

# Premenstrual Dysphoric Disorder (PMDD)

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Premenstrual dysphoric<sup>1</sup> disorder (PMDD) is a severe form of premenstrual syndrome. PMDD is a condition associated with severe emotional and physical problems that are linked closely to the luteal phase of the menstrual cycle. Symptoms occur regularly in the second half of the cycle and end when menstruation begins or shortly thereafter.

PMDD affects about 5% of menstruating women and is considered to be a very severe form of PMS (premenstrual syndrome), which affects as many as 75% of menstruating women.

Both PMDD and PMS share symptoms in common that include depression, anxiety, tension, irritability and moodiness. What sets PMDD apart is its severity, which has a very disruptive effect on their lives.

The cardinal symptom of PMDD is irritability. At least five of the 11 specified symptoms must be present for a diagnosis of PMDD. These symptoms should be limited to the luteal phase and should not represent amplification of preexisting depression, anxiety, or personality disorder. In addition, they must be confirmed prospectively by daily rating for at least two consecutive menstrual cycles. (Bhatia and Bhatia 2002)

- A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):
  - 1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
  - 2. Marked anxiety, tension, feelings of being "keyed up" or "on edge"
  - 3. Marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
  - 4. Persistent and marked anger or irritability or increased interpersonal conflicts
  - 5. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
  - 6. Subjective sense of difficulty in concentrating
  - 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 subjective sense of being overwhelmed or out of control
  - 11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," or weight gain

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<sup>1</sup> Dysphoria is derived from the Greek word dysphoros, which means difficult to bear. It is generally characterized as an unpleasant or uncomfortable mood, such as sadness (depressed mood), anxiety, irritability, or restlessness.

- B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).
- C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).
- D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

## ***Etiology***

The cause of PMDD has not been definitively established.

A leading theory suggests it is due to the lack of serotonin (a neurotransmitter) and mediated by the fluctuations of the levels of sex hormones (progesterone, estrogen, and testosterone) in the luteal phase of the menstrual cycle. (Guille, Spencer et al. 2008)

One study found that luteal phase concentrations of estradiol were lower, and SHBG was higher in women with PMDD when compared to those without. (Thys-Jacobs, McMahon et al. 2008)

In general, estradiol practices excitatory actions and progesterone inhibitory effects on CNS.

Several studies have found changes the GABA system to be associated with the sex hormone abnormalities in PMDD. (Epperson, Haga et al. 2002) (Vickers and McNally 2004) (Sundstrom Poromaa, Smith et al. 2003)

The adrenal glands produce GABA steroids during stress. Examples of GABA-steroids are 3 $\alpha$ -hydroxy-5 $\alpha$ / $\beta$  metabolite testosterone and stress hormone desoxycorticosterone (tetra-hydrodesoxycorticosterone [THDOC]). (Backstrom, Andersson et al. 2003)

## ***Differential Diagnosis***

The following conditions may include dysphoria as a major component or symptom:

- Clinical depression (unipolar) and dysthymia
- Premenstrual Syndrome
- Bipolar disorder
- General anxiety disorder
- Gender identity disorder, sometimes called gender dysphoria
- Personality disorders such as borderline personality disorder and avoidant personality disorder
- Substance withdrawal
- Body dysmorphic disorder
- Hypoglycemia
- Schizophrenia

## ***Premenstrual Syndrome***

PMDD and PMS share many symptoms. Premenstrual syndrome can be divided into four subgroups.

**PMS Type A**, the most common subgroup, consists of premenstrual anxiety, irritability and nervous tension, sometimes expressed in behavior patterns detrimental to self, family and society. Elevated blood estrogen and low progesterone have been observed in this subgroup.

**PMS Type H**, the second-most-common subgroup, is associated with symptoms of water and salt retention, abdominal bloating, mastalgia and weight gain. The severe form of PMS Type H is associated with elevated serum aldosterone.

**PMS Type C** is characterized by premenstrual craving for sweets, increased appetite and indulgence in eating refined sugar followed by palpitation, fatigue, fainting spells, headache and sometimes the shakes. PMS Type C patients have increased carbohydrate tolerance and low red-cell magnesium.

**PMS Type D** is the least common but most dangerous because suicide is most frequent in this subgroup. The symptoms are depression, withdrawal, insomnia, forgetfulness and confusion. PMS Type D has been associated with low estrogen and high progesterone levels, and high lead levels in hair tissue and chronic lead intoxication.

## ***Lab Tests***

PMDD and PMS are diagnosed by symptoms. Several lab tests may help rule out other diagnosis.

Blood sugar tests, including fasting blood sugar and glucose and insulin tolerance tests are indicated if there is a craving for sweets and carbohydrates (PMS-C).

Hormone status may be assessed in serum or saliva. The latter commonly measures all three estrogens (estrone, estradiol and estriol), progesterone, testosterone and DHEA. Many panels measure estradiol and progesterone once a week over one month to assess how they vary over the menstrual cycle.

Adrenal function tests of cortisol and DHEA may be indicated if there is fatigue. Melatonin tests may be indicated if there is insomnia or sleep disturbance.

## ***Conventional Treatment***

### **Selective Serotonin Reuptake Inhibitors**

The U.S. FDA has approved three medications for the treatment of PMDD:

- Fluoxetine (Prozac),
- Sertraline (Zoloft), and
- Paroxetine HCl (Paxil).

