EVIDENCE-BASED MANAGEMENT OF PREMENSTRUAL DISORDERS (PMDs)

Note: This guide is intended primarily as a resource for healthcare providers. If you are a patient, we recommend you also check out our treatment options page designed for patients: iapmd.org/treatment-options.

Premenstrual Disorders such as Premenstrual Dysphoric Disorder (PMDD) and Premenstrual Exacerbation (PME) of psychiatric disorders are complex to diagnose and treat. Below, we provide guidelines to help healthcare providers educate and treat their patients effectively.

ASSESSMENT AND DIAGNOSIS OF PMDs:

Ultimately, each patient with premenstrual symptoms is unique and deserves a compassionate healthcare provider who will work with them to find an effective treatment--or set of treatments-- for their unique needs. To confirm the diagnosis, **two months of daily symptom ratings are recommended to differentiate between PMDD** (symptoms present only premenstrually), **PME** (symptoms always present but worsened premenstrually), and **non-cyclical symptoms.** Daily ratings can also be continued in the context of treatment to evaluate effectiveness over time. A daily symptom rating form can be downloaded at iapmd.org/provider-resources. If desired, standardized scoring of these daily ratings to determine diagnosis can be accomplished using the C-PASS scoring system available at iapmd.org/c-pass-- this is especially encouraged in research contexts.

Please note that it is possible to have both PMDD (five symptoms that are present only in the luteal phase) and also PME of other underlying disorders.

TREATMENT OF PMDs:

Since this is a relatively new area of medical science, the number of randomized controlled trials for PMDs remains relatively small. However, several treatments **have been found to be effective**, and more are currently under investigation. Below, we outline what the scientific evidence indicates about how the *average* person with a premenstrual disorder (typically PMDD - PME is less well-studied) will respond to various treatments. Many patients utilizing IAPMD services have already tried many of the treatments below with no relief, whereas others have tried none.

The purpose of this document is not to provide a "one-size-fits-all" recommendation for the treatment of premenstrual disorders; rather, it is to help those seeking information about effective treatments by reviewing the best evidence about general efficacy and safety of each treatment in those with premenstrual disorders.

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Please visit iapmd.org for more information and resources. Join the IAPMD Professional Community to increase your skills and knowledge in treating PMDs: iapmd.org/pro.

This guide was prepared by the IAPMD Clinical Advisory Board under the direction of Dr. Tory Eisenlohr-Moul.

TREATMENTS WITH STRONG SCIENTIFIC EVIDENCE FOR EFFICACY AND SAFETY IN PMDD

Important Note: Because nearly all clinical trials in this area have focused on PMDD, the tables below are organized according to effectiveness and safety of treatments for PMDD; however, please note accompanying information about possible efficacy in PME of psychiatric disorders.

TREATMENT	EFFICACY IN PMDD	EFFICACY IN PME	SIDE EFFECTS AND SAFETY	MECHANISM OF ACTION
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS) - fluoxetine 20mg ("Prozac") - sertraline 50-150mg ("Zoloft") - paroxetine 20-30mg ("Paxil") - citalopram 20-30mg ("Celexa") - escitalopram 10-20mg ("Lexapro") Dosing Schedule: Symptom-Onset, Luteal, or Continuous	Strong evidence of efficacy for PMDD in many trials. Response rates in randomized controlled trials are around 60%. SSRIs tend to have a rapid effect, often performing better than placebo after just one day.	Untested for PME of psychiatric disorders, but is a rational treatment choice for PME of disorders for which SSRIs are the first-line treatment (i.e., depression and anxiety).	Well tolerated in general, but side effects are common. Most frequent side effects are nausea, low energy, sleepiness, and decreased libido.	Normalizes altered premenstrual serotonin function in PMDD, and alters metabolism of progesterone to its neuroactive metabolites.
DROSPIRENONE-CONTAINING ORAL CONTRACEPTIVE PILL WITH SHORTENED HORMONE-FREE INTERVAL - drospirenone 3mg/ ethinylestradiol .02mg daily (e.g., "Yaz") Dosing: 24-4 or continuous dosing (i.e., shortened or eliminated hormone-free interval)	Evidence of efficacy for PMDD from two randomized controlled trials. Usually effective in first month of treatment. Response rates were 48% and 61%. Effects may be smaller than SSRIs.	One study shows no benefit for PME of depressive disorders when given as an adjunctive treatment to SSRI.	Well tolerated, generally few side effects. Risk of blood clot and estrogen-dependent cancers should be considered based on individual risk profiles. Some individuals do not tolerate progestins and develop chronic symptoms similar to PMDD; progestin treatment should be discontinued in these patients.	Prevention of ovulation and related hormone flux in PMDD.

