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Treatment of Premenstrual Syndrome with Vitamin B_6

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Dr. Milan reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

THE LARGE MAJORITY OF WOMEN EXPERIENCE UNPLEASANT PREMENstrual symptoms at some times during their lives. Although 75-80% of women report some emotional or physical changes during the luteal phase of their menstrual cycle,[1,2] 40-50% experience these symptoms as annoying and 3-8% have symptoms severe enough to produce dysfunction in some aspect of their lives.[3-5] The characteristic symptoms of premenstrual syndrome (PMS) include a mix of mood (i.e., irritability, affective lability, depression, anxiety), physical (i.e., fatigue, bloating, weight gain, breast tenderness, change in appetite), and cognitive (i.e., confusion, difficulty concentrating) changes. The hallmark of PMS is that these symptoms occur within the two weeks before menses, remit within two days of menstruation, and are absent until ovulation.[4] Women typically begin to experience PMS symptoms in their 20s but usually do not seek care until their 30s.[4,5] Of the women who report bothersome premenstrual symptoms, 30-40% will seek help from their primary care provider.[6] It is not clear whether PMS symptoms worsen with age or whether older women are more likely to seek help for the problem.[4]

PMS Etiology/Theories

The exact pathophysiology of PMS is not entirely clear. (*See sidebar for more information on diagnosing PMS.*) It is clear that for PMS to occur, a woman must ovulate in that cycle.[7] There is an obvious link between the symptoms of PMS/premenstrual dysphoric disorder (PMDD) and the rise and fall of sex steroids associated with ovulation. Cyclical PMS symptoms do not occur with pregnancy and resolve after menopause.[8] Although suppression of ovulation with a synthetic androgen (danazol) and gonadotropin-releasing hormone agonists seems to be an effective therapy for PMS,[9-13] suppression of ovulation with oral contraceptives (OCPs) has not been shown to be as reliably effective.[7,8] There is, however, some evidence that an OCP formulated with drospirenone (a progestin and spironolactone

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analog) may be effective in reducing PMS symptoms.[8,14] One theory, espoused by Katarina Dalton, was that progesterone deficiency is the underlying cause of PMS.[15] Although some early evidence also suggested that PMS could be treated effectively with micronized progesterone,[16] a subsequent large randomized controlled trial was negative.[17] It has been shown that progesterone levels are not altered in women with PMS.[18] There is ample evidence to suggest alterations in serotonergic functioning during the luteal phase in women with PMS/PMDD. In addition, selective serotonin reuptake inhibitors that have been studied for treating PMS have produced an average response rate of approximately 60%.[8]

CAM for PMS

In the 1970s and 1980s, many investigators focused on supplementation with a variety of vitamins and minerals, both singly and in combination, to treat PMS. Although calcium and magnesium both have been shown to have some potential as effective therapies for PMS/PMDD, their mechanism of action remains unclear.[19-21] Vitamin E has been studied in the treatment of premenstrual mastalgia with highly variable results.[7,19] Vitamin B_6 as a cofactor in the synthesis of neurotransmitters was studied as a treatment for depression related to OCP use.[22] These data produced interest in vitamin B_6 as a treatment for PMS. Vitamin B_6 has been studied both alone and in combination with other vitamins and minerals.

Mechanism of Action

Pyridoxine HCL is the standard form of vitamin B_6 available as a supplement and is the least expensive form to produce commercially. Pyridoxine HCl is absorbed in the upper small intestine but is not metabolically active until it is phosphorylated in the liver into pyridoxal 5'phosphate (P5P). P5P is exported from the liver bound to albumin and is the most relevant measure of vitamin B_6 status.[23] Vitamin B_6 nutritional status has a significant and selective modulatory impact on central production of both serotonin and gamma-aminobutyric acid,[24] as P5P is a cofactor in the synthesis of these neurotransmitters. It is this biochemical activity that is behind the rationale for the use of vitamin B_6 in PMS/PMDD.