## **Progesterone**

Progesterone has consistently failed to show efficacy for severe PMS/PMDD in large, randomized, placebo-controlled trials. (Freeman 2004)

One study found that progesterone administration was associated with increased confusion, fatigue, and reduced confidence, even after controlling for placebo-associated mood change, in all women in the study (23 with PMDD and 29 non-PMDD controls). (Klatzkin, Morrow et al. 2006)

Depression may be a confounding factor in studies of PMDD. One study found that women with a history of depression showed a blunted allopregnanolone response to stress, and did not show the expected correlation between progesterone and allopregnanolone, (Klatzkin, Morrow et al. 2006)

## **Yaz**

Yaz (drospirenone 3mg and ethinyl estradiol 20mcg) is the first birth control pill to gain FDA approval for treating PMDD. Drospirenone is a synthetic progestin that is an analog to the diuretic spironolactone. (Fenton, Wellington et al. 2007)

## ***Lifestyle Changes***

Lifestyle changes that are recommended for PMDD include: (Bhatia and Bhatia 2002)

- Regular, frequent, small balanced meals rich in complex carbohydrates and low in salt, fat, and caffeine

- Regular exercise

- Smoking cessation

- Alcohol restriction

- Regular sleep

Non-pharmacologic treatments include:

- Stress reduction and management

- Anger management

- Self-help support group

- Individual and couples therapy

- Cognitive-behavioral therapy

- Patient education about the cause, diagnosis, and treatment of PMS/PMDD

- Light therapy with 10,000 Lx cool-white fluorescent light.

## **Natural Therapies**

### **L-tryptophan**

L-tryptophan, a serotonin precursor, was found in two studies to provide significant relief when supplemented daily in a large dose of (six grams) per day. (Rapkin 2003; Freeman 2004)

### **St. John's wort**

St. John's wort was found to be of benefit in one case study. It is contraindicated with SSRIs. (Huang and Tsai 2003)

### **Vitex agnus castus**

Vitex agnus castus was found to be as effective as Fluoxetine. Fluoxetine was more effective for psychological symptoms while the Vitex extract diminished the physical symptoms. (Atmaca, Kumru et al. 2003)

### **Calcium**

Alterations in calcium homeostasis have long been associated with affective disorders. One study compared calcium metabolism in women with and without premenstrual dysphoric disorder (PMDD). Both groups showed variations over the menstrual cycle in calcium-regulating hormones, total serum, ionized and urine calcium, pH, intact PTH, and 1,25-dihydroxyvitamin D [1,25(OH)(2)D]. The PMDD group, when compared with controls, had significantly: (Thys-Jacobs, McMahon et al. 2007)

- lower ionized calcium at phase 1 (menses) ( $1.166 \pm 0.072$  vs.  $1.182 \pm 0.087$  mmol/liter;  $P = 0.027$ ),
- lower urine calcium excretion at three of the five phases (late follicular phase 2, midcycle phase 3, and early luteal phase 4), and
- lower 1,25(OH)(2)D at luteal phase 4 ( $45.0 \pm 27.5$  vs.  $50.6 \pm 33.8$  pg/ml;  $P = 0.032$ ).

### **Magnesium**

Several articles have proposed that magnesium deficiency may be common, and magnesium may be of therapeutic benefit in PMS and PMDD.

One study, however, found no evidence of magnesium deficiency in women with PMDD compared with control subjects, and that magnesium was not superior to placebo in the mitigation of mood symptoms in women with PMDD. (Khine, Rosenstein et al. 2006)

### **Melatonin**

Melatonin has a diurnal rhythm and regulates sleep. The peak concentrations of melatonin in plasma normally occur between 0200 and 0400 hours. Abnormal nocturnal melatonin secretion patterns have been observed in premenstrually depressed patients compared to those in healthy control women. (Parry 1997; Parry, Berga et al. 1997; Parry, Udell et al. 1997)

## **Gamma-Aminobutyric Acid**

One study found that cortical GABA levels declined across the menstrual cycle in healthy women, whereas women with PMDD experienced an increase in cortical GABA levels from the follicular phase to the mid luteal and late luteal phases. (Epperson, Haga et al. 2002)

## **Inositol**

A cross-over, double-blind, placebo-controlled trial of eleven female patients with PMDD diagnosed according to DSM-IV compared myo-inositol (12 g daily) and placebo (d-glucose) administered during the luteal phase only (14 days prior to menses) for six menstrual cycles. No beneficial effect was demonstrated for inositol over placebo. (Nemets, Talesnick et al. 2002)

## **Kamishoyosan**

Kamishoyosan (TJ-24) is a traditional Japanese herbal formula (kampo) that consists of ten crude herbs. It is commonly prescribed, and has been found to be effective for PMS. (Kimura, Takamatsu et al. 2007)

Thirty patients with PMDD were treated with TJ-24 for six menstrual cycles. Nineteen patients (63.3%) had >50% improvement in the total score of the Hamilton Depression Rating Scale (HAM-D) Scale (17 items) in the late luteal phase. Fourteen patients (46.7%) went into remission (total HAM-D score <7). (Yamada and Kanba 2007)

## **Feverfew**

Feverfew (*Tanacetum parthenium*) contains a sesquiterpene lactone, parthenolide, which has been associated with maintaining healthy platelet function and serotonin release, supporting cranial blood vessel integrity and function.

Feverfew has been shown to be effective for migraine headache. (Modi and Lowder 2006) (Diener, Pfaffenrath et al. 2005) (Pittler and Ernst 2004)

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