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GNRH ANALOGUES Dosing: Monthly outpatient injections *- leuprolide 3.75mg monthly injection ("Lupron")* *- goserelin 3.6mg monthly injection ("Zoladex")*	Many trials demonstrate effectiveness for severe PMDD. *Typically reserved for those who have failed to respond to both SSRI and OCs.* *Not effective when ovulation is not suppressed.*	Two studies (1, 2) show no benefit for subsamples with PME of depressive disorders. However, no evidence is available regarding effectiveness when long-term hormone addback is provided (see below). *Note:* If PME (e.g., of depression) is comorbid with other symptoms (e.g., anxiety, irritability) that DO show a PMDD-like confinement to the luteal phase, treatment may still be indicated for PMDD.	Menopausal symptoms. Requires Suppression of ovulation and hormone replacement to prevent related hormone flux bone loss.	Suppression of ovulation and related hormone flux.
GNRH ANALOGUES + STABLE HORMONE ADDBACK *- transdermal estradiol addback ("Climara")* *- progestogen addback for endometrial protection ("Prometrium")*	Many trials demonstrate effectiveness for severe PMDD. *Typically reserved for those who have failed to respond to both SSRI and OCs.*	Untested for PME of depressive disorders, but represents a rational option to trial for treatment-resistant patients. *Note:* If PME (e.g., of depression) is comorbid with other symptoms (e.g., anxiety, irritability) that DO show a PMDD-like confinement to the luteal phase, treatment may be indicated for PMDD.	In two studies, the first month of stable oral estrogen + vaginal progesterone addback caused a resurgence of PMDD symptoms, but symptoms remitted after 1 month. Patients should be informed of possible short-term symptom flare and appropriate supports should be provided.	Suppression of ovulation and related hormone flux.

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TOTAL HYSTERECTOMY WITH BILATERAL SALPINGO-OOPHORECTOMY (THBSO) *- removal of both ovaries is required* *- removal of uterus is indicated to eliminate need for progestin addback post-surgery*	Studies indicate that THBSO is Untested, but a rational effective for those patients who treatment choice for a patient improve during GnRH agonist who has improved during GnRH trial. agonist trial. If patient does not tolerate GnRH analogues (and therefore cannot get a "fair GnRH trial"), THBSO may still be indicated given may still be indicated given evidence of severe cyclicity.	Untested, but a rational treatment choice for a patient who has improved during GnRH agonist trial. If patient does not tolerate GnRH analogues (and therefore cannot get a "fair GnRH trial"), THBSO may still be indicated given evidence of severe cyclicity.	A very routine and safe gynecologic procedure, but still major abdominal surgery with risks (including bleeding, infection, and death). Risk increases with other medical conditions (heart, lung, liver, or kidney disease, obesity, diabetes, history of prior surgery). Permanent. Requires hormone replacement to prevent bone loss.	Complete cessation of ovarian activity and related hormone flux.
COGNITIVE-BEHAVIORAL THERAPIES *Dosing: Weekly sessions with a qualified therapist with appropriate training in CBT and DBT.* *- Cognitive Behavioral Therapy (CBT)* *- Dialectical Behavior Therapy (DBT)* *Close attention should be paid to the quality of the therapy being provided; providers not engaging in skills training or providing behavioral homework assignments to patients should be replaced with providers more adherent to CBT principles.*	CBT is a useful tool for reducing functional impairment related to emotional symptoms across disorders, and some evidence suggests it may be supportive for patients with PMDD specifically. DBT is effective for preventing suicidal behaviors, a common outcome in severe cases of PMDD.	Untested for PME of psychiatric disorders but is a rational treatment choice given the widespread effectiveness of CBT for psychiatric disorders.	Well tolerated, generally few side effects when provided by a qualified professional.	Reduction in neurobiological stress responses, improved coping and relationships.

