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**Title**

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**Permalink**

<https://escholarship.org/uc/item/61r9p16k>

**Journal**

Annals of Internal Medicine, 145(12)

**ISSN**

1056-8751

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**Publication Date**

2006-12-19

**DOI**

10.7326/0003-4819-145-12-200612190-00009

Peer reviewed

## A Randomized Trial of Alternative Medicines for Vasomotor Symptoms of Menopause

Menopause occurs in women as part of normal aging. Many go through this transition with few or no symptoms, while some have substantial or even disabling symptoms (1). The vasomotor symptoms of hot flashes—sudden sensations of intense heat with sweating and flushing typically lasting 5 to 10 minutes—and night sweats are the most prevalent perimenopausal symptoms (2). Vasomotor symptoms vary by race and ethnicity, and the late phases of the menopausal transition are associated with the highest frequency of these events (10% to 60%) (3).

A variety of treatments has been studied in randomized clinical trials (RCTs) for the management of menopausal symptoms (2). The most intensively studied treatment is estrogen. It is often combined with progestin, and when used by itself or with progestins, it is the most effective therapy for vasomotor symptoms, reducing their frequency by about 77% (4).

In 2002, results from the Women's Health Initiative's (WHI) showed that estrogen therapy with or without medroxyprogesterone increases the risk for serious disease events. This substantially dampened the enthusiasm for use of this hormone as a treatment for menopausal symptoms (5)—annual dispensed prescriptions for estrogen declined from 91 million in 2001 to 57 million in 2003 (6). The "quick time to serious event" observed in the WHI and other estrogen RCTs raised further concern that even short-term use of estrogen may carry unacceptable health risks. However, some women have such severe vasomotor symptoms that they and their physicians are willing to assume the risks of estrogen.

During the post-WHI era, the search for safer and effective treatments for menopausal symptoms intensified, and a growing number of RCTs are examining the effectiveness of other hormones, antidepressants, isoflavones and other phytoestrogens, botanicals, acupuncture, and behavioral interventions (7). However, many studies cannot support reliable conclusions because of faults in study design, conduct, or analysis. In this context, Newton and colleagues' (8) report of the Herbal Alternatives for Menopause Trial (HALT) is especially important: The study is a well-designed, adequately powered RCT that makes an important contribution, albeit one that will disappoint women who have been hoping for an effective, safe alternative to estrogen.

The HALT randomly assigned 351 women who were 45 to 55 years of age (approximately one half were in menopausal transition and one half were postmenopausal) and had at least 2 vasomotor symptoms a day to 1 of 5 groups: 1) black cohosh; 2) multibotanical with black cohosh and 9 other ingredients; 3) multibotanical plus dietary soy counseling; 4) conjugated equine estrogen, 0.625

mg daily, with or without medroxyprogesterone acetate, 2.5 mg daily; or 5) placebo. After publication of the results of the WHI, the authors stopped randomly assigning participants to the hormone group of HALT. Participants completed symptom diaries and the Wiklund Vasomotor Symptom Subscale at 3, 6, and 12 months. The trial found no statistically significant reduction in the number or intensity of vasomotor symptoms per day between the herbal intervention and placebo groups at any of the follow-up times. Of importance for the overall interpretation of this trial, and as would be expected, hormone therapy significantly reduced vasomotor symptoms by an average of 4.06 symptoms per day more than placebo.

The focus on black cohosh (*Actaea racemosa* or *Cimicifuga racemosa*), multibotanical supplements, and dietary soy and the trial's negative results are important because use of these herbs and supplements has grown dramatically, even though little is known about their long-term safety or interactions with other medications. Population-based studies of the use of complementary and alternative medicine suggest that approximately 12% of U.S. women are taking herbal preparations on an annual basis. The highest use is in precisely the group studied in this trial: white women between the ages of 45 and 55 years (9).

