

# Premenstrual syndrome

## *Evidence-based treatment in family practice*

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### ABSTRACT

**OBJECTIVE** To evaluate the strength of evidence for treatments for premenstrual syndrome (PMS) and to derive a set of practical guidelines for managing PMS in family practice.

**QUALITY OF EVIDENCE** An advanced MEDLINE search was conducted from January 1990 to December 2001. The Cochrane Library and personal contacts were also used. Quality of evidence in studies ranged from level I to level III, depending on the intervention.

**MAIN MESSAGE** Good scientific evidence shows that calcium carbonate (1200 mg/d) and selective serotonin reuptake inhibitors are effective treatments for PMS. The most commonly used therapies (including vitamin B<sub>6</sub>, evening primrose oil, and oral contraceptives) are based on inconclusive evidence. Other treatments for which there is inconclusive evidence include aerobic exercise, stress reduction, cognitive therapy, spironolactone, magnesium, nonsteroidal anti-inflammatory drugs, various hormonal regimens, and a complex carbohydrate-rich diet. Although evidence for them is inconclusive, it is reasonable to recommend healthy lifestyle changes given their overall health benefits. Progesterone and bromocriptine, which are still widely used, are ineffective.

**CONCLUSION** Calcium carbonate should be recommended as first-line therapy for women with mild-to-moderate PMS. Selective serotonin reuptake inhibitors can be considered as first-line therapy for women with severe affective symptoms and for women with milder symptoms who have failed to respond to other therapies. Other therapies may be tried if these measures fail to provide adequate relief.

### RÉSUMÉ

**OBJECTIF** Évaluer la validité des preuves à la base des différents traitements du syndrome prémenstruel (SPM) et, à partir de cette analyse, formuler des directives pratiques pour le traitement de cette affection en médecine familiale.

**QUALITÉ DES PREUVES** Une recherche avancée a été effectuée dans Medline entre janvier 1990 et décembre 2001. On a également eu recours à la Cochrane Library et à des contacts personnels. Dans les études retenues, les preuves étaient de niveau I à III selon le type d'intervention utilisée.

**PRINCIPAL MESSAGE** L'efficacité du carbonate de calcium (1200 mg/d) et des inhibiteurs sélectifs du recaptage de la sérotonine dans le traitement du SPM repose sur des données scientifiques solides. Les traitements les plus fréquemment utilisés (incluant la vitamine B<sub>6</sub>, l'huile d'onagre et les contraceptifs oraux) ne sont pas fondés sur des données probantes. Les autres traitements pour lesquels les preuves ne sont pas concluantes incluent les exercices aérobies, la réduction du stress, la thérapie cognitive, la spironolactone, le magnésium, les anti-inflammatoires non stéroïdiens, divers traitements hormonaux et un régime alimentaire riche en glucides complexes. Malgré l'absence de preuves concluantes, l'adoption d'habitudes de vie plus saines peut être préconisée, vu les avantages globaux d'un tel changement. Même si la progestérone et la bromocriptine sont largement utilisées, elles ne sont pas efficaces.

**CONCLUSION** Le carbonate de calcium devrait être recommandé comme traitement de première ligne pour les femmes qui présentent un SPM léger à modéré. En présence de symptômes affectifs sévères ou de symptômes moins sévères ne répondant pas aux autres formes de traitement, l'utilisation d'inhibiteurs sélectifs du recaptage de la sérotonine peut être envisagée. Si ces mesures ne procurent pas un soulagement adéquat, d'autres traitements peuvent être essayés.

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*Cet article a fait l'objet d'une évaluation externe.*

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**P**remenstrual syndrome (PMS) is a common cause of substantial psychological and physical distress for women during their reproductive years. Forty percent of women have symptoms that are severe enough to disrupt some aspect of their daily lives; 5% are incapacitated by their symptoms.<sup>1,2</sup>

Despite the magnitude of this problem, a lot of confusion exists in medical and lay communities alike about what is and is not effective for treatment of PMS. This in part reflects the fact that the cause of PMS is still unknown, although several theories have been proposed including hormonal imbalances, micronutrient deficiencies, and neuroendocrine dysfunction.<sup>2</sup> A range of treatments currently available reflect this theoretical diversity.<sup>2</sup> Consequently, it has become increasingly difficult to counsel patients on what is safe and effective for treatment of PMS.

