Arch Womens Ment Health (2002) 4: 111–119

Archives of
Women's
Mental Health

Review article

New perspectives on the treatment of premenstrual syndrome and premenstrual dysphoric disorder

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Summary

Premenstrual dysphoric disorder was discussed by a panel of European researchers. The criteria for diagnosis of the condition, its categorisation as a mental disorder, and its differentiation from depression and premenstrual syndrome are all considered. Data on the treatment of premenstrual dysphoric disorder, using serotonin reuptake inhibitors and other therapies, are reviewed. An algorithm for the treatment of premenstrual dysphoric disorder is proposed.

Keywords: Premenstrual dysphoric disorder; premenstrual syndrome.

Introduction

Following a roundtable discussion in Washington DC, in which the clinical characteristics of premenstrual dysphoric disorder (PMDD) were extensively discussed by a panel of experts from North America (Endicott et al., 1999), a second meeting was convened in the summer of 1999 with a panel of delegates mainly from Europe. The purpose of this meeting was to discuss this disorder from a European perspective, and in particular to discuss different forms of treatment and suggest a treatment algorithm for PMDD.

Characteristics of the disorder

Diagnostic criteria

This disorder was first defined as Late Luteal Phase Dysphoric Disorder (LLPDD) in the DSM-III-R (American Psychiatric Association, 1987). The criteria in the DSM-III-R focused on the difference in symptom severity between luteal and follicular phases of the menstrual cycle: symptoms must worsen during the late luteal phase then disperse shortly after the onset of menses. Another key feature of the disorder is that, to fulfil diagnostic criteria, symptoms should be severe enough to interfere with the woman's social and/or occupational functioning. The symptomatology defined was primarily that of dysphoric mood, rather than physical symptoms (although most women seen for treatment have both types of symptoms).

In DSM-IV, the term premenstrual dysphoric disorder (PMDD) was adopted for the disorder, and it was listed, in appendix B, as a "depressive disorder not otherwise specified" (American Psychiatric Association, 1994). Criteria include at least one year's duration of symptoms, and the presence of at

least five out of eleven specified symptoms, at least one of which must be dysphoric mood. Depression is the first mentioned symptom but irritability appears to be the most commonly reported and troublesome symptom in women presenting for treatment, as further discussed below. The symptoms must be so severe as to interfere seriously with the woman's occupational and/or social functioning. Indeed, functional impairment produced by the disorder may be as severe as that following major depression (Pearlstein et al., 2000). In addition, the symptoms of PMDD must not simply represent a cyclical exacerbation of another mental disorder.

A controversial aspect of the diagnostic criteria is the requirement for prospective daily ratings of symptoms for at least two consecutive cycles. This is an extremely stringent diagnostic requirement for any mental disorder, and can be difficult to achieve in clinical practice. Nevertheless, prospective rating, at least for one cycle, can prove useful in distinguishing PMDD from cyclical exacerbations of other disorders, such as dysthymia or panic disorder. In addition, such symptom ratings can allow women to monitor their disorder, identify the warning signs, and feel some control. As such, it constitutes a form of psychological treatment.

Another controversial aspect of the DSM-IV criteria is the requirement that the patient should display at least five of the symptoms listed. In fact, a condition characterised by only one or a few of the symptoms (such as irritability and depressed mood) might well be as disabling as a condition characterised by five different symptoms or more. In addition, it may be questioned if all the symptoms listed in the DSM-IV definition of PMDD are indeed of clinical significance, and whether these symptoms should all be regarded as parts of one syndrome, or as different syndromes coinciding in time. Although some researchers believe that the somatic symptoms have been given too little emphasis in the PMDD criteria, others argue that they should not be included at all, as they may represent a different condition (or several disparate conditions).

PMDD as a mental disorder

The categorisation of PMDD as a mental disorder is consistent with its mood-disorder symptomatology and its treatment, but may cause certain problems (Yonkers, 1997). Some women may feel stigmatised by this diagnosis, and there is uncertainty about which medical specialists should be responsible for its treatment – psychiatrists or gynaecologists. Furthermore, there is much discussion about whether PMDD should be categorised as a variant of depression, or as a separate mental disorder. There are however several important differences between depression and PMDD; for example, irritability, rather than depressed mood, is the primary symptom of PMDD. Many clinicians and researchers would argue that PMDD should be categorised as a distinct entity in the DSM, rather than as a variant of depression (see below). Any categorization of PMDD as a mental disorder may however be regarded as provocative by women who present to ob/gyn specialists with what they regard as "hormonal problems", as may the suggestion that they should be treated with an antidepressant drug. Part of this stigma may be ameliorated by the acknowledgement that there is a spectrum of psychiatric conditions associated with hormonal changes.

