

POSITION STATEMENT

Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society

ABSTRACT

Objective: To create an evidence-based position statement regarding the treatment of vasomotor symptoms associated with menopause.

Design: The North American Menopause Society (NAMS) enlisted clinicians and researchers acknowledged to be experts in the field of menopause-associated vasomotor symptoms to review the evidence obtained from the medical literature and develop a document for final approval by the NAMS Board of Trustees.

Results: For mild hot flashes, lifestyle-related strategies such as keeping the core body temperature cool, participating in regular exercise, and using paced respiration have shown some efficacy without adverse effects. Among nonprescription remedies, clinical trial results are insufficient to either support or refute efficacy for soy foods and isoflavone supplements (from either soy or red clover), black cohosh, or vitamin E; however, no serious side effects have been associated with short-term use of these therapies. Single clinical trials have found no benefit for dong quai, evening primrose oil, ginseng, a Chinese herbal mixture, acupuncture, or magnet therapy. Few data support the efficacy of topical progesterone cream; safety concerns should be the same as for other progestogen preparations. No clinical trials have been conducted on the use of licorice for hot flashes. Among nonhormonal prescription options, the antidepressants venlafaxine, paroxetine, and fluoxetine and the anticonvulsant gabapentin have demonstrated some efficacy for treating hot flashes and were well tolerated. Two antihypertensive agents, clonidine and methyl dopa, have shown modest efficacy but with a relatively high rate of adverse effects. For moderate to severe hot flashes, systemic estrogen therapy, either alone (ET) or combined with progestogen (EPT) or in the form of estrogen-progestin oral contraceptives, has been shown to significantly reduce hot flash frequency and severity. Clinical trials have associated ET/EPT with adverse effects, including breast cancer, stroke, and thromboembolism. Several progestogens (both oral and intramuscular formulations) have shown efficacy in treating hot flashes, including women with a history of breast cancer, although no definitive data are available on long-term safety in these women.

Conclusions: In women who need relief for mild vasomotor symptoms, NAMS recommends first considering lifestyle changes, either alone or combined with a nonprescription remedy, such as dietary isoflavones, black cohosh, or vitamin E. Prescription systemic estrogen-containing products remain the therapeutic standard for moderate to severe menopause-related hot flashes. Recommended options for women with concerns or contraindications relating to estrogen-containing treatments include prescription progestogens, venlafaxine, paroxetine, fluoxetine, or gabapentin. Clinicians are advised to enlist women's participation in decision making when weighing the benefits, harms, and scientific uncertainties of therapeutic options. Regardless of the management

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strategy adopted, treatment should be periodically reassessed as menopause-related vasomotor symptoms will abate over time without any intervention in most women.

Key Words: Menopause – Vasomotor symptoms – Hot flashes – Estrogen – Progestogen – Hormone therapy – Antidepressants – Isoflavones – Black cohosh – Vitamin E – Gabapentin.

In response to the need to define standards of clinical practice in North America, The North American Menopause Society (NAMS) has created this evidence-based position statement on the treatment of menopause-associated vasomotor symptoms.

METHODOLOGY

An Editorial Board composed of experts from both clinical practice and research was enlisted to review the published data, compile supporting statements and conclusions, and reach consensus on which recommendations to endorse. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was established. (Practice parameter standards related to NAMS position statements were described in a previous editorial.¹)

For this position statement, a search was conducted of the medical literature for clinical trials that presented data specific to the treatment of vasomotor symptoms using the database MEDLINE. Priority was given to evidence from randomized, controlled clinical trials as well as systematic reviews and meta-analyses of such trials, using criteria described elsewhere for evaluating the evidence levels.²⁻⁴ Conclusions from other evidence-based guidelines also were reviewed. The NAMS Board of Trustees was responsible for the final review and approval of this document. Updates to this position statement will be published as developments in scientific research occur that substantially alter the conclusions.

The overall objective of this position statement is to provide a review of clinical data relating to treatment of peri- and postmenopausal vasomotor symptoms and to recommend the most effective treatments. Research often does not distinguish between vasomotor symptoms resulting from spontaneous menopause and those from induced menopause, although anecdotal reports suggest that induced menopause may result in more frequent and/or severe symptoms. This position statement will not specifically address vasomotor symptoms associated with causes other than menopause, such as hypogonadism, low serum gonadotropin levels, or gonadotropin-releasing hormone agonist therapy. However, it will include research conducted among peri- and postmenopausal women who have had breast

cancer. Although their vasomotor symptoms may be related to breast cancer treatment (eg, tamoxifen), it is reasonable to assume that the therapeutic results may be applicable to naturally postmenopausal women, even though the physiologic mechanisms can differ. Finally, although the information is relevant internationally, the focus is limited to therapies available in clinical practice in the United States and Canada.

OVERVIEW

The symptoms of vasomotor instability associated with menopause are commonly termed *hot flashes*. Hot flashes are recurrent, transient episodes of flushing, perspiration, and a sensation ranging from warmth to intense heat on the upper body and face, sometimes followed by chills.⁵ Hot flashes that occur with perspiration during sleep are termed *night sweats*.

The terms *hot flash*, *hot flush*, and *vasomotor symptoms* are often used to describe the same phenomenon. NAMS defines vasomotor symptoms as a global term that encompasses both hot flashes and night sweats. NAMS prefers the term *hot flash* rather than *hot flush*.

Hot flashes are considered one of the hallmark signs of perimenopause. The exact cause of hot flashes has not been determined, although it seems that the changing endogenous estrogen concentrations associated with menopause may play a role. However, endogenous estrogen concentrations alone are not predictive of hot flash frequency or severity.

Most hot flashes are mild to moderate in intensity and typically stop over time without therapy, but the exact timing cannot be predicted. Nevertheless, many North American women experience hot flashes severe enough to seek treatment. Although the available therapies do not “cure” hot flashes, they can provide significant relief.

The main focus of this paper is on treatment options for hot flash symptoms; however, it first presents some background information on epidemiologic, etiologic, and physiologic characteristics.

EPIDEMIOLOGIC CONSIDERATIONS

Hot flashes are an early, readily apparent sign of approaching menopause. A review⁵ found that the incidence of hot flashes typically increases during peri-

menopause, reaches its highest rate during the first 2 years postmenopause, then declines over time. In a prospective, longitudinal study of 436 community-based US women aged 35 to 47,⁶ 31% experienced hot flashes before noting any observable irregularity in menstrual cycles or changes in serum estrogen levels.

Most women experience hot flashes for 6 months to 2 years, although some women have them for 10 years or longer.⁵ A Swedish study found that about 9% of 72-year-old women have hot flashes.⁷

During perimenopause, hot flashes can occur infrequently (monthly, weekly) or frequently (hourly), but there is usually a consistent within-woman pattern. A circadian rhythm has been observed, with hot flash frequency peaking in the early evening hours, about 3 h after the peak in core body temperature.⁸

Reports of the incidence of hot flashes vary widely. In the United States, the Massachusetts Women's Health Study,⁹ a longitudinal, population-based study of 454 women, found that about 75% of the women experienced hot flashes during the transition from perimenopause to postmenopause, which lasted a median of 3.8 years. Other US studies report different figures.

Outside the United States, the reported hot flash rates vary even more widely, from about 10% in Hong Kong¹⁰ to 62% in Australia,¹¹ 68% in Canada,¹² and up to 83% in the United Kingdom.^{13,14} Reasons for these differences are not known.

