Nonhormonal Therapies for Hot Flashes in Menopause

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Numerous reports in the medical literature and popular media have discussed the effectiveness of various nonhormonal agents in reducing menopausal hot flash symptoms. Data for these therapies are limited, and most of the studies have been conducted in women with a history of breast cancer. Selective serotonin reuptake inhibitors and venlafaxine have been shown to reduce hot flashes by 19 to 60 percent and were well tolerated by study participants. Soy isoflavones reduced hot flashes by 9 to 40 percent in some trials, but most trials showed no difference compared with placebo. Black cohosh and red clover also have had inconsistent results, with some trials showing benefit and some no difference compared with placebo. Soy isoflavones, black cohosh, and red clover were well tolerated in clinical trials. Other agents that have been used to alleviate hot flashes include belladonna/ergotamine tartrate/phenobarbital combination, dong quai, evening primrose oil, gabapentin, ginseng, mirtazapine, trazodone, vitamin E, and wild yam, but few data regarding their effectiveness have been published. Further randomized controlled trials are needed. (Am Fam Physician 2006;73:457-64, 467. Copyright © 2006 American Academy of Family Physicians.)

▶ **Patient information:** A handout on nonhormonal options for hot flashes is provided on page 467.

The results of the Women's Health Initiative (WHI) study[1] of hormone therapy in postmenopausal women, published in 2002, have prompted many women and primary care physicians to reconsider the use of estrogen and progesterone hormone therapy to alleviate hot flashes. In the study,[1] 16,608 healthy, postmenopausal women with an intact uterus were randomized to receive therapy with conjugated equine estrogens plus medroxyprogesterone acetate, or placebo. The study was stopped early because researchers found increased incidences of breast cancer (number needed to harm [NNH] = 1,250), coronary heart disease (NNH = 1,428), stroke (NNH = 1,250), and pulmonary embolism (NNH = 1,250) in the treatment group when compared with the placebo group.[1] Many women find the risks associated with hormone therapy to be unacceptable and are requesting nonhormonal therapies to manage their hot flash symptoms. There have been numerous reports in the medical literature and general media as to the effectiveness of various over-the-counter and prescription agents in reducing menopausal hot flash symptoms. The following is a review of the published data for several of these agents *(Table 1)*. Key recommendations for different regimens are listed in the strength of recommendations (SORT) table, with the study duration and the dosages used. Study considerations and limitations are listed in *Table 2*.[2-33] A potential confounder in most hot flash trials is the placebo response rate, which in the studies evaluated for this review was reported as between 18 and 40 percent. This is similar to

TABLE 1
Nonhormonal Agents Used as Therapy for Hot Flashes

Prescription	Nonprescription
Belladonna/ergotamine tartrate/phenobarbital combination (Bellergal,* Bellamine)	Black cohosh
Clonidine (Catapres)	Dong quai
Fluoxetine (Prozac)	Evening primrose oil
Gabapentin (Neurontin)	Ginseng
Mirtazapine (Remeron)	Melatonin
Paroxetine (Paxil)	Red clover isoflavones
Trazodone (Desyrel)	Soy isoflavones
Venlafaxine (Effexor)	Vitamin E
	Wild yam

**—Bellergal is no longer available commercially in the United States.*

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Daily dosages used in studies*	*Study durations*	*Evidence rating*	*References*
Black cohosh may be effective for short-term treatment of hot flashes.	16 to 127 mg	Eight weeks to one year	B	29-33, 40
Clonidine (Catapres) is an effective option for treating hot flashes.	0.1 mg	Eight to 12 weeks	B	10-12
Fluoxetine (Prozac) is an effective option for treating hot flashes, based on limited evidence.	20 mg	Nine weeks	B	5
Paroxetine (Paxil) is an effective option for treating hot flashes.	20 to 40 mg	Four weeks	B	3, 4
Soy and other isoflavones may be helpful in the short-term treatment of hot flashes.	40 to 164 mg	Seven to 12 weeks	B	16, 19, 20, 28
Venlafaxine (Effexor) is an effective option for treating hot flashes.	37.5 to 150 mg	Four to 12 weeks	B	7-9

NOTE: *See Table 2 for study considerations and limitations. All dosages and durations listed are those used in the specific studies, not necessarily the recommended dosage or duration of therapy.*

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 374 or http://www.aafp.org/afpsort.xml.

rates found in studies of hormonal agents, but makes it more difficult to ascertain the true effects of therapy on hot flashes.