Prevalence

Several studies conducted in the United Kingdom (UK) before 1997 found that vitamin B_6 was the most commonly used therapy for PMS,[25] with one survey finding 68% of general practitioners prescribing it for this indication. A similar survey of primary care providers in the United States and Canada, however, found the most prescribed treatment for PMS was progesterone.[26] In 1997, the UK Department of Health proposed to limit the sales of vitamin B_6 because of possible neurotoxic side effects at higher doses. A UK study that measured prescribing practices for PMS from 1993 to 1998 found a sudden 50% decrease (from 22% to 11%) in prescriptions for vitamin B_6 for PMS from 1997 to 1998.[27]

Clinical Evidence for PMS/PMDD

Many of the studies evaluating vitamin B_6 as a therapy for PMS were done before there were well-outlined clinical criteria emphasizing the need to distinguish PMS from PMDD, a more severe form of the syndrome. Therefore, studies have somewhat heterogeneous inclusion criteria and outcome measures. In addition, studies on PMS, similar to those evaluating therapies for depression, have notoriously high placebo response rates. Not surprisingly, the results of these studies have been quite variable.

A 1990 review by Kleijnen of 12 controlled trials found four trials with negative results, three with positive results, and five with ambiguous results.[28] All of the

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studies were small (n < 50) and had some important methodological problems.

A more recent review and meta-analysis identified 25 trials: nine of which were placebo-controlled and had data that could be pooled for meta-analysis.[29] The methodological quality of the trials was evaluated by Jadad[30] score as well as by a second quality scale developed by the authors. The overall quality of the trials was poor with only three of the trials achieving the recommended Jadad score of 3.[31-33] Of the nine trials included in the meta-analysis, three[31,34,35] used a high-dose multivitamin product (Optivite) which, at the recommended dose of 6-12 tabs per day, provides 300-600 mg/d vitamin B_6, 12,500-25,000 IU/d vitamin A, 250-500 mg/d magnesium in addition to a long list of other vitamins and minerals in amounts in excess of the recommended daily allowance.[7,19] These multivitamin studies also divided patients into four symptomatic subgroups, so their analyses were done differently than the other studies. The other six studies used vitamin B_6 alone in doses of 500 mg/d[36] or 50-200 mg/d.[32,33,37-39] In one study subjects took the vitamin supplement during the luteal phase only,[32] while subjects in the other trials received the supplement throughout the menstrual cycle. Two of the studies evaluated only mastalgia,[33,35] while the others measured effects on a variety of physical, emotional, and cognitive symptoms.

The outcome measures of the nine studies were too disparate to compare directly, so the authors of this meta-analysis calculated odds ratios (OR) by dichotomizing patients into "better" or "not better" groups. After excluding one trial for failing the homogeneity test, the

Definitions and Diagnosis of Premenstrual Syndrome

While aspects of premenstrual mood changes were described by Hippocrates, premenstrual tension syndrome was first delineated as a disorder in the 1930s and the term premenstrual syndrome (PMS) was first defined in the 1950s.[1] Although many recognized that a subset of the population suffered from a particularly severe form of PMS resulting in a significant level of dysfunction, clear clinical definitions were not outlined until recently. The American College of Obstetrics and Gynecology (ACOG) established clinical guidelines for PMS in 2000[2] and criteria for Premenstrual Dysphoric Disorder (PMDD) was included in DSM-IV.[3] Both the ACOG criteria for PMS and the DSM-IV criteria for PMDD require confirmation of the luteal nature of the problem through the use of prospective symptom charts or a daily rating instrument for a minimum of two menstrual cycles. A number of valid and reliable diagnostic instruments are available to document symptoms including the Calendar of Premenstrual Experiences,[4] the Premenstrual Syndrome Diary,[5] and the Daily Record of Severity of Problems.[6] One expert recommends that women record daily the presence and severity of five of their most bothersome symptoms.[7] The use of prospective symptom recording is important in both clinical and research settings as the literature shows that more than half of the women who present with complaints of "severe PMS" are found not to have a pure luteal phase pattern based on prospective charts.[3,7]

It is necessary to establish a diagnosis of either PMS or PMDD and rule out other psychiatric disorders. One study found that of 426 women recruited from primary care obstetrics and gynecology practices who reported having PMS, 22% (93) were found to have major depressive disorder and 14% (61) had panic disorder.[8] Of the women in that study who charted their symptoms for a cycle, only 22% were confirmed to have PMS.[8] The symptom diaries also can identify women who present with complaints of PMS but are found to have psychological symptoms present throughout their cycle that worsen between ovulation and menstruation. This phenomenon is referred to as "menstrual magnification."[7] Many women find the information gleaned from charting their symptoms helpful in identifying potential triggers or lifestyle habits that may exacerbate them. Lastly, several experts[7,9] have recommended that women try certain lifestyle changes or nutritional interventions during the cycles when they are recording their symptoms. ❖