In the United States, prevalence rates also differ among racial/ethnic groups. According to a multiethnic cross-sectional survey of 16,065 women aged 40 to 55 in the Study of Women's Health Across the Nation (SWAN), African American women report hot flashes most frequently (45.6%), followed by Hispanics (35.4%), Caucasians (31.2%), Chinese (20.5%), and Japanese (17.6%).¹⁵ More recent data from SWAN indicate that differences in body mass index (BMI) may be a more important predictor of hot flashes than ethnic differences.¹⁶

After bilateral oophorectomy, acute symptomatology may be worse than for women experiencing spontaneous menopause. In US women who undergo bilateral oophorectomy, hot flash rates of up to 90% have been reported.^{17,18} Over time, symptom rates become similar to those for women who have reached menopause naturally.¹⁸

A history of premenstrual complaints is significantly associated with hot flashes in perimenopausal women, according to data from the Melbourne Women's Midlife Health Project.¹¹ Approximately 47% of perimenopausal women with a history of moderate to severe premenstrual complaints experienced hot flashes

compared with 32% of women without a history (odds ratio, 1.42; 95% CI, 1.04-1.93).

Various lifestyle and social factors also seem to be related to hot flash frequency:

- Warm ambient air temperatures increase a woman's core body temperature and make her more likely to reach the sweating threshold. Cooler air temperatures are associated with a lower incidence of hot flashes.^{19,20}
- Previously, it was believed that hot flash risk was inversely related to BMI, as estradiol is elevated as a result of aromatization in adipose tissue. However, in SWAN, which enrolled women aged 40 to 55, a high BMI (≥ 27 kg/m²) was found to be a predictor of hot flash frequency (OR, 1.15-1.18; 95% CI, 1.04-1.32).¹⁵ A cross-sectional study among 1,087 women aged 40 to 60 found that a high BMI (> 30 kg/m²) was associated with an increased risk for moderate to severe hot flashes compared with a low BMI (< 24.9 kg/m²) among pre- or perimenopausal women; an increased risk between hot flashes and BMI was not found in postmenopausal women.²¹ It has been postulated that, at least in pre- and perimenopausal women, any increase in estradiol is offset by increased insulation from body fat, resulting in a higher core body temperature and more hot flashes.
- In SWAN,¹⁵ cigarette smoking (past and current) increased the relative risk of hot flashes (OR, 1.24-1.68; 95% CI, 1.12-1.94), perhaps because of its effect on estrogen metabolism. This finding has also been observed in other studies.^{21,22} The Whiteman et al study²¹ found that current smokers were at an increased risk for both moderate and severe hot flashes and for daily hot flashes; among current smokers, hot flash risk increased with greater amounts smoked.
- SWAN also found that less physical activity increased the relative risk of hot flashes (OR, 1.33-1.71; 95% CI, 1.16-2.07).¹⁵ Another study, however, found that exercise could trigger hot flashes in symptomatic women.²³ Although strenuous exercise may elicit hot flashes in unconditioned women, daily exercise is associated with an overall decreased incidence.^{24,25}
- Low socioeconomic status was identified in SWAN as another factor associated with an increased relative risk for hot flashes (OR, 1.22-1.85).¹⁵
- No clinical trial evidence supports a relationship between the frequency and severity of hot flashes and certain triggers, such as emotional stress and

consuming particular types of foods (eg, thermally hot or spicy food) or drinks (eg, caffeine, alcohol), although this has been reported anecdotally. The Melbourne Women's Midlife Health Project¹¹ found no significant association between alcohol intake and hot flash rates.

ETIOLOGIC CONSIDERATIONS

The precise cause of hot flashes is not known, although they seem to have a hypothalamic origin. Menopause, however, is not the only condition associated with hot flashes. Other conditions that have the potential to result in hot flashes include thyroid disease, epilepsy, infection, insulinoma, pheochromocytoma, carcinoid syndromes, leukemia, pancreatic tumors, autoimmune disorders, and mast-cell disorders. Drugs such as tamoxifen and raloxifene also are known to cause hot flashes.

Endocrinology

Estrogen plays a role in the genesis of hot flashes as these symptoms are encountered by most women experiencing spontaneous menopause, when estrogen levels are known to fluctuate, and induced menopause, when estrogen levels decline abruptly. Hot flashes are more likely to occur after a relatively acute decrease in endogenous plasma estrogen concentrations or the withdrawal of estrogen therapy, rather than low levels per se. In studies of postmenopausal women in whom endogenous estrogen concentrations were measured, ambient estradiol levels did not predict the presence or absence of hot flashes.²⁶⁻²⁸

Several other factors are thought to mediate the estrogen signal and predict a woman's sensitivity to the phenomenon of hot flashes. Considerable evidence supports the hypothesis that α_2 -adrenergic receptors within the central noradrenergic system are involved²⁹ and that norepinephrine levels, which play an important role in thermoregulation, at least partly regulate this process.³⁰ Additionally, one study showed that hot flash frequency was significantly reduced through therapy with oral clonidine, an α_2 -adrenergic agonist, even though circulating estrogen levels were not changed.³¹ There is also considerable evidence that gonadal steroids modulate central noradrenergic activity.³²

Compared with asymptomatic postmenopausal women, symptomatic postmenopausal women have higher levels of plasma 3-methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite of norepinephrine, and these levels further increase significantly with the occurrence of each hot flash.³³ Higher plasma lev-

els of MHPG are associated with increased whole-body sympathetic activation.³⁴ In contrast, plasma levels of the peripheral metabolite of norepinephrine, vanillylmandelic acid, do not change with hot flashes.³⁵ This lends support to the hypothesis that central norepinephrine levels are involved in the initiation of hot flashes.

Furthermore, hot flashes are known to be affected by drugs that influence sympathetic activation. In clinical trials, the α_2 -adrenergic agonist clonidine reduced central noradrenergic activation and hot flash frequency.^{36,37} Conversely, the α_2 -adrenergic antagonist yohimbine increased central noradrenergic activation and triggered hot flashes.²⁹

Gonadotropins and opiates have also been investigated for a possible role in hot flash onset, but no link has been substantiated. Elevations of gonadotropin concentrations at menopause, primarily luteinizing hormone, led to studies evaluating a potential link with hot flashes. Although some temporal associations were shown,^{38,39} subsequent studies with more specific endpoints found no causative connection.⁴⁰⁻⁴³ Thus, acute increases in luteinizing hormone levels have been ruled out as a cause for hot flashes.

An opioidergic system link to hot flashes was investigated after a small study reported that naloxone, an opioid antagonist, significantly reduced the frequency of hot flashes.⁴⁴ However, a subsequent randomized, placebo-controlled trial in postmenopausal women found no causal connection between naloxone and hot flashes.⁴⁵ Furthermore, two studies evaluating hot flash occurrence and β -endorphin plasma concentrations found no conclusive evidence of a causative correlation.^{46,47}

Thermoregulation

Recent evidence suggests that control of the core body temperature (T_c) has a role in initiating hot flashes. Around the time of menopause, whether natural or induced, increased sensitivity to heat (ie, a narrowed thermoneutral zone) often occurs. One study²³ found that women who suffer hot flashes have a significantly smaller thermoneutral zone than women without hot flashes (0.0°C v 0.4°C, respectively). Small elevations in T_c have been shown to precede most hot flashes in postmenopausal women.^{8,35,48} This indicates that T_c elevations, acting within a narrowed thermoneutral zone, trigger hot flashes. However, T_c elevations alone do not explain the entire triggering mechanism, because they have been observed in asymptomatic women.⁴⁹

Animal studies have shown that increased brain norepinephrine narrows the width of the thermoneutral

zone.³⁰ Clonidine reduces norepinephrine release, raises the sweating threshold, and reduces hot flashes in symptomatic women.⁵⁰ Thus, it is proposed that elevated brain norepinephrine narrows the thermoregulatory zone in symptomatic postmenopausal women, and that small elevations in T_c trigger hot flashes when the sweating threshold is crossed.