The relationship between PMDD, PMS and other menstrual symptomatology

PMDD can be regarded as a severe subtype of PMS. PMS is defined in the ICD-10 under the category of obstetric/gynaecological diseases, and the symptoms are predominantly physical and do not necessarily interfere with social functioning. As discussed below, the estimated prevalence of this condition is very high. On the other hand, PMDD is defined mainly by its psychological symptomatology, and by its functional impairment. Its prevalence is much smaller than that of PMS. Whereas many researchers emphasise the importance of separating premenstrual complaints from other perimenstrual symptomatology, such as dysmenorrhea, others have suggested that there is a considerable overlap between premenstrual and menstrual symptoms (Bancroft, 1993).

Distinguishing PMDD from major depression

PMDD is categorised as a mental/depressive disorder and is often treated with antidepressant medication. This has resulted in much discussion of whether PMDD and major depression are indeed separate disorders. Nevertheless, several key features of PMDD distinguish the two disorders (Endicott et al., 1999). Its cyclical variation is unique

among the mood disorders, in that symptoms are absent during the follicular phase. In other mood disorders that show some cyclical variation, the symptoms are present throughout the cycle and are merely exacerbated during the luteal phase. Biological markers associated with depression are usually not displayed by women with PMDD (Yonkers, 1999). Multivariate genetic analysis suggests genetic and environmental factors of importance for premenstrual complaints are separate from those implicated in depression (Kendler et al., 1992).

Treatment strategies are also different. PMDD can be treated effectively by suppression of circulating gonadal hormones, which has no effect on major depression. Both of the disorders can be treated effectively with serotonergic antidepressants, but differences remain. Whereas depression can be treated with drugs influencing either serotonin or noradrenaline, only serotonin reuptake inhibitors (SRIs) are effective in relieving PMDD. Moreover, the doses of SRIs (and especially of clomipramine) used in treating PMDD are lower than those that are effective in major depression. In addition, when SRIs are used for PMDD, a rapid symptom improvement (usually within days) is seen, and there is also a rapid return of symptoms on cessation of treatment. This is, of course, also what happens in the untreated condition: symptoms emerge within days and resolve within days of menses. This contrasts with the development of depression, in which emergence and resolution of depressive symptoms (with or without treatment) is usually much slower, and the onset of action of antidepressants typically takes at least 2 weeks.

Epidemiology of PMDD

The prevalence of mild premenstrual complaints is reported to be extremely high – between 50 and 90% – in both clinical and non-clinical samples of women. A severe form – possible equating PMDD – usually is reported by 5–10% (Hargrove and Abraham, 1982; Andersch et al., 1986; Brown and Doran, 1996; Campbell et al., 1997; Cleckner-Smith et al., 1998; Deuster et al., 1999; Hallman, 1986; Haskett et al., 1987; Johnson et al., 1988; Logue and Moos, 1986; Monagle et al., 1993; Ramcharan et al., 1992; Rivera-Tovar and Frank, 1990; Serafty and Magneron, 1997; Singh et al., 1998; Van Keep and Lehert, 1981; Wilson and Keye, 1989; Woods et al., 1982). Studies performed in Europe have usually yielded similar prevalence figures as studies conduced in the United States. When interpreting these figures, it should be taken into consideration that prospective symptom rating is usually not undertaken in epidemiological studies, and that DSM criteria have been applied in only a few studies.

A longitudinal study of a cohort of women that has been ongoing in Zurich for more than 20 years has confirmed a high prevalence of premenstrual symptoms. This study highlighted irritability as the most common and distressing of all premenstrual complaints, and showed that it is often present without concomitant depressed mood (Merikangas et al., 1993; Angst et al., 2001).

Sex steroids in PMDD

The involvement of sex steroids in the pathophysiology of PMDD is suggested by the cyclicity of the symptoms and by the fact that they disappear during pregnancy and at menopause. The first experimental indication of sex steroids being important to PMDD came when it was discovered that ablation of the ovaries rid women of PMS (Frank, 1931). More recent data have shown that PMS is eliminated by the suppression of ovulation and circulating gonadal hormones using gonadotrophin releasing hormone (GnRH) analogues (Bancroft et al., 1987; Hammarback and Backstrom, 1988; Hammarback et al., 1991; Hussain et al., 1992; Leather et al., 1999; Mezrow et al., 1994; Muse et al., 1984; Muse, 1989; Schmidt et al., 1998) or estrogen (Magos et al., 1986; Watson et al., 1989). The initial findings in this area led to more than 50 years of research into possible hormonal changes that might lead to PMS. However, these have produced contradictory results (Korzekwa and Steiner, 1997), and the conclusion of this research is that patients with PMS probably do not differ from those without symptoms with respect to serum levels of sex steroids, but do differ with respect to how sensitive they are to these hormones. This assumption gains support from the observations that administration of estradiol and/or progesterone may provoke symptoms in women in whom administration of a GnRH analogue or natural menopause has led to improvement (Henshaw et al., 1996; Schmidt et al., 1998).

