remit altogether. It is also important to inform about the possibility of a resurgence of PMDD symptoms during the first month of addback therapy and highlight that these symptoms should diminish with time and stable addback treatment.[12]

During the initial month of treatment, the GnRHa injection can be given with or without addback hormones. Prior recommendations to postpone the addback in service of ensuring that GnRHa improved symptoms is not necessary with prospectively diagnosed PMDD and may cloud the picture more than it helps given the occurrence of postmenopausal symptoms with GnRHa alone. We advocate that it is reasonable for the clinician and patient to discuss the possibility of starting addback with the first cycle to avoid the occurrence of postmenopausal symptoms, acknowledging that 30% of patients will not respond to this treatment paradigm.[23] It is well understood that some patients may not respond to leuprolide plus addback at all, but is reasonable to start simultaneously and assess whether the combination was effective. The monthly injection dose of leuprolide for PMDD is 3.75 mg; this dose and regular monthly appointments should be used until the patient has demonstrated consistent benefit from leuprolide injections with addback hormones. After at least 1 month of improved symptoms on the combination of GnRHa plus addback, the provider can consider transitioning the patient to a leuprolide injection every 3 months with a dose of 11.25 mg.[21,30]

Administration of Addback HRT

Initiating addback despite temporary symptom resurgence. It is important to inform patients that they may experience an increase or return of PMDD symptoms in the first month of addback that will subside in the subsequent months.[12] Many patients are distressed during the first month of addback and become convinced that they must stop or adjust levels of hormone addback. This is not advisable,

as clinical trials support the hypothesis that PMDD is generally a delayed reaction due to sensitivity of the brain to hormone *changes* triggering symptoms, and symptoms remit once those hormonal doses have been stable for at least 1 month. If patients are at high risk of psychosocial impairment or have a history of suicidal thoughts, it may be advisable to initiate weekly check-ins or psychotherapy in order to monitor for and avoid severe decompensation during the first month of addback.

Combination therapy is necessary in patients with a uterus. Estradiol therapy appears to be the critical element for reduction of side effects and medical risks. However, unopposed estradiol addback (ie, estrogen without a progestin to "oppose" its effects) is typically not recommended in patients with a uterus since there can be a risk of endometrial hyperplasia and subsequent risk of uterine cancer that is fully reversed with progestogen addback (to precipitate endometrial shedding/menses). If the patient does not have a uterus, these concerns are not present, and estradiol-only addback can be provided.

The unique need for stable hormone addback in PMDD. Longer-term GnRHa trials, which have been conducted almost exclusively in the context of endometriosis, have largely focused on stable doses of estrogenic compounds along with cyclical administrations of progestogens. While similar stable doses of estradiol may be appropriate for addback in PMDD, the cyclical approach to progestin addback may not be ideal for PMDD, since shifting levels are more likely to trigger emotional symptoms.[12] Therefore, consistent with other expert guidelines,[25–27] we recommend stable daily addback of both estradiol and progesterone.

Addback formulation. Transdermal estradiol has the most favorable safety profile for clotting, stroke, and lipid level changes compared to other administration routes[67–70] and is also the preferred route for patients with migraine headache with auras.[71–73] Transdermal estradiol is recommended in PMDD as well; if not feasible, oral micronized estradiol is also a well-studied and widely available option.

Oral micronized progesterone is generally preferred over medroxyprogesterone acetate (MPA) and other progestins, although both offer endometrial protection. Unlike MPA, which has been associated with breast cancer and cardiovascular risks, micronized progesterone is considered metabolically neutral based on limited data.[74–77]

LNG-IUS are contraceptive agents that are *not* FDA approved for endometrial protection for postmenopausal HRT; yet, they have been approved in over 90 countries for this indication as well as for treatment of simple endometrial hyperplasia in perimenopausal patients in the United Kingdom. LNG-IUS combined with estrogen therapy are a good or better option for prevention of endometrial hyperplasia as compared to systemic estrogen/progestin treatment[78,79] and may be considered as an off-label use for addback in patients who cannot tolerate progestins,[80] who experience heavy vaginal bleeding, or who desire highly efficacious prevention of pregnancy.[81] This recommendation is based on clinical guidelines from the United Kingdom.

Addback dosing. Dosing of hormonal addback is typically aimed at achieving an average premenopausal level, starting at 0.05 mg/wk transdermal estradiol patches (with oral equivalents around 1 mg/d oral micronized estradiol or 0.0625 mg conjugated equine estrogens). If menopausal symptoms persist, estradiol dosages can be increased. Dosing of oral micronized progesterone is typically started continuously at 100 mg/d (a dose roughly equivalent to 2.5 mg MPA). Adjustments can be made as needed to ensure endometrial protection. Again, it is critical in PMDD that addback be given in a stable, non-cyclical regimen to avoid triggering hormone-change–sensitive mood symptoms.

Birth Control and Fertility

Although GnRHa leads to anovulation in the vast majority of instances, some patients may still ovulate during the initial administration and can become pregnant.[82] Therefore, barrier contraception is generally recommended to prevent pregnancy. GnRHa treatment is not known to have long-term effects on fertility when initiated in adults. Among patients who require more effective contraception, use of LNG-IUS for endometrial protection (in lieu of an oral progestogen) may be a reasonable approach,[27] although this can be painful upon insertion and, although less often, upon removal in the event that it is not tolerated.[83]

When to Consider Referral for Oophorectomy (Surgical Menopause)

Depending on an individual's reproductive life goals, proceeding with a hysterectomy with bilateral oophorectomy (surgical menopause) after successful treatment with a GnRHa (chemical menopause) can be a viable option. Of note, if the uterus is removed, stable addback of unopposed estradiol can be initiated following surgical treatment to reduce side effects and risks of hypogonadism. However, if the uterus remains, both estradiol and progesterone will be necessary (see above).

