

Alternative Therapies for Traditional Disease States: Menopause

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With growing concern about the use of hormone replacement therapy, some women are looking for alternative treatments for menopausal symptoms and preventing postmenopausal cardiovascular disease and osteoporosis. In observational trials, exercise has been associated with decreased vasomotor symptoms. One trial suggested that black cohosh may reduce menopausal symptoms. Soy has been shown to decrease vasomotor symptoms, lower lipid levels, and increase bone density. However, large amounts of soy must be consumed, and it is not clear whether soy consumption causes a decrease in cardiovascular events or fractures. The evidence for St. John's wort is equivocal. Fish oil is helpful for secondary prevention of coronary artery disease. (Am Fam Physician 2002;66:129-34. Copyright© 2002 American Academy of Family Physicians.)

For most women, menopause is a normal phase of life that does not require medical intervention. However, some perimenopausal women seek treatment for vasomotor symptoms, while postmenopausal women may need treatment that can reduce their risk of cardiovascular disease and osteoporosis. In the United States, one half of perimenopausal women will report feeling irritated or depressed;¹ and about one third will experience dyspareunia, vaginal dryness, or decreased libido. Conventional treatment for menopausal vasomotor symptoms usually consists of hormone replacement therapy (HRT). Prevention of osteoporosis usually consists of HRT, bisphosphonates, selective estrogen receptor modifiers (SERMs), calcitonin, exercise, or calcium and vitamin D supplements. Cardiovascular disease prevention traditionally includes smoking cessation, lowering of lipid levels, blood pressure control, weight control, diabetes management, and exercise. The role of Hrt in this area is still unclear.

Concerns about safety and effectiveness are causing a retreat from the blanket use of HRT. An estimated 30 to 45 percent of women who receive prescriptions for HRT will not have their prescriptions filled or will discontinue therapy within 12 months of initiation.² Side effects of breast tenderness and breakthrough bleeding, concerns about breast^{3,4} and ovar-

ian cancer,^{5,6} gall bladder disease, and thromboembolic events,⁷ may all contribute to low adherence rates.

Treating Vasomotor Symptoms

Although 85 percent of perimenopausal women have vasomotor symptoms (hot flashes), only one half of these women find them disturbing.⁸ Twenty percent of women will experience symptoms for less than one year, but approximately 50 percent of women may experience symptoms for five years or more.⁹ Conventional estrogen therapy is effective in controlling symptoms in more than 90 percent of women.¹⁰

PROGESTERONE

Although synthetic progesterone (oral and intramuscular injection) has previously been shown to decrease vasomotor symptoms,^{11,12} its use has been limited because of side effects and its adverse effect on lipid profiles. The latest randomized trial¹³ involving progesterone used progesterone transdermal cream (one-fourth teaspoon or 20 g progesterone cream per day) and found that 83 percent of subjects noted improvement or resolution of vasomotor symptoms in the treatment group, compared with a 19 percent improvement in the placebo group.¹³

Recently, "natural" progesterone extracted from plant sources and "micronized" to

Soy has been found to significantly reduce the incidence of hot flashes associated with menopause.

enhance its bioavailability has become available. This product has been shown to have no adverse effect on mood or serum high-density lipoprotein (HDL) cholesterol levels.¹⁴ The most common side effects are fatigue and sedation, which can be minimized by taking the drug at bedtime. Despite the benefits of other forms of progesterone in treating vasomotor symptoms, no randomized trials have specifically addressed the effects of micronized progesterone on vasomotor symptoms.

EXERCISE

Recent observational studies^{15,16} showed that women who regularly exercise are less likely than their sedentary counterparts to experience severe hot flashes. In one observational study of 1,323 women in Sweden,¹⁵ 15 percent of sedentary women experienced "severe" hot flashes, compared with only 5 percent of the subjects who exercised. These differences were not explained by differences in body mass index, smoking habits, or HRT use. However, they may be explained by selection bias.