TREATMENTS WITH LIMITED BUT PROMISING SCIENTIFIC EVIDENCE FOR EFFICACY AND SAFETY IN PMDD

TREATMENT	EFFICACY IN PMDD	EFFICACY IN PME	SIDE EFFECTS AND SAFETY	MECHANISM OF ACTION
5-ALPHA REDUCTASE INHIBITORS *- dutasteride 2.5mg/day ("Avodart")* *Note: finasteride is untested in clinical trials but is sometimes used in clinical practice due to its shorter half-life, which may reduce the risk of birth defects in the event of pregnancy.* **Available primarily in USA**	One study shows improvement in PMDD symptoms with dutasteride; dosage must be high enough to inhibit formation of allopregnanolone.	Untested for PME of psychiatric disorders. Given evidence of reduced biosynthesis of GABAergic neurosteroids (e.g., allopregnanolone) in chronic depressive and anxiety disorders, this medication is not recommended for PME of psychiatric disorders as it may further exacerbate neurosteroid deficits.	Causes birth defects if conception occurs while on the drug; a period of washout is needed prior to pregnancy to avoid birth defects. Patients should be monitored closely for side effects since no long-term trials exist in PMDD. In other populations, these medications can cause depression.	Prevents formation of (and flux in) neurosteroid metabolites of progesterone.
OVULATION SUPPRESSION USING TRANSDERMAL ESTRADIOL + CYCLICAL PROGESTOGEN *.1mg Transdermal E2* Patch (twice weekly; "Vivelle") + *norethisterone 1mg/day, 10 days per cycle*18 *Alternative Progestogen for Endometrial Protection:* *- levonorgestrel-containing IUD ("Mirena")* **Available primarily in the UK**	There have been two positive trials (1,2). May represent alternative to OCs for those who cannot tolerate synthetic progestins if anovulation can be achieved at safe doses. More work is needed to determine the safety and efficacy of various doses.	Not tested.	Increased risk of blood clots, increased breast cancer risk, and increased endometrial thickening/cancer risk can occur in at-risk women, particularly with inadequate progestogen opposition.	Suppression of ovulation and related hormone flux.
QUETIAPINE (LUTEAL PHASE; ADJUNCT TO SSRI) *- 25mg quetiapine/day during the luteal phase ("Seroquel")*	One small trial demonstrated benefit as an adjunctive treatment to SSRI.	Not tested.	Generally safe and well tolerated, but potential for serious and life-threatening side effects.	Unknown.

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ISOALLOPREGNANOLONE **INJECTIONS** ("Sepranolone") *Varying; dosages in development* **NOT YET AVAILABLE**	Two clinical trials have tested Sepranolone against placebo in PMDD. In the first randomized controlled trial, Sepranolone showed effectiveness for PMDD. However, Sepranolone failed to beat placebo in the second trial, which may have been due to a very large and persistent placebo response.	One study demonstrated no benefit for PME of psychiatric disorders.	Initial studies show few side effects.	Blocks or reverses paradoxical effects of progesterone-derived neurosteroids (e.g., allopregnanolone) at GABA-A receptor in PMDD.
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TREATMENTS WITH NO EVIDENCE, MIXED EVIDENCE, OR NEGATIVE EVIDENCE FOR EFFICACY IN PMDD

