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Premenstrual Dysphoric Disorder

Self-Study

Contributors
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For additional reading:

- PMDD/PMS Review Article:
  Yonkers, K. A., & Simoni, M. K. (2018). Premenstrual disorders. *American Journal of Obstetrics and Gynecology*, *218*(1), 68–74. https://doi.org/10.1016/j.ajog.2017.05.045

- Etiology of PMDD:
  Raffi, E. R., & Freeman, M. P. (2017). The etiology of premenstrual dysphoric disorder: 5 interwoven pieces: a better understanding of the causes of PMDD can lead to improved diagnosis and treatment. *Current Psychiatry*, *16*(9), 21-. https://womensmentalhealth.org/specialty-clinics/pms-and-pmdd/the-etiology-of-pmdd/

- RCOG treatment guidelines: https://www.rcog.org.uk/globalassets/documents/guidelines/gt48managementpremensturalsyndrome.pdf

- Carlini SV, Lanza di Scalea T, McNally ST, Lester J, Deligiannidis KM. Management of Premenstrual Dysphoric Disorder: A Scoping Review. Int J Womens Health. 2022 Dec 21;14:1783-1801. doi: 10.2147/IJWH.S297062. PMID: 36575726; PMCID: PMC9790166.

Introduction

- Premenstrual symptom severity varies among women from mild-moderate to severe and debilitating.
- Most women of reproductive age have some emotional or physical symptoms in the week before menstruation.
- A diagnosis of PMDD requires prospective mood charting for at least 2 menstrual cycles.
- Risk factors for PMDD include biological, dietary, psychological, and behavioral factors.

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- First line treatments for PMDD include vitamin B6, oral contraceptives, CBT, SSRIs and calcium supplementation.
- Treatment with a GnRH agonist or should be reserved only for treatment-resistant or the most severe cases. Surgical intervention should only be contemplated after a successful trial with a GnRH agonist.

Definitions

1. Premenstrual Symptoms (PMS) is not listed in DSM-V-TR
    a. A diagnosis of PMS typically captures women who experience distress but do not have the 5 symptoms required for a PMDD diagnosis or for women who have predominantly physical symptoms.
    b. PMS is defined by the American College of Obstetricians and Gynecologists (ACOG) as at least one symptom associated with "economic or social dysfunction" that occurs during the five days before the onset of menses and is present in at least three consecutive menstrual cycles. Symptoms may be affective (angry outbursts, depression, anxiety, confusion, irritability, social withdrawal) or physical (breast pain, bloating, headaches, joint or muscle pain, swelling in extremities, weight gain).

2. Premenstrual Dysphoric Disorder (PMDD) is listed under depressive disorders in DSM-V TR

3. Both PMS and PMDD require that women have symptom expression during the luteal phase of the cycle with a symptom-free period starting after the onset of menses

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Premenstrual Dysphoric Disorder

Diagnostic Criteria F32.81

A. In the majority of menstrual cycles, at least five symptoms must be present in the final week before the onset of menses, start to *improve* within a few days after the onset of menses, and become *minimal* or absent in the week postmenses.

B. One (or more) of the following symptoms must be present:

1. Marked affective lability (e.g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection).
2. Marked irritability or anger or increased interpersonal conflicts.
3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts.
4. Marked anxiety, tension, and/or feelings of being keyed up or on edge.

C. One (or more) of the following symptoms must additionally be present, to reach a total of *five* symptoms when combined with symptoms from Criterion B above.

1. Decreased interest in usual activities (e.g., work, school, friends, hobbies).
2. Subjective difficulty in concentration.
3. Lethargy, easy fatigability, or marked lack of energy.
4. Marked change in appetite; overeating; or specific food cravings.
5. Hypersomnia or insomnia.
6. A sense of being overwhelmed or out of control.
7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," or weight gain.

Note: The symptoms in Criteria A–C must have been met for most menstrual cycles that occurred in the preceding year.

D. The symptoms cause clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).

E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder, or a personality disorder (although it may co-occur with any of these disorders).

F. Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles. (**Note:** The diagnosis may be made provisionally prior to this confirmation.)

G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).