We recommend establishing a relationship with a gynecology practice prior to initiation of GnRHa trials in service of finding a collaborating provider who can assist in completing this surgical intervention as indicated. Depending on the gynecologist's level of familiarity with PMDD, you may need to provide education regarding the diagnosis and treatment of PMDD, as well as the evidence for both GnRHa (chemical menopause) and oophorectomy (surgical menopause) in those with severe PMDD to facilitate a collaboration.

Monitoring Benefit/Improvement

While tracking response to treatment, first-line, second-line, and third-line (GnRHa plus addback) patients should be seen at least monthly until their symptoms are well controlled. Daily symptoms should be monitored throughout the treatment process to provide a clear indication of treatment effectiveness.

CRITICAL AREAS FOR FUTURE RESEARCH

Although the evidence for use of GnRHa in PMDD is sound, there are many limitations of the literature that require future research to optimize treatment protocols.

Comparisons of GnRH Agonists With GnRH Antagonists

GnRH antagonists could hypothetically be superior to GnRH agonists in that they avoid side effects associated with the initial "flare" of estradiol and progesterone early in GnRH agonist treatment and broadly have a better safety profile relative to agonists in males.[84] Additionally, the GnRH antagonist degarelix yields greater suppression of ovarian activity relative to the GnRH agonist triptorelin.[85]

Optimal Timing, Route, and Dosing of Hormone Addback

Although a variety of smaller trials have indicated that GnRHa plus hormonal addback can be tolerated by those with PMDD over the long term, the remaining side effects and setbacks[12] might be reduced by optimizing addback route, dose, and timing. Regarding timing, trials are needed to determine whether immediate addback of estradiol and progesterone (coinciding with the first GnRHa treatment) may be associated with superior outcomes and fewer side effects compared to the traditional timing used for endometriosis treatment, in which hormone addback is initiated in the second month of GnRHa.

Studies to optimize estradiol addback. Clinical trials are needed to determine the optimal estradiol dose for reducing menopausal side effects and protecting other systems in the context of long-term chemical menopause. Since the hypogonadal state induced by GnRHa is similar in many ways to that of primary ovarian insufficiency and surgical menopause, the recommendations of higher estradiol supplementation in these populations (eg, 0.1 mg/d transdermal estradiol[86]) may also be most appropriate for those in chemical menopause; however, a lack of clinical trials to evaluate the safety and efficacy of long-term estradiol dosing in chemical menopause precludes authoritative recommendations.

Studies to optimize progestogen addback. Direct comparisons regarding safety and side effects between oral micronized progesterone and synthetic progestins are needed. Overall, however, oral micronized progesterone appears to be the more conservative approach in that it more similarly mimics the normal premenopausal endocrine state and is metabolized to neuroprotective steroids like allopregnanolone, whereas synthetic progestins are not. On the other hand, synthetic progestins are more potent agonists at the PR and may better control endometrial proliferation and nuisance bleeding during long-term treatment. Studies should also evaluate the tolerability and effectiveness of the LNG-IUS as an alternative form of endometrial protection in PMDD during GnRHa + estradiol addback.[27]

Identification of More Accessible Agents for Ovarian Suppression

In addition to refinement of protocols using widely available GnRHa, more accessible agents should be trialed to establish their long-term safety, tolerability, and effectiveness in PMDD. The GnRH antagonist elagolix, for example, is available in oral formulation and approved for use in endometriosis. In addition, selective progesterone receptor modulators such as oral ulipristal acetate may represent a viable alternative for suppression of ovulation and treatment of PMDD.[87]

CONCLUSION

In this narrative review, we argue that there has been insufficient implementation of clinical trials evidence supporting the use of GnRHa in PMDD. Despite years of compelling evidence for the safety and efficacy of GnRHa (+/– addback) in PMDD, this treatment remains extremely difficult for patients to access in clinical practice. Furthermore, despite the fact that PMDD represents a psychiatric condition characterized by a neurobiological sensitivity to hormone changes, most psychiatrists—even reproductive psychiatrists—do not currently offer GnRHa treatment for severe, treatment-resistant PMDD. Since recent evidence indicates that GnRHa + stable ovarian hormone addback may be safer than surgical menopause, we have outlined practical recommendations for use in clinical practice. We hope that these guidelines will enhance the ability of reproductive psychiatry clinics to provide comprehensive, evidence-based care for patients with PMDD.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: What's Stopping Us? Using GnRH Analogs With Stable Hormone Addback in Treatment-Resistant Premenstrual Dysphoric Disorder: Practical Guidelines and Risk-/Benefit Analysis for Long-term Therapy

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APPENDIX 1

PREMENSTRUAL DYSPHORIC DISORDER - INFORMATIONAL HANDOUT FOR PROVIDERS

What is Premenstrual Dysphoric Disorder (PMDD)?

PMDD is a cyclical, hormone-triggered mood disorder with symptoms arising during the luteal phase of the menstrual cycle (the 10-14 days leading up to menses), improving during menstruation, and subsiding by the week following menstruation. It affects an estimated 5.5% of people with menstrual cycles.

DSM-5 criteria for PMDD requires the cyclical "on-off" pattern in one or more of the core affective symptoms as well as a total of five cycling symptoms overall, which may come from the core affective symptoms or the additional "secondary" symptom list. Of the symptoms listed amongst the criteria below, the most common are irritability and mood swings, with symptoms of anxiety being the next most common, and symptoms of depression being the least common (Pearlstein et al 2005).

