Premenstrual syndrome (PMS) is a regularly recurring cluster of mood and somatic symptoms, occurring during the luteal phase of the menstrual cycle. According to the American College of Obstetricians and Gynecologists, 20–40% of women have some premenstrual symptoms.\(^1\) In ~5% of women of reproductive age, the symptoms are severe enough to seriously disrupt their lives and relationships,\(^2\) thereby meeting the DSM-IV criteria for premenstrual dysphoric disorder (PMDD).

Despite the prevalence of PMDD, its cause is uncertain. Nutritional, hormonal and neurotransmitter imbalances have all been implicated. Because of the substantial placebo response in this disorder,\(^3\) uncontrolled studies have led to an abundance of claims for treatments that have not been substantiated. Some controlled studies have shown benzodiazepines to be effective\(^4\) but, because of the side effects and risks of addiction and abuse, many physicians are reluctant to prescribe them. Surgical or medical induction of an anovulatory state is also effective,\(^5,6\) but the resultant low oestrogen state can increase the risks for cardiac disease and osteoporosis.

Following is a discussion of several placebo-controlled, double-blinded studies of other therapies which appear to be promising. They include continuous and intermittent use of selective serotonin re-uptake inhibitors (SSRIs), calcium supplementation and chaste berry extract.


Tension, irritability and dysphoria are PMDD symptoms that suggest a similar aetiology to depression and anxiety states. Since these states have been linked to serotonergic dysregulation, drugs which affect the serotonin system such as SSRIs have been proposed as treatment for PMDD. In this large, double-blind, placebo-controlled study, the authors test the efficacy of fluoxetine in women with premenstrual dysphoria.

An initial group of 405 women who met criteria for PMDD were enrolled in the trial. The study design included a single-blind placebo washout period in which all women were given placebo for two menstrual cycles, and those who responded were disenrolled from the rest of the study. The remaining 313 women were randomized to receive fluoxetine 20 mg p.o., 60 mg p.o. or placebo daily for four menstrual cycles. The primary outcomes were reductions in tension, irritability and dysphoria, measured by visual analogue scales.

Women using fluoxetine had significant improvements as compared with those given placebo. The differences were largest in the first cycle, where 53% of all cycles with fluoxetine showed at least moderate improvement compared with 28% for placebo.

Only 180 patients, however, completed the study (57% of randomized patients). Most withdrawals were in the 60 mg fluoxetine group (because of side effects) and the placebo group (because of lack of efficacy). Of the remaining patients in the 60 mg fluoxetine group, 86% reported side effects. The percentage of patients in the 20 mg fluoxetine group who reported side effects was not given.

Jermain D, Preece C, Sykes R, Keuhl T, Sulak P. \textbf{Luteal phase sertraline treatment for premenstrual dysphoric disorder.} \textit{Arch Fam Med} 1999; 8: 328–332.

The cyclical intermittent nature of this disorder suggests that intermittent treatment of PMDD might be desirable. In this study, 57 patients with DSM-IV criteria for PMDD who passed the initial screening were randomized in a double-blind crossover trial to receive sertraline 50 mg or placebo daily during the luteal phase of the menstrual cycle for two cycles, followed by two cycles of treatment with the other study agent. The primary outcome was change from baseline in a daily symptom scale during the luteal phase, as measured by COPE, a 22-item patient-rated scale of common behavioural and physical symptoms of PMDD. Forty patients completed the study. After the second cycle of treatment, the treatment effect was significant, with 70% of the patients in the sertraline group showing at least 30% reduction in symptoms, compared with 50% in the placebo group. The number
of patients reporting side effects in the two groups was not significantly different.

Thys-Jacobs S, Starkey P, Bernstein D, Tian J. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Am J Obstet Gynecol 1998; 179: 444–452.

Studies that demonstrate increased bone loss and exaggerated fluctuations of the calcium-regulating hormones in women with PMS suggest that disturbances in calcium regulation may cause the changes seen in PMS.