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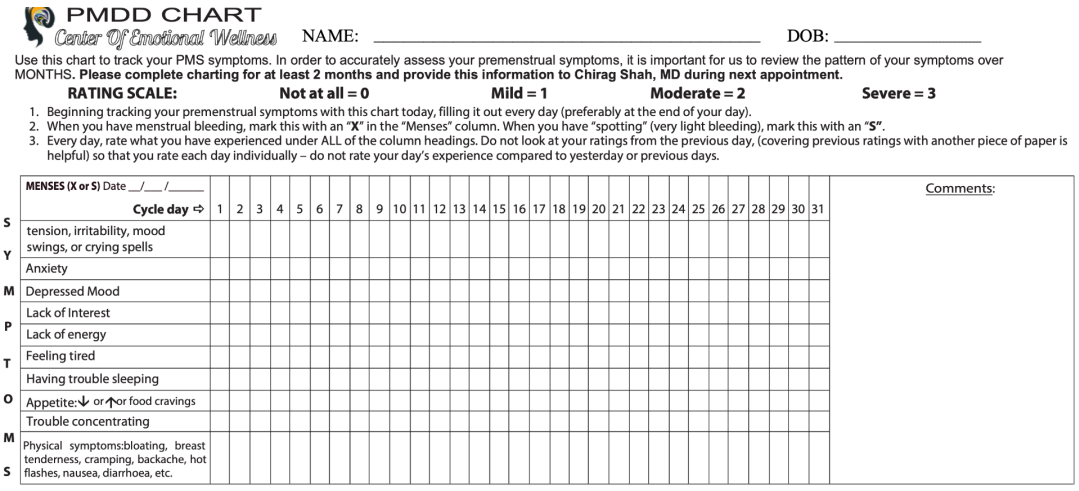
Making the Diagnosis

1. A PMDD diagnosis requires a careful psychiatric, gynecologic, and medical history
2. Thyroid function should be tested in women presenting for PMDD assessment. Thyroid abnormalities may contribute to depression, anxiety, and irritability symptoms seen in PMDD, although thyroid dysfunction would not explain symptoms that occur solely in the luteal phase.
    a. In the presence of abnormal thyroid tests, the thyroid condition should be treated as a first step followed by prospective assessment of mood and physical symptoms to determine PMDD diagnosis independent of the thyroid condition.
3. Accurate diagnosis requires prospective mood charting of at least 1 but preferably 2 menstrual cycles (see the Daily Record of Severity of Problems and the Calendar of Premenstrual Experiences chart)
    a. A mood chart consistent with PMD/PMDD would demonstrate symptoms that begin in the premenstrual period and resolve at the beginning or during menses
    b. Ongoing symptoms that worsen during the premenstrual period is more consistent with premenstrual exacerbation of another disorder

Mood chart Example



PMDD CHART
Center Of Emotional Wellness

NAME: _____ DOB: _____

Use this chart to track your PMS symptoms. In order to accurately assess your premenstrual symptoms, it is important for us to review the pattern of your symptoms over MONTHS. **Please complete charting for at least 2 months and provide this information to Chirag Shah, MD during next appointment.**

RATING SCALE: **Not at all = 0** **Mild = 1** **Moderate = 2** **Severe = 3**

1. Beginning tracking your premenstrual symptoms with this chart today, filling it out every day (preferably at the end of your day).
2. When you have menstrual bleeding, mark this with an "**X**" in the "Menses" column. When you have "spotting" (very light bleeding), mark this with an "**S**".
3. Every day, rate what you have experienced under ALL of the column headings. Do not look at your ratings from the previous day, (covering previous ratings with another piece of paper is helpful) so that you rate each day individually – do not rate your day's experience compared to yesterday or previous days.

	MENSES (X or S) Date __/___ /_____ **Cycle day ⇨**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Comments:
S	tension, irritability, mood swings, or crying spells																																
Y	Anxiety																																
M	Depressed Mood																																
	Lack of Interest																																
P	Lack of energy																																
	Feeling tired																																
T	Having trouble sleeping																																
O	Appetite: ↓ or ↑ or food cravings																																
	Trouble concentrating																																
M	Physical symptoms: bloating, breast tenderness, cramping, backache, hot flashes, nausea, diarrhoea, etc.																																
S																																	

https://www.centerofemotionalwellness.com/wp-content/uploads/2020/01/PMDD-MOOD-CHART-122019.pdf

Epidemiology

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1. Rates & incidence
    a. Fewer women have PMDD than have PMS and women with PMDD may have symptoms of PMS as well. PMS encompasses more physical symptoms.
    b. Studies have been difficult to conduct because of recall bias with retrospective reporting. Of the few studies available, the prevalence of PMS in menstruating women is estimated at 20-30% (Yonkers & Simoni, 2018)
    c. PMDD, as a more severe and less common presentation of premenstrual symptoms, has a prevalence estimated at 1.2%-6.4% (Yonkers & Simoni, 2018)
    d.
2. Across the woman's life cycle
    a. PMS does not occur prior to menarche, during pregnancy, or after menopause.

