Premenstrual Dysphoric Disorder: Diagnosis and Treatment

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Overview
- Epidemiology
- Etiology
- Diagnosis
- Treatment

History of Premenstrual Syndromes

1930s: Described by Dr. Frank
1980s: Researchers began taking notice
1990s: Main stream
2016: PMDD is in DSM-V
Onset from menarche to menopause
Av. age of onset: 26 y/o

3-8% of Women
Typically worsens with age

Onset can be triggered by an obstetrical event

Premenstrual Dysphoric Disorder

Morbidity
- Comparable in severity to depression and generalized anxiety disorder
- 5-15 symptomatic days per month
  - 60-180 days/year
  - 2-6 months/year

Etiology of PMDD
Women with PMDD do not have "abnormal" blood levels of estrogen or progesterone.

Women with PMDD have an abnormal central nervous system response to normal hormonal levels and fluctuations.

Allopregnanolone Production in the Brain

Steroid Biosynthesis
Neuroactive Steroids Modulate GABA<sub>A</sub> Receptor Function

1. Chronic administration of Allopregnanolone results in decrease in GABA<sub>A</sub> receptor sensitivity, cross-tolerance to BZD and increase in α-4 subunits in rodents.
2. Evidence suggests that women with PMDD have a luteal phase sub-sensitivity to effects of BZD and neurosteroids which is greatest in high severity cases.
3. SSRI treatment increases activity of 3α-HSD and increases Allopregnanolone in brain & CSF.

Premenstrual Dysphoric Disorder (PMDD) 
DSM-V Diagnostic Criteria

5/III symptoms for the diagnosis of PMDD

At least one Emotional Symptom:
- Affective Lability
- Irritability/Anger
- Depressed Mood
- Anxiety/tension

Others:
- Decreased Interest in Activities
- Difficulty Concentrating
- Feeling out of control or overwhelmed

Physical Symptoms (counts as 1 sx):
- Breast tenderness, bloating, cravings, muscle pain, headache.

Symptoms MUST:
- Interferes with usual activities
- Regularly occurs during the last week of the luteal phase and remits within a few days of menses
- Not occur during the follicular phase (r/o exacerbation of an underlying mood disorder)

Confirm Diagnosis:
- By prospective daily diary ratings for at least 2 months

Speroff et al., 1994
Not PMS or PMDD

- Mild emotional or physical symptoms 1-2 days before menses
- No distress
- No impairment

Premenstrual Syndrome (PMS)

- Physical, behavioral, or affective/psychological
- Symptoms regularly occur during luteal phase
- Symptoms interfere with some aspects of the woman's life

1-4 symptoms physical, behavioral, or affective/psychological
≥5 symptoms that are physical or behavioral
BUT, if 1 out of 5 is affective (mood swings, anger, irritability, sense of hopelessness, tension, anxiety, on edge) than PMDD
Premenstrual Dysphoric Disorder

- Mood swings, sudden sadness, increased sensitivity to rejection
- Anger, irritability
- Sense of hopelessness, depressed mood, self-critical thoughts
- Tension, anxiety, feeling on edge

Premenstrual Dysphoric Disorder

- Symptoms regularly occur during luteal phase and resolve with menses
- Significant distress or interference with usual activities (e.g., work, school, social life).

Top 10 Luteal Phase Symptoms Reported by Women with PMDD

(Freeman, 2003 Primary Care Companion to JCP)
### Daily Record of Severity of Problems

1 = not at all  
2 = minimal  
3 = mild  
4 = moderate  
5 = severe  
6 = extreme

- Felt depressed, sad, down or blue
- Felt hopeless
- Felt worthless or guilty
- Felt anxious
- Had mood swings
- Was more sensitive to rejection
- Felt angry, irritable
- Had conflicts with other people
- Had loss interest in usual activities
- Had difficulty concentrating
- Felt sad
- Had increased appetite, overate
- Had increased appetite, overate
- Slept more, hard to get up
- Trouble getting staying asleep
- Not overwhelmed
- Had breast tenderness, bloating or swelling
- Had headache
- Had joint or muscle pain
- At least one of these problems interfered with my daily routine, productivity, hobbies or social activities, relationship with other.

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### Patient Example of Daily Ratings for 1 Month

![Graph showing daily ratings for 1 month with key points including ovulation and start of menses.]

