Treating hot flushes without hormone replacement therapy

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Practice recommendations

- Ask your patients about complementary and alternative therapies; 21% of women say they use complementary or alternative therapies only, and another 25% say they use both conventional and alternative methods.
- Women who take 50 mg of soy isoflavones daily report a 10% to 20% absolute risk reduction (number needed to treat, 5–10) in the frequency of hot flashes. The duration of this effect is unknown.
- Black cohosh yields up to an 80% improvement in hot flashes.
- Patients should use an alternative therapy for at least 1 month and keep a symptom diary to adequately assess its effect.

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Physicians may recommend alternative treatments for hot flashes with the same confidence they have in prescription drugs if they understand the expected results, risks and benefits, and interactions with other medications.

For treatment of hot flashes, an increasing number of menopausal women are choosing plant-based alternatives to hormone replacement therapy (HRT). Despite HRT's proven efficacy in treating this plaguing symptom, many patients are fearful that HRT might lead to an increased risk of breast or uterine cancer, increase the risk of vascular disease including heart attack, or cause unpleasant side effects such as mood swings, depression, or continued menstrual periods.[1]

EDITOR'S COMMENT

Dr. Seibel, an expert in non-hormone replacement therapy and a proponent of soy, provides his view of options in this important area. He argues that treatment with the more promising soy and black cohosh preparations is worth considering as part of a careful "N of 1" trial. Read this issue's Clinical Inquiry, "What nonhormonal therapies are effective for postmenopausal vasomotor symptoms?" (pages 324–329), and you be the judge. *—Jeffrey L. Susman, MD*

How pervasive are alternative therapies?

So-called alternative approaches to menopause are used so widely it might be more accurate to consider hormone replacement therapy as the true alternative medicine. Statistics presented at the National Institutes of Health on October 27, 2000, indicate that nearly half of all menopausal women are using complementary therapies—including vitamins, herbs, and soy products—to help treat their symptoms. Twenty-one percent of the women surveyed used complementary or alternative therapies alone, and 25% said they used both conventional and alternative methods.

Taken together, that is more than twice the 19% who said they used conventional hormone replacement therapy only. Given this enormous usage, it should come as no surprise that, in 2001, the dietary supplement industry likely exceeded $12 billion in sales in the United States alone.[4] For many women, the decision to use an alternative is not so much dissatisfaction with conventional treatment, but that they regard the complementary agents as more congruent with their own values, beliefs, and philosophical orientations toward health and life.[5]

One study of 2500 postmenopausal women found that 20% to 30% never fill their initial HRT prescriptions, 10% of those who use estrogen do so only intermittently, an additional 20% discontinue their therapy within 8 months, and only 15% to 20% of women will take HRT for more than a year.[2]

HRT is contraindicated in about 10% of postmenopausal women[3]; the Womens' Health Initiative[4] and the Heart and Estrogen/progestin Replacement Study[5] (HERS) trials have suggested caution in using HRT even for those without contraindications.

With such an enormous number of women either unwilling or unable to take HRT, it is important to consider the alternatives you can offer.[6,7] (See "How pervasive are alternative therapies?") Whichever alternative treatment you and a patient select, give it at least 1 month (and preferably 3 months) to assess its effectiveness. Keeping a symptom diary will allow patients to objectively track their progress.

SOY

Much of the excitement about the health benefits of soy—a staple of the Asian diet for 5000 years—stems from epidemiological studies. The Asian diet, which is rich in isoflavones, is associated with a reduced risk of breast cancer, heart disease, and osteoporosis. Asian women also report fewer hot flashes than do their Western counterparts.[8] One study showed that women in Western countries have an 80% incidence of hot flashes, while Asian women living in China have an incidence of only 20%.[9]

Clearly, factors other than soy also must be considered before we can make a direct cause-and-effect correlation. To that end, many studies have been conducted on the health benefits of soybeans, a rich source of the isoflavones genistein and daidzein.