Core affective symptoms of PMDD as listed in the DSM-5:

1. Mood swings
2. Sudden sadness
3. Increased sensitivity to rejection
4. Anger, irritability
5. A sense of hopelessness
6. Depressed mood
7. Self-critical thoughts
8. Tension, anxiety, feeling on edge

Secondary symptoms of PMDD:

1. Difficulty concentrating
2. Change in appetite, food cravings, overeating
3. Diminished interest in usual activities
4. Easy fatigability, decreased energy
5. Feeling overwhelmed or out of control
6. Breast tenderness, bloating, weight gain, joint/muscle aches
7. Sleeping too much or not sleeping enough

PMDD is included in both the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and the International Classification of Diseases, 11th Revision (ICD-11).

How is PMDD diagnosed?

Retrospective self-report of a cyclical symptom pattern is not an accurate method of diagnosis, as it is strongly prone to false-positive reporting[1]. Therefore, a clinical interview alone cannot be used to make a valid diagnosis of PMDD, and the DSM-5 requires daily ratings of symptoms across two cycles to establish the pattern of symptoms[2,3]. Of note, while daily ratings are necessary to confirm the diagnosis of PMDD, they are not necessary to validate the suffering that the patient is reporting. Expressions of compassionate curiosity are ideal (e.g., "let's use daily ratings to learn more about how these symptoms are changing for you").

Two months of daily severity ratings for each DSM-5 symptom should be evaluated to determine the presence of distressing or impairing symptoms in the premenstrual week that become minimal or absent by the week after menses. We recommend the use of either a pencil-and-paper rating form, or a smartphone app that incorporates the DSM-5 criteria and dimensional symptom severity (e.g., PreMentricS). Pencil-and-paper rating forms for the gold-standard Daily Rating of Severity of Problems (DRSP)[4] are available (https://www.aafp.org/afp/2011/1015/afp20111015p918-fig1.pdf), and can be evaluated using the diagnostic scoring system provided in the original DRSP validation paper[4].

While the DSM-5 diagnosis requires that five cycling symptoms be present to make the diagnosis of PMDD, most clinical experts agree that evaluating the overall cyclicity of distress and impairment is central for determining the need for treatment. The arbitrary five-symptom threshold in the DSM-5 was selected in part to prevent the overdiagnosis of healthy females in response to various academics voicing concern about the "overmedicalization" of the female experience[5]. However, there is evidence that this threshold may be too high; one study found that the optimal cutpoint for prediction of cyclical impairment among patients seeking a diagnosis of PMDD was 4 symptoms[6]. Therefore, in clinical settings, we encourage providers to use daily ratings to evaluate for the presence of clinically-significant cyclical distress or impairment.

Comorbidities and Exacerbations of Underlying Illness

There is a widely-held misconception that PMDD must not be comorbid with other psychiatric conditions (e.g., major depressive disorder, borderline personality disorder); in reality, these diagnostic categories typically intersect, with patients showing some PMDD-pattern symptoms (present only premenstrually), some chronic symptoms that show premenstrual exacerbation (PME; present all the time but worsening premenstrually), and some stable symptoms[7]. We have found that psychiatric comorbidity is the rule rather than the exception, even among patients who have received a prospective diagnosis of PMDD from a medical professional, and that comorbidities do not fully account for adverse outcomes such as suicidality in PMDD[8,9]. Therefore, differential diagnosis of PMDD and PME from other disorders relies on a symptom-by-symptom approach to diagnosis in which each DSM-5 symptom is evaluated separately for cyclical change using daily ratings[7]. While identification and treatment of stable psychiatric comorbidities is certainly important, their presence does not preclude diagnosis and treatment of cyclical symptom changes.

Educating Patients about PMDD and Establishing Shared Understanding

Patients differ widely in their awareness and knowledge about PMDD and its evidence-based treatment. While some patients may have no knowledge of PMDD, other patients may come to treatment with greater knowledge about PMDD than their provider. Of note, many patients with chronic, treatment-resistant PMDD turn to the internet to find information and support. While some online resources are curated by clinical experts in the area with an emphasis on scientific evidence (e.g., www.iapmd.org), many others are confidently written but recommend treatments which lack empirical support for PMDD (e.g., testing for hormone “imbalance”, oral micronized progesterone). Therefore, psychiatrists should provide patients with some basic education about the nature, causes, and evidence-based treatment of PMDD, and correct common misunderstandings. A patient handout (see below) can serve to scaffold the interaction between the patient and the provider by creating shared expectations and understanding, as well as supporting certain aspects of the initial evaluation.

Trialing Selective Serotonin Reuptake Inhibitors (SSRI; First-Line)

Complete reviews of first- and second- line treatments for PMDD are available elsewhere, including evidence-based pharmacologic options[10] and non-pharmacologic options[11]. Here, we highlight the treatments with positive evidence. Trials of at least two first line options, and at least one second line treatment option, is usually required for patients when initially diagnosed with PMDD prior to consideration of GnRHa, although this may depend upon individual differences in tolerance and effectiveness.