Despite inherent challenges, family physicians are in an ideal position to diagnose and treat this common but often overlooked condition. This study aimed to apply the principles of evidence-based medicine to derive a set of recommendations for treating PMS in family practice.

#### Quality of evidence

Several information sources were used including an advanced MEDLINE search, Cochrane Library database, and personal contacts. The advanced MEDLINE and Cochrane Library databases were searched first to determine the strength of evidence arising from clinical trials for various therapies. The MEDLINE search was limited to English articles from January 1990 to December 2001. Premenstrual syndrome and synonymous terms identified by the thesaurus were cross-matched with the MeSH headings diet therapy, drug therapy, prevention and control, rehabilitation, and therapy. These terms were then cross-matched with the MeSH heading "review" to help identify any systematic reviews already published on the topic. Individual searches were performed on identified treatments using the specific treatments as MeSH headings. Appropriate articles were obtained and critically appraised.

Search of the Cochrane Library database obtained review protocols on the use of vitamin B, evening primrose oil, and selective serotonin reuptake inhibitors (SSRIs) for treatment of PMS. Primary authors of the reviews<sup>3-5</sup> were contacted, and they generously

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provided their preliminary conclusions along with a list of supporting references.

Possible treatments were categorized as one of the following: effective, inconclusive evidence, and ineffective. Evidence for effective treatments came from good-quality randomized controlled trials (level I evidence) that showed unequivocally positive benefits of treatment. Evidence was categorized as inconclusive if studies showed positive benefits but had methodologic limitations, including small study size, few trials, lack of true control groups, and questionable clinical significance of positive findings (level II and III evidence). Finally, treatments were categorized as ineffective if good-quality studies showed no significant benefits, if studies showed that the risks and costs clearly outweighed potential advantages, or if studies had serious methodologic flaws that invalidated any positive findings.

#### Effective treatments

**Calcium.** Thys-Jacobs et al<sup>6</sup> conducted a large multi-centre trial (12 sites) involving 466 women diagnosed with moderate-to-severe PMS. Women were randomized to a calcium carbonate (1200 mg/d) or placebo group. Women recorded their symptoms daily over three cycles. Compliance with treatment was measured. Main outcome measure was a 17-parameter complex score. No significant reduction in symptoms was reported after the first cycle. By the third cycle, however, women reported a 48% reduction in their total symptom scores ( $P < .001$ ) compared with baseline. In addition all four-symptom factors (negative affect, fluid retention, cravings, pain) were significantly reduced by the third cycle. Given the study's sound methodology, large size, and size of the treatment effect, these findings provide good evidence for the effectiveness of calcium carbonate as a treatment for PMS. Calcium is also relatively inexpensive and is important in preventing osteoporosis; therefore, it is recommended as first-line treatment for PMS.

**Selective serotonin reuptake inhibitors.** Another significant advance in the treatment of PMS is the use of SSRIs. Premenstrual syndrome has been linked with dysfunctional serotonin metabolism, and experimental evidence suggests that hormonal fluctuations do affect central serotonin levels.<sup>7</sup> Dimmock et al<sup>8</sup> recently published a comprehensive systematic review on the topic including a meta-analysis involving 15 randomized controlled trials. Results of the meta-analysis strongly support the effectiveness of SSRIs in treatment of PMS. Interestingly, the study

group also found no difference in effectiveness between continuous and intermittent therapy during the luteal phase. The effectiveness of SSRIs administered intermittently has been attributed to differences in receptor sites involved in affective and PMS disorders. The doses used for PMS also tend to be lower than those used for depression. Consequently the incidence of side effects tends to be lower as well.<sup>9</sup>

Use of SSRIs is not without drawbacks, however. A host of reported side effects include headache, nervousness, insomnia, drowsiness, fatigue, sexual dysfunction, and gastrointestinal complaints. The SSRIs are also relatively expensive, especially brand-name formulations. Nonetheless, given their proven efficacy, they are recommended, particularly for women with severe affective symptoms for whom other measures have been ineffective.

#### **Inconclusive evidence**

The largest number of treatments had inconclusive evidence. For this diverse group of therapies, evidence supporting effectiveness ranges from likely effective to likely ineffective. Consequently, readers are encouraged to draw their own conclusions about the role of these therapies for management of individual patients.