PHYSIOLOGIC CHANGES

Thermoregulatory and cardiovascular system changes that accompany a hot flash have been well documented. Measurable increases have been observed in T_c , skin temperature, skin conductance, perspiration rate, and the respiratory exchange ratio (metabolic rate measure).

In the 5 to 60 seconds before a hot flash occurs, skin temperature, cutaneous blood flow, and heart rate begin to increase.^{51,52} Increases in T_c of approximately 0.1°C have been shown to occur before a hot flash.³⁵

An individual hot flash generally lasts 1 to 5 min; about 7% are longer, and about 17% are shorter.⁵³ During a hot flash, skin temperatures rise as a result of peripheral vasodilation.^{35,51,52,54,55} This change is particularly marked in the fingers and toes, where skin temperature can increase 1°C to 7°C. Most women experience a sudden wave of heat sensation that spreads over the body, particularly on the upper body and face. Sweating begins, primarily on the upper body, and it corresponds closely in time with the increase in skin conductance.³⁵ Sweating has been observed in women during 90% of hot flashes.³⁵ Modest heart rate increases of about 7 to 15 beats per min occur at approximately the same time as the peripheral vasodilation and sweating.^{54,56} Heart rate and skin blood flow usually peak within 3 min of the onset of a hot flash. Significant elevations in metabolic rate occur simultaneously with sweating and peripheral vasodilation.³⁵ However, because increased metabolic rate and peripheral vasoconstriction do not precede the T_c elevations, they do not account for these elevations.

Skin temperature returns to normal gradually, possibly taking 30 min or longer. Decreases in T_c of 0.1°C to 0.9°C occurring approximately 5 to 9 min after the hot flash begins have been observed,^{52,54,55} probably due to heat loss via perspiration and increased peripheral vasodilation. If the heat loss is significant, the woman may experience chills.

TREATMENT EVIDENCE

Various treatments have been used to relieve hot flashes, including lifestyle modification, nonprescrip-

tion remedies, and prescription therapies. This section reviews their efficacy and safety evidence. It bears noting that the placebo effect is higher in trials of hot flashes than for many other conditions. In well-controlled, randomized clinical trials, placebo treatment has reduced hot flashes by approximately 51%.⁵⁷ Clinical trials for hot flashes are also affected by the fluctuations in symptoms among perimenopausal women and by the abatement of hot flashes seen over time.

It is important to note that for moderate to severe hot flashes, the US Food and Drug Administration (FDA) stipulates that a woman must have seven to eight hot flashes per day or at least 60 per week. Most nonhormonal efficacy studies presented herein enrolled women with lower rates of hot flashes.

Lifestyle modification

One potential approach for mild menopause-associated hot flashes is modification of lifestyle, including manipulating the environment and changing behaviors. The following reviews some of these options.

Core Body Temperature

Because hot flashes can be triggered by small core body temperature elevations in symptomatic women,^{8,35,48} it is rational to assume that practices that lower the core body temperature may be beneficial. Observational studies have shown that lowering air temperature reduces hot flashes.^{19,20} Anecdotally, women report that using a fan, keeping cool by dressing in layers, and consuming cool or cold food and drinks may help prevent hot flashes. Conversely, thermally hot foods or drinks that may raise the core body temperature should be avoided.

Exercise

In observational studies,^{24,25} physically active women reported fewer and less severe hot flashes than an age-matched control group with sedentary lifestyles; significant decreases of more than 50% were noted. In SWAN, less physically active women experienced significantly more hot flashes.¹⁵ However, exercise, especially strenuous exercise that causes perspiration, may trigger hot flashes in symptomatic women.²³ No randomized, controlled trials have examined the efficacy of exercise in managing hot flashes.

Body Mass Index

Evidence from community-based, cross-sectional studies^{15,21} indicates that a high BMI predisposes

women to more frequent or severe hot flashes. However, whether losing excess weight reduces hot flash risk has not been studied.

Smoking

Women who do not smoke cigarettes generally experience fewer hot flashes than do smokers,^{15,21,22} and the risk of experiencing hot flashes increases with the amount smoked.²¹ Stopping smoking may lower the hot flash risk, but no study has specifically tested the effects of smoking cessation on the severity and rate of hot flashes.

Relaxation Techniques

Paced respiration—slow, controlled, diaphragmatic breathing—has shown some efficacy in reducing hot flashes when performed as a hot flash begins. In three randomized, prospective clinical trials,⁵⁸⁻⁶⁰ paced respiration lowered hot flash frequency by approximately 50% more than the controls, a significant difference from baseline. Hot flashes were objectively measured by ambulatory monitoring of sternal skin conductance level.

In the earliest study,⁵⁸ 14 postmenopausal women with hot flashes used either a combination of paced respiration plus muscle relaxation exercises or a control procedure using alpha-wave electroencephalographic (EEG) biofeedback. In a second study,⁵⁹ 33 postmenopausal women experiencing frequent hot flashes were randomly assigned to one of two interventions: paced respiration or muscle relaxation. The control group participated in alpha-wave EEG biofeedback. Only the paced respiration group had a significant decline in hot flashes from baseline. In a third study,⁶⁰ 24 postmenopausal women experiencing at least five hot flashes per day were randomly assigned to use either paced respiration or as a control, alpha-wave EEG biofeedback. Hot flash frequency declined significantly in the paced-respiration group; no significant decline was noted in the biofeedback group.

Another randomized, prospective study⁶¹ also supports the efficacy of behavioral relaxation, including paced respiration. In this trial, 33 women experiencing hot flashes were randomly assigned to one of three groups: behavioral relaxation, reading, or a control. Only the relaxation group had a significant reduction in hot flashes.

Foot reflexology has been evaluated for relief of menopausal symptoms. In a randomized, parallel-group study comparing this technique with foot massage (control group), no significant difference was found regarding hot flash declines from baseline.⁶²

Although not evaluated in controlled clinical trials, some women report that they have fewer hot flashes when they engage in activities to enhance relaxation, such as meditation, yoga, massage, or even just a leisurely bath.

Nonprescription remedies

In the United States and Canada, many women use nonprescription remedies to treat hot flashes, including isoflavones, black cohosh, and topical hormone creams containing progesterone. Less commonly used are dong quai, evening primrose oil, ginseng, licorice, mixtures of Chinese herbs, and other options.

Evidence is generally lacking regarding efficacy and long-term safety of these remedies. Most nonprescription remedies for hot flashes are categorized as dietary supplements and, therefore, are not government regulated as drugs. Demonstrating efficacy and safety is not required before marketing. Also, data regarding the interaction of many of these therapies with each other and with prescription drugs are limited. Interactions will be addressed, when known.

Isoflavones

These are plant-derived diphenolic compounds that exhibit both hormonal and nonhormonal properties. Isoflavones are often called phytoestrogens because they bind to estrogen receptors, with greater affinity to estrogen receptor- β than to estrogen receptor- α , and possess both estrogen agonist and antagonist properties.⁶³ Isoflavones are found in whole foods and commercial preparations, such as purified isoflavone supplements, mixed preparations containing isoflavones, and fortified foods. Two common sources of isoflavones are soy and red clover. No toxicity or adverse effects have been found for whole-food isoflavones, although some people with soy allergies may experience adverse reactions.

Soy-Derived Isoflavones. Randomized, controlled clinical trials have shown that, in general, hot flashes are only slightly reduced in women who consume soy-derived isoflavones when compared with controls (Table 1). Comparing studies is difficult because different products and amounts of isoflavones were used. Symptom indices used to measure efficacy also differed.