Serotonergic treatment of PMDD

The use of serotonergic treatments for a condition characterized by irritability, such as PMDD, is supported by studies showing that serotonin depletion increases in irritability and aggression in rats and mice (Fuller, 1986), and that SRI reduces irritability and aggression in rodents (Fuller, 1986; Ho et al., 2001). The notion that symptoms such as anger, irritability, and affect lability may respond to treatment with SRIs also gains support from clinical studies in conditions other than PMDD (Fuller, 1986; Eriksson, 1999).

Early studies with a serotonergic tricyclic antidepressant

Before any large trials using selective SRIs had been undertaken, clomipramine, a tricyclic antidepressant with strong effect on the serotonin uptake, was reported to be very effective for premenstrual irritability and depressed mood. Open label and controlled trials using small doses of this drug (25–75 mg/day) reduced premenstrual irritability or sadness in almost all the women treated (Sundblad et al., 1992). A subsequent trial demonstrated that the drug could be used intermittently, during the follicular phase of the cycle only, and that this regimen was as effective as continuous administration (Sundblad et al., 1993).

Treatment with fluoxetine

Following early studies demonstrating the efficacy of clomipramine, and of the selective SRI fluoxetine (see Eriksson, 1999), several large trials of selective SRIs in the treatment of PMDD have been conducted, all showing positive effects (for refs, see Eriksson, 1999; Dimmock et al., 2000). The largest of these trials was a placebo-controlled study of fluoxetine (Steiner et al., 1995). Two doses of fluoxetine, 20 mg and 60 mg, were tested in 313 women with prospectively validated PMDD. Both doses yielded equivalent, significant improvements in symptomatology over six cycles of treatment.

A smaller trial comparing fluoxetine, the antidepressant bupropion, and placebo also demonstrated good efficacy of the selective SRI, and lends weight to the argument that PMDD is not simply a variant of depression (Pearlstein et al., 1997). A total of 34 patients were randomised to receive placebo, fluoxetine 20 mg, or bupropion 300 mg, for two cycles. Fluoxetine was significantly more effective than placebo in terms of the Clinical Global Impression (CGI), global assessment score and Hamilton depression rating score, whereas the scores produced by bupropion did not differ from those of placebo.

In all, seven placebo-controlled trials of fluoxetine have been conducted, all of which have demonstrated significant differences in favour of fluoxetine (Romano et al., 1999). The fact that these differences have been recorded in groups as small as ten patients demonstrates the robustness of this treatment effect. Moreover, it has now been demonstrated that fluoxetine can be used intermittently. Treatment in the luteal phase only was as effective as continuous treatment with both treatments producing around an 86% improvement in symptoms over three cycles (Steiner et al., 1997).

Treatment with sertraline

Five placebo-controlled trials of sertraline for the treatment of PMDD have been undertaken (Freeman et al., 1999; Halbreich and Smoller, 1997; Jermain et al., 1999; Yonkers et al., 1997; Young et al., 1998). These include two relatively large trials, involving 243 patients (Yonkers et al., 1997) and 117 patients (Freeman et al., 1999). In these trials, sertraline was significantly more effective than placebo, and more than 60% of patients were much improved (on the CGI or daily symptom rating) after treatment. Like fluoxetine, sertraline was also more effective than a non-serotonergic antidepressant, i.e. desipramine (Freeman et al., 1999). Smaller studies have demonstrated that intermittent treatment with sertraline in the luteal phase only of the menstrual cycle is effective in relieving PMDD (Halbreich and Smoller, 1997; Young et al., 1998).

Treatment with other selective SRIs

The other selective SRIs are less well studied for the treatment of PMDD than fluoxetine and sertraline. Nevertheless, paroxetine has been shown to be more effective than placebo and also more effective than the noradrenaline reuptake inhibitor maprotiline in a trial involving 81 patients (Eriksson et al., 1995). Citalopram has been studied under three different treatment regimens: continuous, semi-intermittent (a small dose in the follicular phase with a larger dose in the luteal phase) and intermittent (dosing in

the luteal phase only), and compared with placebo in 78 patients (Wikander et al., 1998). All the active treatments with citalopram were more effective than placebo. In addition, interestingly, intermittent citalopram treatment was more effective than continuous treatment in relieving irritability in cycles 2 and 3. This result may be interpreted as indicating the development of a certain tolerance to this drug during continuous treatment of PMDD.

