New Treatment Approaches for Premenstrual Disorders

Andrea J. Rapkin, MD

Abstract

Several approaches to alleviating the symptoms of premenstrual disorders are available to women and can be tailored according to individual needs and preferences. This article discusses methods that entail changes to lifestyle and diet and managing life stresses without relying on drug therapy, as well as a variety of medications that may be necessary in addition to or in place of recommended lifestyle modifications. New pharmacologic research is promising and is discussed along with the need to provide empathetic counseling for patients to determine the approach that will work best for each individual.

(Am J Manag Care. 2005;11:S480-S491)

The term "premenstrual disorders" covers a spectrum of premenstrual symptom combinations, from mild premenstrual syndrome (PMS) to premenstrual dysphoric disorder (PMDD) that is severe enough to interfere with work and social functioning. Effective evaluation and treatment of PMS were hampered until the mid-1980s by the lack of established criteria for diagnosing this common condition. The American College of Obstetricians and Gynecologists (ACOG) published a practice bulletin in 2000 that included criteria for PMS, based on an earlier article by Mortola and colleagues, as well as a discussion of different approaches for treating PMS,[1,2] including lifestyle modifications such as regular aerobic exercise and dietary changes. Pharmacologic options studied for treating severe PMS include selective serotonin reuptake inhibitors (SSRIs), anxiolytic agents, gonadotropin-releasing hormone (GnRH) agonists, the diuretic spironolactone, and combination oral contraceptives (OCs).

PMDD is defined as a psychiatric disorder in Appendix B of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*.[3] Currently, selected SSRIs are the only pharmacologic agents with a US Food and Drug Administration (FDA) indication for PMDD.

Prior to the early 1990s when PMDD was defined as "late luteal dysphoric disorder" in *DSM-III*, various severities of PMS and PMDD were often investigated and discussed without differentiation. Therefore, many of the early studies in which the term "PMS" was used probably included patients with PMDD as well. It is necessary to keep this fact in mind when reviewing the literature on premenstrual disorders.

In this article, a number of available nonpharmacologic and pharmacologic treatments are reviewed, as well as recent advances in pharmacotherapy for premenstrual disorders.

Lifestyle Modifications

Lifestyle modification rather than drug therapy may be the most appropriate treatment approach for women with mild PMS symptoms. Physicians should always inform their female patients about lifestyle changes that may ameliorate their premenstrual symptoms and advise them to evaluate the effect of various approaches during the 2 months for which they keep a daily symptom diary. (At least 2 months of prospective daily symptom recording are required for a diagnosis of PMS or PMDD.) Regular aerobic exercise, for example, eases premenstrual symptoms for many women.[4] The decline in

Address correspondence to: Andrea J. Rapkin, MD, David Geffen School of Medicine at UCLA, Department of Obstetrics and Gynecology, 10833 Le Conte, Room 27-165 CHS, Los Angeles, CA 90095-1740; arapkin@mednet.ucla.edu.

endorphin levels that normally occurs in the late luteal phase of the menstrual cycle has been suggested to be an underlying mechanism for premenstrual symptoms in some women. Because regular aerobic exercise leads to the release of endorphins in the central nervous system, physicians should recommend that women perform at least 20 to 30 minutes of aerobic exercise per day for at least 3 days each week.[5]

Dietary and nutritional modifications have also been used over the years to treat premenstrual symptoms. One such approach, calcium supplementation, was studied by Thys-Jacobs and colleagues in 466 evaluable women with moderate-to-severe premenstrual symptoms that had been documented over 2 cycles.[6] Participants were randomized to receive 1200 mg/day of elemental calcium or a placebo for 3 cycles. Premenstrual symptoms were significantly lower in the calcium-treated group than in controls in the second (P = .007) and third (P <.001) treatment cycles. Therefore, calcium supplementation appeared to reduce premenstrual symptoms in some women.

Other studies have suggested that excess alcohol, salt, and caffeine intakes may actually worsen premenstrual symptoms by decreasing magnesium levels.[7] For example, Walker et al conducted a double-blind, placebo-controlled, crossover study in which 41 evaluable women were randomized to 200 mg/day of magnesium or placebo for 2 cycles before being crossed over to the alternate treatment for 2 additional cycles.[8] Walker and colleagues observed that daily magnesium supplementation significantly lowered mild symptoms of fluid retention (ie, weight gain, breast tenderness, swelling of extremities, and abdominal bloating) compared with placebo in the second cycle of administration (P = .0009), but not in the first cycle.[7]

Another study conducted by Freeman and colleagues included 53 women with premenstrual symptom rates that were 30% higher during the late luteal phase than in the follicular phase.[9] Patients were randomized to a commercial carbohydrate-rich beverage or to an isocaloric placebo beverage taken twice daily for 5 days before the anticipated onset of menses. Mood symptoms were decreased in approximately one third of women consuming the carbohydrate-rich beverage, compared with 5% of the placebo group.

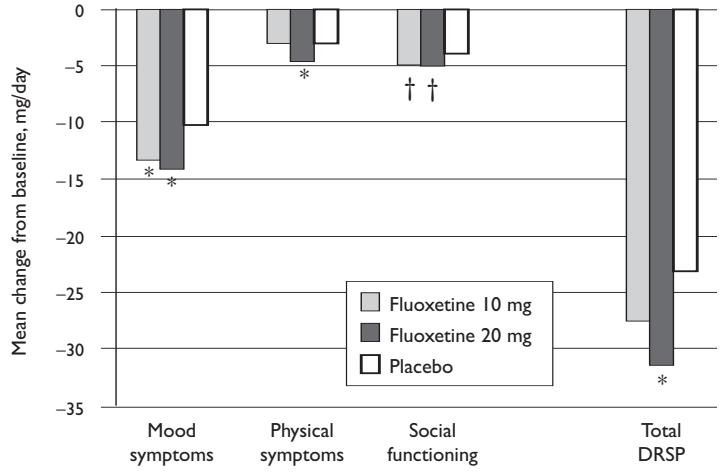
A study indicated that vitamin B_6 had some clinical benefit in reducing premenstrual symptoms,[10] but doses in excess of 100 mg/day can be harmful.[1] Additionally, the herbal product evening primrose oil has not been shown to be effective in treating premenstrual symptoms[11]; however, the ACOG practice bulletin indicated that it may decrease breast tenderness.[1] Finally, with regard to nutrition, reductions in salt, sugar, alcohol, and caffeine intake are often suggested for relieving premenstrual symptoms, but these approaches have not been investigated extensively in controlled studies.[12]

