Peer reviewed article

Premenstrual dysphoric disorder: current status of treatment

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Summary

Objective: Premenstrual dysphoric disorder (PMDD), also referred to as premenstrual syndrome (PMS), is a recurrent luteal-phase condition involving regular occurrence, prior to the onset of menstrual bleeding, of a cluster of symptoms of sufficient severity to result in the deterioration of interpersonal relationships and normal activity. Several treatment options for PMDD with varying degrees of efficacy have been proposed. The literature is reviewed and treatments of proven efficacy are reported.

Study design and methods: A MEDLINE/Cochrane Library search for all studies on PMS and PMDD published between 1983 and 2001 was performed. Only randomised trials were included.

Results: Several treatments appear to be effective. Among these are increased physical activity, dietary change, mineral salt supplementation and ovulation inhibitors. The most effective seems to be administration of selective inhibitors of serotonin reuptake (SSRIs).

Conclusion: Therapy should begin with non-medicated approaches and pharmacological treatment should only be envisaged if symptoms persist.

Key words: premenstrual dysphoric disorder; premenstrual syndrome

Introduction

Premenstrual dysphoric disorder (PMDD) has also been referred to as late luteal phase dysphoric disorder and simply premenstrual syndrome (PMS) [1]. The essential symptoms are markedly depressed mood, appreciable anxiety, pronounced affective lability, and decreased interest in activities [2]. For a precise definition of the syndrome these symptoms should have regularly occurred during the last week of the luteal phase in most menstrual cycles during the past year. They should also remit within a few days of the onset of menses (follicular phase) and are always absent in the week following menses [2]. The research criteria for PMDD are summarised in table 1.

In the DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders, PMDD is included in category F39 (296.90) "depressive disorder not otherwise specified" and replaces the "late luteal phase dysphoric disorder" of the previous version, DSM-III-R, which included it in the category "unspecified mental disorder". It is estimated that at least 75% of women report minor or isolated premenstrual changes, and some studies suggest that 3–8% of women experience symptoms meeting the criteria for PMDD [2, 3]. According to Mimoun, only one woman out of eight consulting for PMS presents with a PMDD meeting the DSM-IV criteria [4].

The causes of PMDD have not been clearly elucidated and have been attributed to hormonal change, neurotransmitters, prostaglandins, diet, drugs, and lifestyle, thus rendering treatment difficult [5].

The disorder could result from an abnormally high oestrogen-to-progesterone ratio [1]. It has been suggested that the biogenic amine neurons of affected women are abnormally influenced by hormonal changes and that the disorder is an example of a chronobiological phase disturbance [1].

In addition to biological theories, social and personal issues relating to menstruation and womanhood may affect the symptoms in individual patients [1]. To understand a woman's feelings during the premenstrual period it is necessary to take into account her personal history and the psychosocial factors involved, such as social and cultural beliefs and mother-daughter communication [6]. In psychoanalytical theory the premenstrual syndrome was associated with an ambivalent pregnancy desire and unconscious conflicts relating to sexual preference [6].

Among the various treatments proposed to

No financial support to declare.

Table 1

DSM-IV research criteria for premenstrual dysphoric disorder.

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 (eg, 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 (eg, 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," weight gain
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).
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).
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.)

date, some have been shown to be effective and others have no proven clinical efficacy. The aim of this article is to review the literature on therapeutic options and identify the treatments of proven clinical efficacy.

Study design and methods

A systematic search of the literature in all languages from 1983 to 2001 was performed by MEDLINE and the Cochrane Library (CCTR, updated quarterly) using the following key words: premenstrual syndrome, premenstrual dysphoric disorder, late luteal phase dysphoric disorder. Only randomised trials were considered.

Results

Physical activity, nutrition, dietary supplements

Aerobic physical exercise modifies endorphin levels and can improve mood. Epidemiological studies confirm the positive effect of physical exercise on PMDD symptoms [7]. Aganoff (1994) investigated the effects of regular, moderate exercise on mood states and menstrual cycle symptoms and compared 97 female regular exercisers with a second group of 159 female non-exercisers [8]. Multivariate analyses of covariance revealed significant effects of exercise on negative mood states and physical symptoms.

Dietary changes often recommended as a treatment for PMDD are a reduction in salt, sugar, alcohol, and caffeine intake, with an increase in carbohydrates. Of these, only the effectiveness of increased carbohydrate intake has been confirmed by a controlled study [9].

In an in-hospital study Wurtman et al. (1989) compared the occurrence and coincidence of depressed mood and excessive carbohydrate intake in 19 patients claiming to suffer from severe psychological symptoms with that in 9 control subjects during the early follicular and late luteal phases of their menstrual cycles [9]. Consumption of a carbohydrate-rich, protein-poor evening test meal during the late luteal phase improved depression, tension, anger, confusion, sadness, fatigue, alertness and calmness scores among patients with PMDD.