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### Premenstrual Dysphoric Disorder

- Comorbidity with mood disorders
- Women with PMDD at high risk of developing major depressive disorder
- 30% to 70% of women with PMDD have a history of depression

PMDD: A Complex Pattern of Symptoms

- Anxiety
- Panic attacks
- OCD
- Guilt
- Depression
- Anger
- Insomnia
- Anger
- Affective lability
- Appetite
- Anhedonia
- Difficulty concentrating
- Physical symptoms
- Depressed mood
- Suicidal ideation
- Sleep
- Fatigue

PMDD needs ovulation, not menstruation

Premenstrual Syndrome (PMS) Treatment

- Few, Well Controlled Studies
  - Regular Exercise
  - Smoking Cessation
  - Alcohol Restriction
  - Regular Sleep
  - Diet


Steiner et al., 2006
Premenstrual Syndrome (PMS) Treatment

- Few, Well Controlled Studies
  - Diet
    - Reduce caffeine use
    - Calcium 1200-1600 mg daily
    - Vitamin B₆ 50-100 mg daily
    - Magnesium 500 mg daily
    - Chasteberry 30-40 mg daily (Luteal phase)

(Pawer et al., 2006)

PMS and PMDD Treatment

- Few, Well Controlled Studies
  - Education about diagnosis
  - Stress Reduction and Management
  - Anger Management
  - Individual and Couples Therapy
  - Cognitive Behavioral Therapy

(Pawer et al., 2006)

Premenstrual Dysphoric Disorder

- SSRIs
  - Most Commonly Used Treatment
  - Reduce irritability
  - Reduce depressed mood/dysphoria
  - Improve physical symptoms
    - Bloating
    - Breast tenderness
    - Appetite changes
  - Improve Psychosocial Functioning

(Pawer et al., 2006)
Allopregnanolone (ALLO) and Tetrahydroprogesterone (THP) are metabolites of progesterone. 5 alpha-dihydroprogesterone is a substrate for 3alpha-hydroxysteroid dehydrogenase, which converts it into ALLO and THP (Belelli, 2005).

SSRI's are effective in treating Premenstrual Dysphoric Disorder (PMDD), which is preferentially responsive to treatment with SSRI's. Luteal phase administration is effective. Women with PMDD have an abnormal central nervous system response to normal hormonal levels & fluctuations.
### Premenstrual Dysphoric Disorder Treatment

- **Continuous Dosing**
  - Daily Medication
- **Intermittent Dosing**
  - Luteal Phase - Start of Menses
  - Start at Ovulation, Stop at 1-2 days after onset of menses
- **Semi-Intermittent Dosing**
  - Daily Medication w/ increasing dose during luteal phase

(Steiner et al., 2006)

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**Estradiol pg/mL**

- Continuous Dosing
- Intermittent Dosing
- Semi-Intermittent Dosing

**Progesterone ng/mL**

- Ovulation
- Luteal Phase

(Speroff, 1994; Steiner et al., 2006)

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### Improvement of PMDD with Continuous Fluoxetine or Placebo

**Percent Improvement**

- Fluoxetine 20 mg
- Fluoxetine 60 mg
- Placebo

(With permission from Steiner et al., N Engl J Med. 1995;23:1529. Copyright © 1995 Massachusetts Medical Society. All rights reserved.)
Mean DRSP Total Score In PMDD With Continuous Sertraline

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline (N = 116)</td>
<td>64</td>
<td>49</td>
<td>58</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>Placebo (N = 118)</td>
<td>44</td>
<td>44</td>
<td>53</td>
<td>53</td>
<td>54</td>
</tr>
</tbody>
</table>

Yonkers et al. JAMA. 1997;278:983.

Continuous Paroxetine CR VAS Mood Score In PMDD

Adjusted mean change from baseline (+/− 2S.E.)*

TC1 = treatment cycle 1
TC2 = treatment cycle 2
TC3 = treatment cycle 3

Adjusted for center group, baseline score and age
*decrease in mean=improvement


Luteal Phase Administration

Day 1  Day 14  Day 28

Sertraline 50 mg/d
Fluoxetine 20 mg/d
Paroxetine 30 mg/d
**Intermittent Sertraline in PMDD**

Mean DRSP Total Score

Mean Cycle 3 Dose:
Sertraline: 73.8 ± 21.7 mg
Sertraline (N = 119) → 107
Placebo (N = 110) → 67

<table>
<thead>
<tr>
<th>DRSP Score</th>
<th>Baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>72.6</td>
<td>71.3</td>
<td>60.8</td>
<td>56.5</td>
<td>54.3</td>
</tr>
</tbody>
</table>

* P<.001
** P<.01


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**Effect Of Intermittent Daily Fluoxetine On PMDD**

Change From Baseline to Mean Luteal Treatment Response

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine 10 mg</td>
<td>-10</td>
<td>-10</td>
<td>-10</td>
<td>-10</td>
</tr>
<tr>
<td>Fluoxetine 20 mg</td>
<td>-5</td>
<td>-5</td>
<td>-5</td>
<td>-5</td>
</tr>
</tbody>
</table>

* Vs placebo, P<.05.
** Vs fluoxetine 10 mg, P<.05.


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**Utility of Paroxetine as an Intermittent Treatment**

<table>
<thead>
<tr>
<th>Study End Point</th>
<th>Placebo</th>
<th>Intermittent Paroxetine</th>
<th>Continuous Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Study End Point</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

* Percentage of Responders

Intermittent vs placebo, P<.001; Continuous vs placebo, P<.01.

* Based on a CGI score of 1 or 2 during the luteal phase of each menstrual cycle.