Pharmacotherapeutic Options

Compared with the nonpharmacologic approaches, pharmacotherapeutic options for managing premenstrual disorders have been investigated in greater detail. However, the study techniques employed have varied widely, including methods of diagnosis, outcomes analyzed, and methods of outcome measurement. Studies should include procedures for recording improvements in psychological symptoms and physical symptoms as well as overall improvement. Daily self-report diaries constitute the primary measurement, but some clinician-rated scales have also been validated. In addition, symptom assessment should include several months of tracking to confirm the diagnosis before entry into the study and placebo run-in periods to exclude placebo responders.

Antidepressants. Of numerous options available, antidepressants from the class of the SSRIs may be considered the therapy of choice for PMDD in many patients. Currently, the only agents with an FDA indication for PMDD are fluoxetine hydrochloride, sertraline hydrochloride, and paroxetine hydrochloride. Unlike tricyclic antidepressants, which interact with several receptors, the SSRIs interact minimally with receptors other than the serotonin (5-HT) reuptake receptor.[13] Fluoxetine has a recom-

Figure 1. Luteal-phase Daily Fluoxetine for PMDD: DRSP Scores



*P <.01.
†P <.05.
PMDD indicates premenstrual dysphoric disorder; DRSP, Daily Record of Severity of Problems.
Source: Reprinted with permission from Cohen, et al. *Obstet Gynecol.* 2002; 100:435-444.

mended dose of 20 mg/day (**Figure 1**); in clinical studies, no added benefit was observed with increasing the dosage to 60 mg/day. Sertraline is initiated at a dose of 50 mg/day and can be increased up to 150 mg/day for daily dosing or up to 100 mg/day for dosing only during the luteal phase of the cycle. Paroxetine is initiated at a dose of 12.5 mg/day and can be increased to 25 mg/day.[14] Clinical trials that formed the basis for approval of these 3 SSRIs for managing PMDD symptoms and additional trials with other SSRIs are listed in **Table 1**.

Several adverse effects are associated with daily use of the SSRIs that have received an FDA indication for PMDD (**Table 2**). Individual response to these side effects may lead to poor adherence or discontinuation of these medications.

In a study to investigate compliance to antidepressant agents prescribed for PMS, Sundström-Poromaa and colleagues noted reasons given by these patients for discontinuing antidepressant use.[15] A total of 170 (84.2%) of the 202 women who were prescribed an SSRI or a tricyclic antidepressant for PMS during a 4-year period completed a written questionnaire. The 22 (12.9%) women who never started treatment listed their primary reasons as fear of negative side effects (54.5%) and not wishing to take this type of drug (54.5%). (A woman could give more than 1 reason for not initiating antidepressant therapy.) Of the 148 (87.1%) women who did start therapy, 91 (61.5%) had discontinued the antidepressant by the end of 2 years. **Table 3** lists the reasons for discontinuation of therapy.

Women who experience severe side effects can be advised to switch to a different SSRI. Should they choose to switch to a different drug class, the SSRI dose must be tapered slowly to avoid discontinuation symptoms. In addition, the FDA recently revised the safety labeling for SSRIs to advise against their use in patients younger than 18 years and to warn patients with major depressive disorder of the risk for worsening symptoms and/or for suicidal ideations.

Studies with non-SSRI/selective norepinephrine antidepressants have had less favorable results compared with SSRIs. A comparative study of treatment with sertraline and desipramine (flexible dosage range 50-150 mg/day) vs placebo in 189 subjects with PMS/PMDD showed that sertraline was significantly more effective than placebo on the Penn Daily Symptom Report (>50% symptom decrease in 65% of subjects in the sertraline groups), whereas desipramine was not (symptom decrease in 36% of subjects in the sertraline group and 29% in the placebo group).[16] Another comparative study investigated fluoxetine 20 mg/day, bupropion 100 mg/day, and placebo in 34 women with PMDD. Fluoxetine was superior to both bupropion and placebo in efficacy by Global Clinical Impression ratings. Posttreatment Hamilton Rating Scale for Depression and Global Assessment Scale rating scores were intermediate between but not significantly different from fluoxetine or placebo.[17]

On the whole, studies conducted with antidepressants in women with PMS and PMDD indicate that serotonergic activity is required for efficacy. The SSRIs have been investigated for both continuous and luteal-phase (intermittent) administration, and fluoxetine, paroxetine CR (controlled release),

