Pre-menstrual Dysphoric Disorder

A NATUROPATHIC APPROACH

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Pre-menstrual Dysphoric Disorder (PMDD) is a severe type of premenstrual syndrome. It is characterised by moderate to severe affective and behavioural symptoms that occur post ovulation and peak in the luteal phase of the menstrual cycle, becoming minimal or absent at the onset of menstruation.[1] PMDD is believed to affect 3-8%[2] of women worldwide.

Diagnostic criteria

In 2022, PMDD was added to the International Classification of Diseases 11th Revision (ICD-11) and placed under the category of gynaecological diseases.[3] PMDD is also listed in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) as a separate entity under depressive disorders.

Pathophysiology

Hormones such as pregnenolone, progesterone, oestradiol, and corticosterone can be synthesised in the brain where they function as neuro-active steroids (NAS's).[5] Here they act on neuron receptors in parts of the brain that influence mood, cognition and behaviour, influencing the release of neurotransmitters (NT's) such as serotonin, GABA and dopamine.[6] Symptoms of PMDD are partially driven by central nervous system sensitivity to normal fluctuations in neuroactive steroid hormones (NASs) and their subsequent action on NT's.[7]

Allopregnanolone

A sensitivity to rising levels of progesterone in the luteal phase and its metabolite, allopregnanolone (ALLO) have been implicated in the pathogenesis of PMDD.[8] In women without PMDD, modulation of the GABA-a receptor by ALLO results in reduced anxiety and mild sedation. Paradoxically women with PMDD show altered GABA-a receptor sensitivity to rising levels of ALLO, resulting in mood and behavioural disturbances such as aggression, anxiety and poor executive function.[9,10]

DSM-5 Diagnostic criteria for PMDD

CORE SYMPTOMS

At least 1 of the first 4 core symptoms listed should be present in the week before menses:

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

1 or more of the following symptoms must also be present:

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

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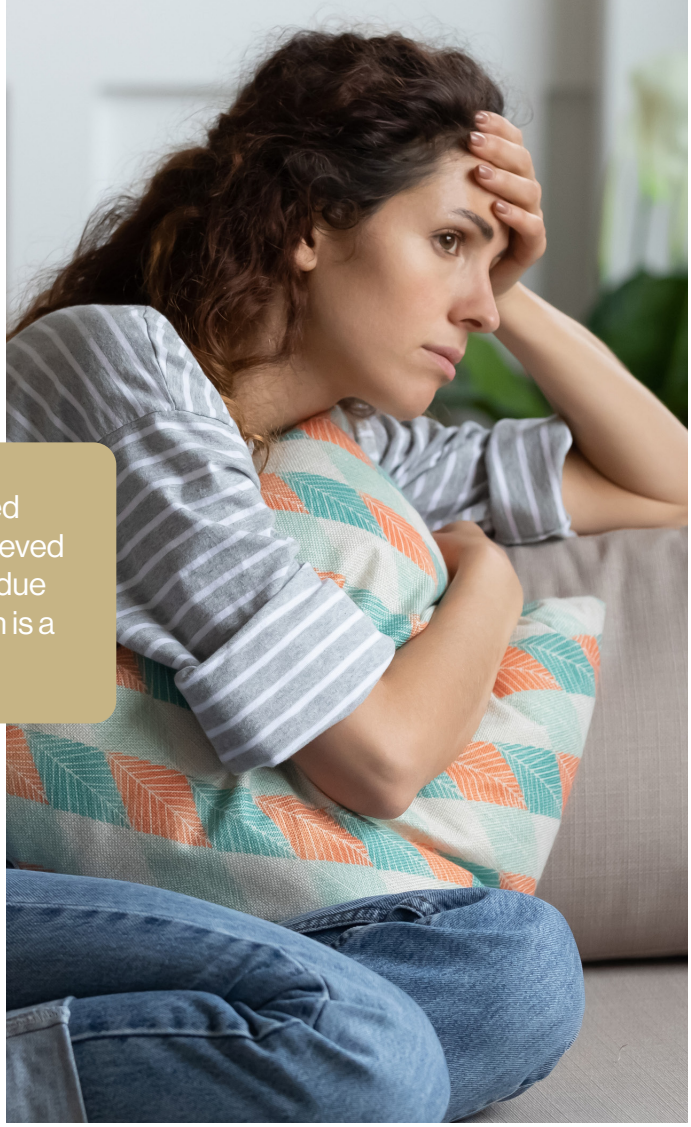
- Symptoms are associated with clinically significant distress, interference with work, school, usual social activities, or relationships with others.
- Symptoms must not be an exacerbation of another disorder e.g., MDD, hypothyroid
- Should be confirmed by prospective daily ratings during at least 2 symptomatic cycles (although a provisional diagnosis may be made prior to this confirmation)

Serotonin

Women with PMDD demonstrate altered serotonergic activity in the luteal phase of the menstrual cycle. This is largely driven by withdrawal of oestrodiol. Oestrodiol is known to increase serotonergic activity via multiple mechanisms including:

- increasing serotonin transporter mRNA, particularly in brain areas involved with emotion and behaviour, [11]
- increasing production of tryptophan hydroxylase, the enzyme responsible for the conversion of tryptophan to serotonin.[12]

Plasma melatonin has been shown to be delayed in the luteal phase of women with PMDD and is believed to contribute to mood disturbances. This may be due to blunted serotonin production, the latter of which is a precursor for melatonin production.