Only a few of the botanical products on the market have been carefully studied. As noted in the National Institutes of Health State-of-the-Science report (1), progress has been slow, in part because of methodological challenges. For example, the content of the botanicals is not uniform, in part because of variation in nature and because manufacturers use different methods to make the end product. Because of these concerns, Newton and colleagues were careful to test the content of the one batch of black cohosh used in this RCT. Interpretation of the trials evaluating botanicals has also been hampered by small sample sizes, short follow-up, and lack of comparable control groups.

Black cohosh, one of the main agents studied in HALT, has been the most studied botanical for the treatment of menopausal symptoms. Taken in aggregate, the results from previous trials have been inconclusive. Because of the inclusion of a placebo and an estrogen replacement group in HALT, a 12-month follow-up, and a 92% trial completion rate, HALT provides strong evidence that black cohosh is ineffective for the treatment of vasomotor symptoms.

Although most trials evaluating soy products for the treatment of vasomotor symptoms are negative (2), HALT's negative dietary soy results are not definitive because it seems that the majority of the participants ran-

domly assigned to this group did not achieve the target level of soy intake (at least 2 soy-containing foods a day).

The HALT has other important strengths. The authors selected a clinically important minimum effect size: one half of the observed benefit from hormonal therapy. Researchers paid close attention to between-group imbalance among patient-level characteristics associated with the severity of vasomotor symptoms. Finally, they did a carefully selected set of sensitivity analyses, none of which changed the main results.

As with many clinical trials, little can be said about the applicability of the results to a widely representative population. The women who enrolled in HALT were highly selected. The recruitment procedure included mailing 157 493 brochures, which led to 3443 responses and attendance at a screening visit by 509 women. At this visit, 398 women were deemed eligible and 351 enrolled. Given this steep funnel to enrollment, it is likely that the average HALT participant was much more symptomatic than most women who are going through menopause. Newton and colleagues report that the women in HALT experienced an average of 6 vasomotor symptoms a day—a frequency much higher than that reported in many population-based studies. The women also were more educated and were predominantly white. Therefore, we cannot be sure that the findings from HALT would apply to all symptomatic women in menopause transition.

The HALT provides important information for women who are having moderate to severe vasomotor symptoms: Black cohosh is not effective. Because most participants in the multibotanical plus dietary soy counseling groups did not increase their soy intake to the target level, this trial was probably not an adequate test of dietary soy for treatment of vasomotor symptoms. On the other hand, it is easy and probably safe for symptomatic women to try to increase dietary soy and determine whether symptoms are better.

The good news from HALT has to do with the natural history of vasomotor symptoms. Women in the placebo group experienced an approximately 30% reduction in the severity and frequency of vasomotor symptoms during the 12-month follow-up period. This finding is consistent with the observed 30% to 35% decline in vasomotor symptoms among the placebo groups in a number of the large, well-designed clinical trials (2). This high rate of spontaneous resolution of symptoms may be part of the natural progression of menopausal symptoms or may be due to other treatments, self-care practices, or possibly regression to the mean. Because of this consistent finding, any trial evaluating new treatments must have a randomized design and must include a placebo or control groups. Because of the emphasis in the lay press on the negative symptoms associated with menopause, many women enter this phase of

normal aging expecting to have severe symptoms, yet population-based studies suggest otherwise. Therefore, if a woman is not severely bothered by her vasomotor symptoms, it is important to reassure her that she has a good chance of having fewer symptoms within 6 to 12 months. Indeed, she may not need treatment at all.

This study reminds us of the need to perform RCTs to evaluate new biologically plausible agents and behavioral treatments in multiethnic populations of women. Although only some women will have severe, prolonged vasomotor symptoms, they clearly need treatment options that are safe and effective. Therefore, we must continue the search for new treatments and behavioral approaches to managing vasomotor symptoms, and we must test them carefully. The HALT shows us how.

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**Potential Financial Conflicts of Interest:** None disclosed.

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