Table 1. Pivotal Studies Supporting Approval of SSRIs for Use in PMDD

Study	Agent	Dosing	Duration	Primary Outcome Measure	Results
Cohen 2002	Fluoxetine	I	3 cycles	DRSP	Fluoxetine 20 mg/day was significantly more effective than placebo; fluoxetine 10 mg/day was not significantly effective on DRSP total score but improved mood-related and social functioning symptoms
Steiner 1995	Fluoxetine	C	6 mo	VAS	Fluoxetine 20 or 60 mg/day was significantly more likely than placebo to produce moderate or marked improvement on VAS total score
Menkes 1993	Fluoxetine	C	3 mo ea. (crossover)	VAS	Fluoxetine 20 or 60 mg/day was significantly more effective than placebo in decreasing (improving) the VAS total score; score on placebo was 3.8 times higher than score on fluoxetine
Prescribing Information	Paroxetine CR	C	3 cycles	VAS	Paroxetine CR 12.5 mg/day or 25 mg/day were significantly more effective than placebo for change from baseline to end point on luteal-phase VAS total score (pooled study results)
Steiner 2005	Paroxetine CR	I	3 mo		Paroxetine CR as luteal-phase dosing was significantly more effective than placebo as measured by change from baseline luteal-phase VAS total score
Yonkers 1997	Sertraline	C	3 cycles	DRSP	Sertraline was significantly more effective than placebo on change from baseline to end point in DRSP total score and other measures
Halbreich 2002	Sertraline	I	3 cycles	DRSP, CGI-I	Sertraline was significantly more effective than placebo on change from end point
Agents Not (Yet) Approved for Treatment of PMDD Symptoms					
Freeman 2005	Citalopram	I	3 cycles	Penn DSR	Total premenstrual DSR scores improved significantly: decreased 57% in group given citalopram throughout the luteal phase and 51% in group given citalopram starting at symptom onset
Freeman 2001	Venlafaxine	C	4 cycles	Penn DSR	60% of venlafaxine-treated subjects showed more than 50% improvement in DRSP vs 35% of placebo subjects. Approximately 80% of symptom reduction occurred during first cycle
Cohen 2004	Venlafaxine	I	2 cycles	DRSP, CGI-S, PTSQ	Favorable changes in DRSP scores and subscores and in PTSQ scores were significant ($P < .05$), and 9 subjects (81.8%) showed satisfactory response based on CGI-S ≤ 2

SSRIs indicate selective serotonin reuptake inhibitors; PMDD, premenstrual dysphoric disorder according to *DSM-IV* criteria or LLPD according to *DSM-III* criteria; I, intermittent dosing (luteal phase); DRSP, Daily Record of Severity of Problems; C, continuous dosing throughout cycle; VAS, visual analogue scale; CR, controlled release; CGI-S, Clinical Global Impression-Severity; CGI-I , Clinical Global Impression-Improvement; Penn DSR, University of Pennsylvania Daily Symptom Report; PTSQ, Premenstrual Tension Syndrome Questionnaire.

Sources: Cohen L. *J Clin Psychopharmacol.* 2004;24:540-543, Cohen L. *Obstet Gynecol.* 2002;100:435-444; Freeman E. *J Clin Psychiatry.* 2005;66:769-773; Freeman E. *Obstet Gynecol.* 2001;98:737-744; Halbreich U. *Obstet Gynecol.* 2002;100:1219-1229; Menkes D. *Int Clin Psychopharmacol.* 1993;8:95-102; Steiner M. *Am J Obstet Gynecol.* 2005;193:352-360; Steiner M. *N Engl J Med.* 1995;332:1529-1534; Yonkers K. *JAMA.* 1997;278:983-988.

and sertraline are approved for use in PMDD without specification of the regimen, so can be employed continuously or intermittently. Onset of efficacy is rapid: therapeutic benefit is seen in the first menstrual cycle after initiation of treatment with these agents. Patients on systemic hormonal contraceptives were excluded from many of the SSRI trials, so the efficacy of SSRIs in combination with systemic (including oral) hormonal contraceptives for the continuous daily treatment of PMDD is unknown.

Table 2. Frequency of Common Side Effects With Daily Use of SSRIs

	Fluoxetine	Sertraline	Paroxetine
Anxiety	+++	+	+
Sedation	+	++	++++
Insomnia	++++	++++	+++
Nausea	++++	++++	++++
Decreased libido	+	+	+
Weight gain	0/+	+	++

Frequency based on populations reported in *Physicians' Desk Reference,* 54th ed, 2000. 0/+ = <1.0%; + = 1.0%-5.0%; ++ = 5.1%-10.0%; +++ = 10.1%-15.0%; ++++ = ≥15.1%.
SSRIs indicates selective serotonin reuptake inhibitors.
Source: Ferguson JM. *Prim Care Companion J Clin Psychiatry.* 2001;3:22-27. Copyright 2001. Physicians Postgraduate Press. Adapted with permission.

Table 3. Reasons for Discontinuation of Antidepressant Agents*

Reason	Number (%)†
Unacceptable side effects, especially reduced libido	39 (42.9)
Aim to deal with symptoms "naturally"	21 (23.1)
Unwillingness to use this type of drug	18 (19.8)
Fear of drug dependence	17 (18.7)
Wanted to find out if symptoms disappeared	16 (17.6)
No improvement or deterioration	16 (17.6)
Bad publicity of antidepressant drugs in media	5 (5.5)
Lack of information	4 (4.4)
Advised to discontinue	3 (3.3)
Other (eg, menopause, desire pregnancy, economics)	26 (28.6)

*Includes tricyclic agents and selective serotonin reuptake inhibitors.
†91 women total; more than 1 possible reason could be given.
Source: Reproduced from Sundström-Poromaa I, et al. *J Psychosom Obstet Gynaecol.* 2000;21:205-211. Used with permission.

Anxiolytics. The anxiolytic agent alprazolam has not shown consistent results in studies evaluating its effectiveness in alleviating premenstrual symptoms, according to the ACOG practice bulletin.[1] In a study conducted by Evans and colleagues, women with premenstrual symptoms were given either alprazolam (0.25, 0.50, or 0.75 mg) or placebo during both the luteal and follicular phases of the cycle under controlled laboratory conditions.[18] It was observed that acute doses of alprazolam did not improve negative premenstrual mood and actually were associated with an increase in negative mood in the follicular phase.[18] Also, alprazolam impaired task performance in both phases of the cycle. As a result, acute administration of alprazolam was not deemed a clinically useful treatment for premenstrual symptoms. In addition, continued use of alprazolam can lead to dependency, and some users develop a tolerance to this agent.