SOY

The consumption of soy has been found to significantly reduce the incidence of hot flashes. In a recent double-

TABLE 1
Soy Products*

Source	Soy protein content	Approximate calories
1 cup soy milk	3 to 10 g	90 (low fat) 140 (regular)
3 oz tofu	10 g	90
½ cup soy flour	20 g	220
2 tablespoons soy protein isolate	25 g	110

*—Soy lacks cysteine and methionine, and must be combined with other plant proteins (e.g., rice, corn, wheat) to supply all essential amino acids.

blind, placebo-controlled study,¹⁷ hot flashes were reduced by 45 percent in the women who received 60 g of soy protein isolate daily (isoflavone content was not standardized). This reduction was significantly greater than in the subjects who received placebo, although the placebo group also experienced a 30 percent reduction in hot flashes. In one pilot study,¹⁸ a significant reduction in the incidence of hot flashes was found at six weeks in participants who took 400 mg of soy extract and 50 mg isoflavone daily. Other studies have documented significant decreases in the frequency¹⁹ or severity²⁰ of vasomotor symptoms. Because hot flashes vary in frequency, severity, and duration, future research involving the use of soy should address these variables. The caloric intake of soy must also be considered in the overall health of the patient (Table 1).

BLACK COHOSH

The mechanism of action of black cohosh is not fully understood. Several studies²¹⁻²⁴ have demonstrated that black cohosh significantly improves menopausal symptoms, but most of these studies had design flaws or were sponsored by the manufacturer. The one double-blind placebo-controlled trial²⁵ that studied black cohosh was performed in Germany in 1987. The effects of black cohosh (8 mg per day) versus estrogen (0.625 mg conjugated estrogen) and placebo were studied in 80 postmenopausal women. The women in the black cohosh group had a statistically significant improvement in menopausal vasomotor symptoms and vaginal epithelium after 12 weeks. This group also had significantly greater

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symptom relief than the placebo and estrogen groups. However, contrary to a vast number of earlier studies, this one found that the estrogen group fared no better than the placebo group. This finding calls into question the overall quality and validity of the study.²⁵ Black cohosh appears to be free of significant side effects and drug interactions.²⁶ Long-term effects of its use are unknown. In Germany, where the herb is approved for use in treating menopausal symptoms, it is recommended only for short-term (fewer than six months) use.

DONG QUAI

This root, which has vasodilatory and antispasmodic effects, has been used in Chinese medicine for more than 2,000 years, but it was not scientifically studied until 1997. In one double-blind randomized, placebo-controlled study,²⁷ 71 women with menopausal symptoms, including hot flashes or night sweats, were assigned to receive dong quai or placebo for 24 weeks. The results showed no significant difference in relief of menopausal vasomotor symptoms between the two groups. The study also showed no difference in endometrial thickness, maturation of vaginal cells, serum estradiol, or estrone levels. The authors concluded that dong quai, when used alone, was no more useful than placebo in the treatment of menopausal symptoms.²⁷

Traditional Chinese herbalists have faulted this study because dong quai is not usually used as solo therapy, but is used in conjunction with other herbs. They maintain that the synergistic effect of dong quai acting with other herbs accounts for the beneficial effects. To date, however, it can only be concluded that dong quai used alone is no better than placebo in reducing menopausal vasomotor symptoms.

EVENING PRIMROSE OIL

Evening primrose oil is commonly used for the treatment of menopausal symptoms, but only one randomized trial²⁸ has studied its effects on menopausal symptoms (MEDLINE search: evening primrose oil/gamolenic acid/menopause/hot flashes/vasomotor symptoms). This study of 56 symptomatic women found evening primrose oil to be no more effective than placebo in controlling vasomotor symptoms.

