Article Review

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Premenstrual Disorders: An Expert Review

Yonkers et al.
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Introduction

- The spectrum of premenstrual disorders:

1. *Premenstrual syndrome*
2. *Premenstrual dysphoric disorder:* The most severe one
3. *Premenstrual worsening of another medical condition*

DSM 5 PREMENSTRUAL DYSPHORIC DISORDER

A. In most menstrual cycles, the following 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 post- menses. At least one of the symptoms must be either (1), (2), (3), or (4) and the individual must experience at least five total symptoms:

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, feelings of being “keyed up,” or “on edge”
5. decreased interest in usual activities (e.g., work, school, friends, hobbies)
6. subjective difficulty in concentration
7. lethargy, easy fatigability, or marked lack of energy
8. marked change in appetite, overeating, or specific food cravings
9. hypersomnia or insomnia
10. a sense of being overwhelmed or out of control
11. physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of “bloating,” weight gain

DSM 5 PREMENSTRUAL DYSPHORIC DISORDER (continued)

B. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships.
C. The disturbance is not merely an exacerbation of the symptoms of another disorder.
D. Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)
E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication or other treatment) or another medical condition (e.g., hyperthyroidism).

Premenstrual Syndrome

1) Physical and/or emotional symptoms
2) Symptoms are present during the luteal phase and abate as menstruation begins
3) A symptom-free week
4) Symptoms are associated with significant impairment during the luteal phase

The criterias’ shared features

- Symptom expression during the luteal phase with a symptom-free period
- Functional impairment

◉Consider recall bias problems; recommend menstrual calendars!

Variant premenstrual disorders

- Including;
    - Premenstrual exacerbation of any other medical condition
    - Progestin-induced disorders

- Biological bases different from the core premenstrual disorders

PMS symtpoms

- The most problematic complaints include;
  - ✓Bloating
  - ✓Mood swings
  - ✓Lethargy
  - ✓Irritability
  - ✓Breast tenderness
  - ✓Anxiety/tension
  - ✓Fear of being rejected
- The most severity: the day before and first day of menses

Epidemiology

- The point prevalence of:
  - PMS: 20-30%
  - PMDD: 1.2-6.4%

Risk Factors

- White race
- High potassium intake
- Adiposity and metabolic syndrome (esp. in BMIs over 27.5 kg/m^2)
- Use of nicotine cigarettes
- Early sexual abuse and trauma
- Depressive and/or anxiety disorders
- Familial factors

◉Risk does not differ among different age groups.

◉Protective dietary factors: thiamine, riboflavin, non-heme iron and zinc

Etiopathology

- Pathological response to either withdrawal from or exposure to the progesterone metabolite, and gamma amino butyric acid (GABA) agonist, allopregnanolone
- Depletion of the serotonin’s precursor, tryptophan/ serotonin receptor antagonist/dysregulation of serotonergic transmission
- Difficult top-down control of the frontal cortex

Evidence Based Treatments

- 4 main categories:

1. Non-pharmacological approaches: diet, exercise and psychotherapy
2. Psychotropic treatment
3. Hormonal agonists and antagonists
4. Vitamins and botanicals

Non-pharmacological Approaches

- A complex carbohydrate diet during the luteal phase;
    - Increasing the amount of serotonin
- Exercise;
    - As a mood stabilizer
- Cognitive behavioral therapy (CBT)

Serotonin Reuptake Inhibitors

- Strong efficacy if administered either throughout the cycle or only during the second half of the menstrual cycle

- Rapid onset of action for PMDD

Hormone Agonists & Antagonists

- COC comprised of 3 mgs of the progestin drospirenone and 20 micrograms of ethinyl estradiol, taken for 24 days of a 28-day cycle : efficacious for PMDD
- OCPs are approved for treating PMDD in women who desire contraception;
    - Consider FDA warnings of blood clots risks in drospirenone-containing pills
- Estrogen; regardless of intake method: not proven to be effective
- Progesterone: advocated as a treatment but not supported yet

Hormone Agonists & Antagonists (continued)

- GnRH agonists:
  - just for severe cases or as the third line treatment after SSRIs & OCPs due to high costs and adverse effects
  - suppress ovarian estrogen release and ovulation
  - Injection of leuprolide acetate 3.75 mgs, monthly
  - Common adverse effects: vaginitis, vasomotor symptoms & decreased bone density

Surgery

- Indication: refractory symptoms
- Total hysterectomy with bilateral salpingo-oophorectomy
- To ensure the benefit of this method, GnRH agonists should be used;
  - Assessment of the benefit and tolerance of hypoestrogenic state

Complementary medicines

- The most frequently studied ones:

  - ✓Vitamin B6 (pyridoxine)
  - ✓Vitex Agnus Castus (Chasteberry)
  - ✓St. Johns Wort
  - ✓Gingko Biloba
  - ✓Evening Primrose Oil

Complementary medicines (continued)

- Vitamin B6:
  - Beneficial in doses up to 100 mgs per day
  - Peripheral neuropathy in doses of 200 mgs per day

Complementary medicines (continued)

- Vitex Agnus Castus extracts:
  - Binds to the dopamine-2 receptor, opioid receptor and β-estrogen receptor
  - Beneficial in doses of 20-40 mgs/day

Complementary medicines (continued)

- Ginkgo biloba L. :
  - Antioxidant
  - Anti-inflammatory
  - Effective on stress and depressive symptoms

Complementary medicines (continued)

- Hypericum perforatum (St. John’s Wort) :
  - Effective on neuromodulator synthesis
  - Common symptoms such as bloating, food cravings, headache and fatigue were significantly decreased with daily 900 milligram tablets while mood and physical symptoms involving pain remained unaffected.