GnRH agonists. A third treatment option is the class of GnRH agonists, which use a hormonal approach to suppress ovarian steroid hormone production and prevent ovulation, in effect by inducing medical oophorectomy.[4] These agents have demonstrated efficacy in alleviating several premenstrual symptoms. For example, in a small study conducted by Mortola and colleagues,[19] GnRH monotherapy was associated with at least a 75% improvement from baseline in the Calendar of Premenstrual Experiences (COPE) scores for behavioral (P <.01), physical (P <.05), and total (P <.01) symptoms. However, because GnRH agonists induce medical menopause, estrogen and progestin must be added back to prevent bone loss and potentially for cardioprotection.[4] According to an additional, small study, 10 women with PMS symptoms given leuprolide acetate at 3.75 mg/mo for 3 months had a significant decrease in symptoms measured using a Daily Rating Form and the observer form of the Rating Scale for Premenstrual Tension Syndrome. Addition of either progesterone vaginal suppositories or a 17β-estradiol patch or the leuprolide regimen resulted in significant return of symptoms. No changes in mood occurred in 15 normal women who received the same regimen. The authors conclude that in women with PMS, the occurrence of symptoms represents an abnormal response to normal hormonal changes.[20]

Synthetic androgens. Danazol, a synthetic androgen indicated in the United States

for the treatment of endometriosis, menorrhagia, fibrocystic breast disease, and hereditary angioedema, has also been investigated for the management of PMS and premenstrual mastalgia, with moderate results. Luteal-phase–only danazol was not effective for treating the general symptoms (daily analogue scale scores) of premenstrual syndrome, but appeared highly effective for relieving premenstrual mastalgia in a study conducted on 100 women.[21] A smaller study, conducted in 31 women meeting rigorous criteria for a diagnosis of severe PMS, evaluated effects of danazol treatment using the Premenstrual Tension Self-Rating Scale, the Beck Depression Inventory, and a visual analogue scale. Danazol 200 mg bid provided greater symptom relief than did placebo.[22] Potential adverse effects of danazol are a cause for concern with this agent.[23]

Diuretics. Another therapeutic consideration is spironolactone, an aldosterone receptor agonist derived from 17α-spirolactone. According to the ACOG practice bulletin, thiazide diuretics have not been demonstrated to be beneficial in alleviating premenstrual fluid retention, but spironolactone has, in fact, been shown to have benefit in PMS.[1] Spironolactone also has been shown to relieve other symptoms associated with the premenstrual phase of the cycle,[4] as noted in a double-blind, parallel-group study over 3 cycles conducted by Vellacott and colleagues.[24] Sixty-three women, aged 16 to 45, with a history of at least 6 months of cyclic symptoms were randomized to spironolactone 100 mg/day or to placebo, given from day 12 of the menstrual cycle to the onset of menses. Spironolactone was significantly superior to placebo in relieving the general feeling of bloating ($P = .001$). By cycle 3, more than half of the 26 women using spironolactone also experienced improvement of abdominal swelling, swelling of the hands and feet, breast discomfort, irritability, depression, anxiety, tension, and increase in sexual interest.

Spironolactone was also examined in a double-blind, crossover study conducted by Wang and colleagues in 35 women with PMS.[25] Two pretreatment cycles were used to diagnose PMS, after which the treatment phase began, consisting of two 3-month periods. Women were randomized to 100 mg/day of spironolactone or placebo administered daily from day 14 of the menstrual cycle until the onset of menses. The primary outcome measure was the prospective daily visual analogue scale. During the intervals when women were taking spironolactone, they experienced significant improvements in negative symptoms (ie, anxiety and tension, irritability, fatigue, and depression) and in physical symptoms (ie, headache, feelings of swelling, cravings for sweets, and breast tenderness) compared with baseline values and with placebo ($P < .01$ for all measures). Spironolactone treatment was also associated with an improvement in positive symptoms (cheerfulness, well-being, friendliness, feeling energetic) compared with baseline values ($P < .01$).

Oral contraceptives. Another hormonal option, combination OCs, is a popular choice for helping to relieve several premenstrual symptoms. In the United States, OCs contain estrogen as ethinyl estradiol (EE) in combination with a variety of progestins. EE causes a rise in serum aldosterone levels, which lead to sodium and water retention, thereby contributing to bloating and breast tenderness.[26] All progestins have progestogenic activity, but they can differ in terms of other pharmacologic effects. The pharmacologic profiles of progesterone and various progestins used in OCs (as found in animal models) are demonstrated in the work of Krattenmacher.[27]

Until recently, very few controlled studies had evaluated the efficacy of OCs in reducing premenstrual symptoms, and those that had been conducted yielded mixed results. For example, in 1992 Graham and Sherwin studied 82 women with moderate-to-severe premenstrual symptoms in a double-blind, placebo-controlled trial.[28] The women charted daily symptoms for 1 cycle, after which they were randomly assigned to a triphasic OC containing EE 35 µg and norethindrone (0.5 mg, 1.0 mg, and 0.5 mg) or to placebo for 3 cycles. A total of 23 women (28%) dropped out of the study (18 in the OC group and 5 in the placebo group). Com-

pared with placebo, the OC significantly reduced premenstrual breast pain and bloating (P <.03) but did not have significantly better effects on mood symptoms.