Between 30% and 50% of women convert daidzein, one of the isoflavones found in soy, to a metabolite known as equol (ie, “equol producers”).⁷⁸ Equol is a nonsteroidal estrogen with estrogenic effects.⁷⁹ In a re-

TABLE 1. Efficacy of soy-derived isoflavones in hot flash treatment: controlled clinical trials

Lead author	Trial design	Tx length	N (age)	Daily dosage	Hot flash decreases		
					Soy	Control	Significance
Soy foods							
Albertazzi ⁶⁴	R, DB, PC	12 wk	104 (45-62)	76 mg iso	45%	31%	S
Burke ⁶⁵	R, DB, PC	24 mo	241 (mean 51)	42 mg iso	42%	77%	NS
				58 mg iso	59%	77%	NS
Dalais ⁶⁶	R, DB, CO	12 wk	52 (45-65)	45 g soy grits (53 mg iso)	22% ^a	51% ^b	—
Knight ⁶⁷	R, DB, PC	12 wk	24 (mean 53)	77 mg iso	43%	20%	NS
Murkies ⁶⁸	R, DB	12 wk	58 (mean 54-56)	45 g soy flour	40%	25%	NS
				45 g wheat flour			
St. Germain ⁶⁹	R, DB, PC	24 wk	69 (42-62)	40 g iso-rich soy protein	57%	76%	NS
				40 g iso-poor soy protein	54%	76%	NS
Van Patten ⁷⁰	R, DB, PC	12 wk	123 (mean 54)	500 mL soy beverage (90 mg iso)	30%	40%	NS
Soy isoflavone supplements							
Faure ⁷¹	R, DB, PC	16 wk	75 (mean 54)	soy iso extract (70 mg iso)	61%	21%	S
Han ⁷²	R, DB, PC	16 wk	82 (45-55)	150 g soy protein (100 mg iso)	27%	1%	S
Nikander ⁷³	R, DB, PC, CO	12 wk	62 (mean 54)	114 mg iso	10%	14%	NS
Penotti ⁷⁴	R, DB, PC	24 wk	62 (45-60)	72 mg iso	40%	40%	NS
Quella ⁷⁵	R, DB, PC, CO	4 wk	177 (18 to >50)	600 mg soy tablets (50 mg iso)	35%	38%	NS
Scambia ⁷⁶	R, DB, PC	6 wk	39 (mean 53-54)	400 mg soy extract (50 mg iso)	44%	24%	S
Upmalis ⁷⁷	R, DB, PC	12 wk	177 (55)	soy iso extract (50 mg iso)	28%	19%	NS

Superscript numbers refer to citations in the reference list. Tx, treatment; R, randomized; DB, double-blind; PC, placebo-controlled; OL, open label; CO, crossover; iso, isoflavones; S, statistically significant vs control; NS, not statistically significant vs control.

^aNS v baseline; no between-group comparison.

^bS v baseline; no between-group comparison.

cent study of 180 Japanese women,⁸⁰ equol producers derived the most hot flash relief from their soy consumption. In a randomized, controlled trial of soy isoflavones in 62 postmenopausal women,⁷³ no difference in hot flash efficacy was found between women in the high- and low-equol groups. Although an association between production of equol and hot flash control has not been disproved, it seems less likely given the recent trial results.

Most hot flash studies used isoflavone amounts of 40 to 80 mg/day. The potential for adverse effects from isoflavones and soy foods in these amounts seems minimal. Data are inconclusive regarding the estrogenicity of isoflavones.

Red Clover-Derived Isoflavones. Red clover (*Trifolium pratense*) contains several phytoestrogen compounds, including a rich supply of the isoflavones daidzein and genistein.

Three randomized, double-blind, placebo-controlled clinical trials of the red clover supplements Rimostil (57 mg/day isoflavones) or Promensil (40 mg/day isoflavones) found no benefit for hot flash treatment at one tablet per day for 3 months using study populations of

252,⁸¹ 51,⁸² and 37⁸³ peri- and postmenopausal women. One randomized, double-blind, placebo-controlled trial in 30 women aged 49 to 65 years reported that, after a 4-week placebo run-in, Promensil at 80 mg/day for 8 weeks reduced hot flashes.⁸⁴ However, the placebo response was lower than expected (16.7%), which may have affected the results.

The adverse effects reported with red clover isoflavones seem minimal, although the long-term safety of red clover has not been confirmed.

Black Cohosh

Preparations made from the rhizomes of black cohosh (*Cimicifuga racemosa* syn. *Actaea racemosa*) have been studied for relieving hot flashes, although the precise mechanism of action in humans is unknown. Among the substances in black cohosh thought to have an active therapeutic role are the triterpene glycosides, including actein, 27-deoxyactein, and cimifugoside. Almost all studies used the commercial preparation Remifemin. The currently available tablet form is standardized to the 27-deoxyactein content (1 mg per 20 mg tablet), although the formulation and

dose have changed over time, making it difficult to compare trials.

Three randomized, double-blind, placebo-controlled clinical trials have compared black cohosh with estrogens for treating hot flashes.⁸⁵⁻⁸⁷ A recent 3-month trial⁸⁵ tested BNO 1055 (Klimadynon, Menofem), a standardized black cohosh preparation, against conjugated equine estrogens (CEE) or placebo in 62 postmenopausal women aged 40 to 60 years. Black cohosh, at a dose equivalent to 40 mg/day, had no significant effect on hot flashes compared with placebo; only CEE increased endometrial thickness. The other two trials used Remifemin. One of these trials⁸⁶ evaluated black cohosh at a dose of 40 mg/day for 2 months in 85 breast cancer survivors older than 18 years (44 were aged 50-60 years), 59 of whom were taking tamoxifen. In this trial, black cohosh provided no benefit over placebo, although the study did report a substantially lower incidence of sweating. In the other trial, a study of 80 women aged 45 to 58 years (41 postmenopausal),⁸⁷ treatment with an earlier formulation of Remifemin (4-mg tablets twice daily for 3 months) was more effective than either CEE (0.625 mg/day) or placebo in improving the Kupperman menopausal symptom index scores and vaginal epithelium.

In 60 women aged 45 to 60 years with menopause-related symptoms, a Remifemin liquid extract (40 drops twice daily), CEE (0.625 mg/day), and diazepam (2 mg/day) all reduced Kupperman menopausal index scores.⁸⁸ Another randomized, treatment-controlled trial⁸⁹ of 60 symptomatic women aged 40 years or older found similar improvement with Remifemin tablets (standardized to 4 mg triterpene glycosides), estriol (Ovestin) at 1 mg/day, CEE (Presomen) at 1.25 mg/day, or an estrogen/progestogen combination product (Trisequens). Neither trial was placebo controlled.

Previous reports, including the 1989 monograph from the German government's Commission E (which regulates herb efficacy and safety), postulated that black cohosh has estrogenic effects. However, more recent reports suggest that it is not estrogenic.⁹⁰⁻⁹² Because currently available data are contradictory, caution dictates that the use of black cohosh not be presumed safe in women with breast cancer.

There are no known reports of serious adverse effects or drug interactions with black cohosh. Moderate side effects are rare and include gastrointestinal upset.⁹³ The effects of long-term use are unknown as no clinical trial has lasted longer than 6 months. However, longer trials are in progress.

Dong Quai

This herb is commonly used in traditional Chinese medicine (TCM) for treating gynecologic conditions. TCM practitioners traditionally do not use dong quai (*Angelica sinensis*) alone, but as part of an individually tailored herbal mixture.

The only randomized, double-blind, placebo-controlled study of dong quai for hot flashes evaluated 71 postmenopausal women (mean age, 52 years) using 4.5 g/day dong quai root for 6 months. During the study, the hot flash incidence decreased by approximately 25% to 30% from baseline in the dong quai group; this was not significantly different from placebo.⁹⁴

Data are inconclusive regarding the estrogenicity of dong quai.^{90,94} Dong quai is contraindicated in women using warfarin.

