

Brice A. Labruzzo, PharmD
University of Louisiana at
Monroe College of Pharmacy/
Baton Rouge General Family
Health Center, Baton Rouge

Robert Chasuk, MD
Baton Rouge General Family
Medicine Residency Program,
Baton Rouge

**Susan Kendall, PhD,
MS (LIS)**
Michigan State University
Libraries, East Lansing



**Long-term use
of pyridoxine in
doses >200 mg/d
can cause
neuropathy.**

Q / Which complementary therapies can help patients with PMS?

EVIDENCE-BASED ANSWER

A / **CHASTEBERRY TREE AND CALCIUM** have demonstrated efficacy and safety in treating symptoms of premenstrual syndrome (PMS) (strength of recommendation [SOR]: **A**, randomized controlled trials [RCTs]). Pyridoxine and saffron may be effective, but high doses of pyridoxine can cause neuropathy (SOR: **B**, RCT and meta-analysis of lower-quality studies).

Insufficient evidence exists to recommend magnesium. St. John's wort and evening primrose oil aren't effective for managing PMS (SOR: **B**, inconsistent or limited quality patient-oriented evidence). No evidence was found to support black cohosh or vitamin E.

statistically significant differences were noted between the 2 groups. Chasteberry tree was well tolerated; most adverse effects occurred in patients receiving fluoxetine. The most frequent adverse effects with chasteberry tree were nausea in 5 patients and headache in 4.³

Symptoms decrease significantly after 3 calcium treatment cycles

Two RCTs (33 and 466 patients) comparing 1000 and 1200 mg of calcium with placebo found a significant decrease in PMS symptoms after 3 treatment cycles.^{4,5} Calcium improved negative affect, water retention, food cravings, and pain. In the first study, 73% of patients preferred taking calcium, compared with 15% who preferred placebo.

The second study found that, by the third treatment cycle, patients taking calcium had an overall 48% reduction in total symptom scores, compared with a 30% reduction in the control group. The most common adverse effects were headache, rhinitis, and nonspecific pain.

Watch out for neuropathy with high doses of pyridoxine

A meta-analysis of pyridoxine in doses from 50 to 600 mg per day for PMS included 9 RCTs. Relative to placebo, pyridoxine improved PMS symptom scores (odds ratio=2.32, 95%

Evidence summary

A double-blind RCT comparing chasteberry tree with placebo in 170 patients found a decrease in self-reported PMS symptom scores and an increase in response rate (defined as a 50% reduction in symptoms)—52% vs 24%—in the intervention group (number needed to treat [NNT]=3.5). Patients taking chasteberry tree had 1 occurrence of multiple abscesses and 1 of urticaria.¹

A prospective, open-label study of chasteberry tree for PMS symptoms in 43 patients found a 42% decrease in self-assessed PMS symptom scores, with the greatest improvement in pain, behavior changes, negative feelings, and fluid retention. No serious adverse events occurred.²

A third study comparing chasteberry tree with fluoxetine in 19 patients found a decrease in premenstrual symptom scores for both fluoxetine (13 of 19 patients) and chasteberry tree (11 of 19 patients). No

CONTINUED ON PAGE 559

CONTINUED FROM PAGE 552

confidence interval, 1.95-2.54). The overall quality of studies was poor, however, with few subjects, widely varying doses, and different outcome measurements.⁶

Two subsequent RCTs of 40 and 96 patients that weren't included in the meta-analysis failed to demonstrate reduced premenstrual symptoms.^{7,8} Long-term use of pyridoxine in doses >200 mg/d can cause neuropathy.

Saffron shows promise in small study

A recent double-blind RCT evaluated the effect of 2 cycles of treatment with saffron (*Crocus sativus L*), 30 mg twice daily, on PMS symptoms in 50 patients. Nineteen patients in the saffron group showed a response, defined as 50% reduction in symptom severity, compared with 2 patients in the placebo group (NNT=2). The study found no statistically significant difference in frequency of adverse effects.⁹

Evidence for magnesium is sparse

Two RCTs comparing magnesium with placebo had low precision because of small numbers and short treatment duration.^{10,11} The first (N=28) demonstrated reduced total Moos Menstrual Distress Questionnaire scores.¹⁰ The second study reported a decrease in fluid retention symptoms by 2 points on an 80-point

scale ($P<.009$) at 2 months, but no difference in total score.¹¹

A further study, begun as an open trial of magnesium infusion for premenstrual dysphoric disorder (N=6), found a dramatic reduction in mood symptom scores. After converting to a randomized, blinded design (N=10), no difference was found compared with placebo.¹²

