Premenstrual dysphoric disorder (PMDD) – an overview

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Abstract
Premenstrual dysphoric disorder (PMDD) is a disabling condition that affects women of reproductive age. It is not frequently conversed, is often mistaken for Premenstrual Syndrome (PMS) or can be misdiagnosed due to its array of symptoms and periodicity. Women experience severe and distressing symptoms which can lead to dysfunction. PMDD symptoms usually begin around the luteal phase of the menstrual cycle and reduce upon menstrual bleeding.

Treatment options include diet and lifestyle modification, medication and psychological interventions. This article aims to review the condition and treatments options that are available.

Keywords: menstruation, premenstrual dysphoric disorder (PMDD), luteal phase, reproduction

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Introduction
Premenstrual dysphoric disorder (PMDD) is a condition distinguished by mood and physical symptoms in the week prior to menstruation. Approximately 5% of women are affected and often go undiagnosed.1 Assigned in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), it is distinguished by cognitive–affective symptoms that are distinctive from those of other mood disorders.2

Cognisance of the synchronised variation in mood with menstrual cycle phases has amplified noticeably over the past two decades. Traditionally the term premenstrual syndrome (PMS) has been more familiar. PMS has a number of symptoms such as which occur in the late luteal phase and subside at the commencement of menstruation:3

• irritability
• tension
• fatigue
• dysphoria
• distractibility
• impaired motor coordination
• changes in eating and sleeping, and
• libido changes

Distinction between PMDD and PMS is the severity of PMDD symptoms and the ability to affect functioning.

Clinical phenomenology
The DSM-5 diagnosis is established upon a pre- and perimenstrual repetition of at least five physical, affective, and/or behavioural symptoms (Table I).

As per DSM-5 criteria, these symptoms must have occurred during at least two menstrual cycles in the past year to meet criteria for PMDD diagnosis. The greatest severity of symptoms is noted from three to four days prior to onset of menstruation to up to three days postmenstrual onset. There must be an absence of symptoms in the postmenstrual week.5

Pathophysiology
PMDD symptoms occur due to hormonal actions following ovulation. The hormones progesterone and oestrogen control certain neurotransmitters that impact mood and behaviour e.g. serotonin, Gamma-aminobutyric acid (GABA), dopamine, norepinephrine.6 When serotonin levels are decreased, sleep, appetite and moods are affected. It has been postulated that women with PMDD have lower levels of serotonin in the last 10 days of the menstrual cycle.6 Allopregnanolone (ALLO), which is a metabolite of progesterone, has also been shown to play a role

<table>
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<tr>
<th>Table I: Physical, affective, and behavioural symptoms of PMDD*</th>
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<tr>
<td>Physical</td>
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<td>Breast tenderness</td>
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on GABA-A receptors in the pathophysiology of PMDD.6,7 ALLO has anxiolytic effects comparable to benzodiazepines.7 Genetics, stress and psychosocial factors are other contributors.7 Risk factors include anxiety, depression, PMS, family history of PMDD or mood disorders, personal history of trauma, abuse or other highly stressful events.7

PMDD can worsen during the years of perimenopause. The symptoms may be more severe, and as periods become increasingly irregular, symptoms can be more frequent and much less predictable, making PMDD harder to manage.2

Treatments
The goals of the treatment of PMDD are:
1. Reduction of symptoms
2. Enhanced social and occupational functioning
3. Improved quality of life

Pharmacological interventions
The first-line treatment for PMDD are selective serotonin re-uptake inhibitors (SSRIS) (Table II).

Hormonal interventions are indicated in Table III.

Lifestyle changes and non-pharmacological treatment options include:2,8,9
- Dietary modifications
- Restricted salt –1200 mg/day in divided doses
- Restricted caffeine
- Restricted alcohol – 6 g/day from ovulation to menses

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<tr>
<th>Table II: Pharmacological treatment options for PMDD2,7,8,9</th>
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<tbody>
<tr>
<td><strong>Agents</strong></td>
</tr>
<tr>
<td>Serotonergic agents</td>
</tr>
<tr>
<td>Citalopram</td>
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<tr>
<td>Fluoxetine</td>
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<tr>
<td>Paroxetine</td>
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<td>Sertraline</td>
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<td>Venlafaxine</td>
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<th>Table III: Hormonal therapies for PMDD2,7,8,9</th>
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<tr>
<td><strong>Drug</strong></td>
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<tr>
<td>Leuprolide depot</td>
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<tr>
<td>Leuprolide depot with ovarian hormone supplements</td>
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<tr>
<td>Goserelin with oestrogen supplementation</td>
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<tr>
<td>Danazol</td>
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<tr>
<td>OCPs</td>
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<tr>
<td>Progesterone</td>
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IM = intramuscularly; SC = subcutaneously; OCPs = oral contraceptive pills
- Moderate regular exercise
- Cognitive behavioural therapy
- Stress management
- Supportive therapy
- Patient education about the condition

Nutritional supplements include:2,8,9
- Vitamin B6, up to 100 mg per day
- Vitamin E, up to 600 IU per day
- Calcium carbonate, 1,200 to 1,600 mg per day
- Magnesium, up to 500 mg per day
- Tryptophan, up to 6 g per day

Complementary medicines include:9,10
- Vitex agnus-castus (chasteberry)
- St John wort
- Gingko biloba
- Evening primrose oil

Management

Figure 1 provides an outline for the management of PMDD.

Novel pharmacotherapies

The appearance of evidence associating allopregnanolone in the aetiology of PMDD has led to new drug advances. A phase II study was conducted in a sample of women with PMDD with sepranolone, an allopregnanolone antagonist.13 It was demonstrated that patients receiving the active ingredient had a decrease in symptoms compared to placebo over the menstrual cycle.14,15 It is an injection that inhibits the effects of the GABA steroid allopregnanolone on a GABA-A receptor in the brain.16 This prevents PMDD symptoms from developing.16

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**Figure 1:** Algorithm for the management of PMDD10,11,12
Conclusion

It is imperative that pharmacists and healthcare professionals have the ability to distinguish between PMS, PMDD and psychiatric disorders in order for women to be correctly diagnosed and treated. Future outlooks may include training healthcare professionals for the assessment of PMDD and how to offer support to patients. Women who suspect they have the condition should aim to track their symptoms using journals or apps. PMDD is a cyclical mood disorder distressing a subset of women with a disease burden analogous to other depressive disorders. Additional investigation is required to both continue to clarify the pathophysiology of this disorder and to establish its most effective treatments.

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References