Numerous trials have established SSRIs as the first-line evidence-based treatment for PMDD[12]. In contrast to their longer onset of action in other depressive disorders, some trials have documented an SSRI benefit over placebo in reducing PMDD symptoms of irritability, sadness, anxiety, and mood swings after just 24 hours[13,14] and luteal phase dosing (post-ovulation until menstruation) has been found to be similarly effective to continuous dosing[12] without evidence for adverse withdrawal effects during monthly cessation of SSRI use[15]. Not surprisingly, then, some studies suggest that shorter dosing intervals, only while symptomatic, may also be effective[15]; however, at this time there is insufficient evidence to recommend symptom-onset dosing as a first-

line treatment. Low and moderate SSRI doses appear to be effective (see Table 1); there is limited evidence regarding use of high doses[12]. Decisions regarding SSRI choice, dose-escalation, and duration of use (i.e., symptomatic days vs luteal phase vs continuous) should be based on a discussion between the patient and their provider, including consideration of treatment response, comorbidities, tolerability, and (persistence of) side effects. Treatment for at least one full cycle while monitoring daily symptom ratings and side effects is recommended before changing to an alternate dose or SSRI or moving on to second line options. Given the short onset of action in PMDD, however, improvements with SSRI treatment should be observable in the first cycle. If no response is evident in the first cycle, trial of a different SSRI is usually the next step. If partial response is noted, dose escalation in the subsequent cycle is our typical approach.

Trialing Oral Contraceptives (Second-Line)

If SSRI treatment fails, or if the patient is seeking contraception, we recommend trial of an ovulation-suppressing agent. Combined oral contraceptive (OC) formulations containing the progestin drospirenone, taken on a 24-4 schedule (24 days of active hormone, followed by 4 days of inactive pills) reduced DRSP symptom scores compared to placebo in RCTs[16–18], although a recent meta-analysis suggests a need for more research to understand for whom (or for which symptoms) this treatment is effective[19]. Levonorgestrel-containing OCs on a continuous dosing schedule also reduced DRSP symptom scores compared to placebo in some trials, although evidence is mixed[20]. Similarly, two clinical trials demonstrate ovulation-suppressing doses of estradiol (implants or patches; 100-200mg/day) and progestins (oral) reduce PMDD symptoms compared to placebo[21]. In contrast, clinical trials evaluating other OCs on a 21-7 schedule for PMDD have generally failed to demonstrate efficacy, and some progestin-only contraceptives may hold greater risk of adverse mood reactions[22]. OCs should be trialed for at least two cycles with monitoring of daily symptoms prior to considering third line options. Note that one clinical trial also supports the superiority of combined therapy with drospirenone-containing OCs and SSRI relative to drospirenone-containing OC alone[23]; therefore, if response to monotherapy with either SSRI or OC is partial, addition of the other may be a useful strategy. Drospirenone-containing OCs may pose a greater risk of venous thromboembolism (VTE) relative to other progestins[24]; this should be discussed with patients prior to initiation of treatment. However, at this time, VTE screening is not different for drospirenone-containing OCs and all patients initiating an OC should be screened for VTE risk factors including personal clot history, known hereditary thrombophilia (e.g., Factor V Leiden), age ≥ 35, BMI over 30, and nicotine use; consistent with the CDC guidelines[25].

Trialing Augmenting Agents (Third-Line)

If a patient has partially responded to a first-line agent (SSRI) and/or a second-line agent (drospirenone-containing OCs), augmentation strategies may help achieve a more complete response. Augmentation strategies include medications and behavioral interventions. Psychopharmacologic augmentation strategies with supporting evidence include alprazolam[26], quetiapine[27], and buspirone[28]. However, benzodiazepines should be used sparingly and only after evaluation for a substance use disorder[29].

Although it is unknown whether behavioral psychotherapy addresses the biological mechanisms of hormone change sensitivity in PMDD, it appears to be a useful adjunct to pharmacologic treatment in many cases. Two RCTs using structured CBT do support its use for reduction of PMDD symptom severity and impairment[30,31]. Further, if the patient struggles with a lack of skill for managing extreme emotions during PMDD-- and particularly if there is a pattern of self-injurious or suicidal behaviors-- we recommend referral for dialectical behavior therapy since this treatment has a strong evidence base for improving emotion regulation skills and reducing risk of suicide[32].

Summary

The first step in treating patients with PMDD is compassionate curiosity and validation, as it often takes years for patients to receive accurate diagnosis. After confirming symptom cyclicity with daily ratings and considering comorbidities and exacerbations of other psychiatric diagnoses, medical providers can start first-line treatment for PMDD. SSRIs are first line, and after one month of non-response, trial of another SSRI is often the next

step. Second line treatment is drospirenone-containing oral contraceptives, and third line treatments include pharmacologic augmentation and behavioral interventions. If the patient has still not experienced symptom relief after trialing all evidence-based treatment, we advise patients and providers share informed decision-making to consider use of GnRH analogs. At this point, we offer the associated manuscript with detailed recommendations and risk/benefit analysis for long-term use of GNRHa.

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APPENDIX 2

PREMENSTRUAL DYSPHORIC DISORDER – PATIENT INFORMATIONAL HANDOUT

What is Premenstrual Dysphoric Disorder (PMDD)?

PMDD is a cyclical, hormone-triggered mood disorder with symptoms arising during the luteal phase of the menstrual cycle (the 10-14 days leading up to menses), improving during menstruation, and subsiding by the week following menstruation. It affects an estimated 5.5% of people with menstrual cycles.

Here are the symptoms of PMDD as listed in the DSM-5:

1. **Mood/emotional changes** (e.g. mood swings, feeling suddenly sad or tearful, or increased sensitivity to rejection)
2. **Irritability**, anger, or increased interpersonal conflict
3. **Depressed mood**, feelings of hopelessness, feeling worthless or guilty
4. **Anxiety**, tension, or feelings of being keyed up or on edge
5. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
6. Difficulty concentrating, focusing, or thinking; brain fog
7. Tiredness or low-energy
8. Changes in appetite, food cravings, overeating, or binge eating
9. Hypersomnia (excessive sleepiness) or insomnia (trouble falling or staying asleep)
10. Feeling overwhelmed or out of control
11. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, bloating or weight gain

PMDD is included in both the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and the International Classification of Diseases, 11th Revision (ICD-11).