**Diet.** Dietary restrictions are often recommended to help alleviate the physical and psychological symptoms of PMS. The most common dietary recommendations are to restrict sugar and increase consumption of complex carbohydrates.<sup>10</sup> Of these measures, only an increase in carbohydrate consumption has been studied in a randomized controlled trial. One small trial involving 24 women found that women who consumed a carbohydrate-rich beverage daily during the late luteal phase reported fewer mood changes in the hours following consumption than women who consumed an isocaloric beverage.<sup>11</sup> While the scientific evidence is very limited, given the overall health benefits of a healthy diet rich in complex carbohydrates, it would be reasonable to include this diet as part of initial management of PMS.

**Aerobic exercise.** Women who have PMS are often encouraged to increase their activity level. It has been hypothesized that exercise (particularly aerobic varieties) increases endorphin levels, which in turn improves mood.<sup>10</sup> Several descriptive studies indicate that women who exercise regularly have fewer PMS symptoms than sedentary women.<sup>12</sup> Another study has shown that previously sedentary women as

well as women who already exercise regularly who increase their activity levels report fewer PMS symptoms.<sup>13</sup> Finally, one randomized controlled unblinded trial involving 23 women found that women randomized to an aerobic exercise group did report fewer PMS symptoms after three cycles than women who were in a nonaerobic exercise group.<sup>14</sup> While most of the studies are not randomized or are descriptive in nature, the cumulative evidence suggests that aerobic exercise is likely to reduce PMS symptoms. Given the associated benefits of exercise, it seems reasonable to recommend an aerobic exercise program to help alleviate PMS symptoms.

**Psychological approaches.** Epidemiologic evidence suggests that increased stress levels aggravate PMS symptoms.<sup>15</sup> Various trials suggest that relaxation and cognitive therapies help alleviate PMS symptoms. In one trial, women were randomized to a group instructed to practise a relaxation technique for 20 minutes a day or to 20 minutes in a "quiet time" group. The women in the relaxation response group reported fewer PMS symptoms than women in the "quiet time" group.<sup>16</sup>

In another study, women who reported "severe" PMS symptoms were randomized to groups learning cognitive-behavioural coping skills, "nonspecific behavioural" techniques, and a waiting list. Women in the cognitive-behavioural group reported significantly fewer PMS symptoms than women in the other groups immediately following treatment and at 9-month follow up.<sup>17</sup> In another study, both cognitive-behavioural and information-focused therapy led to substantial reductions in symptoms.<sup>18</sup> These studies involved relatively small numbers and often lacked "true" control groups; their cumulative results suggest that various psychological approaches including instruction on relaxation techniques, cognitive-behavioural strategies, and information on ways to relieve PMS symptoms.

**Pyridoxine (vitamin B<sub>6</sub>).** Pyridoxine, or vitamin B<sub>6</sub>, is one of the most widely used and probably the most controversial treatment for PMS. Vitamin B<sub>6</sub> is believed to correct a deficiency in the hypothalamic-pituitary axis.<sup>10</sup> Vitamin B<sub>6</sub> is a cofactor in the synthesis of tryptophan and tyrosine, which are the precursors of serotonin and dopamine, respectively.<sup>19</sup> Theoretically, low levels of vitamin B<sub>6</sub> lead to high levels of prolactin that in turn produce the edema and psychological symptoms associated with PMS.<sup>3</sup>

There have been at least 24 trials on use of vitamin B<sub>6</sub> for treatment of PMS.<sup>4</sup> Recently, Wyatt et al<sup>4</sup>

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performed a systematic review and meta-analysis on the topic. They included the results of nine randomized controlled trials in the meta-analysis. Overall quality of the trials was considered to be poor. In addition the trials were quite heterogeneous in terms of their inclusion and exclusion criteria as well as the outcome measures examined, which makes interpretation of the findings difficult. The results of the meta-analysis did show "some" benefit of treatment with vitamin B<sub>6</sub> (odds ratio 2.12, confidence interval 1.8 to 2.48). Their overall conclusions, however, were that available data suggested some benefit, but there was insufficient evidence of high enough quality to confidently recommend vitamin B<sub>6</sub> for treatment of PMS.