Calcium and magnesium supplements have been shown to have a favourable clinical effect on physical (fluid retention) and behavioural (mood change) symptoms in PMDD [10, 11]. A double-blind randomised study in 38 women has demonstrated the clinical efficacy of magnesium supplementation in the treatment of mood change in PMS [12]. Tyhs Jacobs conducted a controlled, multicentre clinical trial in a group of 466 women to assess the effect of calcium carbonate on the luteal and menstrual phases in PMDD. Calcium

did indeed result in an overall 48% reduction in total symptom scores from baseline, compared with a 30% reduction with placebo. It was concluded that calcium supplementation is a simple and effective treatment for PMDD [11].

Vitamins (E and B6) have been recommended for a number of years as an effective treatment for cyclic mastalgia, particularly tocopherol. London et al. (1983) conducted a randomised trial among 75 women to compare the effect of tocopherol with placebo in mastodynia, and found a significant decrease in symptoms in the tocopherol group [13]. However, another randomised study showed only slight benefit [14]. Randomised controlled studies with pyridoxine versus placebo showed no significant benefit [15]. Moreover, high doses of pyridoxine were associated with peripheral neurotoxicity.

Ovulation suppressors

The agonist analogues of GnRH, such as busereline (Suprefact Dépôt), gosereline (Zoladex), or leuproreline (Lucrin Dépôt) represent an effective treatment for PMDD [16]. This type of treatment aims to inhibit the endogenous chronobiological system underlying the menstrual cycle. However, due to their prolonged action, these drugs mimic the continued flow of GnRH, cause desensitisation of the pituitary and lower the secretion of gonadotropin and sexual steroids. Consequently, oestrogen concentrations are usually markedly reduced, thus exposing patients to a higher risk of osteoporosis where treatment is prolonged.

Several studies have confirmed the effect of danazol (Danatrol), a synthetic androgen with an anti-oestrogen effect which blocks ovulation and eliminates associated symptoms [17–21]. Unfortunately this treatment has several important side effects such as weight gain, increased pilosity and acne. Moreover, it lowers the HDL rate and is not recommended in view of the increased cardiovascular risk.

Psychotropic drugs

The efficacy of psychotropic drugs has been widely studied. The selective-reuptake inhibitors (SSRIs) such as fluoxetine (Fluctine) [22–29], sertraline (Zoloft) [30–33], paroxetine (Deroxat) [34–36], and citalopram (Seropram) have been shown to be effective and are the treatments of choice for PMDD [37, 38].

Two crossover, double-blind, placebo-controlled trials have shown the efficacy of sertraline at a dose of 50 mg/d or 100 mg/d during the luteal phase only [37, 38]. Daamen and Brown (1992) reported that a single dose of fluoxetine prescribed during the early luteal phase was as effective as a daily dose [39]. Other studies have demonstrated that the administration of sertraline or fluoxetine during the premenstrual phase is effective for PMDD [31, 40].

The efficacy and safety of venlafaxine (Efexor), a new-generation antidepressant which selectively inhibits serotonin and norepinephrine reuptake, has been evaluated in a placebo-controlled trial [41]. After three screening cycles, including a single-blind placebo cycle, 164 women were randomly assigned to double-blind treatment with venlafaxine (50–200 mg/d) or placebo for four menstrual cycles. Venlafaxine was significantly more effective than placebo in reducing PMDD symptoms.

In a double-blind, placebo-controlled study to assess the efficacy of citalopram in the treatment of PMDD during three menstrual cycles, Winkader et al. (1998) showed that intermittent administration of citalopram (20 ± 10 mg/d) during the luteal phase (18 patients) and a placebo (17 patients) during the follicular phase was clearly more efficacious than placebo alone during the complete cycle [38]. Moreover, this treatment appeared to be more effective than continued administration (20 ± 10 mg/d) during the complete cycle, or semi-intermittent (20 ± 10 mg/d) during the luteal phase and 5 mg/d during the follicular phase [38].

Alprazolam (Xanax) was investigated in seven double-blind, placebo-controlled studies. Four studies showed that it was more efficacious than placebo, and three others concluded that it was only as effective as placebo [42]. In the study by Evans et al (1998) in 20 patients, alprazolam not only improved depressive mood state during the premenstrual phase but also induced it in asymptomatic patients during the follicular phase [41].

Buspirone (Buspar), a 5-HT agonist anxiolytic, was effective at a dose of 20 mg/d during the luteal phase [43].

Psychotherapy

Morse (1999) showed during two cycles that cognitive-behavioural-based psychotherapy can significantly reduce symptoms compared with a group not undergoing therapy [44]. Over a 12-week period Blake et al. (1998) compared a group of patients undergoing cognitive therapy once a week with a control group. The results showed that the cognitive therapy was significantly more effective [45]. In a randomised study comparing two different cognitive-behavioural approaches and a therapy centred on information, Christensen (1995) reported a reduction in symptoms [46]. Although none of these studies shows definitive results, they suggest that cognitive therapeutic approaches can be useful, at least as adjuvant therapy.