References

1. Rapkin A. A review of treatment of premenstrual syndrome and premenstrual dysphoric disorder. *Psychoneuroendocrinology* 2003;28:39-53.
2. American College of Obstetrics and Gynecologists. Premenstrual Syndrome. ACOG Practice Bulletin No. 15. 2000; April.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association; 1994:715-718.
4. Mortola JF, et al. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: The calendar of premenstrual experiences. *Obstet Gynecol* 1990;76:302-307.
5. Thys-Jacobs S, et al. Comparative analysis of three PMS assessment instruments—the identification of premenstrual syndrome with core symptoms. *Psychopharmacol Bull* 1995;31: 389-396.
6. Endicott J. Severe premenstrual dysphoria: Differential diagnosis and treatment. *J Am Med Womens Assoc* 1998;53:170-175.
7. Johnson SR. Premenstrual syndrome, premenstrual dysphoric disorder, and beyond: A clinical primer for practitioners. *Obstet Gynecol* 2004;104:845-859.
8. Yonkers KA, et al. Premenstrual disorders: Bridging research and clinical reality. *Arch Women Ment Health* 2003;6:287-292.
9. Grady-Weliky TA. Clinical practice. Premenstrual dysphoric disorder. *N Engl J Med* 2003;348:433-438.

overall OR was 2.32 (95% confidence interval [CI] 1.95-2.54) in favor of vitamin B_6 over placebo and 1.57 (95% CI 1.40-1.77) when that trial was included.[29] The authors also extracted data from five trials with outcome measures looking specifically at depressive symptoms[31,32,35,37,38] and calculated an OR of 1.69 (95% CI 1.80-2.48) in favor of vitamin B_6. No dose-response relationship was found among the nine studies. An additional problem with the study is that four of the nine trials used doses of vitamin B_6 that are higher than what is currently considered safe. One of the larger (n = 617) and better quality studies (Jadad score of 3) randomized women with PMS to receive placebo or vitamin B_6 at doses of either 50 mg/d, 100 mg/d, or 200 mg/d for three cycles.[32] Improvement as measured by global assessment was significantly greater in the treatment group ($P < 0.02$).

Another double-blind, randomized controlled trial that was not included in the review by Wyatt treated women with PMS with either 300 mg/d vitamin B_6, alprazolam, propranolol, fluoxetine, or placebo.[40] Although the other groups did better than placebo, the group receiving B_6 did worse than those receiving placebo. A recent systematic review looking at the use of vitamin B_6 as a treatment for depression concluded that while the literature reviewed did not show vitamin B_6 to be valuable in the treatment of depression in general, there did seem to be a consistent indication for its use to treat depression in premenopausal women.[41]

Safety

The Institute of Medicine of the National Academy of Sciences has set the upper limit of vitamin B_6 at 100 mg/d after reports of neuropathy with doses as low as 200 mg/d.[42] Vitamin B_6 can cause nausea, vomiting, abdominal pain, loss of appetite, headache, paresthesia, somnolence, increased serum AST, decreased serum folic acid levels, allergic reactions, breast tenderness and enlargement, and photosensitivity. Large doses (1-6 g/d) can be neurotoxic. Symptoms can include tingling in the hands and feet, decreased muscle coordination, and stumbling gait.[43]

Conclusion and Recommendations

The diagnosis of PMS/PMDD has been aided in recent years by the establishment of clinical criteria for both the milder (PMS) and more severe (PMDD) versions of the disorder. The literature shows very clearly that women who complain of PMS symptoms often are inaccurate in their assessment of the problem. It is therefore essential to screen for other psychiatric comorbidities as well as use laboratory tests to rule out other possible diagnoses. The recommended approach to the treatment of women who have a history consistent with premenstrual symptoms is to use one of the validated instruments for symptom charting. During the cycles when she is charting, a woman can try to identify and then alter lifestyle habits that may improve her symptoms. It is also a time when a trial of vitamin B_6 at 100 mg/d could be tried and assessed for efficacy. After the symptom charts are reviewed, if a diagnosis of PMS is made or if the patient with PMDD does not choose to use a psychotropic medication, a trial of vitamin B_6 could be considered. However, the literature on vitamin B_6 is methodologically very poor and quite equivocal as to its efficacy as a therapy for PMS. ❖