Vitamin B<sub>6</sub> can also cause substantial toxicity and unpleasant side effects. Taken at doses as low as 500 mg daily, it can produce a progressive sensory ataxia and can also cause gastrointestinal side effects, particularly nausea.<sup>20</sup>

**Evening primrose oil.** Evening primrose oil is used extensively to alleviate PMS symptoms. Evening primrose oil contains two essential fatty acids: linoleic and  $\gamma$ -linolenic. Some experts suggest that women with PMS are deficient in  $\gamma$ -linolenic acid, which is necessary for prostaglandin formation.<sup>20</sup> A large body of literature explores this topic; however, the poor quality and methodologic limitations of the studies have made it difficult to draw any firm conclusions about the efficacy of evening primrose oil.<sup>21</sup> Buderer et al<sup>21</sup> systematically reviewed clinical trials done before 1995. Only two of the seven studies were judged to be of high methodologic quality, and these failed to show any significant benefits.

Evening primrose oil is generally well tolerated, but occasionally it can produce nausea, dyspepsia, and headache. Long-term use can be associated with increased risk of inflammation, thrombosis, and immunosuppression.<sup>20</sup> Finally, evening primrose oil is relatively expensive, and current scientific evidence does not support its general use for treatment of PMS.

**Combination oral contraceptives and progestins.** Combination oral contraceptives (OCPs) are also widely used to treat PMS. Despite their popularity, only one randomized controlled trial has compared an OCP (triphasic) to placebo.<sup>22</sup> This trial involved 82 women, of whom only 45 completed the study. There was some improvement in physical symptoms but not mood changes. Several descriptive studies have also looked at the effects of OCPs on mood and PMS and have had very mixed results.<sup>23,24</sup>

It seems counterintuitive that a treatment to suppress ovulation does not also alleviate PMS symptoms. There is some evidence, however, that it is not ovulation per se that underlies PMS, but rather the brain's response to fluctuating hormone levels in susceptible women that triggers symptoms.<sup>2</sup> Because they are associated with changes in hormonal levels, it is not surprising that OCPs can cause similar symptoms. The progestin to estrogen ratio is also probably important in development of negative mood changes. If OCPs are used to treat PMS, a monophasic preparation should theoretically be given continuously.<sup>2</sup>

In another double-blind crossover study involving 48 women with PMS,<sup>25</sup> subjects were given medroxyprogesterone (MPA) or norethisterone (NET) (15 mg daily for 21 days). By the end of the second treatment cycle, women in the MPA group showed significant improvement in their overall psychological scores, whereas women in the NET group showed no difference over placebo. The rate of side effects in the MPA group was significantly higher; 74% of women reported breakthrough bleeding in the MPA group compared with 22% in the NET group.

**Other therapies.** Other therapies used to treat PMS include magnesium, nonsteroidal anti-inflammatory drugs, spironolactone, and various hormonal regimens to suppress ovulation. **Table 1** summarizes the studies and level of evidence for these additional therapies.<sup>26-35</sup>

#### **Ineffective treatments**

**Progesterone and progestogens.** Progesterone has been widely publicized in the lay literature as a treatment for PMS.<sup>10</sup> Treatment with high doses of "natural" progesterone vaginally became popular in the 1970s after publication of many case reports in the lay press, none of which had any true controls.<sup>36</sup> Since then, several randomized controlled trials have failed to show any benefit from topical or oral micronized progesterone over placebo.<sup>37-40</sup> Similarly, a recent comprehensive systematic review and meta-analysis on the topic failed to show any evidence supporting continued use of progesterone in treatment of PMS.<sup>41</sup> Topical progesterone is also expensive. Given the lack of efficacy and the expense, progesterone cannot be recommended as a treatment for PMS.

