Management of premenstrual dysphoric disorder

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Premenstrual dysphoric disorder is a complex disorder characterized by severe physical and psychological symptoms. The pathophysiology and effective treatment of premenstrual dysphoric disorder are presented. Evidence for the effective treatment of premenstrual dysphoric disorder by correction of neuroendocrine abnormalities or suppression of cyclical ovarian activity is reviewed.

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Since its first description in 1931 premenstrual syndrome has been increasingly recognized as a medical condition (Frank, 1931). This article presents evidence that the pathophysiology of premenstrual symptoms is related to cyclical fluctuations in ovarian sex steroid hormones and their interaction with serotonin and other neurotransmitters. Evidence of the effectiveness of non-pharmacological and pharmacological management options for women with premenstrual symptoms is reviewed.

DIAGNOSIS OF PMDD

Over 80% of women of reproductive age experience some premenstrual symptoms. The more severe premenstrual dysphoric disorder (PMDD) affects between 5 and 10% of women (Andersch et al, 1986; O'Brien, 1993). PMDD is included in the American Psychiatric Association (2001)'s *Diagnostic and Statistical Manual of Mental Illness* (DSM-IV) as 'a mood disorder not otherwise specified'. Symptom diaries should be used prospectively over 3–4 months to determine whether the DSM-IV criteria for PMDD are met.

PMDD is diagnosed if five or more symptoms (*Table 1*) are present in the late luteal phase (premenstrually) for most cycles in the previous year and the symptoms resolve or are reduced by at least 75% with the onset of menses. Women may describe a variety of severe physical symptoms but PMDD is only diagnosed if mood or other psychological symptoms are present; at least one symptom should be present from the first four in *Table 1*. Social, medical and psychiatric histories should be obtained to exclude premenstrual exacerbations of other ongoing problems (West, 1989).

TABLE 1.
Making the clinical diagnosis of premenstrual dysphoric disorder*

1.	Clearly unstable mood
2.	Clear and persistent irritability or anger
3.	Clear anxiety, nervous tension or feeling of being overwrought
4.	Clear depressed mood, feelings of hopelessness, or reduction in self esteem
5.	Reduced interest in activities – work, family life, friends
6.	Rapid tiring and lack of energy
7.	Poor concentration
8.	Clear alteration in eating behaviour, food cravings
9.	Sleep disorders, too much sleep or insomnia
10.	Physical symptoms: such as breast pain, bloating, headaches, joint pains

*Five of the above symptoms must be present in the luteal phase of the menstrual cycle, with at least one symptom in group 1–4 to make the diagnosis of premenstrual dysphoric disorder. From *Diagnostic and Statistical Manual of Mental Illness* (American Psychiatric Association, 2001).

PATHOPHYSIOLOGY OF PMDD

Cyclical fluctuations in ovarian sex steroid hormones following ovulation and their subsequent interaction with serotonin and other neurotransmitters are believed to be responsible for the physical and psychological symptoms of PMDD (Steiner and Pearlstein, 2000). Levels of oestradiol and progesterone vary throughout the menstrual cycle: oestradiol is the dominant hormone following menstruation (follicular phase) and following ovulation (luteal phase) both progesterone and oestradiol are produced by the corpus luteum.

Serum sex steroid hormone levels are within the normal range in women with PMDD (Rapkin et al, 1997). Normal cyclical fluctuations in sex steroid hormones may trigger biochemical events within the CNS and other target organs which lead to physical and psychological symptoms (Schmidt et al, 1998).

Progesterone metabolism is altered in women with premenstrual symptoms and there is evidence of an altered brain response to normal levels of

progesterone and to deficiencies in metabolites of progesterone (Rapkin et al, 1997; Monteleone et al, 2000). Two psychoactive metabolites of progesterone, allopregnanolone (3-α-hydroxy-5-α-pregnanolone) and pregnenolone (3-α-hydroxy-5-β-pregnanolone), readily cross the blood–brain barrier (Berga, 1998). Allopregnanolone is produced within the CNS and will stimulate γ-aminobutyric acid A (GABA-A) receptors, upregulate serotonin receptors, reduce depressive symptoms and predispose to anxiety if deficient. Significant decreases in luteal phase allopregnanolone levels have been identified in women with premenstrual symptoms compared to women without symptoms (Rapkin et al, 1997). Pregnenolone inhibits GABA-A receptors and promotes anxiety symptoms.