SSRIs and Venlafaxine

SUMMARY

Studies of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine (Effexor), a serotonin and norepinephrine reuptake inhibitor, have shown an absolute risk reduction (ARR) in hot flashes of 19 to 60 percent with these agents compared with placebo (number needed to treat [NNT] = 2 to 5), primarily in women with a history of breast cancer.[2-9]

MECHANISM OF ACTION

The exact mechanism of action by which these medications alleviate hot flashes is unknown, although hot flashes have been linked to an imbalance in serotonin.[2,6,34]

STUDIES

Initial pilot studies[3,4,6] reported 50 to 67 percent decreases in hot flashes among women with a history of breast cancer; these results prompted larger studies. In a randomized crossover study[5] involving 87 women with a history of breast cancer who received fluoxetine (Prozac), patients experienced a median 19 percent decrease in the frequency of hot flashes ($P = .01$). In another randomized study,[7] researchers evaluated the effectiveness of venlafaxine at three different dosages in reducing hot flashes among 228 women with a history of breast cancer. Forty-five percent of patients receiving low-dosage venlafaxine (37.5 mg daily) experienced at least a 50 percent reduction in hot flashes, compared with 63 percent of patients receiving a moderate dosage (75 mg daily), 55 percent of patients receiving a high dosage (150 mg daily), and 20 percent of patients receiving placebo.

When using a selective serotonin reuptake inhibitor or venlafaxine to treat hot flashes, it is prudent to initiate the medication at a low dosage and titrate to effect.

All venlafaxine treatment groups had a significant change in mean hot flashes compared with the placebo group ($P < .0001$). This trial[7] was continued as an open-label study with 157 participants. The venlafaxine dosages were titrated to desired effect or continued at previous dosages if effective. Overall, hot flashes were decreased by 60 percent compared with baseline. Patients who previously received a high or moderate dosage maintained their initial responses, and patients who previously received a low dosage or placebo experienced significant reductions in hot flashes.[8]

Two studies[2,9] involved women who did not have a history of breast cancer. In one study,[2] 165 postmenopausal women were randomized to receive controlled-release paroxetine (Paxil CR) in a low or high dosage or placebo. Participants experienced reductions in hot flash scores of 37 percent in the placebo group, 62 percent in the low-dosage group, and 65 percent in the high-dosage group ($P < .001$). However, the U.S. Food and Drug Administration (FDA) withdrew Paxil CR from the market in March 2005 because of concerns regarding its manufacturing quality. In a study[9] of 80 postmenopausal women receiving extended-release

venlafaxine (Effexor XR) or placebo for 12 weeks, participants reported decreases in hot flash scores of 51 and 15 percent, respectively.

ADVERSE EFFECTS AND DOSAGE

Most of the studies reported transient, dose-related adverse effects. The most common adverse effects reported were insomnia or excitement, nausea, constipation, and anorexia.[2,5,7] In the trials using venlafaxine for hot flashes there were no reported increases in blood pressure, which is a dose-related adverse effect commonly associated with this agent.[6,8]

The dosage and duration of these medications most appropriate in alleviating hot flashes is unknown; however, regimens using low to moderate dosages seem to be as effective as those using high dosages and have significantly fewer reported adverse effects. Therefore, when using an SSRI or venlafaxine to treat hot flashes, it is prudent to initiate the medication at a low dosage and titrate to effect.

Clonidine

SUMMARY

Clonidine (Catapres) has been found to reduce hot flashes by 15 to 20 percent (ARR) compared with placebo (NNT = 5 to 7) in women with a history of breast cancer.[10-12]

MECHANISM OF ACTION

The exact mechanism of action is unknown, but it is thought to relate to clonidine's ability to reduce vascular reactivity.[10]

STUDIES

In one randomized, crossover study,[10] researchers compared the effectiveness of a clonidine patch with placebo in 110 women with a history of breast cancer. The patch was found to decrease the frequency of hot flashes by 20 percent and the hot flash score by 27 percent compared with placebo ($P < .0001$). Oral clonidine also has been assessed. In 198 women with a history of breast cancer who were randomized to receive oral clonidine at

TABLE 2
Considerations and Limitations of Studies of Nonhormonal Therapies for Hot Flashes in Menopause