**Bromocriptine.** Another theory popular in the 1970s was that PMS was caused by increased levels of, or an increased sensitivity to, prolactin.<sup>10</sup> Consequently, bromocriptine was often prescribed

**Table 1. Characteristics of studies for PMS therapies for which there is inconclusive evidence for effectiveness**

**MAGNESIUM**

Facchinetti et al (1991)<sup>26</sup>

- **Design:** Double-blind RCT; all women received magnesium during last cycle
- **Participants:** 32 eligible women; four drop-outs (one for pregnancy, one lost to follow up, two for side effects)
- **Diagnosis:** Moos menstrual distress questionnaire; 2-month baseline
- **Inclusion:** Severe PMS affecting social and work activity
- **Exclusion:** OCP use, kidney or hepatic disease, or concurrent psychiatric diagnosis
- **Intervention:** Magnesium in divided doses (360 mg daily; 120 mg tid) for two cycles in treatment group and on second cycle in placebo group
- **Results:** Significant improvement in affective, pain, and “arousal” symptoms and overall Moos questionnaire scores
- **Comments:** Would results be similar in women with less severe symptoms? How clinically significant are results?

Walker et al (1998)<sup>27</sup>

- **Design:** Controlled crossover RCT (Was it double blinded?)
- **Participants:** Volunteers recruited from a university community; 38 of 54 recruited subjects completed the study. Reasons for withdrawal not obtained
- **Diagnosis:** Retrospective questionnaire data on 27 symptoms
- **Inclusion:** Women who had 30% or more difference in premenstrual and postmenstrual scores on questionnaire
- **Exclusion:** No restrictions placed on OCP use, medical conditions, or medication use
- **Intervention:** Magnesium (200 mg daily or placebo) for two menstrual cycles; switch over for two cycles
- **Results:** No difference in symptoms after 1 month. Reduction in symptoms related to fluid retention after 2 months in magnesium group compared with placebo ( $P = .009$ ). No significant differences found for other symptom groups
- **Comment:** Failure to explore reasons for withdrawal and any differences in characteristics between groups could have significantly affected results. Inclusion of women using OCPs ( $n = 12/36$ ) could have also affected results
- **Bottom line:** Magnesium could be of some benefit in treatment of PMS, particularly for fluid retention. Generally considered safe at doses up to 483 mg/d in healthy adults but should be avoided among those with serious heart and kidney disease<sup>20</sup>

**VITAMIN E**

London et al (1987)<sup>28</sup>

- **Design:** Double-blind RCT
- **Participants:** 46 eligible minus five drop-outs (four of five in placebo group)
- **Diagnosis:** Apparently based on screening interview over telephone
- **Inclusion:** Women with diagnosis based on questionnaire and baseline measurements
- **Exclusion:** No concurrent use of vitamins, medications, or drugs. Positive response on Minnesota multiphasic inventory
- **Intervention:** 400 IU of vitamin E for three therapy cycles
- **Results:** Improvement in most affective and cognitive symptoms from 28% to 42%, but improvement did not reach statistical significance ( $P < .058$  to  $.085$ )
- **Comment:** Lack of clear diagnostic criteria for PMS severely limits generalizability. Size of study also limits ability to detect treatment effect (type I error)
- **Bottom line:** Supporting data for vitamin E are very limited. More studies are needed to confirm effectiveness

**SPIRONOLACTONE**

O'Brien et al (1979)<sup>29</sup>

- **Design:** Double-blind crossover RCT
- **Participants:** 28 women recruited from hospital staff (England)
- **Diagnosis:** Self-reported history of PMS
- **Exclusion:** History of hepatic, renal, or gynecologic diseases; hypertension; use of OCPs
- **Intervention:** Spironolactone (25 mg qid or placebo on days 18 to 26 of menstrual cycle for four cycles (two treatment and two placebo cycles per patient)

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- **Results:** Main outcome measure was aldosterone and progesterone levels; premenstrual mood index consisted of a visual analogue scale for eight affective symptoms. Treatment resulted in improvement in mood for 80% of treated cycles ( $P < .5$  for "asymptomatic" women and  $P < .005$  for "symptomatic" women)
- **Comment:** Difficult to translate statistical findings into size of treatment effect, particularly as women without PMS apparently benefited from treatment. Did not assess somatic symptoms. Generalizability also an issue because of absence of diagnostic criteria and lack of demographic information on participants