Similarly, in a double-blind crossover study of 3 OCs, 36 women aged 20 to 40 who either had PMS or experienced symptoms throughout their entire menstrual cycle with premenstrual aggravation were examined.[29] The study consisted of 2 treatment cycles followed by a crossover to the alternate preparation for 2 additional treatment cycles. Nineteen women were randomly assigned to a monophasic OC containing EE combined with either desogestrel (DSG) or levonorgestrel (LNG), and 17 women were randomized to treatment with either monophasic EE/DSG or a triphasic OC containing EE plus LNG. Mood scores improved from baseline for all 3 OCs, but Bäckström and colleagues concluded that the beneficial effect observed in the study was no higher than that reported for placebo in other studies. The monophasic DSG pill resulted in less change in mood parameters than did the monophasic and triphasic LNG OCs. However, physical complaints were less frequently reported during the use of the triphasic preparation as compared to the monophasic DSG preparation.[29]

Finally, a nested case-control study conducted by Joffe and colleagues examined a cohort of 976 women, aged 36 to 45.[30] Of the 658 women who had previously used a variety of OCs, 107 (16.3%) reported pill-related premenstrual mood deterioration, 81 (12.3%) reported premenstrual mood improvement, and 470 (71.4%) reported no effect of OCs on premenstrual mood. Therefore, it was concluded that OCs do not affect premenstrual mood in most women.[30]

All but one of the progestins being used in OCs in the United States are derived from 19-nortestosterone. The exception is the progestin drospirenone, which is derived from 17α-spirolactone and is an analogue of spironolactone. The pharmacologic profile of drospirenone closely resembles that of natural progesterone in that it has potent progestogenic, antiandrogenic, and antimineralocorticoid activities, and no androgenic activity.[26] The antimineralocorticoid activity of 3 mg of drospirenone is comparable with 25 mg of spironolactone.[31] Drospirenone acts by binding to aldosterone receptors, blocking aldosterone action in the kidneys, resulting in a substantial rise in sodium and water excretion and some retention of potassium (**Figure 2**).[27]

In recent years, several studies have examined the efficacy of the OC formulation containing EE 30 µg plus drospirenone 3 mg (30EE/drospirenone) on premenstrual symptoms. For example, a double-blind trial included 82 women with PMDD who were randomized to 30EE/drospirenone (n = 42) or placebo (n = 40).[32] The drospirenone-containing OC was observed to have a positive effect on symptoms of PMDD, with the between-group differences reaching statistical significance in appetite, food cravings, and acne (P = .03). In addition, Apter and colleagues conducted an open, 6-cycle study of 336 women to evaluate the actions of 30EE/drospirenone on fluid-related symptoms during the luteal phase of the cycle and the effects of these symptoms on overall well-being.[33] Use of 30EE/drospirenone was associated with a significant reduction in the incidence and severity of the abdominal bloating and breast tenderness (both P <.001) associated with the menstrual cycle. Also, the significant beneficial effect of 30EE/drospirenone on psychologic well-being (P <.0001), as measured by the Psychological General Well-Being Index, observed at cycle 3 was maintained at cycle 6.

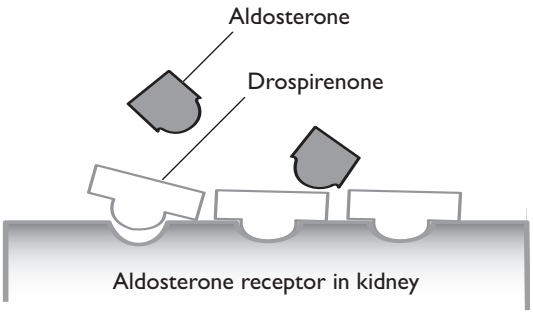
Further, an open-label, 26-cycle study was conducted by Foidart and colleagues of 627 evaluable women: 310 were randomized to 30EE/drospirenone and 317 to EE 30 µg plus DSG 150 µg.[34] Compared with the EE/DSG group, women who were given 30EE/drospirenone experienced a greater incidence of premenstrual symptoms before the study and a lesser incidence throughout the study. The between-group differences were not statistically significant. More recently, Sangthawan and Taneepanichskul conducted an open-label, 6-cycle study of 99 evaluable women who were randomized to either 30EE/drospirenone or EE 30 µg plus LNG 150 µg.[35] The prevalence of premenstrual symptoms was reduced from 58.0% at baseline to 32.0% at cycle 6 in the 30EE/drospirenone group and rose from

59.2% at baseline to 61.2% at cycle 6 in the EE/LNG group. The between-group difference was statistically significant (P = .005).

Positive results with drospirenone were also noted by Borenstein et al, who analyzed responses of 858 women who completed a survey when initiating 30EE/drospirenone and again after 2 cycles of treatment.[36] Compared with baseline values, 30EE/drospirenone use was associated with significant reductions in premenstrual symptoms (P <.001) and improvement in the women's sense of well-being (P <.05). Finally, Sillem and colleagues conducted an observational study of 1433 women using 30EE/drospirenone, 175 of whom continuously took this OC between 42 and 126 days using an extended regimen.[37] Although it was not designed specifically to evaluate premenstrual symptoms, this study did monitor some symptoms associated with PMS and PMDD. A reduction in edema was experienced by 31% of new users and 40% of the switchers and by 34% of the women receiving the standard regimen compared with 49% of the women receiving the extended regimen (P <.001). A decrease in breast tenderness was reported by 40% of new users and 42% of the switchers and by 40% of the women receiving the standard regimen compared with 50% of the women receiving the extended regimen (P = .046). A reduction in bloating was experienced by 31% of new users and 30% of the switchers and by 29% of the women receiving the standard regimen compared with 37% of the women receiving the extended regimen. **Table 4** summarizes the results of the studies of OCs in women with premenstrual symptoms.

The beneficial results observed in the studies cited should be considered in light of potential side effects associated with OC use in some women, including nausea, breakthrough bleeding, weight gain, breast tenderness, and headache, as well as contraindications with certain coexisting medical conditions. However, as with SSRIs, women can switch to a different OC if side effects make this necessary. Given the known noncontraceptive health benefits of OCs, especially their favorable effects on several premenstrual symptoms, they are strong candidates for patient use.