St. John's wort, evening primrose oil don't work

One randomized, double-blind controlled trial (N=125) of 600 mg St. John's wort vs placebo over 2 cycles of treatment found no significant changes in symptom score from baseline.¹³ Two double-blind crossover studies of 27 and 38 patients found that evening primrose oil had no effect on PMS symptoms.^{14,15}

Recommendations

The Premenstrual Syndrome Guidelines of the American College of Obstetricians and Gynecologists (ACOG) state that calcium and magnesium have been shown to be effective in small trials and must be validated in larger trials before a strong evidence-based recommendation can be made. ACOG's guidelines also report minimal effectiveness with vitamin B6 and vitamin E.¹⁶

JFP

References

- Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ*. 2001;322:134-137.
- Berger D, Schaffner W, Schrader E, et al. Efficacy of *Vitex agnus-castus L* extract Ze 440 in patients with premenstrual syndrome (PMS). *Arch Gynecol Obstet*. 2000;264:150-153.
- Atmaca M, Kumru S, Tezcan E. Fluoxetine versus *Vitex agnus-castus* extract in the treatment of premenstrual dysphoric disorder. *Hum Psychopharmacol*. 2003;18:191-195.
- Thys-Jacobs S, Ceccarelli S, Bierman A, et al. Calcium supplementation in premenstrual syndrome: a randomized crossover trial. *J Gen Intern Med*. 1989;4:183-189.
- Thys-Jacobs S, Starkey P, Bernstein D, et al. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. *Am J Obstet Gynecol*. 1998;179:444-452.
- Wyatt KM, Dimmock PW, Jones PW, et al. Efficacy of vitamin B6 in the treatment of premenstrual syndrome: systematic review. *BMJ*. 1999;318:1375-1381.
- Diegoli MS, da Fonseca AM, Diegoli CA, et al. A double-blind trial of four medications to treat severe premenstrual syndrome. *Int J Gynaecol Obstet*. 1998;62:63-67.
- Kashanian M, Mazinani R, Jalalmanesh S. Pyridoxine (vitamin B6) therapy for premenstrual syndrome. *Int J Gynaecol Obstet*. 2007;96:43-44.
- Agha-Hosseini M, Kashani L, Aleyaseen A, et al. *Crocus sativus L* (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. *BJOG*. 2008;115:515-519.
- Facchinetti F, Borella P, Sances G, et al. Oral magnesium successfully relieves premenstrual mood changes. *Obstet Gynecol*. 1991;78:177-181.
- Walker AF, De Souza MC, Vickers MF, et al. Magnesium supplementation alleviates premenstrual symptoms of fluid retention. *J Womens Health*. 1998;7:1157-1165.
- Khine K, Rosenstein DL, Elin RJ, et al. Magnesium (Mg) retention and mood effects after intravenous Mg infusion in premenstrual dysphoric disorder. *Biol Psychiatry*. 2006;59:327-333.
- Hicks SM, Walker AF, Gallagher J, et al. The significance of "non-significance" in randomized controlled studies: a discussion inspired by a double-blinded study on St. John's wort (*Hypericum perforatum L.*) for premenstrual symptoms. *J Altern Complement Med*. 2004;10:925-932.
- Khoo SK, Munro C, Battistutta D. Evening primrose oil and treatment of premenstrual syndrome. *Med J Aust*. 1990;153:189-192.
- Collins A, Cerin A, Coleman G, et al. Essential fatty acids in the treatment of premenstrual syndrome. *Obstet Gynecol*. 1993;81:93-98.
- American College of Obstetricians and Gynecologists. Premenstrual Syndrome. *ACOG Practice Bulletin No. 15*. Washington, DC. April 2000.

CLINICAL INQUIRIES
 Online this month at jfponline.com

• Do Rx alternatives relieve URI-associated cough?

Get the answer to this Clinical Inquiry by going to www.jfponline.com and clicking on "Online Exclusives" in the left-hand navigation bar.

THE JOURNAL OF **FAMILY PRACTICE**