Risk Factors

- Higher rates in white women than African American women
- High potassium diet
- Adiposity and metabolic syndrome (especially if BMI > 27.5)
- Use of nicotine
- Intake of alcohol
- Early sexual abuse and history of trauma
- High co-morbidity with anxiety and/or depression, though not clear if these predispose women to PMS/PMDD
- Associated with lower education status
- Family history of PMS/PMDD (PMDD is thought to have a heritability between 30-80%)

Etiology

1. Hormonal Influence
    a. It is not absolute concentrations of gonadal steroids but rather a woman's response to changes in levels of gonadal steroids that is thought to precipitate PMS/PMDD symptoms
    b. Of great clinical interest is the role of allopregnanolone (ALLO) in PMDD; There are a few lines of evidence
        i. Women with PMDD have higher levels of ALLO and ALLO/ testosterone ratios in the luteal phase than women without PMDD (Girdler studies)

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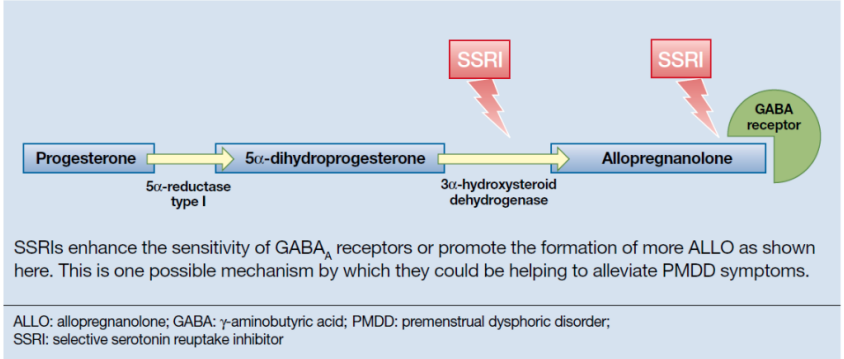
ii. Reducing the conversation of progesterone to ALLO has been demonstrated to reduce PMDD symptoms.
iii. The first pharmacologic preparation of ALLO was recently approved by the FDA to treat postpartum depression, and there is some speculation that the use of ALLO in PMDD may have paradoxical, beneficial effects in PMDD.
iv. As such, SRIs (one of the main treatments for PMDD) lead to changes in ALLO levels and may increase GABA-A receptor sensitivity to ALLO

Conversion of progesterone to ALLO and the SSRI influence



SSRIs enhance the sensitivity of $GABA_A$ receptors or promote the formation of more ALLO as shown here. This is one possible mechanism by which they could be helping to alleviate PMDD symptoms.

ALLO: allopregnanolone; GABA: γ-aminobutyric acid; PMDD: premenstrual dysphoric disorder; SSRI: selective serotonin reuptake inhibitor

Raffi & Freeman, 2017

2. Serotonin Influence
    a. Sex steroids and sex steroid receptors are prevalent in areas that regulate emotion in the brain (i.e. the amygdala). Sex steroids also modulate serotonin transmission.
        i. Depletion of tryptophan (a serotonin precursor) may elicit PMS symptoms
        ii. Women with PMS have dysregulated indices of serotonergic transmission
3. Brain Functional Changes
    a. Women with PMS (due to certain hormonal influences) may have more difficulty exerting top-down control of the frontal cortex on areas that integrate emotional and physical input (i.e. the amygdala)
        i. This could lead to symptoms of impulsivity, impaired executive function, and the expression of emotional symptoms

Psychological Factors

- Women with PMDD have been found to have psychological traits that may amplify the severity of premenstrual emotional symptoms

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- Traits include difficulty with emotional regulation, behavioral impulsivity, impaired social connectedness, higher levels of brooding rumination, greater self-focused attention in response to negative affect, and elevated perceived stress
- These traits serve as a target for cognitive behavioral therapy

Associated Medical Factors

- Women with PMDD have alterations in their calcium homeostasis (and thus vitamin D) that may be related to both their somatic and affective symptoms
    - Calcium is known to influence neuromodulation, some studies posit that women with PMDD have low calcium and thus secondary hyperparathyroidism
- Pain tolerance may change throughout the menstrual cycle related to ovarian hormones. This may lead to exacerbation of pain conditions

Evidence-Based Treatment Interventions

1. Non-Pharmacologic
    a. Exercise
    b. Complex carbohydrate diet during the luteal phase – likely mediated through increase in the amount of serotonin that is centrally available
    c. Cognitive Behavioral Therapy – typically administered in ~12 sessions

2. Pharmacologic
    a. Serotonin Reuptake Inhibitors (SRIs)
        i) SRIs have a more rapid onset of action for PMDD than for depression. As such, the mechanism that makes SRIs efficacious for PMDD may be different than for depression/anxiety
        ii) SRIs can be administered throughout the menstrual cycle or only during the second half of the menstrual cycle (starting shortly after ovulation for approximately 2 weeks)
        iii) If one SRI has difficult to tolerate side effects or is ineffective, consider switch to a different SRI before declaring treatment failure with this class of medications
    b. Hormone Agonists and Antagonists
        i) Combined oral contraceptive pills (OCPs) are commonly used as treatments for PMS/PMDD though evidence is sparse
            (1) Yaz (drospirenone and ethinyl estradiol) is the only OCP that has established efficacy for PMDD via RCT