Placebo

Placebo has also been shown to be effective as a therapeutic tool in this disorder. Many placebo-controlled studies show significant placebo effect in premenstrual symptoms [47, 48]. In a longitudinal study in 68 women, Magos found an initially strong placebo response rate but the placebo effect gradually waned [49].

In a recent study including 101 women, Free-

man observed in some patients with severe PMS a significant and sustained improvement under placebo medication, but the majority report only partial or no improvement [50].

Discussion

One of the major difficulties in research and therapeutic choice is the fact that the definitions of SPM are diverse and the diagnostic criteria have changed over the years.

DSM-IV suggests criteria for PMDD to help researchers and clinicians in the correct diagnosis of the syndrome [1]. In spite of the wide dissemination of diagnostic criteria in international psychiatric classifications, the premenstrual syndrome remains a complex and polymorphous disorder.

The aetiology of PMDD is probably multifactorial, with the involvement of a synergic response underlying the disorder. PDMM appears to arise from various biological factors, both psychological and social, which are capable of influencing the central nervous system and the female reproductive and endocrine systems [4]. The most widely studied and frequently forwarded aetiopathogenic hypothesis is serotonin dysregulation. Serotonin is closely involved in the expression of irritability and anger, and also in the occurrence of the depressive symptoms and specific food cravings often seen in the premenstrual dysphoric disorder [6]. Among their various effects, oestrogens increase the density of serotonin receptors and enhance sensitivity to serotonin agonists [6]. There is a consensus that the therapeutic approach should begin with non-medicated means: a good doctor-patient relationship; information and completion of a daily self-evaluation calendar of symptoms; and advice on lifestyle (stress limitation, release of nervous tension, appropriate diet, explaining the problem to the family) [51].

If symptoms persist, drug therapy can be envisaged [51]. The most effective medication for the treatment of severe psychological or physical symptoms causing functional impairment are the SSRIs [52]. As reported by Dimnock et al. (2000), these are an effective first-line therapy for severe PMS with low side effects [53]. Intermittent administration of SSRIs is suggested as an even more effective treatment [6].

However, the treatment of PMS and PMDD appears to require a strategy which will avoid therapeutic changes often prompted by the patients themselves, exasperated by the variety of symptoms and the consequences for their everyday and married lives [7].

In agreement with Johnson (1998), it would seem judicious as a first move to advise patients to modify their nutritional habits by increasing carbohydrate intake and cutting down sugar, salt, caffeine and alcohol [7]. These dietary changes should be accompanied by calcium and magnesium supplementation, with an increase in aerobic physical activity and lowering of stress levels [7]. If patients do not respond to this approach during two to three cycles, the introduction of an SSRI would seem to the treatment of choice, either to be taken intermittently or during the complete cycle. In terms of cost-effectiveness the initial treatment should be given during the luteal phase and, if no response is obtained, a daily dose may be prescribed. In the event of non-response to SSRI treatment, the introduction of therapy with GnRH may be required despite the possible side effects.

Cognitive-behavioural psychotherapy, whose efficacy has been shown in different studies [44–46], can be proposed as adjuvant therapy.

In conclusion, PMDD is a complex clinical syndrome which is notoriously difficult to treat. Nevertheless, a well-defined therapeutic strategy should enable the majority of women to obtain relief from their symptoms.

With special thanks to Mrs R. Sudan for editorial assistance.

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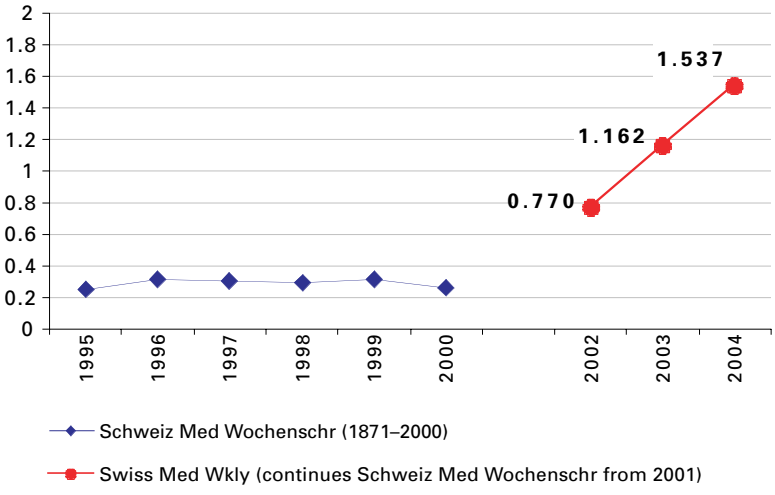

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