Evening Primrose Oil

Preparations made from the oil of evening primrose (*Oenothera biennis*) seeds have been used for menopause-associated hot flashes. However, the only randomized, double-blind, placebo-controlled clinical trial conducted⁹⁵ found no benefit over placebo from using evening primrose oil (2,000 mg gamma-linolenic acid plus 40 mg vitamin E twice daily for 6 months) for treating hot flashes (daily mean 7.2-7.6) in 56 women aged 45 to 67 years. No significant improvement in the number of hot flashes from baseline was found for the treated group, whereas the placebo group had significant improvement. Reported side effects include nausea and diarrhea.

Ginseng

A commonly used TCM ingredient is ginseng root (*Panax ginseng* and other *Panax* species). A randomized, double-blind, placebo-controlled clinical trial in 384 postmenopausal women aged 45 to 65 years found that *P. ginseng* (Ginsana brand containing 100 mg of standardized extract G115) for 14 weeks had no benefit over placebo on hot flash scores.⁹⁶

Case reports have associated ginseng with uterine bleeding.^{97,98} These reports, however, did not examine the ginseng products for adulterants. Mastalgia with diffuse breast nodularity also has been reported. Ginseng should not be used with monoamine oxidase (MAO) inhibitors, anticoagulants, or stimulants. Data are inconclusive regarding the estrogenicity of ginseng.

Licorice

The root of the licorice plant (*Glycyrrhiza glabra*) is used in many TCM preparations, including those used

for menopause-related symptoms. However, there are no clinical data regarding its safety or efficacy for treating hot flashes.

Large chronic doses of licorice may result in pseudoprimary aldosteronism, with symptoms that may include edema, hypertension, and hypokalemia. Cardiac arrhythmias and cardiac arrest have occurred in users of massive amounts of licorice. Licorice should not be used with diuretics. Reports differ as to the estrogenic effect of licorice root.⁹⁰ (Note: Most licorice candy in the United States is not made from real licorice.)

Chinese Herb Mixtures

In the only randomized, double-blind, placebo-controlled clinical trial of a Chinese herb mixture, 55 postmenopausal women aged 45 to 70 years found that the herb mixture taken for 3 months provided less benefit than placebo in treating hot flashes.⁹⁹ However, this study did not represent a typical use of TCM in that all women in the treatment group received the same mixture, not individualized preparations.

Vitamin E

The first well-controlled trial of vitamin E was a double-blind, 3-year study reported in 1953¹⁰⁰ that found vitamin E (50-100 IU/day) was no more effective than placebo in 658 women in relieving an 11-symptom menopause index (hot flashes were not analyzed separately).

Vitamin E therapy has also been evaluated in women with breast cancer. A randomized, double-blind, placebo-controlled crossover study tested 400 IU vitamin E succinate twice daily in 120 breast cancer survivors with hot flashes.¹⁰¹ After two 4-week periods (vitamin E followed by placebo or vice versa), results with vitamin E were statistically superior to placebo only in women who received placebo followed by vitamin E rather than vitamin E followed by placebo. However, the difference between groups was small (one hot flash reduction per person per day).

No acute adverse effects have been noted with vitamin E use at doses of up to 1,200 IU/day. Individuals with vitamin K deficiency may experience increased bleeding with high doses of vitamin E. This may have led to the common misperception that vitamin E increases bleeding risk. However, a generalized increase in bleeding risk has not been observed in studies designed to assess bleeding risk,¹⁰² even with vitamin E dosages up to 1,200 IU/day for 1 month in individuals on chronic warfarin doses.¹⁰³

Topical Progesterone

The use of nonprescription progesterone creams for the treatment of hot flashes is growing among US and Canadian women. So-called “natural” progesterone is synthesized commercially by a chemical process using plants such as soybeans and wild yam (*Dioscorea villosa*), and it is identical to endogenous progesterone. However, diosgenin, the precursor of progesterone found in these plants, cannot be converted to progesterone by the body.

Commercial topical progesterone preparations vary widely in dosages, formulations, additional ingredients, and recommended application sites. Many products labeled as wild yam cream contain only progesterone precursors; however, some of these creams may be adulterated with progesterone. Progesterone creams are regulated as dietary supplements, not drugs.

A 1-year randomized, double-blind, placebo-controlled study found that topical progesterone mixed with vitamin E and aloe vera (Pro-Gest), at 20 mg/day, significantly reduced hot flashes (a secondary endpoint) in 102 healthy postmenopausal women (mean age, 52 years).¹⁰⁴ Hot flash incidence was reduced in 83% of the active treatment group as compared with 19% of the placebo group, a significant between-group difference.

A 12-week randomized, double-blind, placebo-controlled study of 80 postmenopausal women having hot flashes evaluated 32 mg/day of progesterone in a topical formulation containing vitamin E and other oils (Pro-Feme).¹⁰⁵ Among the 72 participants who completed the study (mean age, 54 years; range, 43-69), no detectable changes in hot flashes were observed, despite a slight elevation of serum progesterone levels.

A randomized, double-blind, placebo-controlled, crossover trial¹⁰⁶ found that a topical cream containing wild yam extract, vitamin E, and other oils (BioGest) had no significant effects, when compared with either baseline or placebo, on hot flashes or night sweats in 23 postmenopausal women (average age, 53.3 years) treated for 3 months. Participants applied 1 teaspoonful to the skin twice daily.

No adverse effects associated with progesterone creams have been reported in the medical literature. Whether they are safe for women with a history of a hormone-dependent neoplasm is unknown. Although some topical progesterone preparations may increase serum levels of progesterone, there is little evidence

that any of these creams can prevent estrogen-induced endometrial hyperplasia.

Other Approaches

Several other nonprescription approaches have been used to treat hot flashes. Two such approaches, acupuncture and magnet therapy, are discussed.

Acupuncture. A study of acupuncture for hot flashes randomized 24 postmenopausal women to either electroacupuncture (electrical stimulation of acupuncture needles) or control (shallow acupuncture needle insertion) at standardized points.¹⁰⁷ Both groups improved, with no statistical difference between groups.

Magnet Therapy. In the only randomized, placebo-controlled trial,¹⁰⁸ a crossover study in 15 postmenopausal breast cancer survivors, investigators found no significant hot flash relief using magnetic devices placed on acupuncture points commonly used to treat hot flashes.

Prescription therapies: hormonal options

Many women suffer persistent hot flashes that respond only to prescription medications. Hormones are often prescribed, although their mechanism of action is unclear. The most commonly prescribed hormone is estrogen, either alone or with a progestogen for women with a uterus. Other hormones that have been used include progestogens alone, oral contraceptives (OCs), androgen-estrogen, and custom hormonal preparations.

ET and EPT

Over the past few decades, dozens of randomized, controlled clinical trials have provided evidence regarding the clinical efficacy of both estrogen therapy (ET) and estrogen plus progestogen therapy (EPT) in relieving menopause-related hot flashes, although 4 weeks or longer may be required to get the full effect. All oral and transdermal estrogen formulations and one vaginal estrogen product are government approved for this indication. (In this manuscript, “government approved” indicates approval for marketing by US and/or Canadian institutions responsible for regulating therapies.)

Most clinicians consider systemic ET/EPT to be the therapeutic standard for the treatment of hot flashes. According to NAMS recommendations, treatment of moderate to severe menopause symptoms (including hot flashes) is the primary indication for systemic ET and EPT.¹⁰⁹

A meta-analysis conducted by the Cochrane Group⁵⁷ of 21 randomized, double-blind, placebo-controlled tri-

als enrolling 2,511 women found that systemic ET/EPT significantly reduced both hot flash frequency and severity compared with placebo. Overall, hot flash frequency was reduced by 77% relative to placebo, whereas symptom severity was reduced by 87% (95% CI, 0.08-0.22). Among placebo recipients, a significant reduction in hot flashes of 51% from baseline to end of study also was reported. Trial durations ranged from 3 months to 3 years.

