Premenstrual disorders in the perimenopause: a review of the evidence for dietary, lifestyle and complementary medicine management.

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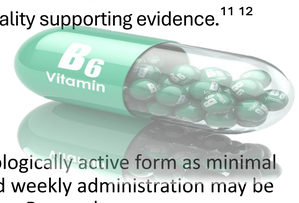
While the aetiology of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) remains uncertain, there are two recognised theories:
1. Some individuals assigned female at birth (AFAB) are "sensitive" to progesterone and progestogens.
2. Abnormal response of the hormonal receptors of the neurotransmitters serotonin and γ-aminobutyric acid (GABA), to (normal levels) of oestrogen, or progesterone or allopregnanolone (ALLO) respectively.[1 2]
Furthermore, growing evidence suggests that the hallmark symptoms of PMDD - mood lability, anxiety and irritability, which are often exacerbated by stress, reflect suboptimal $GABA_A$receptor ($GABA_A$-R) sensitivity to ALLO.[2]

Gonadal hormones are potent neurosteroids and during the perimenopause, the level of these hormones fluctuate. This hormone fluctuation could, in some individuals, create mental health changes.[3]Additionally, a subset of AFABs with a menstrually related mood disorder, such as PMS/PMDD may experience an increased mood sensitivity to the declining ovarian hormones associated with the late menopause transition and early postmenopausal phase. [4]
Oestrogen therapy is indicated to manage the low oestrogen symptoms associated with the menopausal transition as well as to improve mood. However, in non-hysterectomized individuals, a progestogen must be administered to prevent endometrial neoplasia, and this may be associated with a return or exacerbation of the premenstrual mood symptoms. [5]

Epigenetic changes, mediated by hormonal fluctuations, may influence the vulnerability to PMDD. 50% of PMDD patients have alteration of the Extra Sex Combs/Enhancer of Zeste (ESC/E(Z)) gene network. [6]
There is emerging evidence on inflammation and neuroinflammation and the potential role in PMDD.[7]

Targeting the GABA system to alleviate anxiety, with herbal medicine and nutraceuticals that modulate GABA, may provide a novel treatment alternative or adjunctive option to existing anxiolytic or anti-depressant medications[8]

Vitamin B 6 is considered first line intervention for PMDD in the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines,[1] with arguably limited high quality supporting evidence.[11 12]



- Cofactor in the synthesis of monoamines and GABA. [13]
- Supplementation of pyridoxal 5'-phosphate (PLP), the biologically active form as minimal neurotoxicity observed in neuronal cell viability tests, and weekly administration may be preferable over daily use to prevent toxicity.[14] Arguably as a B-complex
- Doses of 50-100 mg and monitor for peripheral neuropathy. An expert panel consensus provided five key recommendation statements that cover the function of vitamin B6, complications due to vitamin B6 deficiency, dosage recommendations, adverse events, and monitoring guidance throughout the course of treatment.[15]

Lemon Balm, *Melissa officinalis*

1200 mg daily, for 3 months, effectively reduced PMS symptoms in double-blind randomised, placebo-controlled trial (n=100 high), however, the cohort was schoolgirls.[16]

Calcium

- RCT of calcium carbonate 500 mg BD for 3 months reduced early tiredness, changes in appetite and depression in women with PMS[17]
- 500 mg of calcium/day reduced PMS symptoms over (2 cycles) (n=66)
  - Improvement in symptoms of anxiety, depression, emotional changes, water retention and somatic changes in calcium group compared with placebo group. [18]

Magnesium

- Anecdotally, Magnesium is often self-prescribed with theorized mechanisms of action, including reduction of anxiety via moderation of the stress response (HPA), but very limited scientific evidence to support a role[19 20]

Serotonin sparing herbal medicine [9] or dopamine agonist herbs[10]may be considered.

Saffron, *Crocus sativus*

- Proposed mechanism: Serotonin sparing action
- Active constituents of Saffron, crocin, and safranal potentially inhibit the reuptake of dopamine, norepinephrine, and serotonin; thereby increasing circulating levels of serotonin.
- Significant improvement in symptoms observed in the Total Premenstrual Daily Symptoms and Hamilton Depression Rating Scale15 mg BD in RCT (n=50) of women aged 20-45 years over 6 months[7]
- Significant improvement in Daily record of severity of problems (DRSP) with Saffron (15 mg BD) administered for 2 weeks in the luteal phase over 2 menstrual cycles, compared to placebo (P = 0.027) but not compared to Fluoxetine (20 mg BD) in RCT (n=120) females, (aged 20-45) who met DSMV criteria for PMDD[21]

***Vitex agnus -cactus* (Chaste tree),**

- Proposed mechanism of action as a dopamine agonist.[10]
- Despite some methodological limitations, has demonstrated benefit as an effective and well tolerated treatment for the relief of PMS.[22 23]
- Dosages and dosing regimens vary. The most prescribed dose is 40 mg of dried fruit equivalent administered once daily for the entire month.
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Potential role of dietary phytoestrogens, to mitigate the premenstrual oestrogen drop, specifically in the management of menstrual migraines[24]

Heavy drinking, considered to be ≥1 standard drink per day, is associated with a moderate increase of the risk of PMS[25]

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