References

1. Campbell EM, et al. Premenstrual symptoms in general practice patients: Prevalence and treatment. *J Reprod Med* 1997;42:637-646.
2. Committee on Gynecologic Practice. American College of Obstetricians and Gynecologists. ACOG committee opinion. Premenstrual syndrome. Number 155—April 1995. *Int J Gynaecol Obstet* 1995;50:80-84.
3. Johnson SR. The epidemiology and social impact of premenstrual symptoms. *Clin Obstet Gynecol* 1987;30:367-376.
4. Johnson SR. Premenstrual syndrome, premenstrual dysphoric disorder, and beyond: A clinical primer for practitioners. *Obstet Gynecol* 2004;104:845-859.
5. Grady-Weliky TA. Clinical practice. Premenstrual dysphoric disorder. *N Engl J Med* 2003:348:433-438.
6. Kraemer GR, Kraemer RR. Premenstrual syndrome: Diagnosis and treatment experiences. *J Womens Health* 1998;7:893-907.
7. Johnson SR. Premenstrual syndrome therapy. *Clin Obstet Gynecol* 1998;41:405-421.
8. Rapkin A. A review of treatment of premenstrual syndrome and premenstrual dysphoric disorder. *Psychoneuroendocrinology* 2003;28:39-53.
9. Sarno AP Jr, et al. Premenstrual syndrome: Beneficial effects of periodic, low-dose danazol. *Obstet Gynecol* 1987;70:33-36.
10. Watts JF, et al. A clinical trial using danazol for the treatment of premenstrual tension. *Br J Obstet Gynaecol* 1987;94:30-34.
11. Hahn PM, et al. A randomized, placebo-controlled, crossover trial of danazol for the treatment of premenstrual syndrome. *Psychoneuroendocrinology* 1995;20:193-209.
12. Muse KN, et al. The premenstrual syndrome. Effects of "medical ovariectomy." *N Engl J Med* 1984;311:1345-1349.
13. Hammarback S, Backstrom T. Induced anovulation as treatment of premenstrual tension syndrome. A double-blind cross-over study with GnRH-agonist versus placebo. *Acta Obstet Gynecol Scand* 1988;67:159-166.
14. Parsey KS, Pong A. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new