Figure 2. Antimineralocorticoid Effect of Drospirenone



Source: Adapted from Krattenmacher R. *Contraception.* 2000;62:29-38. Copyright 2000, with permission from Elsevier.

Recent Research Findings for OC Formulations and Regimens

Recently, several studies have assessed the efficacy of a new OC formulation containing EE 20 µg and drospirenone 3 mg (20EE/drospirenone) administered for 24 days, followed by a 4-day hormone-free interval (24/4), in the treatment of PMDD. Yonkers and Foegh reported on a double-blind, placebo-controlled, crossover study of 20EE/drospirenone that consisted of two 3-cycle treatment periods separated by a washout cycle.[38] Of the 64 women, aged 18 to 40 years, with PMDD symptoms who were randomized, 34 women initiated active treatment with 20EE/drospirenone followed by placebo, and 30 women initiated placebo followed by the new OC formulation. The change from baseline with drospirenone/20EE was significantly superior to that with placebo in the DRSP, which was the primary outcome measure, and in the secondary outcome measures (ie, the CGI-Efficacy and CGI-Severity indexes), the self-rated rating scale for premenstrual tension syndrome (PMTS), and the Endicott Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) items 1 to 14 and item 16 (**Table 5**).

More recently, Yonkers and colleagues conducted another double-blind, placebo-controlled, parallel-group study with 20EE/drospirenone used in a 24/4 regimen in women with PMDD symptoms.[39] The study design consisted of 2 run-in menstrual

Table 4. OC Study Results in Women With Premenstrual Symptoms

Study	Agent	Study Type	Results
Bäckström, et al 1992	DSG/EE, LNG/EE (MP and TP)	RCT	Mood scores improved from baseline for all 3 OCs; benefit no different from placebo
Graham and Sherwin 1992	NET/EE	RCT	Decreased premenstrual breast pain and bloating; no beneficial effect on mood
Freeman, et al 2001	Drospirenone/30EE	RCT	Beneficial effect on symptoms of PMDD, primarily appetite and food cravings compared with placebo
Apter, et al 2003	Drospirenone/30EE	Cohort	Decreased incidence and severity of somatic symptoms; increased general well-being compared with baseline
Foidart, et al 2000	Drospirenone/30EE vs DSG/EE	Open label, random	Symptoms lower in women using drospirenone/30EE compared with DSG/EE
Sangthawan and Taneepanichskul 2005	Drospirenone/30EE vs LNG/EE	Open label, random	Symptoms decreased in drospirenone/30EE group and increased in LNG/EE group
Borenstein, et al 2003	Drospirenone/30EE	Cohort	Decreased premenstrual symptoms and increased health-related quality of life
Sillem, et al 2003	Drospirenone/30EE	Cohort	Decreased edema, bloating, and breast tenderness; reductions greater with extended regimen

OC indicates oral contraceptive; DSG, desogestrel; EE, ethinyl estradiol; LNG, levonorgestrel; MP, monophasic; TP, triphasic; RCT, randomized, controlled trial; NET, norethindrone; PMDD, premenstrual dysphoric disorder.
Sources: References 28, 29, 32-37.

cycles (the qualification phase) followed by 3 treatment cycles. Of the 449 women who were randomized, 231 were in the active-treatment group and 218 received placebo. The primary outcome measure was the 21 individual items in the DRSP. When these individual items were grouped into physical, mood, and behavioral symptoms, 20EE/drospirenone was observed to be statistically superior to placebo for all symptom groupings. Improvement occurred as early as cycle 1 and continued during all 3 cycles. In addition, 20EE/drospirenone was significantly more effective than placebo in the observer-rated (P = .023) and self-rated (P = .004) rating scale for PMTS, the observer-rated (P = .004) and self-rated (P = .014) Clinical Global Impression (CGI)-Improvement scales, the 3 functional items of the DRSP (productivity and enhanced enjoyment in social activities, both P = .003; better quality of relationships, P = .0003), and the Q-LES-Q, items 1 to 14 (P = .05). (All P values have normality correction.)

One means of assessing the effects of various agents on premenstrual symptoms is to compare response rates using the same definition. For example, response rate was defined as a score of "much" or "very much" improved on the CGI-Improvement scale in 2 studies of the SSRI sertraline and in the crossover and parallel studies of 20EE/drospirenone 24/4. In a double-blind study, women with PMDD were randomized to a flexible daily dose (50-150 mg/day) of sertraline (n = 121) or to placebo (n = 122).[40] At end point, 62% of the women in the active-treatment group and 34% of the women in the placebo group were classified as responders (P <.001). In a study of intermittent sertraline, the response rate was 58% in the women receiving active treatment and 45% in the placebo group (P = .036).[41] The

response rates in these 4 studies are compared in **Figure 3**.

Counseling Women With Premenstrual Disorders

To provide effective counseling for a woman with bothersome or severe premenstrual symptoms, physicians must be empathetic and caring communicators as well as knowledgeable about this complex area of women's health. It is important to assure the patient that her symptoms are real, with a physiologic basis, and that she is not "crazy."[42] The clinician or other counselor should explain the details of the menstrual cycle to the patient, especially how premenstrual symptoms occur on a cyclic basis. Because patients usually retain only part of the information they receive during a visit, physicians should provide them with interesting and practical educational materials to reinforce what is discussed. Patients should keep a daily symptom diary for at least 2 months to ensure that an accurate diagnosis of PMS or PMDD is achieved. Clinicians or other counselors should provide the diary for prospectively recording the patient's symptoms, making certain that she knows how to use it properly.