There are many government-approved systemic ET and EPT preparations, routes of administration, regimens, and doses. No evidence indicates that one product or regimen is superior to another for symptom relief.

Among ET products, conjugated equine estrogens, synthetic conjugated estrogens, 17 β -estradiol, ethinyl estradiol, estradiol acetate, esterified estrogens, estropipate (piperazine estrone sulfate), and estriol have all been shown to be effective treatments for hot flashes.

The most commonly used ET product in the United States and Canada is oral conjugated equine estrogens (CEE) dosed at 0.625 mg/day. Another commonly used estrogen therapy is 17 β -estradiol at 0.5-1.0 mg/day (oral) or 0.025-0.075 mg/day (patch).

The vaginal ring that delivers either 0.05 or 0.1 mg/day of estradiol acetate over a 3-month period is the only vaginal estrogen preparation that has been shown to effectively treat hot flashes.^{110,111} Other vaginal estrogen preparations at doses used to treat atrophic vaginitis have not been found to deliver ample estrogen to the circulatory system to relieve hot flashes.

Because of the increased risk of endometrial hyperplasia and adenocarcinoma with ET alone, all women with an intact uterus should receive systemic progestogen with estrogen.¹¹² Medroxyprogesterone acetate (MPA), 2.5 mg/day, is the most commonly used progestogen for EPT. Other oral progestogens used for EPT include norethindrone (also known as norethisterone, 0.35 mg/day), norethindrone acetate (5 mg/day), norgestrel (0.075 mg/day), and micronized progesterone (100-200 mg/day).

An oral tablet of CEE (0.625 mg/day) with MPA (2.5 mg/day) is the most commonly used combined EPT in hot flash trials; lower doses (0.45 mg/day CEE with 1.5 mg/day MPA) have been found to be effective for hot flashes, but long-term endometrial safety is unknown.¹¹³ Other oral tablets offering combined EPT include ethinyl estradiol (0.05 mg/day) with norethindrone acetate (1 mg/day), 17 β -estradiol (1 mg/day) with norethindrone acetate (0.5 mg/day), and 17 β -estradiol (1 mg/day) with norgestimate (0.09 mg intermittently for 3 days every 3 days). Combined EPT is

also available transdermally as 17 β -estradiol (0.05 mg/day) with norethindrone acetate (0.14 mg/day), applied twice weekly and either used continuously for 28 days or used for 2 weeks on and 2 weeks off, as well as 17 β -estradiol (0.45 mg/day) with levonorgestrel (0.15 mg/day), applied once a week for 28 days.

A dose-response relationship between hot flash efficacy and systemic ET/EPT has been observed.^{114,115} Individual responses vary widely, with some women responding to very low doses of estrogen and others requiring higher doses.

Current data from the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS) support a link between EPT and increased risks for breast cancer, coronary heart disease, thromboembolism, stroke, and dementia.¹¹⁶⁻¹²¹ Data from these studies should be extrapolated only with caution to women younger than 50 years of age who initiate ET/EPT. WHI and HERS involved women aged 50 and over (with mean ages of 63 and 67, respectively), and HERS was conducted solely in women with known coronary artery disease. The data should not be extrapolated to women experiencing premature menopause (< 40 years of age) and initiating HT at that time. Breast cancer risk is increased with ET and, to a greater extent, EPT use beyond 5 years.^{121,122} Progestogen may contribute substantially to that adverse effect. EPT and, to a lesser extent, ET increase breast cell proliferation, breast pain, and mammographic density.¹⁰⁹

ET/EPT is contraindicated in women with a history of hormone-sensitive cancer, liver disease (oral estrogen is of particular concern), history of blood-clotting disorders, and confirmed cardiovascular disease.

Potential adverse effects of ET include uterine bleeding, breast tenderness, nausea, abdominal bloating, fluid retention in extremities, headache, dizziness, and hair loss. Additional adverse effects when progestogen is added to estrogen (EPT) include mood changes and the potential for more uterine bleeding than with estrogen alone.

Progestogen

NAMS has determined that the primary menopause-related indication for progestogen use is endometrial protection from unopposed ET.¹¹² Progestogen alone, however, may be considered as a treatment for hot flashes if the benefit-risk profile is acceptable to the woman. Two chemical types of progestogens are available: progesterone (identical to the hormone secreted by the human ovary) and progestin (synthetic proges-

terone). Although each progestogen has unique properties, studies have found that several progestogens effectively treat hot flashes, leading to the conclusion that, as with estrogens, it is a drug class effect.

In women with a history of breast or endometrial carcinoma, there are no data demonstrating safety of progestogen on the breast, although progestogen seems to contribute substantially to the increased breast cancer risk seen with EPT use.¹¹² Mammographic density, linked in some studies to greater breast cancer risk, is increased with progestogen use, although this effect will reverse with discontinuation of use.¹²³⁻¹²⁵

Medroxyprogesterone Acetate (MPA). This progestin has been shown in several double-blind, placebo-controlled trials to relieve menopause-associated hot flashes in healthy women, as well as in women with breast or endometrial cancer. Both intramuscular and oral forms have demonstrated efficacy.

- **Intramuscular MPA.** In a double-blind, placebo-controlled trial in 69 women, the contraceptive depot-medroxyprogesterone acetate (DMPA), injected intramuscularly at a dose of 150 mg/month, reduced hot flashes by 90%, as compared with a 25% reduction for placebo.¹²⁶ Uterine bleeding was the major side effect, observed in 43% of participants. In a randomized, double-blind, placebo-controlled trial of 36 postmenopausal women, DMPA (50, 100, and 150 mg) exhibited a dose-response relationship.¹²⁷ By week 4, hot flashes were reduced by 75%, 90%, and 100% versus placebo on doses of 50 mg, 100 mg, and 150 mg, respectively. Only two participants had uterine bleeding.

Hot flash treatment with DMPA was compared with CEE in a randomized trial of 42 women who had reached menopause spontaneously or surgically.¹²⁸ Women received either DMPA (150 mg) or CEE (0.625 mg) for 25 days each month for 3 months. Hot flashes decreased significantly from baseline in both groups; no between-group difference was noted. Among women who benefited from treatment (82% of women in each group), hot flashes were reduced by 62% with CEE and by 69% with DMPA. During the treatment period, no hot flashes were reported by 18% of those using CEE and by 33% of those using DMPA. Side effects were similar between the two treatment groups.

In women with a history of breast cancer, a randomized trial¹²⁹ of 71 postmenopausal women compared DMPA (500 mg on days 1, 14, and 28) with oral megestrol acetate (40 mg/day). After the

6-week treatment period, 67% of DMPA recipients had at least a 50% reduction in hot flashes, which was statistically similar to the megestrol acetate group. An observational study of 15 women with a history of breast cancer found that DMPA (3 bi-weekly injections of 500 mg) reduced hot flashes by 90%.¹³⁰ Improvement remained for months after discontinuing DMPA in many of the women.

Contraindications of DMPA are the same as for estrogen. Adverse effects include weight gain, irregular uterine bleeding, amenorrhea, and nervousness. Evidence is inconclusive regarding associating DMPA therapy with a decrease in bone loss.¹³¹⁻¹³⁴

- **Oral MPA.** In clinical trials, oral MPA has shown efficacy similar to DMPA in relieving hot flashes; however, oral MPA is associated with less uterine bleeding and has been associated with no adverse effect on BMD. Contraindications are the same as with DMPA.