How is PMDD diagnosed?

Because the reproductive system and ovarian hormones are normal in PMDD, there is no blood test to diagnose it. Instead, the diagnosis is made by tracking the eleven symptoms listed above against your menstrual cycle for at least two cycles. A diagnosis of PMDD requires that at least five of the eleven symptoms (one of which must be from the first four listed above) are moderately distressing or impairing in the weeks before menses and become minimal or go away in the week after menses. Smartphone apps like Prementrics can be used to track symptoms, or pencil-and-paper methods can also be used (https://www.aafp.org/afp/2011/1015/afp20111015p918-fig1.pdf).

PMDD is defined as a reaction to “ovulatory” menstrual cycles (that is, cycles in which an egg is released from the ovaries); therefore, it cannot be diagnosed if you are not currently ovulating. Ovulation does not happen when taking hormonal contraceptives (with the exception of some hormonal intrauterine devices, IUDs), when pregnant (and often when breastfeeding), and after the menopause transition. While similar mood symptoms can arise without ovulation when medication changes cause hormone flux, these are not typically considered PMDD (since PMDD is a reaction to cyclical ovulation) and are instead referred to as medication-induced mood disorders.

What Causes PMDD?

While PMDD is directly triggered by the hormone changes of the menstrual cycle, it is not a hormone imbalance. PMDD is an abnormal neurobiological sensitivity to the natural rise and fall of estrogen and progesterone that happen following ovulation. There are several lines of research ongoing, but so far they

suggest that there are differences in how luteal phase hormones affect the brain's signaling molecules (especially serotonin) that are probably responsible for symptoms in most cases.

How is PMDD Treated?

Given the causes noted above, treatments are usually aimed at either (1) using medications to buffer the brain against cyclical serotonin changes, or (2) suppressing ovulation so that they do not make fluctuating hormones (so that the brain's sensitivity is not triggered).

Below, we will review each of the typical treatment options for PMDD in the order that they are usually given. Keep in mind that this is a general list, and not all medications are safe for all people. Your doctors will need to evaluate whether each treatment option is safe and appropriate for you given your unique medical history.

Selective Serotonin Reuptake Inhibitors (SSRIs; pills). For buffering the brain against cyclical serotonin changes, SSRIs are the most common medications, and there are many studies showing they work better than a placebo (sugar pill). These medications work faster in PMDD than in depression-- in fact, studies show that they work better than placebo for PMDD after just 24 hours. If the first SSRI doesn't work for you, your provider will likely change the dosage or prescribe a different SSRI (e.g., Prozac (fluoxetine), Zoloft (sertraline), Lexapro (escitalopram)) before other treatments are explored. Because SSRIs work quickly in PMDD, many people are able to take them only during the luteal phase of their cycle, and studies show that this is often equally effective and well-tolerated by patients. In addition to the many clinical trials showing that SSRIs benefit symptoms in PMDD[1], one elegant experiment demonstrated that, following remission of PMDD symptoms on SSRI, randomization to metergoline (a serotonin receptor agonist) was associated with a resurgence of symptoms relative to placebo.[2] This experiment provides strong evidence that SSRIs benefit PMDD via a serotonergic mechanism.

Combined Oral Contraceptives (COCs; pills). For suppressing the ovaries and related hormones, COCs are a common approach -- but the best studies indicate that they need to be dosed on an "extended cycle" (that is, on a 24 active-4 inactive, or continuous active schedule rather than a 21 active-7 inactive schedule) in order to reduce hormone fluctuations. Some studies find that drospirenone-containing COCs work the best, whereas other studies find no difference between pills as long as continuous or extended-cycle dosing (24-4, continuous) is used.

Other Options for Symptom-Management. When SSRIs or COCs have failed, most patients work with a psychiatrist to consider **alternative medications** that might alleviate their symptoms. **Cognitive behavioral therapy** can also be helpful to cope with chronic symptoms and can be tried without additional medications or in conjunction with treatment options.

Gonadotropin-releasing hormone analogs (GnRHa; monthly injections). If all of the treatments above haven't worked, and you're still experiencing upsetting or impairing symptoms each month, it may be time to seek a consultation for a different, stronger method for suppressing the ovaries. Medications called GnRHa (e.g., leuprolide) can be used as a way to create a low, stable hormone state like menopause. In order to prevent all of the risks and side effects associated with an early menopausal state, **stable hormone replacement therapy (estrogen and progesterone)** is needed to make this approach safe long-term. Sometimes, symptoms can flare temporarily during the early phases of this treatment process, but generally go down after hormones have been stable for about one month.

Although GNRHa injections (usually monthly) have been found to work better than a saline injection in many clinical trials, they are not currently FDA approved for PMDD (because this approval has never been sought). That means that it can be difficult to get this medication covered by insurance; usually, the diagnosis must be documented using daily symptom ratings, and full medical records indicating failures of other treatments (listed above) are necessary. Your doctor will usually have to write a special letter to the insurance company to convince them to cover this medication. In some cases this fails, and the treatment cannot be covered by insurance.

Oophorectomy (removal of both ovaries). In some complex cases, surgical removal of the ovaries (which creates a permanent low-hormone menopause state) can be used to treat PMDD. However, this is usually only considered when GnRHa therapy has been effective but cannot be continued for some other medical reason. The uterus is also removed in most cases, which eliminates the need for progesterone addback-- that means that estrogen-only hormone replacement therapy can be given. Given the major risks of this surgical approach, we recommend that all other options be exhausted before it is considered.