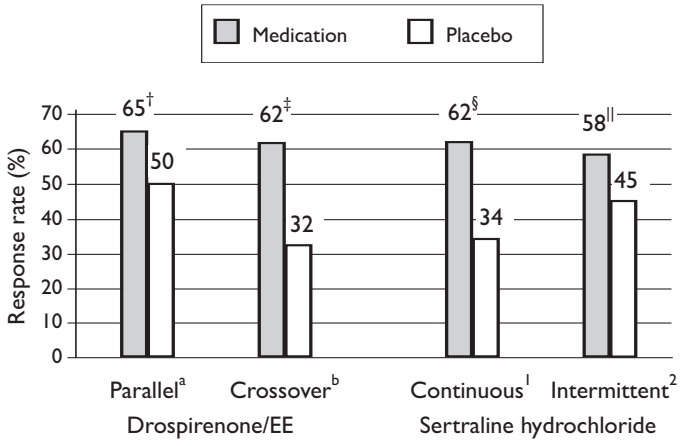
Even before a diagnosis of PMS or PMDD has been made, the physician or counselor can help the patient identify ways to adjust her lifestyle to manage stress that can contribute to premenstrual symptoms. Patients should be encouraged to seek nonthreatening support from family and friends. In addition, they should be instructed about how to initiate lifestyle modifications, such as exercise, dietary changes, appropriate use of vitamin and mineral supplements, and stress management, including relaxation and cognitive behavioral approaches. Available pharmacotherapeutic options should be discussed, keeping in mind the patient's personal preferences, side effects, the cost of the treatments being considered, and her needs. For example, use of an OC might be the best first-line treatment choice for a woman who also has contraceptive needs, which can be reversed if so desired. OCs also have noncontraceptive health benefits of which the patient should be informed. Finally, the patient should be assured that

Table 5. Crossover Study of 20EE/Drospirenone Versus Placebo in Women With Symptoms of PMDD

Outcome Measures	Change From Baseline: 20EE/ Drospirenone	Change From Baseline: Placebo	*P* Value
DRSP items 1-21	–22.94	–10.46	<.0001
CGI			
Efficacy	2.39	1.77	.006
Severity	–1.17	–0.42	.01
PMTS, self-rated	–13.02	–5.60	.01
Q-LES-Q*			
Items 1-14	13.93	6.58	.045
Item 16	0.79	0.33	.044

*Because item 15 deals with medication satisfaction, it does not have a change-from-baseline measure.
EE indicates ethinyl estradiol; PMDD, premenstrual dysphoric disorder; DRSP, Daily Record of Severity of Problems; CGI, Clinical Global Impression; PMTS, rating scale for premenstrual tension syndrome; Q-LES-Q, Endicott Quality of Life Enjoyment and Satisfaction Questionnaire.
Source: Reference 38.

Figure 3. Comparison of Response Rates*



*Response rate was defined in all 4 studies as being very much or much improved on the CGI-Improvement scale.
†$P = .002$.
‡$P = .009$.
§$P \leq .001$.
||$P = .036$.
CGI indicates Clinical Global Impression; EE, ethinyl estradiol.
[a]reference 39; [b]courtesy of Pearlstein T. [Data on file, Berlex corporation]; [1]reference 40; [2]reference 41.
Source: Adapted from Yonkers KA. *JAMA.* 1997;278:983-988 with permission from the American Medical Association.

she can try different therapeutic options until she finds the one most suitable for her.

Conclusion

A variety of approaches have been used to treat premenstrual symptoms. Lifestyle modifications, such as regular physical activity and dietary/nutritional changes, can reduce premenstrual symptoms in some women. Nonpharmacologic options are the easiest forms of treatment to implement, based on appropriate counseling, and can be tried by any woman as she charts her symptoms in a daily symptom record for at least 2 cycles to enable her physician to arrive at a correct diagnosis.

Several pharmacologic options have been shown to be effective and should be evaluated in light of the patient's individual needs and preferences. Some agents, such as particular SSRIs, are effective in many patients but also can be expensive and cause unwanted side effects. Other options, such as GnRH agonists, may be of limited use for similar reasons. Combination OCs are often used to treat premenstrual symptoms, even with a lack of evidence-based support, although new research is revealing more supportive data. OC formulations containing progestin drospirenone have been shown to be effective in treating symptoms of PMDD in controlled studies.

Counseling women about the nature of their symptoms and the variety of treatment possibilities provides much-needed reassurance in many instances and makes it feasible to individualize therapy based on the patient's preferences, treatment cost, and the most likely means of restoring patient comfort, function, and overall health.

REFERENCES

1. ACOG Practice Bulletin. Premenstrual syndrome. *Obstet Gynecol.* 2000;95:end of issue 4.

2. Mortola JF, Girton L, Beck L, Yen SS. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: the calendar of premenstrual experiences. *Obstet Gynecol.* 1990;76:302-307.

3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Washington, DC: American Psychiatric Association; 2000.

4. Steege JF, Blumenthal JA. The effects of aerobic exercise on premenstrual symptoms in middle-aged women: a preliminary study. *J Psychosom Res.* 1993;37:127-133.

5. Ginsburg KA, Dinsay R. Premenstrual syndrome. In: Ransom SB, ed. *Practical Strategies in Obstetrics and Gynecology.* Philadelphia, Pa: WB Saunders Co; 2000:684-694.

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

7. Johnson S. The multifaceted and widespread pathology of magnesium deficiency. *Med Hypotheses.* 2001;56:163-170.

8. Walker AF, De Souza MC, Vickers MF, Abeyasekera S, Collins ML, Trinca LA. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. *J Womens Health.* 1998;7:1157-1165.

9. Freeman EW, Stout AL, Endicott J, Spiers P. Treatment of premenstrual syndrome with a carbohydrate-rich beverage. *Int J Gynaecol Obstet.* 2002;77:253-254.

10. Wyatt KM, Dimmock PW, Jones PW, Shaughn O'Brien PM. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *BMJ.* 1999;318:1375-1381.

11. Budeiri D, Li Wan Po A, Dornan JC. Is evening primrose oil of value in the treatment of premenstrual syndrome? *Control Clin Trials.* 1996;17:60-68.

