Non-Antidepressant Treatment of Premenstrual Syndrome

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Although selective serotonin reuptake inhibitors are considered the first-line treatment option for premenstrual syndrome, several other such options are also available. Multiple studies have indicated that medications that suppress ovulation alleviate premenstrual emotional and physical symptoms. However, the use of such medications, such as the gonadotropin-releasing hormone agonists, leads to prolonged low estrogen levels and cardiac and osteoporotic health risks. A recent double-blind, placebo-controlled study of 466 women with premenstrual syndrome reported that calcium was effective in reducing emotional, behavioral, and physical premenstrual symptoms. Recent preliminary trials have suggested efficacy for cognitive therapy, light therapy, and tryptophan. Future studies of diet recommendations, exercise, relaxation, magnesium, nonsteroidal anti-inflammatory drugs, diuretics, opiate antagonists, and alternative therapies are needed. *(J Clin Psychiatry 2000;61[suppl 12]:22–27)*

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The treatment literature of premenstrual syndrome (PMS) has suggested multiple therapies over the past few decades, and the options studied have generally been targeted to treat specific symptoms or to affect possible etiologic factors. Recent treatment studies that use specific diagnostic criteria for PMS or premenstrual dysphoric disorder (PMDD)[1] and that require prospective symptom charting have reported several effective treatment options. In particular, the selective serotonin reuptake inhibitors (SSRIs), discussed in the article by Steiner (this supplement),[2] and the gonadotropin-releasing hormone (GnRH) agonists have been reported to be effective in several double-blind, placebo-controlled studies. There are many other proposed treatments with anecdotal support, support from open trials, or support from preliminary controlled trials that deserve further study. This article will review the literature of hormonal medications, anxiolytics, vitamins, minerals, and psychosocial and other non–antidepressant medication treatments. The reader is also referred to comprehensive reviews of the treatment of PMS and PMDD[3–7] and reviews of recent trials.[8,9]

BACKGROUND

Two recent community surveys examined the prescription and over-the-counter (OTC) treatment patterns currently in use for PMS. One survey of women in the United States, the United Kingdom, and France reported that 3% to 11% of the 1045 women surveyed used prescription medicine for PMS that included analgesics, oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAIDs), and progesterone (particularly in the United Kingdom).[10] OTC preparations for PMS were used by 20% to 50% of all women surveyed, and these included NSAIDs, acetaminophen, aspirin, evening primrose oil, and vitamins. Another survey of 1052 women in the United States reported similar results; i.e., 3% of women used similar prescription medication, and 24% used OTC analgesic preparations for PMS.[11] In addition, 18% used exercise, 4.5% used changes in diet, and less than 2% used alternative treatments such as mind-body techniques, homeopathy, acupuncture, massage, and herbs. Other survey studies have also reported that OTC preparations, pain medications, and lifestyle modifications are the first line of treatment for PMS.[12–14] It is noteworthy that the treatment patterns in the community do not reflect recommendations for PMS or PMDD from the treatment literature. This may be due in part to the efficacy of OTC preparations or prescription analgesics for milder or specific premenstrual symptoms, but it may also be due in part to the need for increased awareness in the lay literature and by health professionals of the available treatments substantiated by research.

Rationale for Treatment

The etiology of PMDD is considered to involve several systems, including the hypothalamic-pituitary-gonadal axis, neurotransmitters, endocrine factors, and circadian rhythms. PMDD is likely to involve the interaction of normal menstrual cycle hormonal fluctuations at ovulation with dysregulated neurotransmitter systems, such as serotonin, norepinephrine, and gamma-aminobutyric acid (GABA).[9,15–18] Recent treatment strategies try to affect this

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interaction by suppressing ovulation or by "correcting" the neurotransmitter dysregulation with antidepressants or anxiolytics.[19] Other somatic therapies and psychosocial therapies may indirectly affect the interaction of gonadal hormones with neurotransmitters and other parameters at ovulation.

TREATMENT

Ovulation Suppression Treatments

Ovulation suppression therapies studied in the treatment of PMS and PMDD include GnRH agonists, danazol, estrogen, and progesterone. Although ovulation suppression with each of these agents has been reported to alleviate premenstrual symptoms, the low estrogen levels that result from these medications lead to long-term health concerns of cardiac disease and decreased bone density.