TREATMENT	EFFICACY IN PMDD	EFFICACY IN PME	SIDE EFFECTS AND SAFETY	MECHANISM OF ACTION
LIFESTYLE CHANGES - Improved diet - Increased exercise - Reduced caffeine intake - Reduced alcohol intake	A healthy lifestyle improves general mental and physical health. However, only low-quality evidence is available linking these outcomes to premenstrual symptoms, and findings are mixed. May be more appropriate for mild premenstrual symptoms than for PMDD.	Not studied.	N/A	N/A
VITAMIN AND MINERAL SUPPLEMENTS	Mixed evidence. May be more appropriate for mild premenstrual symptoms than for PMDD. Some evidence that calcium, magnesium, Vit D, and Vit B6 supplements may improve premenstrual symptoms.	Not tested.	Supplements are readily available, but also poorly regulated in the United States. Risk of overdose or toxicity. Very safe if taken in consultation with a provider.	N/A
LEVONORGESTREL-CONTAINING CONTINUOUS ORAL CONTRACEPTIVE PILL *- levonorgestrel .09mg + .02mg ethinylestradiol daily with no pill-free interval ("Lybrel")*	Four studies show inconsistent effects in PMDD, with some demonstrating benefit and others not.	Not tested.	Risk of blood clot and estrogen-dependent cancers should be considered based on individual risk profiles. Some individuals do not tolerate oral contraceptives and develop chronic or cyclical symptoms similar to PMDD; progestin-containing medications should be discontinued for these patients.	Prevention of ovulation.

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COMBINED EE + PROGESTIN VAGINAL RING CONTRACEPTIVE RING ("Nuvaring")	Not yet tested, but is known to consistently suppress ovulation and may be a rational treatment given efficacy of other ovulation-suppression agents in PMDD; however, patient should be monitored for progestin-induced mood symptoms.	Not tested. Given the lack of efficacy of other ovulation-inhibiting agents in PME of depression, a beneficial effect is not necessarily expected.	Risk of blood clot and estrogen-dependent cancers should be considered based on individual risk profiles. Can be easily removed by patient.	Efficacy not yet established.
LEVONORGESTREL-CONTAINING INTRAUTERINE DEVICE (IUD) ("Mirena", "Skyla")	No evidence available, but not a rational treatment given that they do NOT consistently suppress ovulation.	No evidence, but not a rational treatment given that they do NOT consistently suppress ovulation	May have adverse effects on physiological stress responses; many women discontinue due to depressive symptoms.	N/A; not expected to be effective.
COPPER IUD ("Paragard")	No evidence available, but not a rational treatment given its inability to suppress ovulation.	No evidence, but not a rational treatment given its inability to suppress ovulation.	Heavy periods.	N/A; not expected to be effective.
DANAZOL ("Danocrine")	Not effective for emotional PMDD symptoms when considering the whole cycle.	Not tested. Not recommended given side effect profile.	Common side effects include acne, weight gain, hirsutism, deepening of the voice; some changes may be irreversible. May cause birth defects.	Efficacy not yet established.

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BENZODIAZEPINES *- alprazolam ("Xanax")*	Mixed evidence, with well-controlled studies showing either no benefit or some benefit. Tolerance and reduced efficacy expected with long-term use. Not indicated for those with marked impulsivity or family/personal history of drug abuse. Not indicated for daily or long-term use.	Not tested for PME.	High risk of addiction and abuse; indicated for those with marked tolerance often develops. Withdrawal can be life-threatening.	Sedation.
ORAL MICRONIZED PROGESTERONE OR PROGESTINS ONLY. - usually given in the luteal phase only	Several studies show that this is ineffective, and is likely to worsen symptoms in the first month.	Not tested in PME.	Progestins can trigger mood symptoms, particularly acutely.	N/A, not effective.

RECOMMENDED READING:

- Up-to-Date Guidelines for Management of Premenstrual Syndrome and PMDD
- Royal College of Obstetrics and Gynecology Guidelines for the Management of Premenstrual Syndrome
- International Society for Premenstrual Disorders Consensus Guidelines