There is evidence of serotonergic receptor dysfunction in women with PMDD (Parry, 2001). Treatments that enhance serotonergic function and increase serotonin can improve symptoms and selective serotonin-reuptake inhibitors (SSRIs) are effective treatments for PMDD (Wyatt et al, 2002).

TREATMENT OPTIONS FOR PMDD

A variety of treatments are available including non-pharmacological, pharmacological and surgical. Treatment should be tailored to individual needs. Symptoms may be exacerbated by environmental factors, psychosocial factors, stress, relationship problems, self esteem and general health issues (Deutser et al, 1999). Therefore many non-pharmacological treatments may be beneficial first-line options including relaxation techniques, dietary changes, homeopathic remedies, self-help groups, vitamin and mineral supplementation.

For some women with severe symptoms pharmacological correction of the neuroendocrine abnormality or suppression of cyclical fluctuations in ovarian hormones is appropriate. The effects of placebo should not be underestimated in PMDD; in a randomized trial 20% of women described a sustained reduction in symptoms of at least 50% with placebo, 41% described partial improvement with placebo and 39% had no improvement (Freeman and Rickels, 1999). Surgical management involving removal of the ovaries may be appropriate for a small number of women.

Non-pharmacological management

Cognitive and information-focused therapy: Cognitive behavioural therapy, which modifies beliefs about negative premenstrual symptoms, and information-focused therapy, which discusses relaxation training, nutritional and vitamin guidelines, dietary and lifestyle recommendations, aspects of child management training and assertion training, can reduce physical and psychological symptoms (Blake et al, 1998). Positive effects are achieved after the first treatment and improvement is maintained (Morse et al, 1991).

Dietary advice: Dietary advice is no different from advice about healthy eating. Carbohydrate food cravings may occur premenstrually and some women increase their carbohydrate consumption significantly (Wurtman et al, 1989). Fernstrom et al (1979) found that carbohydrates consumed without proteins increase tryptophan uptake in the CNS, leading to serotonin synthesis and release. There is insufficient evidence to support radical dietary changes in the management of PMDD.

Vitamin and mineral supplementation: Many dietary supplements have been advocated for treatment of premenstrual symptoms but evidence for their use is limited. Vitamin B_6 (pyridoxine) is a cofactor in the metabolism of tryptophan, tyrosine and glutamate. Tryptophan is the precursor of serotonin, tyrosine is involved in the production of dopamine and noradrenaline, and glutamate is involved in GABA production. The recommended daily intake of vitamin B_6 is around 2 mg/day and deficiency is rare. A peripheral neuropathy can occur as a result of overdose (200–600 mg/day) (Schaumburg et al, 1983). A meta-analysis of vitamin B_6 use in treatment of premenstrual symptoms suggested that a daily dose of 100 mg is likely to benefit women with premenstrual syndrome (Wyatt et al, 1999).

Zinc and magnesium deficiencies have been identified in the luteal phase in women with premenstrual symptoms (Chuong and Dawson, 1994; Posaci et al, 1994). Small randomized trials have suggested that magnesium supplements (200 mg/day) reduce weight gain, swelling of extremities, breast tenderness and abdominal bloating associated with PMDD (Walker et al, 1998). A synergistic effect of magnesium 200 mg and vitamin B_6 50 mg has been shown to reduce anxiety-related symptoms (De Souza et al, 2000).

Herbal therapies: The fruit of *Vitex agnus castus* (the chaste tree) contains a mixture of iridioids and flavenoids, compounds similar to the sex steroids. A prospective randomized controlled trial demonstrated that daily agnus castus fruit extract was superior to placebo in the treatment of physical and psychological symptoms (Schellenberg, 2001).

Pharmacological management of PMDD

SSRIs are highly effective in the treatment of physical and psychological premenstrual symptoms when used continuously or in the luteal phase only (Wyatt et al, 2002). Fluoxetine has been shown to be effective if given in the 14 days before menstruation (Dimmock et al, 2000; Cohen

et al, 2002) and a dose of 20 mg daily appears to be as effective as 60 mg (Steiner et al, 2001). The side effects of fluoxetine (most commonly nausea, disturbed sleep, fatigue and tremor) may limit its use and are more common with higher doses. Other SSRIs, e.g. sertraline, are effective in the treatment of PMDD when given continuously (Yonkers et al, 1997) or in the luteal phase only (Jermain et al, 1999). Venlafaxine may be useful in treating PMDD in women who are unable to tolerate fluoxetine (Freeman et al, 2001).

