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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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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Appendix 1** Premenstrual Dysphoric Disorder - Informational Handout for Providers
2. **Appendix 2** Premenstrual Dysphoric Disorder – Patient Informational Handout
3. **Appendix 3** Risk Factor Assessment
4. **Appendix 4** Treatment Side Effects
5. **Figure 1** PMDD Treatment Decision Tree: First, Second, and Third Line Treatments, Plus Augmenting Agents
6. **Figure 2** GnRHa Administration for Treatment-Resistant PMDD: Prototypical Treatment Paradigm

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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.

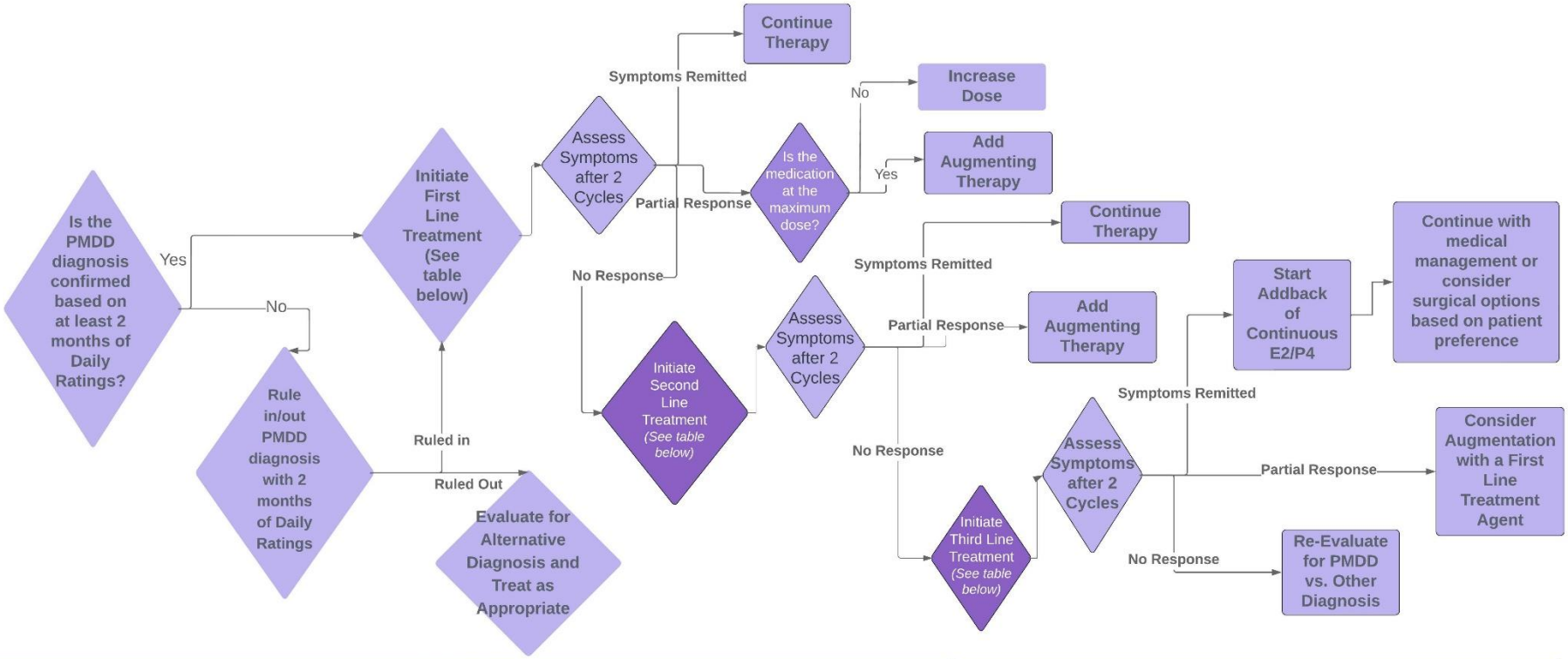
- Hot flashes
- Headaches
- Fatigue
- Increased sweating
- Changes in sleep
- Nervousness
- Dizziness
- Nausea
- Vomiting
- Constipation
- Diarrhea
- Palpitations (heart racing)
- Vaginal dryness
- Changes in weight
- Decreased libido
- Vaginitis
- Flu-like symptoms