GnRH agonists cause anovulation by the chronic down-regulation of GnRH receptors in the hypothalamus, leading to decreased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release from the pituitary and subsequent decreased estrogen and progesterone release. GnRH agonists are administered parenterally (e.g., nasal spray, depot injections), because oral preparations are metabolized by the liver. The administration of GnRH agonists has been associated with dysphoria in women without PMS.[20] Ten double-blind, placebo-controlled studies of GnRH agonists have been published, and 8 have reported superiority over placebo,[21–28] while 2 have reported efficacy equal to placebo.[29,30] Although most studies indicate efficacy, GnRH agonists may be less effective for women who have premenstrual dysphoria and more severe premenstrual symptoms,[21] as well as women who have premenstrual exacerbation of depression.[22]

Add-back regimens of replacement estrogen and progesterone have been studied in an attempt to decrease the health risks associated with the prolonged decreased estrogen resulting from long-term GnRH agonist use. A small, older controlled report suggested the return of some mood and anxiety symptoms with add-back estrogen and progesterone given sequentially.[31] A recent double-blind, placebo-controlled study confirmed the reappearance of mood and anxiety symptoms with the addition of estradiol valerate, 2 mg/day, and norethisterone, 5 mg days 22–28, in women with PMS who were asymptomatic after monthly depot implants of goserelin.[25] A study by Schmidt and colleagues[27] compared the effects of estrogen and progesterone separately in women with PMS and control women who were anovulatory for 3 cycles after leuprolide monthly injections. The control women did not develop mood or anxiety symptoms for 4 weeks after the addition of estradiol or progesterone. However, the women with PMS, although asymptomatic on leuprolide therapy, had a return of several mood and anxiety symptoms with either estradiol or progesterone. The results of this study suggest that women with PMDD may have an intolerance of estrogen as well as progesterone in replacement strategies, and this suggestion deserves further study.

A few controlled studies have examined the efficacy of parenteral estrogen for PMS and have reported that estradiol may be effective for PMS.[32–34] An older study reported that luteal phase oral conjugated estrogen (0.625 mg/day) was not more effective than placebo.[35] In this study, anovulation was presumed to be absent, since the estrogen was administered only during the luteal phase. The results of this study suggested that estrogen may cause some negative affect in women with PMS, similar to the results of the more recent study by Schmidt and colleagues.[27] Two studies have suggested that progesterone in doses that cause anovulation may be helpful for PMS. One study reported that high-dose medroxyprogesterone was superior to norethisterone and placebo,[36] and another study reported that norethisterone was superior to oral contraceptives.[37] Controlled studies are needed to determine the effect of levonorgestrel on PMS.

Danazol, a synthetic steroid, has been studied for the treatment of PMS at various doses. As reported and reviewed, doses of 200 to 400 mg/day can be helpful for PMS,[38] and efficacy has been reported to correlate with anovulation.[39] Although an older, small crossover study with luteal phase danazol (200 mg/day) in 14 subjects reported efficacy,[40] a recent crossover study of this same dose in 100 women with PMS during the luteal phase reported efficacy only for reducing mastalgia but not other premenstrual symptoms.[41] Limitations of this medication include several adverse effects in addition to the risks associated with prolonged anovulation. Adverse effects include weight gain, nausea, acne, facial hair, decreased high-density lipoproteins, and depression.

One of the most extensively studied hormonal treatments for PMS has been luteal phase progesterone, as recently reviewed.[6,15] Progesterone has been of recent theoretical interest as a treatment due to the anxiolytic properties of some of its metabolites, particularly allopregnanolone.[15,18] Oral micronized progesterone is a form of progesterone with increased bioavailability and a less adverse effect on lipid profiles. However, almost all controlled trials of progesterone, oral micronized progesterone, and synthetic progestins have failed to demonstrate efficacy over placebo. Two large, well-designed studies failed to show efficacy of progesterone compared with placebo[42] or of oral micronized progesterone compared with alprazolam and placebo.[43]

Oral contraceptives have been subject to some investigation in the treatment of PMS. As mentioned above, these medications are one of the most frequently prescribed treatments for women in the community seeking treatment for PMS. Small randomized trials to date have not indicated relief of premenstrual symptoms with oral contraceptives,[44,45] and one study indicated worsening of premenstrual dysphoria.[46]