#### Vellacott et al (1987)<sup>30</sup>

- **Design:** Double-blind RCT
- **Participants:** 63 women enrolled minus four drop-outs (four from placebo, three from treatment group; reasons for withdrawal not stated)
- **Diagnosis:** Self-reported history of PMS for minimum of 6 months
- **Inclusion:** Women ages 16 to 45 with more than 6-month history of PMS symptoms
- **Exclusion:** Pregnancy, chronic diseases, psychiatric illness, use of OCPs during preceding 6 months, hypersensitivity to treatment drug
- **Intervention:** Spironolactone (100 mg) or placebo for two consecutive cycles from day 12 of cycle to first day of bleeding
- **Results:** Improvement was noted in eight of 12 symptoms. Approximately twice as many women in treatment group reported improved mood by the second treatment cycle, but only general bloating reached statistical significance ( $P < .001$ ). On global assessment, twice as many women in treatment group showed improvement, but  $P$  value reached only .054
- **Comment:** Study showed trend toward improvement in most physical and affective symptoms, but might not have had sufficient power to confirm these findings. Quite marked improvement was noted in general swelling
- **Bottom line:** Spironolactone could be of some benefit in treating PMS, particularly symptoms related to fluid retention. Larger studies are needed to confirm this finding, however

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## NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

#### Wood and Jakubowicz (1980)<sup>31</sup>

- **Design:** Double-blind crossover RCT
- **Participants:** 39 women ages 25 to 50 recruited on radio program
- **Diagnosis:** Based on telephone interview?
- **Exclusion:** Taking OCPs
- **Intervention:** Mefenamic acid, 250 mg tid, at "start of PMS symptoms." One baseline, treatment, and placebo cycle each
- **Results:** Main outcome measure was daily symptom ratings for 18 symptoms. Mefenamic acid improved general symptoms ( $P < .002$ ). Symptoms most affected included tension, irritability, depression, and pain
- **Comment:** Generalizability difficult to assess, given questionable diagnostic criteria. Also could be difficult to replicate treatment effects at particular times in women's cycles

#### Mira et al (1986)<sup>32</sup>

- **Design:** Double-blind crossover RCT for six cycles (three 2-month placebo and treatment cycles)
- **Participants:** 19 women referred to PMS clinic with minimum 2 years of symptoms. Four women withdrew (two placebo, two treatment, for unknown reasons)
- **Diagnosis:** 3-month baseline; daily questionnaire (22 questions on mood, 41 on symptoms)
- **Exclusion:** Psychiatric history, serious medical conditions, OCPs
- **Intervention:** Mefenamic acid, 250 mg tid, starting day 16 of cycle to day 3 of menses
- **Results:** Main outcome measure was daily symptom record. Significant improvement in fatigue ( $P < .001$ ), general malaise ( $P < .001$ ), headache ( $P < .005$ ), irritability ( $P < .01$ ), and depressed mood ( $P < .01$ ). No improvement in breast symptoms, swelling, food cravings, agitation, or poor concentration
- **Comment:** Well designed but small trial. Mefenamic acid effective only for specific symptoms

#### Facchinetti et al (1989)<sup>33</sup>

- **Design:** RCT (unclear whether blinded)
- **Participants:** 34 patients with PMS for 2 to 7 years; six patients dropped out (reasons unclear, from which groups unspecified)
- **Diagnosis:** Criteria not stated
- **Exclusion:** Women with other medical or gynecological treatments, receiving OCPs, taking other treatments for PMS within 3 months of start of study
- **Intervention:** Naproxen sodium, 550 mg bid, from 7 days before menses to day 4 of menstrual cycle. Group A: 2-month baseline, 3-month placebo, 3-month active treatment. Group B: 2-month baseline, 6-month active treatment
- **Results:** Outcome measure was Moos menstrual questionnaire during baseline period and third and sixth month (minimum 10 times per cycle). Improvement in "pain," "arousal," "negative affect," and "behavioural changes" clusters in patients taking active treatment during first 3 months. (Measured differences in symptoms during PMS and menstrual phase with intermenstrual symptoms)

- **Comment:** Paper was confusing and difficult to follow. Absence of clear diagnostic criteria and some inconsistencies between text and data call the validity of this study into question
- **Bottom line:** NSAIDS, particularly mefenamic acid, could be effective in alleviating depression and many general somatic symptoms (except swelling) during the luteal phase. This finding would be particularly helpful for women who also have hypermenorrhea and dysmenorrhea