ANTIDEPRESSANTS

Recently published lay and scientific literature has publicized the benefits of antidepressants (e.g., selective sero-

Dong quai, which has vasodilatory and antispasmodic effects, has been used in Chinese medicine for more than 2,000 years, but results from a recent randomized controlled trial have shown it to be ineffective in relief of menopausal vasomotor symptoms.

tonin reuptake inhibitors [SSRIs] and St. John's wort) in the treatment of vasomotor symptoms. The *Prescriber's Letter*²⁹ recently stated that venlafaxine hydrochloride and other SSRIs reduce hot flashes by at least 50 percent. However, a close look at the studies^{30,31} reveals that all had design flaws. Even the authors of the studies concluded that SSRIs may be a promising new treatment for vasomotor symptoms, but that well-designed randomized trials are needed before any clinically useful conclusions can be drawn.

When treating menopausal vasomotor symptoms, depression, fatigue, irritability, and fluid retention, herbalists often recommend St. John's wort. Although the literature supports its use in mild to moderate depression,³² there is no unequivocal evidence for its use to treat menopausal symptoms.

OTHER HERBAL SUPPLEMENTS AND HOMEOPATHY

There is no good evidence in the literature to support the use of any of the following supplements to treat vasomotor symptoms: flaxseed oil, fish oil, omega-3 fatty acids, red clover, ginseng, rice bran oil, wild yam, calcium, gotu kola, licorice root, sage, sarsaparilla, passion flower, chaste berry, ginkgo biloba, and valerian root. In addition, no studies were found that substantiated the purported effects of homeopathic remedies.³³

Preventing Cardiovascular Disease

Roughly one half of postmenopausal women die of coronary heart disease (CHD) or stroke, making CHD the leading cause of death in women in this category. Though HRT was once believed to reduce cardiac events, new evidence appears to contradict these earlier observational studies.^{34,35} Some discussion of alternative methods to reduce risk in this population is warranted. Of course, traditional risk-reduction measures should also be employed (e.g., smoking cessation, lipid control, weight loss, hypertension and diabetes control).

SOY

The U.S. Food and Drug Administration has recently allowed labeling of soy-rich foods as “capable of decreasing the risk of heart disease.” This claim is based on the well-documented lipid lowering effects of soy. One meta-analysis³⁶ showed a 9 percent decrease in total cholesterol levels and a 13 percent decrease in low-density lipoprotein (LDL) levels in patients taking 50 g of soy per day. However, the role of soy in preventing cardiovascular disease, specifically in postmenopausal women, has yet to be studied. Long-term studies need to be undertaken to determine if this observed lipid-lowering effect translates into a decreased incidence of cardiovascular events and cardiovascular mortality in postmenopausal women.

VITAMINS C, E, AND B CAROTENE

Earlier observational studies seemed to indicate that patients with a higher consumption of vitamins C, E, and B carotene had lower incidences of ischemic heart disease. However, subsequent randomized controlled trials and systematic reviews indicate that no reduction in cardiovascular disease occurs in patients who supplement their diets with vitamins C, E, or B carotene.³⁷⁻³⁹ The literature does not specifically address this question with regard to postmenopausal women.

FISH OIL: OMEGA-3 FATTY ACIDS AND N-3 POLYUNSATURATED FATTY ACIDS

All three prospective randomized trials assessing fish oil for the secondary prevention of cardiac events showed positive results.⁴⁰⁻⁴² In the largest trial,⁴¹ over 11,000 postinfarction patients who received 850 mg of omega-3 fatty acids per day experienced a 45 percent reduction in the rate of sudden cardiac death and a 20 percent reduction in the total mortality rate. What is impressive about this trial is that benefits occurred in patients already receiving “standard” postinfarction therapy (e.g., angiotensin-converting enzyme inhibitors, beta blockers, antiplatelet

Hormone replacement therapy was once believed to reduce cardiac events in postmenopausal women, but recent evidence seems to contradict earlier observational studies.