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Anxiolytics

Alprazolam is the anxiolytic medication that has been studied the most in PMS. Theoretically, administration of a benzodiazepine could "correct" a subsensitive benzodiazepine/$GABA_A$ receptor complex in women with PMS or could modulate the action of progesterone metabolites at that receptor complex.[15,18] Recent studies report different pharmacodynamic and behavioral responses to benzodiazepines at different menstrual cycle phases in women with PMS,[18,47] but not in women without PMS.[48,49] Four studies have reported that luteal phase treatment (with doses up to 0.25 mg t.i.d. in most studies) relieves several premenstrual symptoms.[43,50–52] One of these studies reported that alprazolam was ineffective for the premenstrual exacerbation of mood or anxiety disorders.[50] The largest study reported a 37% improvement with alprazolam,[43] a considerably lower effect size than in studies with SSRIs. One double-blind, placebo-controlled study that compared various alprazolam doses and full- and partial-cycle dosing reported that alprazolam was not superior to placebo.[53] An older, positive controlled report of the luteal administration of buspirone has not been replicated.[54] Single doses of both alprazolam[55] and buspirone[56] have been reported to increase food intake premenstrually, and alprazolam administered for 2 luteal weeks did not decrease premenstrual carbohydrate cravings in women with PMS.[57] These reports suggest that the anxiolytics are not helpful for the food cravings common in PMS.

Calcium

Reduced bone mineral density has been associated with both depression[58,59] and PMS,[60] and some abnormality of calcium or parathyroid hormone homeostasis may be an etiologic factor in PMS.[61] A recent large multicenter trial examined the efficacy of calcium (1200 mg/day in 2 divided doses) compared with placebo.[62] Calcium was reported to be 48% effective compared to 30% with placebo. Although the diagnosis of PMS in the women in the sample was prospectively confirmed by daily ratings, there was no follicular symptom maximum score as an exclusion criterion, and the sample of 466 women may have included some women with premenstrual exacerbation of chronic Axis I disorders. Also, approximately 25% of the sample took oral contraceptives. These 2 factors differentiate this large sample from the samples in the published multicenter SSRI trials to date, which stringently exclude women with concurrent Axis I disorders and women taking hormonal medications. The results of this study indicated that calcium was more effective than placebo in reducing all of the emotional and physical symptoms of the PMDD diagnostic criteria except for fatigue and insomnia. The comprehensive effect of calcium on the spectrum of PMDD symptoms is very similar to that of the SSRIs. However, the efficacy rate of 48% is lower than that reported in SSRI trials. Clearly, calcium seems to be a promising and inexpensive treatment option for women with PMS and PMDD.

Magnesium

An earlier controlled study reported that the luteal administration of magnesium (360 mg/day) was helpful for premenstrual emotional and physical symptoms,[63] but a recent report indicated that the daily administration of magnesium (200 mg/day) was helpful only for reducing premenstrual fluid retention and was not helpful for emotional symptoms in women with retrospectively defined PMS.[64] It has been suggested that PMS may be related to an increased Ca^{2+}/Mg^{2+} ratio,[65,66] and increasing magnesium intake and decreasing dairy products have been common dietary recommendations in the past. How the efficacy of calcium supplementation fits into such a model remains to be explored.

Vitamin B_6

Because of its metabolic action,[67] vitamin B_6 has been of theoretical interest as a treatment for PMS, depression, and other disorders. An earlier review of several studies[68] and a recent study[69] have indicated a lack of efficacy of vitamin B_6 for PMS. However, a recent meta-analysis of 940 women with PMS from 9 controlled trials indicated weak support for vitamin B_6 (50–100 mg/day) in reducing premenstrual symptoms and a lack of neurotoxicity in this dose range.[70]

Other Somatic Treatments

Older studies of various somatic therapies have been reviewed extensively, and the reader is referred to these reviews of the studies of other vitamin and mineral preparations, evening primrose oil, lithium, β-blockers, calcium channel blockers, bromocriptine, thyroxine, diuretics, light therapy, sleep deprivation, and hysterectomy and oophorectomy.[3,4,7] Older studies that have indicated some promise and deserve replication include those of NSAIDs,[71,72] spironolactone,[73] naltrexone,[74] vitamin E,[75] and doxycycline.[76] The efficacy of the antibiotic doxycycline may be related to the introduction of bacteria into the pelvic cavity as an etiology of some cases of PMS.[77]

Some recent studies of note will be mentioned. A recent crossover trial[78] reported that 30 minutes of evening light therapy for the 2 luteal weeks was superior to placebo in 14 women with PMS. These authors suggested that the effect of bright light might be mediated through the serotonin system. An open study[79] reported that daily photic stimulation reduced emotional and physical premenstrual symptoms. A recent study[80] reported that the dietary serotonin precursor L-tryptophan (6 mg/day) during the 2 luteal weeks was superior to placebo in 37 women with PMDD. A recent controlled trial[81] reported that the synthetic steroid tibolone improved premenstrual symptoms and increased beta-endorphin levels.