	Study considerations and limitations		
Agent	*Durations*	*Populations*	*Other*
SSRIs[2-5] and venlafaxine (Effexor)[6-9]	Relatively short; long-term efficacy unknown	Primarily women with a history of breast cancer receiving tamoxifen (Nolvadex), and predominantly white	Worsening hot flash symptoms could be associated with a rapid decline in estrogen as well as the adverse effects of chemotherapy, radiation, and tamoxifen therapy.
Clonidine (Catapres)[10-12]	Relatively short; long-term efficacy unknown	Primarily women with a history of breast cancer receiving tamoxifen	Few studies have been performed. Exclusion criteria were numerous and could limit application to a larger population.
Soy isoflavones[13-24]	Relatively short; long-term efficacy unknown	Varied greatly, including women who were perimenopausal, women who were menopausal, and women with a history of breast cancer	Results were inconsistent. Studies that reported significant positive results with soy isoflavones compared with placebo were conducted in women with moderate to severe hot flashes. Studies did not use consistent commercial, standardized products and dosages.
Red clover[25-28]	Relatively short; long-term efficacy unknown	Menopausal, predominantly white women	Studies did not use consistent commercial, standardized products and dosages.
Black cohosh[29-33]	Most relatively short; long-term efficacy unknown	Varied greatly, including women who were premenopausal, women who were menopausal, and women with a history of breast cancer	Results were inconsistent. Studies were weak in design. Studies did not use consistent commercial, standardized products and dosages.

SSRI = selective serotonin reuptake inhibitor.

Information from references 2 through 33.

bedtime or placebo, hot flashes decreased by 38 percent in the clonidine group and by 23 percent in the placebo group ($P < .006$).[11] Another study,[12] in which clonidine was administered transdermally in 30 postmenopausal women, showed that clonidine decreased the number and the severity and duration of hot flashes compared with placebo.

ADVERSE EFFECTS AND DOSAGE

Adverse effects occurred more commonly with the clonidine patch compared with placebo; the most commonly reported side effects were dry mouth, constipation, drowsiness, and application site irritation.[10] There was little difference in adverse effects with oral clonidine compared with placebo.[11]

The most appropriate dosage and duration of clonidine is unknown.

Soy Isoflavones

SUMMARY

Soy isoflavones may have a modest benefit for hot flashes, but study results are inconclusive.[13-24]

MECHANISM OF ACTION

Soy has been linked to reduced vasomotor symptoms in Asian women who consume a soy-rich diet.[35,36] It contains large quantities of phytoestrogens and is one of the richest sources of isoflavones available. Isoflavones are similar to endogenous estrogen: they compete with estrogen for the same receptors and exert estrogenic and antiestrogenic effects. The agonist/antagonist effects are determined largely by concentrations of isoflavones and endogenous estrogen, as well as menopausal status.[17,37,38]

STUDIES

Researchers have evaluated the effectiveness of soy isoflavones as tablets, capsules, and liquids in more controlled environments. A small pilot study[13] of the effects of soy isoflavones in 39 menopausal women reported a 20 percent ARR in hot flashes weekly compared with placebo ($P < .01$). Other studies have shown no difference in effectiveness between isoflavones and placebo. One randomized study[14] involving 62 menopausal women reported a 40 percent response rate in both groups; another randomized study[15] involving 157 menopausal women with a history of breast cancer showed a response rate of 30 percent for both groups; a randomized study[16] involving 241 perimenopausal women showed no significant difference between the two groups ($P = .10$); and a randomized, crossover study[17] involving 182 women with a history of breast cancer also showed no difference in soy isoflavones compared with placebo in reducing hot flash symptoms ($P = .78$).

Positive results of soy isoflavone use also have been reported. In a randomized study[18] involving 177 menopausal women, soy isoflavones were found to be superior to placebo in decreasing hot flash severity (27 percent reduction versus 18 percent, respectively; $P = .01$), but not hot flash frequency ($P = .078$). In a randomized study[19] involving 75 menopausal women there was a 61 percent decrease in hot flashes with isoflavones compared with a 21 percent decrease with placebo ($P = .01$), and 68 percent of patients in the isoflavone group experienced a decrease in their hot flashes of more than one half, compared with 32 percent in the placebo group. Also, a randomized controlled trial[20] (RCT) of 82 postmenopausal women reported an improvement in vasomotor symptoms on the Kupperman index (a commonly used menopause symptom index) with the use of soy isoflavones compared with baseline and with placebo ($P < .01$).