Safety considerations

There are no safety issues that are unique to PMDD. Exposure to drugs during pregnancy should be minimal, because treatment will not be needed. Sexual side effects are a major issue for some patients, particularly in the long term. However, intermittent treatment should improve this problem. Little is known about the tolerability of long-term selective SRI treatment in PMDD (although it is well documented in other disorders). Discontinuation symptoms are not uncommon when treatment with SRIs is abruptly stopped after long-term continuous treatment, but does not seem to constitute a problem when SRIs are used intermittently for PMDD. On the other hand, intermittent treatment may sometimes be associated with initial side effects, such as nausea, reappearing each time treatment is restarted.

Summary of selective SRI treatment

Treatment trials with selective SRIs have demonstrated the following features. Serotonergic treatments are highly effective in treating PMDD, as confirmed by a recent meta-analysis (Dimmock et al., 2000); in contrast, non-serotonergic antidepressants are largely ineffective. The selective SRIs produce improvements both in the symptoms of PMDD and in the functioning of the women treated (Pearlstein et al., 2000). The onset of action of the selective SRIs is fast, within a few days of starting treatment, making intermittent treatment a feasible option. (Such an option is often preferred by women, both psychologically and to reduce the duration of side effects.) Studies in which active treatment was discontinued in a double-blind fashion after many cycles of treatment showed that most patients relapsed quickly, within months of discontinuation (de la Gandara and Gilaberte, 1998; Yonkers et al., 1998). Therefore long-term treatment with selective SRIs may be required to manage PMDD effectively. Not only mental symptoms but also somatic complaints seem to respond to treatment with SRIs (Eriksson et al., 1995; Yonkers et al., 1997; Steiner et al., 2001). To what extent SRIs are useful to women reporting only somatic complaints is however not known.

Hormonal treatment of PMS

The symptoms of PMS are effectively reduced by drugs inhibiting ovulation, such as GnRH analogues (see above), estradiol implants or patches (Magos et al., 1986; Watson et al., 1989), and danazol (Sarno et al., 1987), as well as by surgical ovariectomy. The use of these strategies for the long-term management of PMS/PMDD is, however, associated with significant problems. Treatment producing a reduction in estradiol levels induces an early menopause, with an enhanced risk of cardiovascular disease and osteoporosis as probable consequences. To avoid these negative effects, an ovulation inhibitor may be combined with hormone replacement ("add-back"). However, as discussed above, in some but not in all women, progesterone 'add-back' will produce a return of symptoms (Henshaw et al., 1996; Schmidt et al., 1998). Likewise when ovulation is prevented by means of estradiol implants or patches, the cyclical addition of a progesterone analogue required to induce endometrial shedding may lead to PMS-like complaints (Magos et al., 1986; Watson et al., 1989). The combination of estradiol patches and a progesterone-releasing intrauterine device would be an attractive strategy and appears to be effective (PMS O'Brien, unpublished), but, to date, has not been evaluated in controlled trials. Progesterone and various progesterone derivatives have been claimed to be effective for PMS but controlled trials supporting the use of these compounds are lacking, and a recent meta-analysis concluded that they are not superior to placebo (Wyatt et al., 2001). Oral contraceptives are generally assumed to be effective in some patients, particularly with respect to the treatment of breast tenderness (Bäckström et al., 1992). Documentation on the effect of these substances on mood symptoms is not impressive, and in some patients they may even aggravate the symptoms (Bancroft and Rennie, 1993). Aldosterone antagonists have been reported to have some effect, mainly on somatic symptoms (O'Brien et al., 1979).

Other treatments for PMDD

Many other therapies are used to treat PMDD, but usually with little evidence for their efficacy. The benzodiazepine, alprazolam, has been tested, with conflicting results (Freeman et al., 1995; Harrison et al., 1990; Schmidt et al., 1993), but is not widely prescribed because of fears about dependency. The dopamine agonist, bromocriptine, was widely used at one time. However, it is effective only in alleviating symptoms of breast pain, not mood symptoms, and is now reserved for treating severe breast pain (Andersch, 1983). Non-serotonergic antidepressants have been used, but there is little evidence from clinical trials that they are effective (Eriksson et al., 1995; Freeman et al., 1999; Pearlstein et al., 1997). Cognitive behavioral therapy has been tested for PMS in some clinical trials, which have produced both positive and negative results (see e.g. Morse et al., 1991). However, this is difficult to test stringently, as there are inherent difficulties in controlling the process.

