

CLINICAL INQUIRIES

What nonhormonal therapies are effective for postmenopausal vasomotor symptoms?

■ EVIDENCE-BASED ANSWER

Regular exercise may reduce vasomotor symptoms of menopause (strength of recommendation [SOR]: **C**—single observational study).¹

Soy products/isoflavones, either through diet or supplementation, may reduce the incidence of hot flashes (SOR: **D**—inconsistent results of randomized trials).²

Clonidine, as an oral or transdermal preparation, reduces hot flashes (SOR: **A**—randomized clinical trials),³ as does gabapentin (SOR: **A**—single randomized clinical trial).⁴

In cancer patients who have had surgical menopause, selective serotonin reuptake inhibitors⁵ and megestrol⁶ (Megace) have been effective in reducing hot flashes (SOR: **A; B** for extrapolation to the general population).

Other therapies—including Bellergeral (a combination of belladonna, ergotamine, and phenobarbital), methyldopa, evening primrose oil, ma quan, flaxseed, ginseng, and topical wild yam extract—have not been effective.⁷ Black cohosh may be effective, but the evidence for this is of poor quality (SOR: **C**). (See **Table**.)

TABLE

Nonhormonal therapies for postmenopausal vasomotor symptoms

Agent	Effective	SOR [†]	Comments
Soy/isoflavones	Maybe	D	Multiple RCTs with conflicting results, no formal meta-analysis. Does have a positive effect on lipid profile
Clonidine (Catapres)	Yes	A	Multiple small RCTs
Venlafaxine* (Effexor)	Yes	B	Single RCT
Fluoxetine* (Prozac)	Yes	B	Single RCT
Gabapentin (Neurontin)	Yes	A	Single RCT
Megestrol* (Megace)	Yes	B	Single RCT
Exercise	Maybe	C	Single observational study
Black cohosh	Maybe	C	German E commission recommendation positive in 1989, but only 1 of 7 trials cited had placebo control. Recent RCT showed no benefit
Other: Bellergeral, methyldopa, evening primrose oil, ginseng, wild yam extract, ma quan, flaxseed	No	C	All have been advocated but no positive trials for any evidence of effect

*Trials conducted only with patients with breast cancer and interventional menopause, most of whom were on anti-estrogen therapy.
[†]See page 290 for a description of strength of recommendation.
 SOR, strength of recommendation; RCT, randomized controlled trial

■ EVIDENCE SUMMARY

Hormone replacement therapy (HRT) is the standard treatment for vasomotor symptoms of menopause, and it is effective for this indication. With recent studies showing no benefit from long-term HRT for menopausal women and increased adverse effects with its use (especially for women at risk for coronary heart disease), there has been increased interest in nonhormonal treatments for these symptoms.

A small number of randomized clinical trials have studied treatments other than HRT for the control of vasomotor symptoms of menopause. As a group, these trials have been short-term and have involved small numbers of patients. A disproportionate number of trials have been completed in breast cancer survivors, since these patients tend to have more severe vasomotor symptoms as a result of their anti-estrogenic therapies. Whether these results can be generalized to all postmenopausal women with vasomotor symptoms cannot be determined from the evidence.

Eleven randomized trials of *soy protein/isoflavone* used placebo controls. Results were mixed, with 7 trials showing no effect and 4 showing a reduction in hot flushes in comparison with placebo. Studies reporting a positive effect showed approximately a 15% reduction in episodes in comparison with placebo. In one 6-month trial, there was a correlation between hot flushes and urinary isoflavone excretion regardless of treatment group, suggesting a confounding effect of dietary intake of isoflavone.

Five of six randomized controlled trials of *clonidine* have shown a reduction in frequency of hot flushes ranging from 14%–50% compared with placebo. One trial, which used oral clonidine 0.1 mg daily, also reported an improved quality of life for the treatment group. A single randomized trial has shown that *gabapentin*, at a dose of 900 mg/day, is effective in reducing both frequency and severity of hot flashes.⁴

Trials of specific *selective serotonin reuptake inhibitors* have been completed in patients with vasomotor symptoms secondary to breast cancer

therapies. Individual randomized controlled trials of venlafaxine and fluoxetine have proven these agents effective, and a preliminary open-labeled trial of paroxetine has also suggested benefit.

Several reviews suggest *black cohosh* may be effective for short-term treatment, and it is used in Germany for this indication. The trials we found were not placebo-controlled, however, and the safety of this agent is controversial. A single English-language placebo-controlled trial did not show any benefit for black cohosh.

■ RECOMMENDATIONS FROM OTHERS

The American College of Obstetrics and Gynecology clinical management guideline, “The use of botanicals for management of menopausal symptoms,” gives a level C recommendation (consensus and expert opinion) that “Soy and isoflavone may be helpful in short-term (≤ 2 years) treatment of vasomotor symptoms” and “black cohosh may be helpful in the short-term (≤ 6 months) treatment of women with vasomotor symptoms.” They note that “given the possibility that these compounds may interact with estrogen, these agents should not be considered free of potential harm in women with estrogen-dependent cancers.”⁸

The North American Menopause Society notes that behavior changes, such as moderate exercise and avoidance of hot-flush triggers, may prevent some hot flushes, although there is only anecdotal evidence for this. The efficacy of paced respiration—deep, slow abdominal breathing—to lessen hot flushes has been shown in a small trial. The society states that other alternative therapies have not been shown to be efficacious, except for moderate quantities of soy products.⁹

The Medical Letter says the evidence that phytoestrogens are helpful for menopausal women comes mostly from epidemiological studies. The long-term adverse effects of phytoestrogen consumption are not known.¹⁰

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■ CLINICAL COMMENTARY

Behavioral modifications may be the first approach to reduce the incidence of vasomotor symptoms in menopausal women. Recommendations include wearing several layers of breathable clothing; keeping a glass of cold water, ice pack, or small fan by the bedside and nearby at work; performing deep breathing relaxation techniques; and exercising routinely.

Effective nonhormonal treatments include phytoestrogens (≤ 2 years), black cohosh (≤ 6 months), clonidine, selective serotonin reuptake inhibitors, and venlafaxine. Overall, there are few well-designed clinical trials regarding the safety and effectiveness of botanical agents used for vasomotor symptoms. Since the Food and Drug Administration does not regulate the marketing and standardization of these products, patients should be advised to purchase products from reputable companies with internal standardization processes.

Additionally, patients should talk with their health care provider prior to initiating any alternative medication to avoid drug-disease and drug-drug interactions.

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What treatments are effective for varicose veins?

■ EVIDENCE-BASED ANSWER

For larger trunk varicose veins, as in the saphenous vein, therapeutic options include conservative measures (such as leg elevation and compression stockings), injection sclerotherapy, and surgical vein ligation, with or without stripping. Long-term outcomes appear superior with surgical treatment.

For mid-sized reticular veins and spider telangiectasias, several options are available, including sclerotherapy, laser ablation, and thermal ablation. However, no randomized trials have compared the relative effectiveness of these treatments.

Venotonic medications (primarily plant-derived and synthetic flavonoids, such as horse chestnut seed extract, that improve venous tone) provide symptom relief. Head-to-head comparisons are needed to identify the most efficacious therapies (strength of recommendation: **C**, based on case series and extrapolations from small trials.)

■ EVIDENCE SUMMARY

Graduated elastic compression stockings improve lower-extremity hemodynamics (including reflux and residual volume measured by color flow duplex scanning) in patients with varicosities, and can improve symptoms such as swelling, discomfort, and leg tightness.^{1,2}

A Cochrane review concluded that existing evidence supports the use of sclerotherapy for recurrent varicose veins after surgery and