Alprazolam is a benzodiazepine used to treat anxiety, panic disorders and depression; it may be beneficial in the management of premenstrual symptoms at a low dose (0.25 mg three times daily) in the luteal phase (Smith et al, 1987).

Progesterone and progestogens: Progesterone supplementation has been the main treatment for premenstrual symptoms despite little evidence to support its use (Freeman et al, 1990). Natural progesterone undergoes extensive first pass metabolism in the liver, is relatively inactive orally and is administered most effectively via pessary or suppository. Many studies have looked at the effect of progesterone on premenstrual symptoms, most using synthetic progesterone (progestogens). A systematic review of randomized controlled trials highlighted the poor quality of many clinical trials and found that natural progesterone was not significantly better than placebo or progestogen and that improvements in symptoms were not clinically important (Wyatt et al, 2001).

Oestradiol: Transdermal oestradiol (100 μg) inhibits ovulation and is effective in the treatment of premenstrual symptoms, compared to placebo (Watson et al, 1989; Smith et al, 1995). Unopposed oestrogen is associated with an increased risk of endometrial hyperplasia and malignancy so women who have not undergone hysterectomy require concomitant progestogens for 10–14 days each month (Voigt et al, 1991), but these progestogens may lead to a recurrence of symptoms. Use of the levonorgestrel releasing intrauterine system (Mirena, Schering Health Care Ltd, West Sussex) to protect the endometrium is a useful alternative to oral or transdermal progestogens because of the very low systemic absorption of progestogen and consequent low incidence of side effects. There is no convincing evidence that the Mirena alone is effective in the management of premenstrual symptoms.

Danazol: Danazol may be beneficial in the management of premenstrual symptoms when used in doses which suppress ovulation but side effects are common and may limit its use (Halbreich et al, 1991; Hahn et al, 1995). The use of luteal phase danazol (200 mg daily) appears to be effective in reducing premenstrual mastalgia (O'Brien and Abukhalil, 1999).

Contraceptive hormones: There are no published placebo-controlled trials addressing the effectiveness of depomedroxyprogesterone acetate (DepoProvera (Pharmacia Ltd, Milton Keynes, UK), an injectable contraceptive) or the combined oral contraceptive pill in the management of premenstrual symptoms.

Gonadotrophin-releasing hormone analogues: Ovarian suppression with gonadotrophin-releasing hormone (GnRH) analogues reduces premenstrual symptoms in many women (West and Hillier, 1994; Schmidt et al, 1998). Although often very effective they are expensive and can increase the risk of osteoporosis with prolonged use (over 6 months). GnRH analogues are best reserved for inducing a medical oophorectomy to assess the potential benefit of oophorectomy on symptoms of PMDD before considering surgery.

Surgical management of PMDD

Hysterectomy with bilateral salpingo-oophorectomy improves the general affect, mood and quality of life to such a degree that prospectively completed symptom charts are no different from women without premenstrual symptoms (Casper and Hearn, 1990). Surgical management of women with PMDD is only appropriate in women who are unresponsive or intolerant of other treatment, who have completed their family, where PMDD has been prospectively diagnosed and whose symptoms resolve as a result of downregulation with GnRH analogues.

Symptoms can be expected to persist following hysterectomy with ovarian conservation (Backstrom et al, 1981) but bilateral oophorectomy and concomitant hysterectomy is effective in reducing premenstrual symptoms (Casson et al, 1990). Oestradiol replacement is required to prevent menopausal symptoms and osteoporosis and should not result in symptom recurrence. A woman's tolerance of oestrogen replacement therapy can be established by administering it during concurrent downregulation with GnRH analogues.

CONCLUSION

SSRIs are an effective and well-tolerated treatment for women with PMDD. The use of vitamin B_6 has also been shown to be effective but the evidence for benefit from other treatments is less convincing. There is no evidence to support the use of progesterone or synthetic progestogens. Downregulation with GnRH analogues before pelvic clearance is an effective measure for a carefully selected minority of women. HM

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KEY POINTS

- The diagnosis of premenstrual dysphoric disorder should be established by analysis of prospectively collected symptom diaries.
- There is a substantial placebo effect which has resulted in unfounded claims of benefit for a large number of treatments.
- Selective serotonin-reuptake inhibitors are effective when taken continuously or in the luteal phase.
- Downregulation with gonadotrophin-releasing hormone analogues together with concurrent 'add-back' hormone replacement therapy helps to identify the small number of women who will benefit from surgical treatment.