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(a) Shortened hormone-free interval may be pivotal to efficacy (a standard 21 day active treatment phase did not demonstrate efficacy with the same steroids)

ii) Estrogen and Progesterone supplements have low/poor quality research and little evidence

iii) Third Line: GnRH agonists

(1) GnRH agonists are used in a continuous manner to suppress ovarian release of estrogen and ovulation but should not be used for more than 6 months as stand-alone treatment

(a) Following that time, low dose continuous estradiol (transdermal or micronized) and micronized progesterone should be added back to reduce the risks associated with long-term GnRH agonist use and to avoid the potential negative mood effects of progestogens.

(2) A GnRH agonist may be administered as a once monthly injection of leuprolide acetate 3.75mg

(3) Adverse side effects include vaginitis, vasomotor symptoms, and decrease in bone density

c. Fourth Line: Surgery

i) For refractory cases only

ii) Establish efficacy with a trial of GnRH agonists first

3. Complementary Medicines

Please note that complementary medicines recommendations are based on poor quality studies or studies done in only a small number of subjects. As such, while there are no data suggesting that these treatments do not work, there is only limited data suggesting that they may be of some benefit. Moreover, since dietary supplements are not regulated by the FDA, it is difficult to accurately dose these products.

a. Vitamin B6 (pyridoxine)

i) Benefits for PMS/PMDD in doses up to 100mg/day

ii) Peripheral neuropathy can occur with doses of 200mg/day or higher

b. Vitamin B1 (thiamine)

i) In a small RCT, it decreased PMS symptoms

ii) Found to have more benefit when used with calcium

iii) Effective dose is 100mg daily

c. Calcium

i) Influences neuromodulation; some studies indicate that women with PMS may have low calcium and possibly secondary hyperparathyroidism

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ii) 500mg/day significantly reduced symptoms but less effective than fluoxetine

d. Zinc

i) Low levels of Zinc have been found in women with PMDD..

ii) 30 mg daily dose or up to 50mg during the luteal phase

e. Vitex Agnuscastus (chasteberry)

i) Binds to dopamine-2 receptors, opioid receptors, beta-estrogen receptors

ii)20-40mg/day

f. St. John wort

i) Affects neuromodulator synthesis

ii) 900mg daily

g. Gingko biloba

i) Anti-inflammatory properties – may affect stress and depressive symptoms

ii) Dosed three times per day

h. Acupuncture

i) Several studies have shown the benefit of acupuncture for physical and psychological symptom relief.

4. New & Emerging Treatment:

i) Dutasteride:

(1) 5 alpha reductase inhibitor used to treat benign prostatic hyperplasia in men also acts to reduce the conversion of progesterone to allopregnanolone. Hence, it stabilizes the level of allopregnanolone thereby reducing its effects in the luteal phase.

(2) In the pilot, it was dosed at 2.5mg/day.

ii) Ulipristal Acetate:

(1) A selective progesterone receptor modulator initially used for fibroid treatment.

(2) Acts as a progesterone antagonist. It modulates progesterone receptors in the brain and prevents ovulation.

(3) Limited information on safety. Liver function monitoring is advised while taking the medication.

iii) Sepranolone:

(1) A negative allosteric modulator of GABA-A receptor.

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(2) Antagonized the effects of allopregnanolone, which has been implicated as a contributor to PMDD. Mood changes in the luteal phase have also been attributed to the rising levels of progesterone and its metabolite allopregnanolone.

Treatment Algorithm

- First line treatment: exercise, vitamin B6 (100mg/day), CBT, oral contraceptives, and intermittent or continuous SRIs
- If very mild symptoms or patient does not want to undergo treatment with SRI, consider complex carbohydrate diet, vitamin B6, and calcium 1000mg daily
- If moderate to severe symptoms or if the woman fails to respond to other interventions, commence treatment with oral contraceptives (evidence strongest for Yaz) or SRI treatment
- If initiating SRI treatment, for woman who has regular cycles and/or can predict onset of symptoms, may use intermittent dosing and start after ovulation or at symptom onset
- If a woman fails to respond to this, consider daily treatment. There is some evidence that women with greater physical symptoms have better response to daily treatment
- If one SRI does not lead to full response or has difficult to tolerate side effects, switch to a different SRI
- If these approaches fail, may consider GnRH agonist
- If GnRH agonist is effective but GnRH with hormone addback is ineffective as a long-term option, may consider surgical intervention.

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