A double-blind, crossover trial of 27 postmenopausal women found that MPA, 20 mg/day, was significantly more effective than placebo in relieving hot flashes.¹³⁵ A randomized, placebo-controlled, crossover trial in six postmenopausal women determined that MPA at 20 mg/day significantly reduced both the subjectively noted hot flashes and the frequency of recorded temperature elevations more than placebo.¹³⁶

One randomized, double-blind, crossover trial¹³⁷ evaluated the efficacy of MPA in endometrial cancer survivors. In 21 women treated for endometrial carcinoma who had severe menopausal symptoms, MPA (100 mg twice daily) for 12 weeks was significantly more effective than placebo in relieving hot flashes. On average, the maximal effect was achieved after 4 to 6 weeks.

Megestrol Acetate. Another oral progestin, megestrol acetate, has also been studied for treating hot flashes. The only well-controlled clinical trial was in women with a history of breast cancer. In this trial—a randomized, placebo-controlled, double-blind crossover trial¹³⁸—97 postmenopausal women received 4 weeks of relatively low doses of megestrol acetate (20 mg twice daily). At the end of the study, hot flashes were reduced by about 85% in the megestrol acetate group compared with 21% in the placebo group, a significant between-group difference. The primary adverse effect was withdrawal uterine bleeding, generally occurring 1 to 2 weeks after discontinuation of therapy. A follow-up telephone survey of study participants determined that 18 (31%) of 58 women continued to use

megestrol acetate for periods of up to 3 years or longer with continued control of hot flashes and a minimum of side effects.¹³⁹ In a randomized trial comparing megestrol acetate with DMPA in 71 postmenopausal women with a history of breast cancer,¹²⁹ no between-group difference was found.

The full efficacy of megestrol acetate on reducing hot flashes may not be observed until after 3 or 4 weeks of therapy. In women receiving concurrent tamoxifen, there seems to be an increase in hot flashes for a few days after starting megestrol acetate therapy, before any decrease in hot flashes.¹³⁸

Despite the use of higher doses of megestrol acetate to treat metastatic breast cancer, a government-approved indication, concerns exist regarding the adverse effects of low doses of any progestational agent on breast cancer. No definitive data are available regarding the long-term safety of megestrol acetate for treatment of hot flashes in women with breast cancer.

Side effects include increased appetite (one of the drug's approved indications is for treating unwanted weight loss, but at much higher doses, in the 160- to 800-mg/day range) and, possibly, exacerbation of pre-existing diabetes and an increase in thromboembolic events.

Oral Contraceptives

A commonly prescribed therapy for women needing both contraception and hot flash therapy is a low-dose OC. A randomized, double-blind, placebo-controlled Canadian study of 132 healthy, nonsmoking perimenopausal women (aged 40-55) experiencing hot flashes found that an OC containing 0.02 mg ethinyl estradiol and 1 mg norethindrone acetate (Minestrin 1/20, equivalent to Loestrin 1/20) substantially reduced both the number and severity of hot flashes, but it was statistically no more effective than placebo.¹⁴⁰ A 3-year randomized study of a low-dose triphasic OC in 200 perimenopausal women found significant reductions in hot flashes compared with controls.¹⁴¹ The relatively high estrogen and progestin doses found in OCs, compared with menopausal HT, increase the likelihood that OCs might be effective.

Contraindications to the use of OCs include a history of blood clots, cardiovascular disease, migraine, hormone-sensitive carcinoma, jaundice, or liver disease. Smokers over age 35 should not use OCs. The most common adverse effects of OCs include nausea, vomiting, abdominal bloating, breakthrough uterine bleeding, change in menstrual flow, edema, melasma, and migraine.

Androgen-Estrogen Therapy

One androgen-estrogen product, a combination of 0.625 or 1.25 mg esterified estrogens and 1.25 or 2.5 mg methyltestosterone, respectively, is marketed for the treatment of moderate to severe vasomotor symptoms that are not improved by estrogen alone. Published clinical trial data are lacking to support this claim.

Contraindications and adverse effects are the same as for estrogen therapy, along with side effects associated with androgen treatment (including alopecia, acne, deepening of the voice, and hirsutism). However, these effects are infrequent at doses currently available for women. Long-term effects of low-dose testosterone treatment in women are not known. Higher endogenous testosterone concentrations have been linked to increased breast cancer, premature atherosclerosis, and dyslipidemia.^{142,143}

Custom Hormone Preparations

In addition to patented formulations, custom-made formulations prepared by a compounding pharmacist from a prescription are also available. These preparations, although not government approved, offer different types and amounts of estrogen (usually estriol, estrone, or estradiol) and progestogen (usually micronized progesterone) as well as ways to administer these hormones (eg, capsule, skin cream/gel, subdermal implant, sublingual tablet, rectal suppository, nasal spray). Custom preparations have not been adequately studied for any indication, including hot flash efficacy. Neither side effects nor other safety issues have been determined. No data support claims that these preparations are safer than conventional pharmaceutical drugs.

Prescription therapies: nonhormonal options

In women with hot flashes for whom hormones are not an option, other prescription drugs that are government approved for different indications have shown some effectiveness in relieving hot flashes. Some of these drugs were studied in women with a history of breast cancer. Available evidence suggests that data obtained from cancer survivors can be extrapolated to other populations of women. These data are included in the following summaries.

Antidepressants

Certain prescription antidepressants may decrease hot flashes in women, including those with a history of breast cancer. This effect on hot flashes likely results

from alterations of central serotonin or norepinephrine concentrations. Serotonin, injected into the hypothalamus, widens the thermoneutral zone in rats and guinea pigs; no human data are available.³⁰ A review of the data for three antidepressants follows. However, these studies enrolled women with lower hot flash rates than those required by the FDA to prove efficacy with moderate to severe hot flashes.

Venlafaxine. One antidepressant investigated for treating menopause-related hot flashes is venlafaxine HCl, a combined serotonin and norepinephrine reuptake inhibitor (SNRI).

A randomized, double-blind, placebo-controlled clinical trial¹⁴⁴ enrolled 229 women who were experiencing at least 14 hot flashes per week (69% were taking tamoxifen) and either had a history of breast cancer or chose not to take ET/EPT. Women were randomized to 4 weeks of treatment with either placebo or one of three venlafaxine doses: 37.5, 75, or 150 mg/day. At the end of the study, venlafaxine recipients had hot flash score reductions from baseline of 37% for the 37.5-mg/day dosage and 60% for both higher doses, as compared with a 27% reduction for placebo recipients. The effect on reducing hot flashes was relatively rapid, with full effect noted within 1 to 2 weeks. An uncontrolled pilot trial also supports this finding.¹⁴⁵

In the clinical trial, venlafaxine was relatively well tolerated at doses of up to 150 mg/day. (Doses used to treat depression start at 75 mg/day and increase to 150 to 225 mg/day.) The most problematic side effect was nausea or vomiting, which led to drug discontinuation in 5% to 10% of women, depending on the dose. In women who developed nausea but continued therapy, nausea largely dissipated over the following 1 to 2 weeks. In addition, those taking venlafaxine had more dry mouth and a decreased appetite. Only the highest dose arm had more constipation than the placebo arm.