Physiologic activity

Isoflavones are phytoestrogens with a heterocyclic phenol structure that is similar to estrogen. Their potency is between 1×10^4 and 1×10^3 the activity of 17β-estradiol.[10] Although their potency is low, their serum concentrations can reach levels several orders of magnitude higher than those of physiologic estrogens. It is generally believed that isoflavones act as a selective estrogen receptor modulator, exerting antiestrogenic effects in the high-estrogen environment of premenopause and estrogenic effects

TABLE 1

Positive trials* of soy in the treatment of hot flushes

Absolute risk reduction of hot flushes (%)						
Study	**N**	**Design**	**Soy**	**Control**	**NNT**	**LOE†**
Murkies 1995[11]	58	45 g soy flour	42	25	6	1b
Brzezinski 1997[12]	73/72	Mostly soy, 1/4 diet, some flaxseed	54	35		
Albertazzi 1998[13]	51/53	60 g soy protein	43.6	31.3	8.1	2b
Scambia 2000[14]	39	50 mg/d isoflavones	45	25	1b	
Upmalis 2000[15]	177	50 mg/d isoflavones	30	20	1b	

From Seibel MM, *The soy solution for menopause: an alternative to estrogen.* New York, NY: Fireside Press, 2003.

*None of the above trials were of high quality—all either had a large number of dropouts, substantial divergence of outcomes, a small "n" (number of subjects) or other substantive methodological concerns.

NNT, number needed to treat; LOE, level of evidence

†See page 290 for a description of strength of recommendation.

in the low-estrogen environment of postmenopause.

Clinical efficacy

Hot flushes. An increasing number of studies suggest that soy and soy isoflavones—in the form of soy flour, soy protein, and dietary supplements—may play an important role in the treatment of hot flushes. In general, the average amount of isoflavones consumed in a typical Asian diet is approximately 50 mg/day. (One gram of soy protein contains approximately 1 mg of isoflavones.)

Unfortunately, clinical trial data are confounded by varying preparations of soy, length of therapy, outcomes measured, and small sample sizes. The absolute risk reduction of soy preparations versus placebo or comparators in positive trials ranges from 10% to 20% (number needed to treat [NNT]=6–10) when frequency of hot flushes is the outcome measured (**Table 1**).[11–15]

Placebo effect. All soy studies also confirm the existence of a placebo effect on the treatment of hot flushes. The large placebo effect and varied efficacy has left many skeptics questioning the clinical efficacy of soy products.[16]

I believe that thinking is wrong. Women who have hot flushes tend to have lower sleep efficiencies and longer REM latencies than women who do not experience this vasomotor symptom.[17] By lowering the frequency of hot flushes, soy may produce greater sleep efficiencies and improve quality of life.

Safety

Soy has been safely consumed by hundreds of millions of people without complications, with t he possible exception of soy allergies (**Table 2**). The literature suggests it is safe and effective in dosages of either 40 g of soy protein or 50 mg of soy isoflavones per day. Soy does not stimulate the uterine lining and may be protective of the endometrium if taken with estrogen.

The incidence of breast cancer is one fourth as high in Asia as in the US; many studies have shown soy to be protective of breast tissue. However, soy may stimulate breast tissue in women with a his-

TABLE 2

Remedies for hot flushes and their adverse effects, interactions, and contraindications

	Adverse effects	Important drug interactions	Contraindications
Soy	Bloating, flatulence	Thyroid hormone, if taken simultaneously	Use with caution in patients being treated for hypothyroidism (soy may bind thyroid medication, thus lowering absorption; patients on thyroid hormone should use soy only in supplement form or take at a time distant from thyroid medication)
Black cohosh	Abdominal pain, nausea, headaches, dizziness, trembling limbs	Iron therapy medications	Patients with iron deficiencies; use cautiously in patients with breast cancer or high risk of breast cancer
Dong quai	Photodermatitis, rash	Warfarin (effects potentiated)	Patients with coagulopathies or very heavy menstruation and acute viral infections such as colds or influenza; pregnancy
Evening primrose oil	Nausea, softening of stools, headaches, seizures	Anticonvulsant and tricyclic antidepressants	Patients taking anticonvulsants and tricyclic antidepressants (lowers efficacy)
Red clover	Blood thinning	Anticoagulants such as coumadin, heparin, clopidrogel, pentoxifylline, or aspirin	Patients with coagulopathies

tory of breast cancer. The evidence in these areas is conflicting and controversial.