12. Johnson SR. Premenstrual syndrome therapy. *Clin Obstet Gynecol.* 1998;41:405-421.

13. Preston JD, O'Neal JH, Talaga MC. Antidepressant medications. In: *Handbook of Clinical Psychopharmacology for Therapists.* 3rd ed. Oakland, Calif: New Harbinger Publications, Inc; 2002:163-180.

14. *Physicians' Desk Reference,* 58th ed. Montvale, NJ: Thomson PDR; 2004.

15. Sundström-Poromaa I, Bixo M, Bjorn I, Nordh O. Compliance to antidepressant drug therapy for treatment of premenstrual syndrome. *J Psychosom Obstet Gynaecol.* 2000;21:205-211.

16. Freeman EW, Rickels K, Sondheimer SJ, Polansky M. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: a randomized controlled trial. *Arch Gen Psychiatry.* 1999;56:932-939.

17. Pearlstein TB, Stone AB, Lund SA, Scheft H, Zlotnick C, Brown WA. Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. *J Clin Psychopharmacol.* 1997;17:261-266.

18. Evans SM, Haney M, Levin FR, Foltin RW, Fischman MW. Mood and performance changes in women with premenstrual dysphoric disorder: acute effects of alprazolam. *Neuropsychopharmacology.* 1998;19:499-516.

19. Mortola JF, Girton L, Fischer U. Successful treatment of severe premenstrual syndrome by combined use of gonadotropin-releasing hormone agonist and estrogen/progestin. *J Clin Endocrinol Metab.* 1991;72:252A-252F.

20. Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. *N Engl J Med.* 1998;338:209-216.

21. O'Brien PM, Abukhalil IE. Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase-only danazol. *Am J Obstet Gynecol.* 1999;180(1 pt 1):18-23.

22. Hahn PM, Van Vugt DA, Reid RL. A randomized, placebo-controlled, crossover trial of danazol for the

treatment of premenstrual syndrome. *Psychoneuroendocrinology.* 1995;20:193-209.

23. Danocrine® [package insert]. New York, NY: Sanofi-Synthelabo; 1996.

24. Vellacott ID, Shroff NE, Pearce MY, Stratford ME, Akbar FA. A double-blind, placebo-controlled evaluation of spironolactone in the premenstrual syndrome. *Curr Med Res Opin.* 1987;10:450-456.

25. Wang M, Hammarback S, Lindhe BA, Backstrom T. Treatment of premenstrual syndrome by spironolactone: a double-blind, placebo-controlled study. *Acta Obstet Gynecol Scand.* 1995;74:803-808.

26. Oelkers W. Drospirenone, a progestogen with antimineralocorticoid properties: a short review. *Mol Cell Endocrinol.* 2004;217:255-261.

27. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. *Contraception.* 2000;62:29-38.

28. Graham CA, Sherwin BB. A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. *J Psychosom Res.* 1992;36:257-266.

29. Bäckström T, Hansson-Malmström Y, Lindhe BÅ, et al. Oral contraceptives in premenstrual syndrome: a randomized comparison of triphasic and monophasic preparations. *Contraception.* 1992;46:253-268.

30. Joffe H, Cohen LS, Harlow BL. Impact of oral contraceptive pill use on premenstrual mood: predictors of improvement and deterioration. *Am J Obstet Gynecol.* 2003;189:1523-1530.

31. Yasmin®. *Physicians' Desk Reference,* 59th ed. Montvale, NJ: Thomson PDR; 2005:930-938.

32. Freeman EW, Kroll R, Rapkin A, et al. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *J Womens Health Gend Based Med.* 2001;10:561-569.

33. Apter D, Borsos A, Baumgartner W, et al. Effect of an oral contraceptive containing drospirenone and ethinylestradiol on general well-being and fluid-related symptoms. *Eur J Contracept Reprod Health Care.* 2003;8:37-51.

34. Foidart JM, Wuttke W, Bouw GM, Gerlinger C, Heithecker R. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. *Eur J Contracept Reprod Health Care.* 2000;5:124-134.

35. Sangthawan M, Taneepanichskul S. A comparative study of monophasic oral contraceptives containing either drospirenone 3 mg or levonorgestrel 150 microg on premenstrual symptoms. *Contraception.* 2005;71:1-7.

36. Borenstein J, Yu HT, Wade S, Chiou CF, Rapkin A. Effect of an oral contraceptive containing ethinyl estradiol and drospirenone on premenstrual symptomatology and health-related quality of life. *J Reprod Med.* 2003;48:79-85.

37. Sillem M, Schneidereit R, Heithecker R, Mueck AO. Use of an oral contraceptive containing drospirenone in an extended regimen. *Eur J Contracept Reprod Health Care.* 2003;8:162-169.

38. Yonkers KA, Foegh ML. A new low-dose, drospirenone-containing oral contraceptive (OC) with a new dosing regimen is effective in reducing premenstrual dysphoric disorder (PMDD) [abstract]. *Fertil Steril.* 2004;82:O-255, S102-S103.

39. Yonkers KA, Brown C, Pearlstein TB, et al. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. *Obstet Gynecol.* 2005;106:492-501.

40. Yonkers KA, Halbreich U, Freeman E, et al. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. A randomized controlled trial. Sertraline Premenstrual Dysphoric Collaborative Study Group. *JAMA.* 1997;278:983-988.

41. Halbreich U, Bergeron R, Yonkers KA, Freeman E, Stout AL, Cohen L. Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. *Obstet Gynecol.* 2002;100:1219-1229.

42. Griswold D. Menstruation and related problems and concerns. In: Youngkin EQ, Davis MS. *Women's Health: A Primary Care Clinical Guide.* Upper Saddle River, NJ: Pearson Education, Inc; 2004:145-164.