In this study, 497 patients meeting the National Institute of Mental Health Premenstrual Syndrome Workshop criteria were randomized to receive 1200 mg of elemental calcium a day or placebo. Eighty-nine percent of the randomized patients completed a symptom diary for three cycles. The primary outcome measure was the difference between the symptom complex score on active calcium treatment versus placebo. Although there were no significant differences between treatment and control groups after the first cycle, there were significant improvements in the calcium group after the second cycle. By the third cycle, an improvement in symptoms of at least 50% was seen in 55% of the calcium group compared with 36% of the placebo group. Most patients in both groups reported mild side effects, with no significant difference between the two groups.


Chaste tree fruit (Vitex agnus castus) has been used medicinally for hundreds of years. It has been used to decrease libido, initiate menstruation and relieve uterine cramps. Studies indicate that chaste berry may correct prolactin levels in latent hyperprolactinaemia by an effect on dopamine receptors.

In this study, 178 women who met the DSM III-R criteria for PMS were selected from out-patient clinics in Germany. They were randomized to receive either one 20 mg tablet daily of chaste berry (active fruit extract ZE 440, standardized for casticin) or placebo. Women rated six self-assessment items using a visual analogue scale for severity of PMS. The primary outcome measure was change from baseline to end point in the combined scores. Ninety-six percent of the enrolled patients had at least one baseline and one post-baseline value. There was a significant improvement in the mean symptom score of patients taking the treatment compared with those given placebo. Fifty-two percent of the patients receiving agnus castus were responders (>50% improvement in scale from baseline) as compared with 24% in the placebo group. The number of reported adverse effects were few and were not different between the two groups.

Discussion

PMDD is very common, and many types of therapy have been proposed, often without good scientific evidence. Our incomplete understanding of the mechanisms involved in PMS complicate the search for useful treatments. Treatments which essentially induce early menopause, either surgically by oophorectomy or medically with the use of gonadotrophin-releasing hormone analogues have been shown to be effective, but their far-reaching systemic effects suggest they should only be used as last resort. Other treatments that have been used, but for which there is not convincing evidence, include oral contraceptive pills, progesterone, magnesium, tryptophan and B12 supplementation. Additional studies are needed to elucidate the effectiveness of these and other promising treatments such as light therapy, exercise and cognitive therapy.

Several recent studies evaluate the use of SSRIs (notably sertraline, fluoxetine and citalopram) for PMS symptoms. The makers of Prozac (fluoxetine) are even marketing the same drug under a different name as a specific treatment for PMS. The intermittent nature of PMS and the considerable side effect potential of these drugs argue in favour of intermittent use. In the paper discussed in this review, patients given luteal phase sertraline showed only minimal improvement—responders were counted as those showing only a 30% improvement in symptoms, and fully 50% of the placebo group met this criterion. This may be the reason why so many SSRI trials use a placebo washout period to reduce the number of placebo responders and thus increase the apparent effect of the study drug. A similar study using sertraline and a placebo washout period showed an improvement of at least 50% in 65% of the sertraline group and 36% of the placebo group, an effect similar to the other studies discussed here.

In the study reviewed above, chaste tree fruit extract was shown to be effective, with a responder rate similar to the SSRIs studied. Its lower incidence of side effects makes it an attractive alternative. Lack of standardization of herbal supplements in the USA makes it difficult to determine if available supplements have the same formulation as that used in the study. If available, it might be a very useful treatment.

Most intriguing is the use of calcium supplementation. Again, the responder rate was similar to the other treatments discussed, and with relatively few side effects. The linkage between abnormal calcium or parathyroid hormone homeostasis and the association of reduced bone mineral density with PMS are interesting and will require more study. As the authors postulate, it is possible that PMS may be an indicator of low body calcium status. Encouraging such women to increase calcium intake might significantly alter a later risk for osteoporosis. In any case, it is a benign and potentially very useful therapy.
that could be recommended to nearly all women with this difficult condition.

References