In contrast to herbal alternatives to HRT, soy has been thought to lower cholesterol, make blood vessels more elastic (increase vascular elasticity), and slow osteoclast activity in bones. It is also an excellent source of protein, and is lactose- and cholesterol-free.[18]

BLACK COHOSH

A member of the buttercup family, black cohosh (*Actaea* [formerly *Cimicifuga*] *racemosa*) has a long history in folk medicine, especially among Native Americans, who boiled the root in water and drank the resulting beverage to treat dysmenorrhea, labor pain, upset stomach, and arthritis. In Germany, extracts of black cohosh have been used since the 1940s.

Many substances have been identified in the rhizome, but it is uncertain what the majority of them do or, in fact, which are active ingredients.[19] The effectiveness of black cohosh is based on the total amount of triterpenoid glycosides, typically standardized to 2.5%.[20]

Several studies, most of them in the German literature, have shown that black cohosh yields a significant improvement in hot flushes, with reductions of up to 80% reported (level of evidence [LOE]: **2b**).[21–23] The usual dosage is 40 drops of the extract twice daily for 6 to 8 weeks, or one to two 20-mg tablets twice daily with liquid (not to be chewed or sucked).

Side effects are uncommon, but occasional stomach pains and intestinal discomfort, dizziness, nausea, severe headaches, stiffness, and trembling limbs have been noted. Germany's Commission E, which is similar to the US Food and Drug Administration, recommends that black cohosh not be used for more than 6 months, since no studies have been conducted for longer periods.

Black cohosh has weak estrogenic effect on the breast and should be used cautiously in patients with breast cancer or a high risk of breast cancer. A 2-month double-blind, randomized controlled trial of black cohosh in breast cancer survivors demonstrated no short-term side effects; however, therapy was only significantly beneficial in relieving sweating and ineffective in reducing flushes.[24] The long-term effects are unknown. A recent systematic review suggests that the side effects of black cohosh are transient, and severe adverse event reports are unproven (**Table 2**).[24]

DONG QUAI

Dong quai, a common Chinese herb extracted from the *Angelica sinensis* root, has become popular in the US. In contrast to China, where it is sold as part of a mixture that includes several other herbs, dong quai typically is sold in the US as a single herb.

Although some women report improvements in their vasomotor symptoms, there have been very few studies on the effects of dong quai on menopause. In one 24-week study of 71 postmenopausal women, researchers could not demonstrate a significant difference between dong quai and placebo in alleviating vasomotor symptoms (LOE: **2b**).[25] The investigators suggested that studying the effects of dong quai alone, rather than in combination with other herbs, may have been a factor in their findings.

By lowering the frequency of hot flushes, soy may produce better sleep and improve quality of life

Two caveats: Dong quai increases photosensitivity, so women taking the herb should be cautioned that too much exposure to sunlight may result in a rash. Also it has been reported to potentiate the effects of warfarin (**Table 2**). It should not be used during pregnancy.[26]

EVENING PRIMROSE

Native Americans consumed the leaves, roots, and seedpods of evening primrose (*Oenothera biennis*) for food, and made extracts from it to treat a variety of conditions. Today, the flowers and seeds are pressed to make oil that is high in the omega-6 fatty acid gamma-linolenic acid (known as GLA) and essential polyunsaturated fatty acids, which convert into prostaglandins. Evening primrose oil also is a good source of linoleic acid.

Although there are a number of good studies in which evening primrose oil has been used to successfully treat eczema and several other conditions with few side effects, it appears to have no benefit over placebo for hot flushes (LOE: **2b**).[27]

Patients should be warned that mild upset stomach, indigestion, nausea, softening of stools, and mild headaches may occasionally occur. Also, evening primrose is contraindicated in women taking seizure medications or antipsychotics because it lowers the seizure threshold in patients on phenothiazines (**Table 2**).

RED CLOVER

Red clover (*Trifolium pratense*) is a plant that contains the phytoestrogens formononetin, biochanin A, daidzein, and genistein. It was

Evening primrose oil appears to have no benefit over placebo in the treatment of hot flushes

originally used by Native Americans to treat whooping cough, gout, and cancer.

Two clinical trials conducted in Australia failed to demonstrate that red clover extract was more effective than placebo in reducing vasomotor symptoms (LOE: **2b**).[28,29] However, one recent presentation found that women who took 40 mg of red clover per day—the recommended dosage—experienced a significant reduction in hot flushes.[30]

There is still little information on whether red clover will have any effect on the uterine lining or breast tissue. Because red clover contains coumarin-like substances, high dosages may cause the blood to thin (**Table 2**).[31]

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