***This handout was developed by the authors of this paper. Please see the main article references for specific references in addition to the below.**

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APPENDIX 3

Risk Factor Assessment (Patient Version)

	Yes	No
Have you ever been told you have a blood clotting disorder?		
Does anyone in your family have a history of blood clotting disorders?		
Have you ever been told by a doctor that you have a genetic mutation that puts you at risk for blood clots?		
Have you ever been diagnosed with, or do you think you might have ever had, a pulmonary embolism (blood clot in the lungs), deep vein thrombosis (blood clot in the leg), or other blood clots?		
Do you currently smoke or vape nicotine containing products?		
Have you ever been diagnosed with cancer? This includes breast cancer, ovarian cancer, colon cancer, skin cancer, or any other type of cancer.		
Including yourself, has anyone in your family (children, siblings, parents, aunts, uncles, cousins, or grandparents) been told that they have a genetic mutation associated with breast or ovarian cancer (e.g. a mutation in the BRCA1, BRCA2, PTEN, or Tp53 genes)?		
Have you ever been diagnosed with endometriosis or uterine fibroids?		
Have you ever had migraines?		
Have you ever been told you have osteoporosis or low bone mineral density?		
Have you ever been told you have an illness that increases your risk for osteoporosis, including but not limited to anorexia nervosa or bulimia?		
Have you or has anyone in your family been diagnosed with any type of cardiovascular disease, including high blood pressure or coronary artery disease, before age 55?		
Have you or anyone in your family been diagnosed with prolonged QT syndrome or have you been told that you have a prolonged QT interval based on an EKG of your heart?		
Do you have epilepsy or a history of seizures?		
Do you have elevated liver enzymes or liver disease?		

** This table was developed by the authors of this paper.

Risk Factor Assessment (Provider Key)

Screening Questions	Eligibility Determination
Have you ever been told you have a blood clotting disorder?	If the patient answers yes to any of these questions, this is not a rule out as addback hormones should not increase VTE risk above natural cycling levels. However, we recommend discussing the risks of a clot including signs and symptoms of a DVT or PE prior to initiation of therapy and assessing for other comorbidities that elevate clotting risk. If the patient has multiple comorbidities or is on treatment for a hypercoaguable state, we recommend consulting with the provider managing the anticoagulant prior to initiating GnRHa with addback.
Does anyone in your family have a history of blood clotting disorders?	
Have you ever been told by a doctor that you have a genetic mutation that puts you at risk for blood clots?	
Have you ever been diagnosed with, or do you think you might have ever had, a pulmonary embolism (blood clot in the lungs), deep vein thrombosis (blood clot in the leg), or other blood clots?	
Do you currently smoke or vape nicotine containing products?	Smoking or vaping is not a rule out as addback hormones should not increase VTE risk above natural cycling levels. However, counseling on minimizing nicotine use is recommended.
Have you ever been diagnosed with cancer? This includes breast cancer, ovarian cancer, colon cancer, skin cancer, or any other type of cancer.	The patient is ineligible if she has a personal history of breast cancer. If a patient responds with a yes for other cancers, the patient is eligible to move forward. We recommend discussing the following with the patient: cancer risks associated with hormone addback are expected to be lower than use of HRT during menopause due to suppression of underlying ovarian activity.
Including yourself, has anyone in your family (children, siblings, parents, aunts, uncles, cousins, or grandparents) been told that they have a genetic mutation associated with breast or ovarian cancer (e.g. a mutation in the BRCA1, BRCA2, PTEN, or Tp53 genes)?	If a patient responds yes, consider additional consultation with a geneticist or oncologist prior to proceeding with GnRHa with addback.
Have you ever been diagnosed with endometriosis?	In patients with endometriosis the addition of addback hormones is unlikely to cause sustained exacerbations and will likely provide reduction in symptoms, as GnRHa plus addback hormones has been shown to be an effective treatment for endometriosis for up to 6 months.

Have you ever had migraines?	If the patient answers yes to having a history of migraines the patient is eligible to move forward with GnRHa with addback hormones. Counsel the patient on monitoring migraine frequency and intensity. Hormone-sensitive migraine frequency should reduce with GnRHa alone and remain stable with addback. A deviation from this prediction warrants follow up.
Have you ever been told you have osteoporosis or low bone mineral density?	If the patient responds yes, you may move forward with GnRHa with addback. GnRHa without addback will increase the risk of decreased bone mineral density.
Have you ever been told you have an illness that increases your risk for osteoporosis?	
Have you or has anyone in your family been diagnosed with any type of cardiovascular disease, including high blood pressure, coronary artery disease, or a stroke, before age 55?	Studies have demonstrated an increase in serum cholesterol which is known to be related to increased risk of cardiovascular disease and strokes. However the significance of the increased levels is unknown. Consideration of the patients other cardiovascular comorbidities is prudent prior to initiation of therapy. Patients with a personal history of coronary artery disease or stroke should not initiate treatment.
Have you or anyone in your family been diagnosed with prolonged QT syndrome or have you been told that you have a prolonged QT interval based on an EKG of your heart?	Leuprolide is associated with QTc prolongation in men due to the suppression of androgen. It is not thought to cause QTc prolongation in women. However, we recommend counseling the patient and obtaining a baseline EKG if the patient has a personal or family history of QTc prolongation and monitoring QTc with a repeat EKG after initiation of Leuprolide.
Do you have epilepsy or a history of seizures?	There are post-marketing reports of seizures within the first several months after initiation of GnRHa. This event remains rare but those with a history of seizures should be counseled on this rare but possible risk.
Do you have elevated liver enzymes or liver disease?	Without add-back this is not a concern. In dual-hormonal therapy (estrogen plus progesterone) add-back data is also reassuring. Studies using only progesterone addback were associated with increase in liver enzymes and this type of add-back should be avoided. We do not recommend progesterone-only add-back in general.