In one RCT[21] conducted to evaluate the effects of soy isoflavones and melatonin, participants were randomized to one of four different therapies: soy isoflavones monotherapy, melatonin monotherapy, soy isoflavones and melatonin combination therapy, or placebo. Results showed no statistically or clinically significant differences in outcomes among the four groups. Three other studies[22-24] of various isoflavone regimens did not show any significant differences in outcomes between the treatment and placebo groups.

The American College of Obstetricians and Gynecologists (ACOG) states that soy and isoflavones may be helpful in the short-term (i.e., two years or less) treatment of vasomotor symptoms; however, given the possibility of their interacting with estrogen, these agents should not be considered free of potential harm for women, particularly those who have an estrogen-dependent cancer.[39]

ADVERSE EFFECTS AND DOSAGE

Adverse effects were similar when comparing soy isoflavones and placebo.[14-19] The long-term effects of soy isoflavones on estrogen-sensitive tissues is unknown. However, in one study[14] there were no significant changes in endometrial thickness from baseline in the soy-treated patients.

Because a wide range of soy isoflavone dosages and many different commercial products were used, it is difficult to recommend the most appropriate dosage and product.

Red Clover

SUMMARY

Red clover isoflavones do not appear to be more effective than placebo in reducing hot flashes, based on limited data from small clinical trials.[25-28]

MECHANISM OF ACTION

Red clover, like soy, contains isoflavones, which act as agonist/antagonists on estrogenic receptors.

STUDIES

In two small pilot studies,[25,26] researchers compared red clover with placebo in postmenopausal women and found no difference in effectiveness of reducing hot flashes. In a randomized study[27] with 252 menopausal women, researchers compared two different commercial red clover products with placebo. All groups reported significant declines in hot flashes compared with baseline ($P < .0001$), but neither of the red clover products demonstrated superiority over placebo ($P > .20$). In a smaller study[28] involving 30 menopausal women, however, those taking red clover isoflavones experienced an additional 44 percent decrease in hot flashes over the placebo group ($P < 0.01$).

ADVERSE EFFECTS AND DOSAGE

Researchers reported similar adverse effects in women treated with red clover and those treated with placebo.[27,28] The long-term safety of red clover is unknown.

The best dosage and commercial product of red clover isoflavones to use is not clear based on the limited data available.

Black Cohosh

SUMMARY

Black cohosh shows promise for treatment of hot flashes, but study results are inconsistent.[29-33,40]

MECHANISM OF ACTION

The exact mechanism of action of black cohosh is unknown. It was theorized that black cohosh competes with estrogen for binding sites and exerts a positive estrogenic effect, but newer data suggest it may act as a selective estrogen receptor modifier, depending on the tissue receptors,[41] and that it also may exert an agonistic effect on serotonin receptors.[42] In addition, black cohosh may decrease luteinizing hormone, leading to a reduction in hot flashes.[43]

STUDIES

Black cohosh is the most studied and perhaps the most popular herb for treatment of hot flashes. Typically, it is not used on a long-term basis.[40] One randomized study[29] involving 84 women with a history of breast cancer reported that black cohosh was similar to placebo in alleviating hot flashes ($P = .86$). However, in a study[30] in which 80 menopausal women were randomized to receive estrogen, black cohosh, or placebo, the women receiving black cohosh had an 84 percent decrease in their hot flash symptoms compared with a 40 percent decrease in the estrogen and placebo groups ($P < .001$). A study[31] in which 97 menopausal women were randomized to estrogen, black cohosh, or placebo showed black cohosh to be as effective as estrogen and superior to placebo in decreasing hot flash symptoms ($P = .046$).

In an open-label, randomized study[32] involving 136 premenopausal women with a history of breast cancer who received black cohosh or placebo, researchers found that, at the end of the study, 46 percent of women receiving black cohosh were free of hot flashes ($P < .01$). Twenty-nine percent of women receiving black cohosh continued to have severe hot flashes, compared with 74 percent of those receiving placebo ($P < .01$). Results of a study[33] involving 152 postmenopausal women receiving a high or a low dosage of black cohosh showed similar decreases in Kupperman index scores in the two groups (from a median score of 35 at baseline to a median score of 8 at 12 weeks), suggesting that the higher dose was no more effective than the lower dose ($P = .73$). ACOG states that black cohosh may be helpful in the short-term (i.e., less than six months) treatment of women with vasomotor symptoms.[39]

ADVERSE EFFECTS AND DOSAGE

Black cohosh was reported to be well tolerated, and no serious adverse events were linked to its use.[29-32] One 12-week study[31] reported no change in endometrial thickness in women receiving black cohosh. The long-term safety of black cohosh is unknown.