progestogen. *Contraception* 2000;61:105-111.
15. Dalton K. *The Premenstrual Syndrome and Progesterone Therapy.* 2nd ed. Chicago IL: Year Book Medical Publishers; 1984.
16. Dennerstein L, et al. Progesterone and the premenstrual syndrome: A double-blind crossover trial. *Br Med J (Clin Res Ed)* 1985;290:1617-1621.
17. Freeman EW, et al. A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. *JAMA* 1995;274:51-57.
18. Rubinow DR, et al. Changes in plasma hormones across the menstrual cycle in patients with menstrually related mood disorder and in control subjects. *Am J Obstet Gynecol* 1988;158:5-11.
19. Bendich A. The potential for dietary supplements to reduce premenstrual syndrome (PMS) symptoms. *J Am Coll Nutr* 2000;19:3-12.
20. Thys-Jacobs S, 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.
21. Facchinetti F, et al. Reduction of monocyte's magnesium in patients affected by premenstrual syndrome. *J Psychosom Obstet Gynecol* 1990;11:221-229.
22. Villegas-Salas E, et al. Effect of vitamin B_6 on the side effects of a low-dose combined oral contraceptive. *Contraception* 1997;55:245-248.
23. Leklem JE. Vitamin B-6: A status report. *J Nutr* 1990;120:1503-1507.
24. Vitamin B_6 (pyridoxine and pyridoxal 5'-phosphate)—monograph. *Altern Med Rev* 2001;6:87-92.
25. Corney RH, Stanton R. A survey of 658 women who report symptoms of premenstrual syndrome. *J Psychosom Res* 1991;35:471-482.
26. Lyon KE, Lyon MA. The premenstrual syndrome. A survey of current treatment practices. *J Reprod Med* 1984;29:705-711.
27. Wyatt KM, et al. Prescribing patterns in premenstrual syndrome. *BMC Women's Health* 2002;2:4. Available at: www.biomedcentral.com/1472-6874/2/4. Accessed Aug. 7, 2005.
28. Kleijnen J, et al. Vitamin B_6 in the treatment of the premenstrual syndrome—a review. *Br J Obstet Gynaecol* 1990;97:847-852. Erratum in: *Br J Obstet Gynaecol* 1991;98:329-330.
29. Wyatt KM, et al. Efficacy of vitamin B_6 in the treatment of premenstrual syndrome: Systematic review. *BMJ* 1999;318:1375-1381.
30. Jadad AR, et al. Assessing the quality of reports of randomized clinical trials; is blinding necessary? *Control Clin Trials* 1996;17:1-12.
31. London RS, et al. Effect of a nutritional supplement on premenstrual symptomatology in women with premenstrual syndrome: A double-blind longitudinal study. *J Am Coll Nutr* 1991;10:494-499.
32. Barr W. Pyridoxine supplements in the premenstrual syndrome. *Practitioner* 1984;228:425-427.
33. Williams MJ, et al. Controlled trial of pyridoxine in the premenstrual syndrome. *J Int Med Res* 1985;13:174-179.
34. Stewart A. Clinical and biochemical effects of nutritional supplementation on the premenstrual syndrome. *J Reprod Med* 1987;32:435-441.
35. Chakmakjian ZH, et al. The effect of a nutritional supplement, Optivite for women, on premenstrual tension syndrome: Effect of symptomatology, using a double-blind crossover design. *J Appl Nutr* 1985;37:12-17.
36. Colin C. Controlled studies on the oral administration of progestagens, an antiestrogen and vitamin B6 in the treatment of mastodynias [in French]. *Rev Med Brux* 1982;3:605-609.
37. Smallwood J, et al. Vitamin B_6 in the treatment of premenstrual mastalgia. *Br J Clin Pract* 1986;40:532-533.
38. Kendall KE, Schnurr PP. The effects of vitamin B_6 supplementation on premenstrual symptoms. *Obstet Gynecol* 1987;70:145-149.
39. Doll H, et al. Pyridoxine (vitamin B_6) and the premenstrual syndrome: A randomized crossover trial. *J R Coll Gen Pract* 1989;39:364-368.
40. Diegoli MS, et al. A double-blind trial of four medications to treat severe premenstrual syndrome. *Int J Gynaecol Obstet* 1998;62:63-67.
41. Williams AL, et al. The role for vitamin B-6 as treatment for depression: A systematic review. *Fam Pract* 2005 Jun 17 (epub ahead of print).
42. Parry GJ, Bredesen DE. Sensory neuropathy with low-dose pyridoxine. *Neurology* 1985;35:1466-1468.
43. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline.* Washington, DC: National Academy Press; 1999. Available at books.nap.edu/books/0309065542/html/index.html. Accessed Aug. 7, 2005.

Black Cohosh Extract Effectively Treats Climacteric Symptoms—Best Results in Early Menopause

By Donald Brown, ND

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Dr. Brown is a consultant for Nature's Way, Inc.

Source: Osmers R, et al. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol* 2005;105:1074-1083.

Abstract: In a randomized, multicenter, double-blind, placebo-controlled clinical trial, the efficacy of a standardized black cohosh preparation was studied in 304 postmenopausal women. Subjects were at least 45 years of age and were selected from

24 gynecological practices in Germany. Women entered in the trial were required to have an interval of at least 12 months since their last regular menstruation or an interval of at least six months since their last regular menstruation plus follicle-stimulating hormone (FSH) of ≥ 50 U/L. Additionally, climacteric complaints as defined by the Menopause Rating Scale I (MRS) of ≥ 0.4 in at least three items. Participants were randomized to receive either 20 mg of black cohosh (*Cimicifuga racemosa*) extract (Remifemin®, Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany) or placebo bid for 12 weeks.

Clinical examinations were performed pretreatment and at weeks 4 and 12. The primary outcome measure was the intensity of climacteric symptoms as defined by the MRS, a 10-item scale with each item being scored from 0 (no complaints) to 1 (severe complaints) in increments of 0.1. Symptoms rated include hot flashes, sleep disorders, joint and muscle symptoms, nervousness, disorders of sexuality, depressive moods, impaired memory, vaginal dryness, cardiac complaints, and urinary complaints. The primary endpoint was defined as change from baseline in the MRS mean score, analyzed in a linear regression model considering the following cofactors and covariates: age at study onset, MRS at baseline, FSH at baseline, and others that are beyond the scope of this review. Secondary measures included changes in MRS subscores (hot flashes [includes hot flashes, sweating, sleep disorders], psyche [includes depressive moods, nervousness, nervous irritability, impaired memory and performance], soma [includes cardiac complaints, joint and muscle symptoms], atrophy [includes disorders of sexuality, urinary complaints, vaginal dryness], and safety variables).