*** This table was developed by the authors of this paper. Answers provided are supported within the primary paper. Please see references cited in the section '**Assessing Comorbidities and Relevant Risk Factors'.**

APPENDIX 4

Treatment Side Effects

As with any medication, treatment with ***GnRH agonists*** has risks and may result in side effects. Below are some of the common side effects you may notice with treatment initiation. These are expected in some patients and are unlikely to put you at risk for serious complications. Most of these side effects should resolve once hormonal addback has been stable for at least one month.

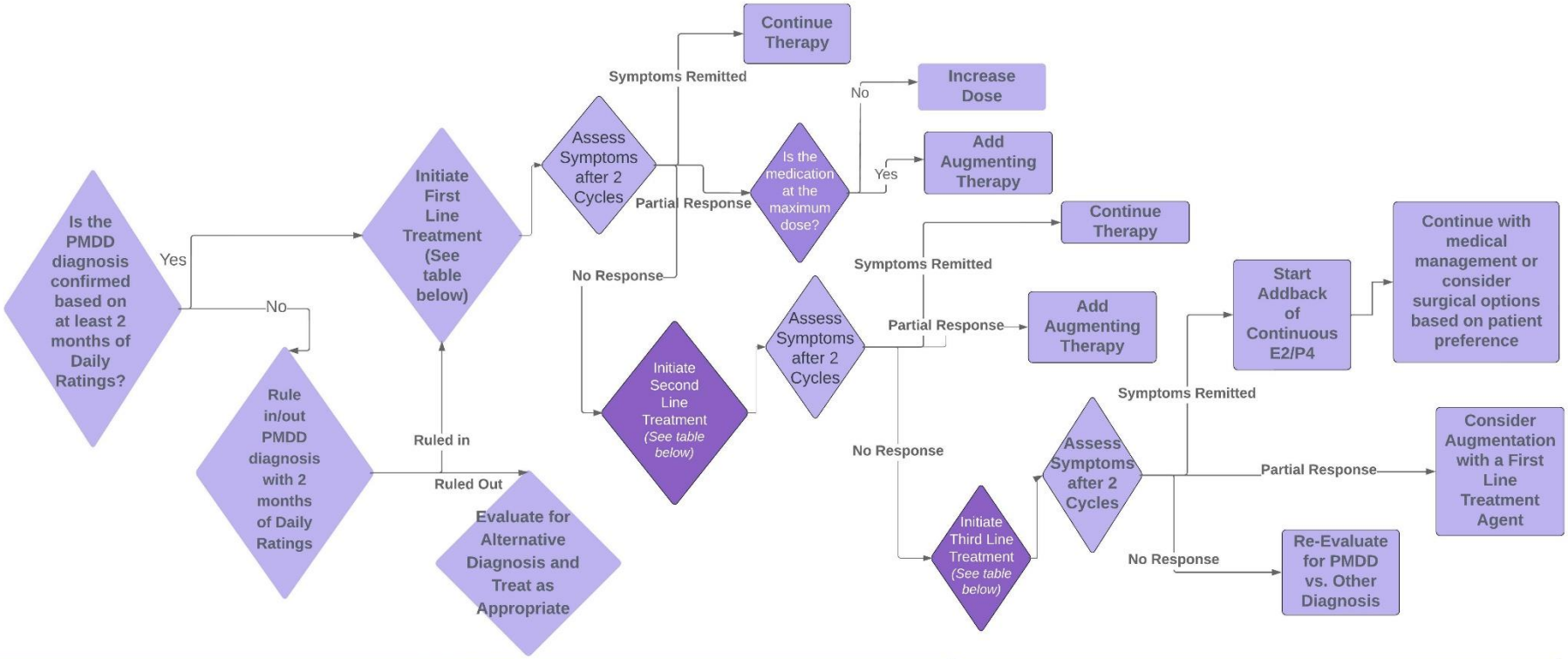
- Hot flashes
- Headaches
- Fatigue
- Increased sweating
- Changes in sleep
- Nervousness
- Dizziness
- Nausea
- Vomiting
- Constipation
- Diarrhea
- Palpitations (heart racing)
- Vaginal dryness
- Changes in weight
- Decreased libido
- Vaginitis
- Flu-like symptoms

Certain side effects are more serious and worrisome than others. Please consult your doctor immediately or go to the Emergency Room if you experience any of the following side effects:

- Chest pain
- Difficulty breathing
- Loss of consciousness
- Seizure
- Pain in your legs, pain behind your knee, or pain behind your calf
- Swelling in one of your legs or feet
- Changes in your vision
- Concerning breast lumps

References: This handout was created by the authors of this paper. Please see the main article, section entitled **'The Role of Addback in Mitigating Risks and Side Effects'** for specific references.

Supplementary Figure 1. PMDD Treatment Decision Tree: First, Second, and Third Line Treatments, Plus Augmenting Agents



First Line Treatment
(SSRIs)

Fluoxetine	Sertraline	Paroxetine ER	Citalopram	Escitalopram
Start: 10-20 mg Increase by 10-20 mg Max Dose: 60 mg	Start: 25-50 mg Increase by 50 mg Max Dose: 150 mg	Start: 12.5 mg Increase by 12.5 mg Max Dose: 25 mg	Start: 5-10 mg Increase by 5-10 mg Max Dose: 20 mg	Start: 5-10 mg Increase by 5-10 mg Max Dose: 20 mg

Second Line Treatment
(Ovulation Suppression with Highly Accessible Agents)