## HORMONAL REGIMENS

### Watson et al (1989)<sup>34</sup>

- **Design:** Double-blind crossover RCT: 3-month active and placebo phases of treatment
- **Participants:** 40 women from PMS clinic with "severe" symptoms (>1 year). Five women withdrew because of side effects: two placebo, three active treatment phases
- **Diagnosis:** Prospective charting of symptoms for 2 months
- **Exclusion:** Irregular cycles, gynecological disease, use of OCPs or other medications
- **Intervention:** 100- $\mu$ g estradiol patch twice weekly (possible suppression of ovulation effect) or placebo patches. All women received norethisterone (5 mg/d) from day 19 to day 26 to bring on withdrawal bleed
- **Results:** Main outcome measure was daily ratings on Moos menstrual distress questionnaire. Significant improvement in six of eight symptom clusters (pain, concentration, negative affect, fluid retention, autonomic, behavioural) by at least 60% ( $P \leq .001$  or  $\leq .05$ )
- **Comment:** Might not be able to generalize findings to women with less severe symptoms. Cyclic progesterone could exacerbate PMS symptoms, especially during placebo phase of treatment

### Smith et al (1995)<sup>35</sup>

- **Design:** Non-blinded RCT for eight cycles. No placebo group
- **Participants:** 107 women referred with "severe" symptoms
- **Diagnosis:** Prospective charting of symptoms for one or two cycles
- **Intervention:** Women randomized to one of four groups: 100- $\mu$ g or 200- $\mu$ g estradiol patch for 2 weeks with dydrogesterone (10 mg) or medroxyprogesterone (10 mg), from day 17 to day 26
- **Results:** Reduction in all symptoms in both groups compared with baseline, by at least 4 months in the groups using 100- $\mu$ g and 200- $\mu$ g estradiol patches. More women in the higher estrogen group dropped out or were dissatisfied with treatment; 75% of women reported side effects. Only 57% and 43% of women in the low- and high-dose estradiol groups were satisfied with treatment at 8 months
- **Comment:** Lower dose of estradiol was as effective and better tolerated than higher doses, but was still associated with a substantial number of side effects attributed to progesterone, or estrogen effects and skin irritation
- **Bottom line:** Hormonal regimens could be of some benefit in treating PMS, particularly for women with severe symptoms. Treatment is associated with several unacceptable side effects, however. Hormonal measures could particularly benefit perimenopausal women who are contemplating hormone replacement therapy

OCPs—oral contraceptives, PMS—premenstrual syndrome, RCT—randomized controlled trial.

to women suffering from PMS, particularly those with substantial fluid retention and breast tenderness. An extensive review by Andersch,<sup>42</sup> which analyzed 14 randomized controlled trials until 1982, found no improvement in general PMS symptoms compared with placebo. One exception was severe cyclic mastalgia, for which bromocriptine might be effective.<sup>42</sup> A more recent double-blind randomized crossover trial involving 21 women did show some improvement in abdominal bloating and mastalgia, but no effect on emotional symptoms.<sup>43</sup> Bromocriptine is also expensive and has several side effects. Consequently its use cannot be recommended for general treatment of PMS.

## Recommendations

How should family physicians interpret all this information? While the strength of evidence is central in making rational management decisions, other factors

must also be taken into account. These include treatment costs, potential health benefits, adverse effects, individual risk factors, comorbidity, and severity of symptoms. In arriving at a set of guidelines, I evaluated the strength of evidence in the context of these other factors (Table 2). Physicians must judge for themselves how to translate these guidelines into individual management plans for patients.

## Conclusion

Optimal management of PMS requires more than scientific knowledge. It also requires a systematic approach to screening and strong patient-centred communication skills to determine patients' ideas about their symptoms and how they affect their lives. Personal relationships with patients are also important in negotiating treatment plans that are acceptable to patients, particularly where lifestyle changes are concerned. Finally, continuity of care is essential, as it can take months before any improvement is noted. ❁

**CME**

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## Premenstrual syndrome

**Table 2. Management of premenstrual syndrome in family practice****MILD TO MODERATE PMS****FIRST-LINE TREATMENTS:** Begin with calcium carbonate (1200 mg/d)\*; consider adding*LIFESTYLE CHANGES:* Aerobic exercise, stress reduction, healthy diet rich in complex carbohydrates during luteal phase of cycle*PSYCHOLOGICAL APPROACHES:* Relaxation training, patient education on PMS, teach positive coping techniques