TABLE 2
Fish Oils

Amount (g) of omega-3 fatty acids per 100 g of fish (about 3 oz)	
Salmon, 1.1	Herring, 1.5
Albacore, 1.3	Mackerel, 1.8
Amount (g) of omega-3 fatty acids per g of oil	
Cod liver oil, 0.19	
80% omega-3 fatty acid concentrate, 0.8	

Adapted with permission from O’Keefe JH, Harris WS. From inuit to implementation: omega-3 fatty acids come of age. Mayo Clin Proc 2000;75:607-14.

agents). It is theorized that these effects are the result of the membrane-stabilizing effect of these oils. Though these results are impressive in women with established CHD, no large trials have yet addressed the use of n-3 polyunsaturated fatty acids as a means of primary prevention in postmenopausal women who are at risk (Table 2).⁴³

RED CLOVER

Red clover is sometimes used as an aid to prevent cardiovascular disease. This supplement has been shown to improve systemic arterial compliance and elasticity, an indicator of cardiovascular risk that decreases after menopause.⁴⁴ Red clover has not been shown to improve plasma lipids, and it has not been studied long-term to determine if increased arterial compliance leads to a decrease in cardiovascular mortality.

Preventing Bone Loss

It is well documented that the rate of bone loss increases significantly after menopause. Alternative therapies, such as soy and magnesium, may be of benefit.

SOY

The effect of soy (i.e., isoflavone) on bone density has recently been evaluated. In one small study,⁴⁵ 66 postmenopausal women consumed 40 g of soy protein (standardized to 2.25 mg of isoflavone per g of protein) per day during a six-month trial. The study noted an increase in lumbar spine bone mineral density of 2.2 percent during the study period. No bone density differences were noted

TABLE 3

Summary of Alternative Treatments for Menopausal Indications

<i>Indication</i>	<i>Agent</i>	<i>Summary of evidence</i>
Vasomotor symptoms: effective treatments	Exercise	Observational trials show an association between exercise and decreased vasomotor symptoms
	Soy	One RCT shows efficacy
	Black cohosh	One RCT of questionable quality shows efficacy
	Progesterone	Effective, but limited by adverse effects
Vasomotor symptoms: ineffective treatments	Dong quai	One RCT shows no efficacy
	Evening primrose oil	One RCT shows no efficacy
Vasomotor symptoms: equivocal evidence	Ginseng	No evidence
	St. John's wort	Equivocal evidence
	Micronized progesterone	No evidence
Prevention of cardiovascular disease: effective treatments	Soy	Lowers lipid levels, but no evidence regarding mortality
	Fish oil	3 RCTs showing benefit for secondary prevention only
Prevention of cardiovascular disease: ineffective treatments	Red clover	No evidence
Prevention of osteoporosis: equivocal evidence	Soy	May increase bone density; no evidence on prevention of fractures
	Magnesium	Observational studies suggest increase in bone density; no evidence on prevention of fractures

RCT = randomized controlled trial.

Information from references 13-17,25,27,28,32,33,40-48.

in the hip.⁴⁵ So far, there have been no studies documenting the role of soy in preventing fractures or increasing hip bone mineral density.

A more recent review⁴⁶ concluded that “the data on naturally occurring isoflavones are limited but suggest that including them in diets results in a reduction in bone resorption caused by estrogen deficiency.” Considering the potentially beneficial effects on bone as well as the previously mentioned cardiovascular benefits, it seems that soy in the diet of postmenopausal women could be beneficial.

MAGNESIUM

Magnesium deficiency might also contribute to decreased bone mineral density. Magnesium suppresses parathyroid hormone, which reduces calcium absorption and retention.

Some animal studies⁴⁶ suggest that magnesium deficiency might result in decreased bone mineral densities, and other observational studies⁴⁷ have shown that elderly patients whose diets have higher intakes of magnesium have increased bone mineral density. However, long-term randomized, placebo-controlled studies evaluating the role of magnesium supplementation in the prevention of osteoporosis and fractures are lacking in the literature.

A magnesium intake of 600 mg per day has been shown to be an adequate amount to maintain bone reserve. However, most dietary surveys conducted in the

United States reveal that the average diet contains less than 300 mg of magnesium per day. *Table 3*^{13-17,25,27,28,32,33,40-48} provides a summary of alternative treatments for menopausal symptoms.

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