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Psychosocial Therapies

The psychosocial therapies that have received the most attention have been dietary recommendations, exercise, cognitive therapy, and relaxation therapy. These treatments are generally taught in individual sessions or in a group psychoeducational format, and controlled studies of individual and group therapies are needed. In addition, multiple treatment modalities are usually included in the individual and group therapies, and studies are needed to identify which treatment components are the most helpful. A recent report[82] suggested that the positive reframing of perceptions of the menstrual cycle was a helpful component of a psychoeducational group therapy.

Dietary recommendations include the increase of complex carbohydrates, reduction of refined sugar, elimination of caffeine, and frequent feedings. As reviewed, the premenstrual increased appetite and carbohydrate craving may be a homeostatic mechanism to increase dietary tryptophan consumption in an effort to increase brain serotonin.[5] Other than one study reporting that consumption of a beverage mixture of simple and complex carbohydrates reduced premenstrual depression, anger, and carbohydrate craving,[83] there are no controlled studies of specific dietary regimens.

Exercise is another frequently recommended treatment for PMS. There is also no controlled study of exercise as a single treatment in women with confirmed PMS that has been published to date. As reviewed, most studies report a reduction in negative affect and other premenstrual symptoms in non-PMS samples, and it is not clear that aerobic exercise is more effective than nonaerobic exercise.[5,84] The efficacy of exercise could be due to raised endorphin levels, physiologic changes, and psychological changes.[84–86]

Cognitive therapy was recently[87] reported to be superior to a wait-list control condition in 23 women with prospectively confirmed PMS. The cognitive therapy consisted of 12 weeks of individual sessions and included reviewing dysfunctional attitudes and increasing coping strategies. The authors reported significant reductions in premenstrual psychological and physical symptoms and improved psychosocial functioning. The only other controlled study[88] in women with prospectively confirmed PMS reported that 13 weeks of group cognitive-behavioral therapy (involving cognitive restructuring and assertiveness training) was as effective as 13 weeks of group information-focused therapy (involving relaxation training, dietary guidelines, and lifestyle modifications) in 33 women. Controlled studies in less well-defined PMS samples indicated that group cognitive-behavioral therapy was superior to group awareness through movement training and wait-list control,[89] and group coping skills training was superior to relaxation training and dydrogesterone.[90] Cognitive therapy seems to be a promising treatment for PMS, and future studies should confirm this in a large sample of women and determine which components are most useful.

Relaxation therapy has been studied as a single treatment in 2 controlled trials of women with PMS (neither with confirmed prospective daily ratings). In one study, relaxation therapy twice daily was superior to charting and leisure reading,[91] and in the other study, relaxation therapy was less effective than coping skills training.[90] Relaxation therapy is a common component of group therapy for PMS, in addition to psychoeducation and lifestyle modifications. Reflexology was reported to be effective in a controlled trial.[92]

CONCLUSION

Due to efficacy and tolerability, the SSRIs are considered by most clinicians to be the first-line treatment of PMS and PMDD. However, several studies have identified a number of alternative effective treatment options. The GnRH agonists have been shown to be effective in multiple double-blind, placebo-controlled trials. These agents, and other agents that suppress ovulation, produce prolonged low estrogen levels with resultant cardiac and bone health risks. Add-back hormone regimens have been associated with the reappearance of affective and anxiety symptoms, limiting their usefulness for PMS. Calcium (1200 mg/day) was reported to be effective for most premenstrual emotional, behavioral, and physical symptoms in a large multicenter study. This is an inexpensive and healthy option for women with PMS. Several other medications and psychosocial therapies deserve further study. Survey studies indicate that women with PMS are prescribed oral contraceptives and analgesics most often and take several OTC preparations, many of which are not supported by the research treatment literature.

Drug names: alprazolam (Xanax and others), bromocriptine (Parlodel and others), buspirone (BuSpar), naltrexone (ReVia).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, the following agents mentioned in this article are not approved by the U.S. Food and Drug Administration for the treatment of PMDD: alprazolam, bromocriptine, buspirone, danazol, doxycycline, estradiol valerate, leuprolide, levonorgestrel, lithium, medroxyprogesterone, norethisterone, and thyroxine.

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