(If first-line treatment is ineffective after three cycles, consider adding second-line treatment\*)

**SECOND-LINE TREATMENTS:** Tailor treatment to symptom**SWELLING†**

- Spironolactone (100 mg/d by mouth); start at midcycle (days 12 to 16)
- Magnesium (360 mg/d)†

**PAIN:** TREAT WITH NSAIDS†

- Mefenamic acid (500 mg tid) starting as early as day 16 of cycle, or start of PMS symptoms†
- Naproxen sodium (550 mg bid) starting 1 week before menses start; continue for the first few days of bleeding†

**PERIMENOPAUSAL SYMPTOMS:** Treat with hormonal therapies†

- Estradiol patch (0.1- or 0.2-µg patches, 2 weekly) plus cyclic medroxyprogesterone acetate (5 mg from days 17 to 26)†

**AFFECTIVE SYMPTOMS:** Treat with SSRIS (2-month trial for all SSRIS during luteal phase only. Switch to daily administration if response inadequate)†

- Fluoxetine (20 mg daily by mouth)
- Sertraline (50 mg daily by mouth)
- Paroxetine (20 mg daily by mouth)
- Fluvoxamine (50 mg daily)

**MASTALGIA:** Treat with evening primrose oil (500 mg three to four times daily)†**CONTRACEPTION:** Use oral contraceptives (monophasic preparations on a continuous basis)†**GENERAL**

- Methylprogesterone acetate (15 mg daily from days 1 to 21)†
- Vitamin B<sub>6</sub> (50 mg once or twice daily)†
- Vitamin E (400 IU daily)

**SEVERE PMS:** TREAT SEVERE AFFECTIVE SYMPTOMS WITH SSRIS; CONSIDER ADDING AT THE OUTSET IN ADDITION TO FIRST-LINE TREATMENTS DESCRIBED ABOVE\***REFERRAL:** If above measures are ineffective, think about referral for consideration of treatment with danazol or gonadotrophin-releasing hormone

NSAIDS—non-steroidal anti-inflammatory drugs, PMS—premenstrual syndrome, SSRIS—selective serotonin receptor inhibitors.

\*Good evidence for effectiveness is based on well designed, large randomized controlled trials.

†Some evidence for effectiveness exists, but strength of evidence is limited by one or more of the following: small study size, lack of true control groups, methodologic problems, and questionable clinical significance of positive statistical findings.

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**Competing interests**

None declared

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**Editor's key points**

- Because premenstrual syndrome (PMS) presents with a variety of symptoms and signs, and its actual pathology is obscure, an individual approach to assessment and management is recommended for each woman.
- Good, level I evidence supports using calcium carbonate and selective serotonin reuptake inhibitors.
- Less conclusive evidence suggests some relief with aerobic exercise, high-complex carbohydrate diets, stress reduction, spironolactone for swelling, magnesium, nonsteroidal anti-inflammatory drugs, hormone treatment, evening primrose oil, oral contraceptives, and vitamins B<sub>6</sub> and E.
- Progesterone and bromocriptine have not been shown to be helpful and should be avoided due to cost and potential complications.

**Points de repère du rédacteur**

- Étant donné que les signes et symptômes du syndrome prémenstruel (SPM) sont très variés et que la pathologie de cette affection est mal connue, il est recommandé d'utiliser une approche personnalisée dans l'évaluation et le traitement de ce syndrome.
- Il y a des preuves solides de niveau I en faveur de l'usage du carbonate de calcium et des inhibiteurs sélectifs du recaptage de la sérotonine.
- Il existe aussi des preuves moins probantes que l'exercice aérobique, les régimes à forte teneur en glucides complexes, la réduction du stress, la spironolactone en cas d'œdème, le magnésium, les anti-inflammatoires non stéroïdiens, certains traitements hormonaux, l'huile d'onagre, les contraceptifs oraux et les vitamines B<sub>6</sub> et E procurent un certain soulagement.
- L'utilité de la progestérone et de la bromocriptine n'a pas pu être démontrée, et ces médicaments devraient donc être évités en raison de leur coût et des complications possibles.

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