Landon et al. Presented at the 155th Annual Meeting of the APA; May 18-23, 2002; Philadelphia, PA.
Luteal Versus Continuous Sertraline Treatment: Percent Improvement

<table>
<thead>
<tr>
<th>Condition</th>
<th>Contin-Sertraline</th>
<th>Luteal-Sertraline</th>
<th>Contin-Placebo</th>
<th>Luteal-Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRSP-Total</td>
<td>32</td>
<td>21</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>DRSP-Depressive Symptoms</td>
<td>36</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>DRSP-Physical Symptoms</td>
<td>23</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>DRSP-Anger/Irritability</td>
<td>19</td>
<td>19</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Mean Baseline DRSP-Physical Score
Yonkers et al, 2015
Halbreich et al, 2012

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Premenstrual Dysphoric Disorder Treatment

- Continuous Dosing: Medication taken daily
  - Comorbid Mood or Anxiety Disorder
  - Subsyndromal Mood/Anxiety Sx in Follicular Phase
  - Erratic/Irregular Menstrual Cycle
  - Unable to Remember to Take/Timing
  - Concern around Starting/Stopping SSRI

(Swiner et al., 2006)

Premenstrual Dysphoric Disorder Treatment

- Continuous Dosing: Medication taken daily
  - Fluoxetine (Prozac): 20-60 mg daily
  - Sertraline (Zoloft): 50-150 mg daily
  - Paroxetine (Paxil): 10-30 mg daily
  - Paroxetine CR (Paxil-CR): 12.5-25 mg daily
  - Citalopram (Celexa): 5-20 mg daily

(Swiner et al., 2006)
Premenstrual Dysphoric Disorder Treatment

- Intermittent Dosing: Medication taken Luteal-Menses
  - Regular Menstrual Cycle
  - No 'On/Off' side effects
  - Side effects (e.g., sexual dysfunction)

(Steiner et al., 2006)

Premenstrual Dysphoric Disorder Treatment

- Intermittent Dosing: Medication taken Luteal-Menses
  - Fluoxetine (Prozac): 20-60 mg daily
  - Fluoxetine (Serafem/Prozac Weekly): 20 mg weekly
  - Sertraline (Zoloft): 50-150 mg daily
  - Paroxetine (Paxil): 10-30 mg daily
  - Paroxetine CR (Paxil-CR): 12.5-25 mg daily
  - Citalopram (Celexa): 5-20 mg daily

(Steiner et al., 2006)

Premenstrual Dysphoric Disorder Treatment

- Semi-Intermittent Dosing: Medication taken daily with increase in dose Luteal-1-2 days of Menses
  - Mood or Anxiety Disorder with Premenstrual Worsening
  - Subsyndromal Mood or Anxiety Sx in Follicular Phase
  - 'On/Off' side effects

(Steiner et al., 2006)
Premenstrual Dysphoric Disorder Treatment

- Semi-Intermittent Dosing: Medication taken daily with increase in dose Luteal: 1-2 days of Menses
  - Citalopram (Celexa): 5 mg daily during follicular phase, 10-30 mg daily during Luteal phase

(Suiner et al., 2006)

SSRIs-Side Effects

- SSRI-Related Side Effects
  - CNS
    - Agitation, Anxiety, Jitter, Nervousness (10%)
    - Fatigue (10-30%)
    - Insomnia, hypersomnia
    - SI ≤ 24 years old
    - Sexual Dysfunction (30-40%)
      - Low libido or anorgasmia
  - Metabolic Weight Gain
    - Weight gain (5-20%) *Mainly w/ Paroxetine
  - GI (10-20%)
    - Nausea, Diarrhea

(McClintock et al., 2011)

SSRIs-Side Effects

- SSRI-Related Side Effects
  - CNS
    - Anxiety, Agitation, SI: Start low dose, increase slowly
      - +/- Benzodiazepine (2 week supply)
    - Insomnia: take med in AM
    - Hypersomnia or Fatigue: take med in PM
  - Sexual Dysfunction (30-40%)
    - Lower dose, drug holiday, switch SSRI
  - Low libido: Add Buproprion SR 100-150 mg BID
  - Anorgasmia: Add Sildenafil 50-100 mg prn

(McClintock et al., 2011)
SSRIs-Side Effects

- SSRI-Related Side Effects
  - Weight Gain (5-20%)
    - Avoid Paroxetine
  - GI (10-20%)
    - Start low dose, increase slowly, usually resolves 7-10 days

Oral Contraceptive Pills

- Somatic Symptoms
  - Spironolactone
    - Improve Mood
    - Reduce Bloating and Weight Gain
  - Oral Contraception
    - Drospirenone (analog of spironolactone)
      - Decrease Food Cravings
      - Increase Appetite
      - Reduce Acne

Premenstrual Dysphoric Disorder Treatment

Women’s Reproductive Behavioral Health Program

MUSC Women’s Services
135 Cannon St., Suite 201
843-792-5300
guille@musc.edu