Complementary medicines (continued)

- Calcium:
  - Effective on neuromodulation
  - Low calcium in women with PMS; possibility of secondary hyperparathyroidism
  - 500 mgs calcium decreased symptoms in moderate-severe PMS.

Management Recommendations

- The first step: accurate diagnosis
  - Based on a careful medical, gynecological, and psychiatric history including diet and exercise

- Laboratory tests, such as gonadal steroid levels, are not useful.
- Thyroid indices can be obtained if the clinician suspects thyroid dysfunction but this would not lead to expression of cyclical symptoms.

Management Recommendations (continued)

- Menstrual calendar:
  - Including at least one but ideally 2 cycles
  - Symptoms with severity score
  - The Daily Record of Severity of Problems (DRSP)
  - The Calendar of Premenstrual Experiences (COPE)

Calendar of Premenstrual Experiences

Bleeding																																												
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	32	33	34	35	36	37	38	39	40			
Date																																											
Weight																																										
SYMPTOMS																																										
Acne																																										
Bloatedness																																										
Brest tenderness																																										
Dizziness																																										
Fatigue																																										
Headache																																										
Hot flashes																																										
Nausea, diarrhea, constipation																																										
Palpitations																																										
Swellings (hands, ankles, breast)																																										
Angry outburst, arguments, violent tendencies																																										
Anxiety, tension, nervousness																																										

Management Recommendations (continued)

- Symptom classification after completion of menstrual calendars:

1. symptoms that began in the premenstrual phase and offset at the beginning of menses or shortly thereafter (PMS or PMDD)
2. ongoing symptoms that worsen during the premenstrual phase (premenstrual worsening of another condition)
3. continuous or sporadic symptoms not related to a phase of the menstrual cycle (neither PMS nor PMDD)

Premenstrual symptoms limited to the premenstrual phase (PMS or PMDD)

- First line treatments:
    - exercise
    - Vitamin B6 (100 mgs)
    - CBT
    - OCPs
    - SSRIs (intermittent or continuous)

Premenstrual symptoms limited to the premenstrual phase (PMS or PMDD) (Continued)

- Start treatment with diet (complex carbohydrates during the late luteal phase), exercise, 100 mgs B6 and calcium (1000 mgs daily) if;

1. Mild symptoms OR
2. Short duration of symptoms OR
3. The patient doesn’t want treatment with OCPs or SSRIs

Premenstrual symptoms limited to the premenstrual phase (PMS or PMDD) (Continued)

- Treatment with OCPs or SSRIs in:
  - Moderate to severe symptoms which lead to functional impairment
  - Patients who do not respond to later discussed treatments

- The choice in women who desire contraception: OCPs
- The choice in women who do not need contraception: SSRIs

Premenstrual symptoms limited to the premenstrual phase (PMS or PMDD) (Continued)

- The strongest efficacy in contraceptives: drosperinone/estrogen preparation with a shortened hormone free interval (24 on and 4 days off)

- In women who are taking another OCP with mood & anxiety symptoms:
  - Switch to a drosperinone/estradiol preparation with a shortened hormone-free interval OR
  - Add an SSRI

Premenstrual symptoms limited to the premenstrual phase (PMS or PMDD) (Continued)

- Initiating medication in SSRIs:
  - Patients with regular cycles who can predict the onset of symptoms: at symptom onset or after ovulation
  - Women who have difficulty predicting the onset of symptoms or ovulation, or who have not fully responded to intermittent SRI treatment: daily treatment

Premenstrual symptoms limited to the premenstrual phase (PMS or PMDD) (Continued)

- In patients with severe physical symptoms:
    - Better response to daily SSRIs rather than intermittent
- Duration of SSRI treatment: at least 1 and ideally 2 months
- Patients not responding to drospirenone/estradiol : consider an SSRI
- Patients not responding to SSRIs: consider another SSRI

Premenstrual symptoms limited to the premenstrual phase (PMS or PMDD) (Continued)

- Not responding to the first line treatment: start a GnRH agonist
  - Consider supplemental estrogen and progestin as add-back therapy.
    - For symptom relief and withdrawal bleeding
    - The lowest dose possible

- Continuous hormone suppression rather than cyclic

Premenstrual symptoms limited to the premenstrual phase (PMS or PMDD) (Continued)

- Consider surgical interventions if:
  - GnRH agonists treatment was successful and the only method that improved symptoms AND
  - The patient has completed child-bearing

- Note that a trial of GnRH agonist treatment prior to consideration of surgical options is CRITICAL!

Ongoing symptoms that worsen in the premenstruum

- Treatment of the underlying disorder
  - If it is a chronic depressive or anxiety disorder: daily treatment with an SSRI
- If premenstrual worsening of symptoms continues despite this treatment:
    - Health habits should be optimized with diet, exercise and the addition of vitamin B6 and calcium.
    - If that is not sufficient, the dose of SSRI may be increased during the luteal phase or it may be combined with a drosperinone/estradiol product.

Continuous or Sporadic symptoms

- Manage the underlying condition

OR

- Refer to another clinician who can do so

Take Home Notes

- Premenstrual disorders vary in terms of the severity and timing of symptom onset.
- Treatments are well studied and include lifestyle changes for women with mild symptoms and use of a SRI or contraceptive with drosperinone/estradiol and shortened hormone free interval for women with moderate to severe premenstrual symptoms, including PMDD.
- Only a fraction of women will require use of a GnRH agonist or surgery.
- Surgical removal of uterus, tubes and ovaries should not be contemplated in the absence of a GnRH trial that shows benefit.

Thanks for Listening!

Any questions?