A total of 268 women successfully completed the trial. At the end of 12 weeks, the difference in the decrease in MRS score was significantly greater in the black cohosh group compared to placebo ($P = 0.027$). When confounders and covariates were considered, this difference became more significant. Notable is the fact that when considering women in the early stages of menopause and lower baseline FSH (FSH = 20 U/L and one year duration of climacteric complaints) compared to women in later stages of menopause (FSH = 40 U/L and three years duration of symptoms), the differences in MRS scores became even greater ($P < 0.001$). The MRS subscore for hot flashes changed most significantly in the black cohosh group compared to placebo ($P = 0.007$), although significant, but smaller differences were noted for the atrophy ($P = 0.012$) and psyche ($P = 0.019$) subscores. The difference on the soma subscore did not reach significance. These differences again were greater among women in early menopause compared to those in later stages.

All 304 women originally enrolled in the trial were included in the safety analysis. In the black cohosh group, 50 (32.7%) women reported 71 adverse events compared to 47 (31.1%) in the placebo group. A causal relationship to the study medication was judged to be at least possible in six events (3.9%) reported in the black cohosh group compared to 7 (4.6%) in the placebo group. Most of the adverse events were mild in nature with gastrointestinal complaints being distributed equally between both groups. There were no notable increases in liver enzymes in either group during the 12 weeks of the trial.

Comments

THIS LARGE RANDOMIZED TRIAL SUPPORTS THE USE OF black cohosh extract to treat menopausal symptoms, most notably hot flashes. However, it is the first successful trial to demonstrate that the duration of menopause symptoms and baseline FSH levels may be a predictor of how effectively it works. Namely, women with symptoms lasting one year or less and with lower baseline FSH levels are more likely to have a reduction of symptoms than women with a longer duration of symptoms and higher baseline FSH. The effect size for the black cohosh group was -0.03 to -0.05 MRS units, similar to the -0.036 MRS units noted for recent studies using conjugated estrogens.[1]

Notable as well is the finding that black cohosh did not appear to have any hepatotoxic effects according to serum enzyme measures. Issues regarding the potential hepatotoxicity of black cohosh have arisen over the past couple of years, including isolated case reports.[2] The authors do report that a longer safety trial is currently underway.

The publication of this trial coincides with a report by the Mayo Clinic that an eight-week placebo-controlled, crossover design trial shows no efficacy for black cohosh in treating hot flashes.[3] This trial studied 132 women and found no difference compared to placebo. The study treated women with black cohosh for four weeks and used a generic black cohosh product that, according to the authors, they procured under the assumption that it duplicated Remifemin. Presented at the American Society of Clinical Oncology in Orlando, Florida (May 13-17, 2005), the study was funded by a grant from the National Cancer Institute. By my scorecard, that makes two poorly designed trials on black cohosh funded by the U.S. government to date—the other being an eight-week trial completed at Columbia University with women with a history of breast cancer, many taking tamoxifen.[4]

Conclusion

The results of this clinical trial suggest that 40 mg/d of black cohosh extract safely and effectively treat symptoms associated with menopause with the most significant effect being on hot flashes. This is the first trial to suggest that duration of menopause and baseline FSH levels may be predictors of the efficacy of black cohosh. The results suggest that women with symptoms for one year or less and with a lower baseline FSH are more likely to benefit from black cohosh therapy than women with a longer duration of symptoms and higher baseline FSH. ❖

References

1. Wuttke W, et al. The *Cimicifuga* preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: Effects on menopause symptoms and bone markers. *Maturitas* 2003;44(Suppl 1):S67-S77.
2. Levitsky J, et al. Fulminant liver failure associated with the use of black cohosh. *Dig Dis Sci* 2005;50:538-539.
3. Study finds black cohosh no better than placebo in treating hot flashes [press release]. Scottsdale, AZ: Mayo Clinic; May 17, 2005.
4. Jacobson JS, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol* 2001;19: 2739-2745.

CE Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

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2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients;
4. offer guidance to patients based on latest science and clinical studies regarding alternative and complementary therapies.