AETIOLOGY

Genetics

Twin studies support a link between genetics and an increasing susceptibility for the development of PMDD. Polymorphisms are observed in many genes, including those coding for:[13]

- Serotonergic 5HT1A receptor
- Oestrogen 1 receptor alpha gene (ESR-1)
- ESC/E(Z).[14]

Trauma

Women who have a history of trauma are significantly more likely to experience PMDD than controls. An Australian study observed 83% of women with PMDD had experienced early life trauma, with emotional abuse being the most prevalent.[15] While the underlying mechanisms are multifaceted, dysfunctional HPA-axis activity and subsequent altered neurotransmission may be responsible.[16]

Chronic stress

Women with PMDD demonstrate a maladaptive response to stressors highlighted by a flattened diurnal cortisol slope,[17] thus suggestive of HPA axis dysfunction. This may explain their perception of daily events as more stressful and their higher arousal of negative feelings in the luteal phase of the cycle. Chronic stress alters the composition of GABA-a receptors reducing tonicity,[18] which may partly explain the paradoxical reaction to rising levels of ALLO, and subsequent heightened stress reactivity.

Comorbidities

Women with PMDD should be considered a high-risk group for suicidality. Meta-analysis of thirteen studies demonstrates that PMDD patients were at an almost seven times higher risk of suicide attempt.[19] Practitioners awareness of working in conjunction with a mental health professional needs to be highlighted to ensure optimal patient care. Women with bipolar [20, 21] and ADHD [22] also demonstrate a higher prevalence of PMDD.

SUPPLEMENTATION

Calcium 600mg/twice daily [23] (luteal phase)

Alterations in cyclical calcium homeostasis have been observed in women with PMDD compared to healthy controls.[24] Calcium channels are involved with the release of monoamines including serotonin and dopamine, it is hypothesised that dysregulated levels of calcium in the luteal phase may drive neuronal dysfunction. Feelings of irritability, depression, anxiety, and mania experienced by individuals with PMDD are enhanced. Oestrodiol has a regulating action on calciotropic hormones, thus withdrawal of oestrodiol will influence cellular calcium concentrations.[25] It is interesting to note that many of the mood symptoms associated with low calcium mimic that of PMDD.

Myo-inositol 2g/day (luteal phase)

Myo-inositol may be useful for the management of PMDD due to its role as a second messenger of serotonin, however contradictory results have been seen. An early 2002 study using a high dose of myo-inositol (12g/day) taken in the luteal phase of the cycle showed no efficacy compared to placebo.[26] However a later study utilising a lower dose of 2g/day of myo-inositol consumed over 6 menstrual cycles was associated with a statistically significant improvement in the Hamilton Depression Rating scale and the Clinical Global Impression-Severity of Illness scale in women with PMDD.[27]

HERBAL

Crocus sativus (Saffron)

Supplementation with *Crocus sativus* (15mg twice daily) over two menstrual cycles has been shown to assist with improving mood in individuals with PMDD.[28] The active constituents, crocin and safranal found with in *Crocus sativus* are believed to inhibit the reuptake of dopamine, norepinephrine and serotonin, contributing to its mood enhancing effects.

Adaptogen & Nervine herbal medicines

Due to the HPA axis dysfunction observed in women with PMDD, herbal medicines with adaptogen and nervine actions may be useful, though no studies have been conducted. Examples include *Withania somnifera*, *Chamomila recutita*, *Centella asiatica* and *Rhodiola rosea* (caution with anti-depressants).

NUTRITION

PMDD is associated with extreme cravings, driven by withdrawal of oestrodiol and serotonin. Women with PMDD should be encouraged to consume adequate whole food carbohydrates. Complex carbohydrates in the luteal phase assist with improving mood symptoms including depression, tension and anger by increasing brain synthesis of serotonin.[29,30]

LIFESTYLE

Light therapy

Light therapy is effective in enhancing mood in a range of mental health conditions, including PMDD. While exposure to sunlight is ideal, use of a light box may also be helpful. Thirty minutes of evening light therapy, administered via a light box in the luteal phase of the menstrual cycle, to women with PMDD has been shown to reduce premenstrual depression and tension scores.[31]

PMDD TREATMENT PROTOCOL

- **Saffron 15mg/day:** luteal phase
- **Adaptogen & nervine herbs:** throughout the menstrual cycle
- **Calcium:** 600mg/BD in the luteal phase
- **Light exposure:** 30mins+/day, every day for serotonin production
- ⬆ **Complex carbohydrates:** luteal phase to promote serotonin
- Meal prep in the follicular phase in preparation for the luteal phase
- ⬇ Stress in the luteal phase (⬇ workload, ⬆ fun) to support HPA axis
- Regular check-ins with psychologist

PMDD RESOURCES:

- **Symptom Tacker and other resources:** https://iapmd.org/toolkit
- **Phone App:** https://mevpmdd.com

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