Drospirenone-Containing OCs (24-4 Schedule)	>	Transdermal Estrogen + Progestogen (to suppress ovulation)	=	Levonorgestrel-Containing Oral Contraceptive (Continuous Schedule)	=	Other Ovulation-Suppressing Birth Control

Augmenting Agents

Psychotherapeutics		*Behavioral Interventions*		*Supplements*	
Buspirone 10mg	Quetiapine 25mg (+)	Cognitive Behavioral Therapy	Exercise	Chasteberry *Vitex agnus castus*	St. John's Wort *Hypericum perforatum*

Third Line Treatment

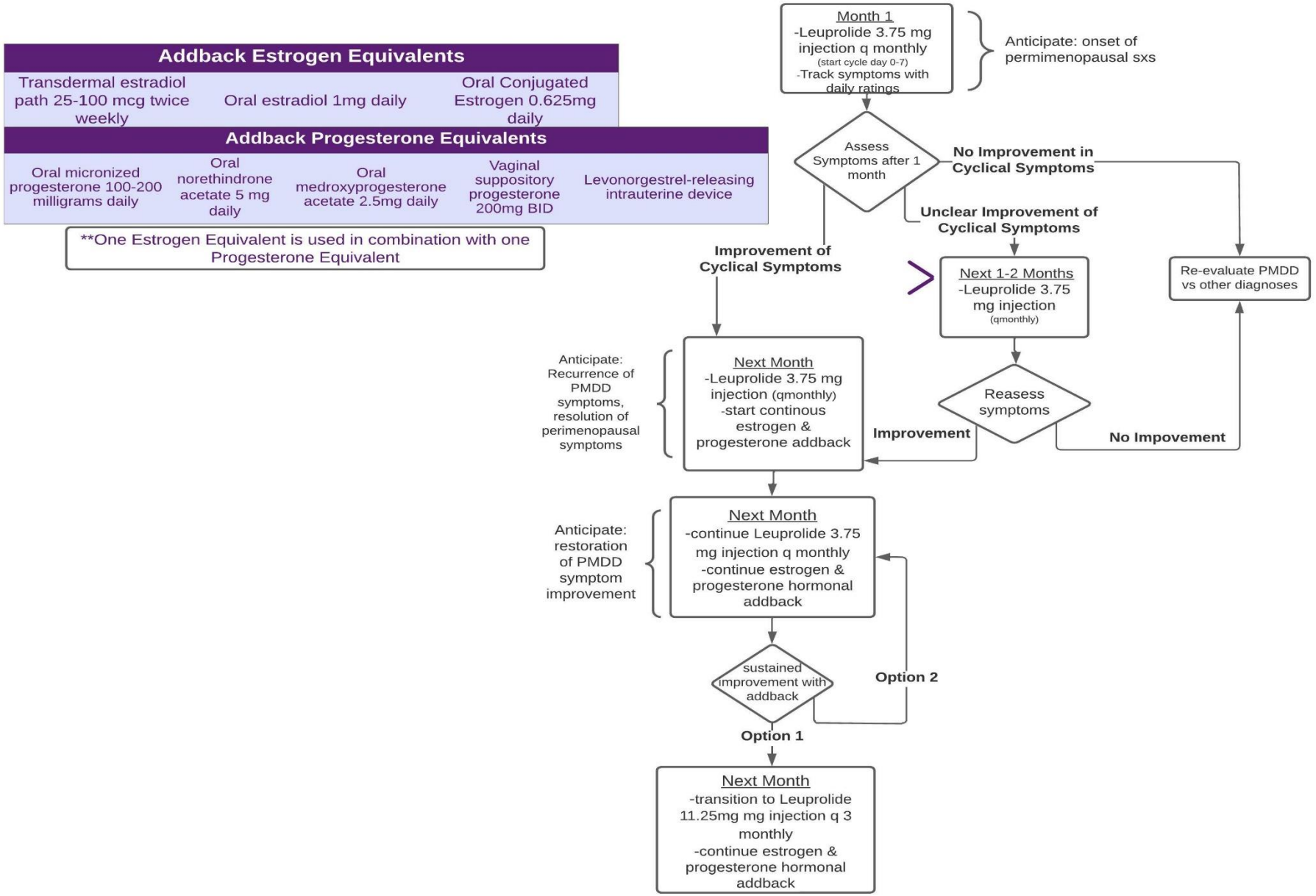
GnRH Analog + Stable E2/P4 Addback	>	Venlafaxine ~50-150mg	=	Duloxetine 60mg	=	Clomipramine 25-75mg

Treatment Implementation

- Treatments should be trialed for two menstrual cycles while daily symptom severity ratings are tracked
- There is no data to suggest superiority of any SSRI over another, only one SSRI is used at a time
- Drospirenone-containing OCs are the preferred agent among the Second Line Treatment agents due to FDA approval (Freeman et al 2012, Yonkers 2018)
- There is not enough data to suggest which Augmenting Agent is preferred
- St. John's Wort should not be combined with an SSRI due to the possibility of serotonin syndrome
- If patient does not want to use a GnRH analog, consider trialing an SNRI or Tricyclic Antidepressant
- If Third Line Treatment is only partially effective, consider augmenting with a First Line Treatment agent
- If Third Line Treatment results in no response, re-evaluate the patient with two cycles of daily symptom severity ratings to determine whether the patient has PMDD or if their symptoms might better be explained by an alternative diagnosis

This flowchart was developed by the authors of this article using a summation of references from the main article. Please see references 10-23 from the primary article reference section.

Supplementary Figure 2. GnRHa Administration for Treatment-Resistant PMDD: Prototypical Treatment Paradigm



This flowchart was developed by the authors of this article using a summation of references from the main article. Please see references 12, 19-23 from the primary article reference section.