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

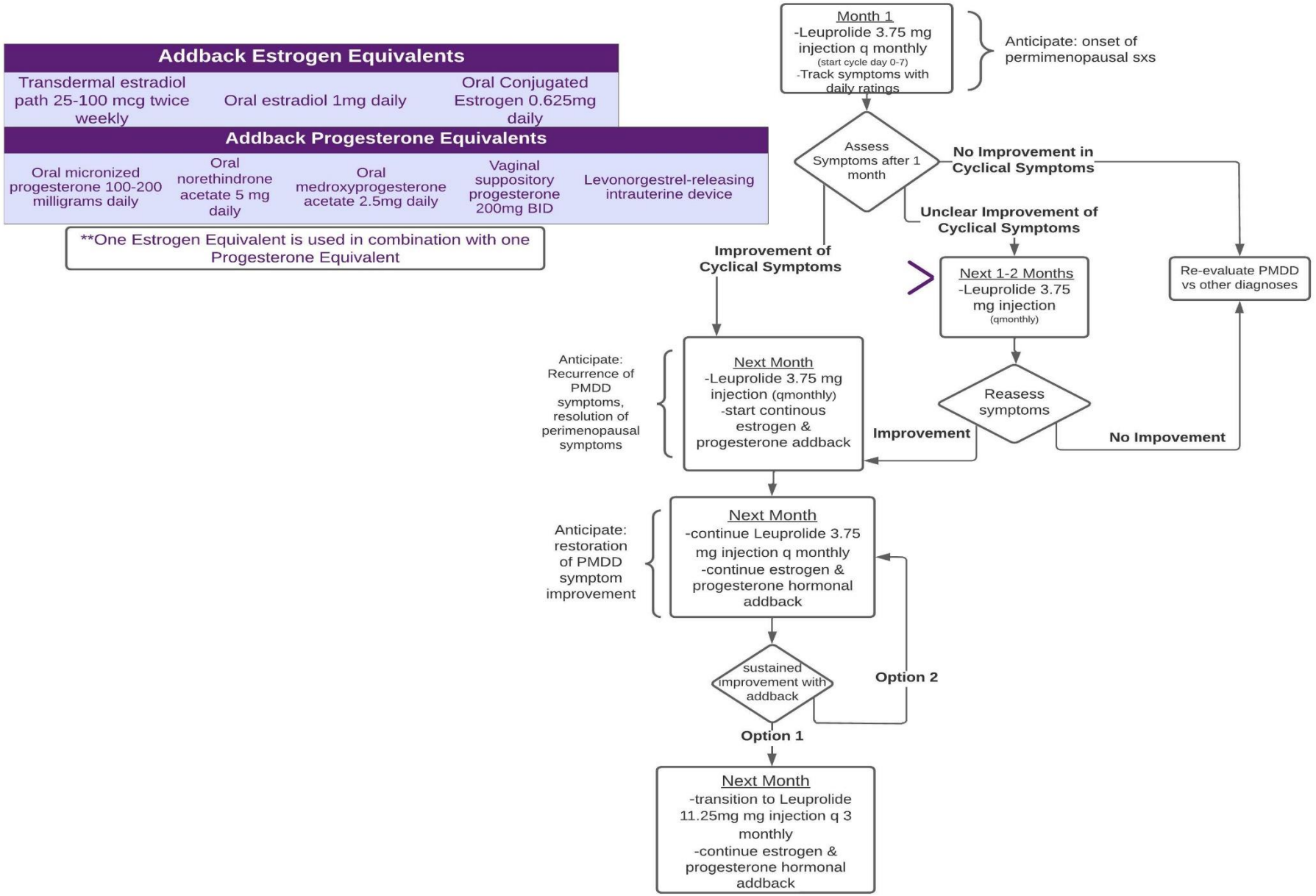
GnRH Analog + Stable E2/P4 Addback	>	Venlafaxine ~50-150mg	=	Duloxetine 60mg	=	Clomipramine 25-75mg

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.