CE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

CE / CME Questions

10. What percent of women report emotional or physical changes during the luteal phase of their menstrual cycle?

a. 3-8%
b. 30-40%
c. 40-50%
d. 75-80%

11. The literature on vitamin B_6 for as a therapy for premenstrual syndrome is methodically poor, and is equivocal as to its efficacy as a therapy for PMS.

a. True
b. False

12. A recent systematic review of vitamin B_6 for depression concluded that there seemed to be a consistent indication for its use to treat depression in premenopausal women.

a. True
b. False

13. A recent trial evaluating black cohosh for treating menopausal symptoms found it to be beneficial for which group?

a. Women experiencing symptoms for longer than one year
b. Women experiencing symptoms for one year or less

Answers: 10. d, 11. a, 12. a, 13. b.

News Briefs

FDA Skeptical that Green Tea Reduces Risk of Certain Cancers

The FDA recently announced the results of a review of qualified health claims that green tea may reduce the risk of breast and prostate cancer. Based on a systematic evaluation of the available scientific data, FDA has made the following statements:

- "Two studies do not show that drinking green tea reduces the risk of breast cancer in women, but one weaker, more limited study suggests that drinking green tea may reduce this risk. Based on these studies, the FDA concludes that it is highly unlikely that green tea reduces the risk of breast cancer."
- "One weak and limited study does not show that

drinking green tea reduces the risk of prostate cancer, but another weak and limited study suggests that drinking green tea may reduce this risk. Based on these studies, the FDA concludes that it is highly unlikely that green tea reduces the risk of prostate cancer."

The FDA also concluded that existing evidence does not support qualified health claims for green tea consumption and a reduced risk of any other type of cancer.

NCCAM Offers Continuing Education Series on Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health (NIH) in Bethesda, MD, is offering a new on-line continuing education series on complementary and alternative medicine (CAM).

This lecture series offers health care professionals and the public the opportunity to learn more about CAM therapies through video lectures by some of the leading experts in the field. Health care professionals can earn Continuing Medical Education (CME) credits; users who complete all the test chapters can generate an on-line certificate. The CME series is free and can be viewed at http://nccam.nih.gov/videolectures.

The series currently has six different lectures. Each lecture includes an overview of the CAM area, a review of research results and ongoing research, and discussion of the historical and practice perspectives.

CAM topics covered are:

- Overview of CAM
- Herbs and other dietary supplements
- Mind-body medicine
- Acupuncture: An evidence-based assessment
- Manipulative and body-based therapies: Chiropractic and spinal manipulation
- CAM and aging

Each lecture includes:

- A video lecture by a scientific expert
- The lecture transcript
- An on-line test that can be taken to receive CME credits (credits for nurses will be added soon)
- Additional resource links

For additional information, call NCCAM's Clearinghouse toll free at (888) 644-6226, or visit the NCCAM web site at http://nccam.nih.gov.

Nationwide Alert Issued for "Liqiang 4" Because of Potential Health Risk

The FDA is warning consumers not to take Liqiang 4 dietary supplement capsules because they contain glyburide—a drug that could have serious, life-threatening consequences in some people.

Glyburide is used to lower blood sugar, and is safe and effective when used as labeled in FDA-approved medications. People who have low blood sugar or those with diabetes can receive dangerously high amounts of glyburide by consuming Liqiang 4, the FDA says. Consumers should stop using these products immediately and seek medical attention, especially if they are currently being treated with diabetes drugs or if they have symptoms of fatigue, excessive hunger, profuse sweating, or numbness of the extremities. Consumers who have this product should get rid of it immediately.

The product is sold as part of a shrink-wrapped two-bottle set. One of the 90-capsule bottles is labeled "Liqiang 4 Dietary Supplement Capsules;" the other bottle is promoted as a "bonus pack" of Liqiang 1. At this time the FDA is evaluating Liqiang 1 and other versions of this line of products to determine their composition and safety. The product is manufactured by Liqiang Research Institute, China, and is marketed throughout the United States in herbal stores and through mail-order by Bugle International of Northridge, CA.

The FDA learned of the potential problem through an anonymous consumer complaint and followed up with testing that revealed the presence of glyburide in this product. The product has also been termed "Liqiang Xiao Ke Ling" (Liqiang Thirst Quenching Efficacious) in ads in Chinese language publications, which also promote it as useful for the control of diabetes and being derived from only natural ingredients. ❖

In Future Issues:

Herbs and Lactation

Evening Primrose Oil for Menopausal Symptoms

Vitamin E and Cardiovascular Disease

***Ginkgo biloba* and Depression**

Acupuncture for Female Infertility