Many women use over-the-counter (OTC) medications to treat PMDD. Herbal treatments are popular, but there is little scientific evidence for their efficacy (see however Schellenberg, 2001). Other commonly used OTC medications often contain a prostaglandin inhibitor, which is useful for treating mild dysmenorrhoea and the headaches that may be associated with PMS, and/or diuretics, which are useful for treating some of the somatic but not the mood symptoms of PMS. Nutritional supplements, such as vitamin B6 and evening primrose oil (essential fatty acids), are used, but there is little evidence for their efficacy (Budeiri et al., 1996; Kleijnen et al., 1990). There is some evidence for an improvement in PMS following calcium or magnesium treatment which warrants further investigation (Thys-Jacob et al., 1998; Facchinetti et al., 1991). Increasing exercise may also help alleviate symptoms (Moline, 1993; Pearlstein and Steiner, 2000).

A treatment algorithm for PMDD

At present, both hormonal and serotonergic treatments are used in PMDD. Women reporting to an ob/gyn specialist are, in general, given hormonal treatment, whereas those who report to psychiatrists are given serotonergic drugs.

As discussed above, the efficacy and tolerability of SRIs for PMDD has been established in a large number of controlled trials, and also gains support from a recent meta-analysis (Dimmock et al., 2000). These compounds are relatively easy to prescribe and use, but their widespread adoption will depend on education of both physicians and patients, so that women do not feel stigmatised by this treatment. It is hoped that ongoing education of both physicians and patients about the prevalence, diagnosis, and ability to treat this disorder will increase the number of women who are recognised, diagnosed and treated successfully. Notably, clinical experience indicates that patients not responding to one SRI may respond to another, and that patients not tolerating the side-effects of one SRI may tolerate those of one of the other drugs within this family. Consequently, it may be worthwhile to test more than one SRI before turning to other therapeutic options.

The efficacy of treatment that disrupts hormonal cyclicity – such as GnRH analogues without hormonal "add-back", or estradiol patches without progesterone addition – is well established; yet, this treatment strategy is associated with major problems in terms of tolerability. There are other forms of hormonal treatments that probably are both effective and acceptable in terms of tolerability – such as estradiol plus intrauterine progesterone – but these remain to be evaluated in large-scaled controlled studies. The adequate position of hormonal treatment in a PMDD treatment algorithm hence was a matter of debate at the meeting. In the enclosed algorithm (Fig. 1), "hormonal suppression

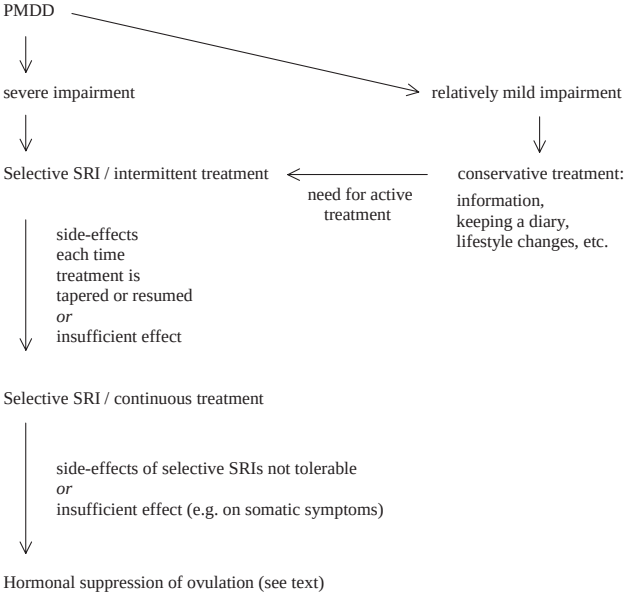

Fig. 1. A treatment algorithm for PMDD

of ovulation" refers to the various forms of treatments disrupting hormonal cyclicity discussed above, and is suggested as an alternative for patients in whom SRIs are not effective or cannot be tolerated. It is however acknowledged that further studies are warranted to clarify the precise role of various forms of hormonal treatment for the management of PMDD and PMS.

For women reporting somatic complaints but no mental symptoms in the luteal phase, the possible efficacy of SRIs has yet not been established. For this subgroup, it is possible that hormonal intervention should be regarded as first-line of treatment; moreover, other treatments may be of value, depending on which symptoms are dominating. In order to present a treatment algorithm for this form of PMS not PMDD, additional studies are however warranted.

Acknowledgements

The meeting was sponsored by Eli Lilly Company. Editorial assistance in the preparation of this manuscript was provided by Jill Gonzales and Rajinder Judge.

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