Because many different dosages and commercial products of black cohosh were used, it is difficult to recommend one as the most appropriate.

Other Agents

Other agents also have been used for the treatment of hot flash symptoms in menopause, including belladonna/ergotamine tartrate/phenobarbital combination (Bellergal [not available in the United States]; Bellamine),[44] dong quai,[45] evening primrose oil,[46] gabapentin (Neurontin),[47] ginseng,[48] mirtazapine (Remeron),[49] trazodone (Desyrel),[50] vitamin E,[51] and wild yam,[52] but there are few published data on their effectiveness. Studies on these agents are summarized in *Table 3*.[44-52] Belladonna/

ergotamine tartrate/phenobarbital combination and gabapentin were more effective than placebo in reducing hot flashes in two small clinical trials.[44,47] However, larger clinical studies are needed to support these initial findings.

Final Comment

Hot flash symptoms can significantly impact a woman's quality of life and should be addressed. Severity of the hot flashes, medical history, and concomitant medications should be considered in determining the best therapy for each patient. As already mentioned, the placebo response rate is a potential confounder in most trials, making it difficult to determine the true success of therapy. Further RCTs are needed to determine more clearly the most effective therapy for alleviating hot flashes in menopausal women for whom hormonal therapy is not appropriate or by whom it is declined.

DATA SOURCES: English-language studies, as well as pertinent references from these articles, were identified through a search of PubMed (1966 to May 2005), the Cochrane

TABLE 3
Agents Used in the Treatment of Hot Flashes with Limited Supporting Evidence

Agent	*Study population*	*Dosage*	*Study duration*	*Results*	*Adverse effects**
Belladonna/ ergotamine tartrate/ phenobarbital combination (Bellergal,† Bellamine)[44]	71 menopausal women	1 tablet three times per day	Eight weeks	75 percent decrease in hot flashes with Bellergal versus 68 percent with placebo ($P < .001$, NNT = 14)	Similar incidence between groups
Dong quai[45]	71 menopausal women	4.5 g per day	Six months	No significant difference compared with placebo	Similar incidence between groups
Evening primrose oil[46]	56 menopausal women	500 mg per day	Six months	No significant difference compared with placebo	Similar incidence between groups
Gabapentin (Neurontin)[47]	59 menopausal women	300 mg three times per day	12 weeks	45 percent decrease in hot flashes with gabapentin versus 29 percent with placebo ($P = .02$, NNT = 6)	Somnolence; dizziness
Ginseng[48]	384 menopausal women	200 mg per day	Four months	No significant difference compared with placebo	Similar incidence between groups
Mirtazapine (Remeron)[49]	Four menopausal women	15 to 30 mg per day	Varied by patient	All four women experienced a decline in frequency and severity (40 to 80 percent) of hot flashes while receiving mirtazapine.	None reported
Trazodone (Desyrel)[50]	25 climacteric women	75 mg per day	Three months	No significant difference from baseline	Drowsiness
Vitamin E[51]	125 women with a history of breast cancer	800 IU per day	Nine weeks	No significant difference compared with placebo	Similar incidence between groups
Wild yam[52]	50 menopausal women	1 teaspoon topically twice per day	Six months	No significant difference compared with placebo	None reported

NNT = number needed to treat.

**— Adverse effects listed are those reported in these trials, and may not be an accurate representation of the overall side-effect profile for each agent.*
†—Bellergal is not available in the United States.

Information from references 44 through 52.

Database, and the Natural Medicine Database. Key search terms included climacteric, hot flash, hot flush, flushing, menopause, postmenopause, therapy, isoflavones, serotonin reuptake inhibitors, clonidine, belladonna, evening primrose oil, ginseng, dong quai, wild yam, gabapentin, vitamin E, and black cohosh.

Members of various family medicine departments develop articles for "Practical Therapeutics." This article is one in a series coordinated by the Department of Family Medicine at the University of Oklahoma College of Medicine, Tulsa, Okla. Coordinator of the series is John Tipton, M.D.

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