Contraindications to using venlafaxine include concomitant use with MAO inhibitors. Other adverse effects observed in venlafaxine trials for depression include somnolence, dizziness, constipation, and sexual dysfunction. There is also a dose-related risk of increased blood pressure with the use of venlafaxine, affecting about 3% of those using less than 100 mg/day.¹⁴⁶

Paroxetine. A selective serotonin-reuptake inhibitor (SSRI), paroxetine HCl has also been associated with decreased hot flash rates. The only randomized, double-blind, placebo-controlled trial used controlled-release paroxetine in 165 women without a history of breast cancer and experiencing 2 or 3 hot flashes per day.¹⁴⁷ At doses of either 12.5 or 25.0 mg/day for 6

weeks, paroxetine significantly decreased hot flash composite scores by 62.2% (12.5 mg/day) and 64.6% (25.0 mg/day), compared with a 37.8% decrease for placebo recipients. Results from two uncontrolled pilot studies also support this study.^{148,149}

Contraindications to using paroxetine include concomitant use of MAO inhibitors or thioridazine. Caution is advised with concomitant administration of warfarin. Adverse effects observed in trials for depression include asthenia, sweating, nausea, decreased appetite, somnolence, insomnia, and dizziness. The recommended initial dose for treating depression is 20 mg/day.

Fluoxetine. Another SSRI, fluoxetine HCl, is government approved to treat depression and premenstrual dysphoric disorder, but it also has been studied for hot flashes at the same dose (20 mg/day) recommended as the initial dose to treat depression.

In a double-blind, placebo-controlled, crossover trial,¹⁵⁰ 81 healthy women with a history of breast cancer or a perceived risk of breast cancer and at least 14 hot flashes per week were randomized to fluoxetine (20 mg/day) or placebo for a 4-week period, with the alternative treatment given for an additional 4 weeks. The crossover analysis found additional reductions in hot flash frequency of about 20% for fluoxetine recipients compared with placebo recipients (no difference in results based on age). The magnitude of benefit in this study, however, did not seem to be as great as was seen with venlafaxine. Fluoxetine was well tolerated in this trial.

Contraindications and side effects with fluoxetine are the same as with paroxetine.

Gabapentin

This anticonvulsant has been studied for treating hot flashes. Its mechanism of action on hot flashes is unknown, although it has been speculated that gabapentin may modulate calcium currents.

A randomized, double-blind, placebo-controlled trial performed in 59 postmenopausal women averaging seven or more hot flashes per day found that, after 12 weeks of gabapentin therapy (900 mg/day, administered in three divided doses), hot flash frequency was reduced by 45%, with a 54% reduction in a hot flash composite score.¹⁵¹ The differences were statistically significant compared with placebo recipients, who had reductions of 29% and 31%, respectively. Gabapentin was relatively well tolerated in this clinical trial, with dizziness and lightheadedness (especially at initiation of therapy) and peripheral edema being the major observed adverse effects. Results from a prospective, single-arm study¹⁵² and an open-case series¹⁵³ also support these findings.

Although higher doses of gabapentin are commonly used for treatment of seizures or neuropathies (up to 3,000-3,600 mg/day), doses as low as 100 mg/day are typically used as starting doses for hot flashes, particularly in older women.

Hypersensitivity to the drug is the only contraindication to gabapentin use. Adverse effects observed in seizure trials include somnolence, dizziness, ataxia, fatigue, and nystagmus.

Antihypertensives

Two older antihypertensive drugs, clonidine HCl and methyldopa HCl, have been studied for treating hot flashes.

Clonidine. Two randomized, placebo-controlled trials (N = 10 and N = 29) found that the α_2 -adrenergic agonist clonidine, given either orally or transdermally, reduced hot flash frequency by 46% (for 0.4 mg/day) and 80%, respectively, in healthy women.^{36,37} However, in one of these studies,³⁶ four women in the clonidine group withdrew because of drug-related side effects, which included nausea, fatigue, headaches, dizziness, and dry mouth.

In breast cancer survivors using tamoxifen, two randomized, placebo-controlled clinical trials also found clonidine effective in relieving hot flashes.^{154,155} An 8-week trial¹⁵⁴ found that oral clonidine (0.1 mg/day) significantly reduced hot flashes in 194 postmenopausal women (by 38% v 20% for placebo), although the clonidine group reported more difficulty sleeping than those receiving placebo (41% v 21%, respectively). In 110 women (median age, 54),¹⁵⁵ transdermal clonidine (equivalent to 0.1 mg/day) for 4 weeks significantly improved hot flash frequency and severity compared with placebo. However, clonidine was associated with more side effects than the placebo, including dry mouth, drowsiness, constipation, and itchiness under the patch.

Contraindications include cardiac sinus node function impairment. Clonidine lowers blood pressure, heart rate, and pulse rate; arrhythmias have been observed at high doses. Adverse effects observed in hypertension trials include dry mouth, drowsiness, dizziness, constipation, and sedation.

Methyldopa. Two randomized, double-blind, placebo-controlled, crossover trials reported that methyldopa, in daily oral doses of 500 to 1,000 mg, decreased menopause-related hot flashes, although improvement was modest.^{156,157} Nesheim et al¹⁵⁶ reported a median reduction in hot flashes of 65% with methyldopa (250 mg/day) compared with 38% for placebo, a significant between-group difference. Hammond et al¹⁵⁷ found

significant reductions in hot flashes in a trial involving 10 women.

Contraindications include active hepatic disease and use of MAO inhibitors. Methyl dopa lowers blood pressure. A positive Coombs test, hemolytic anemia, and liver disorders may occur with methyl dopa therapy. Side effects observed in hypertension trials include sedation, headache, asthenia, edema, and weight gain.

Bellergal Spacetabs

There are limited data to support the efficacy of this older sedative, a combination tablet of low-dose phenobarbital (a barbiturate), ergotamine tartrate, and levorotatory alkaloids of belladonna, in treating menopause-related hot flashes. Its specific mechanism of action is unknown.

A randomized, double-blind, placebo-controlled study in 72 women found that Bellergal significantly reduced hot flashes compared with placebo (60% v 22%, respectively) after 12 weeks of treatment.¹⁵⁸ In a randomized, placebo-controlled, double-blind trial in 66 women,¹⁵⁹ significant decreases in hot flashes from baseline were reported after 8 weeks for both the Bellergal (75%) and placebo (68%) groups. However, the between-group difference was not significant.

Contraindications include cardiovascular or hepatic disease and glaucoma. Adverse effects include visual disturbances, dry mouth, flushing, dizziness, and somnolence. Bellergal reduces the efficacy of certain drugs, including anticoagulants and OCs. Bellergal intoxication can lead to death. Barbiturates are addictive and should not be recommended for long-term use.

Other Drugs

Additional prescription therapies studied for relief of hot flashes are available in many countries but not in North America. Other options can be expected in the future.

CLINICAL MANAGEMENT

The treatment of menopause-associated vasomotor symptoms is a common clinical challenge. Before treatment begins, a detailed patient history of hot flashes is needed, including frequency and severity as well as the effect they have on activities of daily living. Women differ in their attitude toward hot flashes. No treatment is needed unless the hot flashes are bothersome to the woman. Some women seek only to reduce their symptoms slightly, whereas others request more complete amelioration.

The decision to undertake treatment should be based on the severity of the symptoms, an assessment of treatment-related risks, and the woman's personal attitudes about menopause and medication. The clinical goal is to tailor therapy to each individual woman's needs, using the various options. Clinicians are advised to enlist women's participation in decision making when weighing the benefits, harms, and scientific uncertainties of options.

No therapy is government approved in either the United States or Canada for treating hot flashes in women who are at high risk for or have been diagnosed with breast cancer or other hormone-dependent neoplasias. However, a variety of nonprescription and non-hormonal treatments have been used to relieve hot flashes in these populations. Caution is advised when recommending therapies to these women, as some therapies may have estrogenic activity.

Data are inadequate to determine if the physiologic mechanisms for hot flashes in breast cancer survivors using tamoxifen are different from hot flashes in women experiencing menopause-related hot flashes. At this time, it is reasonable to assume that the therapeutic results seen with hot flashes may be applicable to either population.

In most women, hot flashes will abate over time without any intervention. When therapy is desired, various nonpharmacologic and pharmacologic options are available. The recommended clinical management approach includes lifestyle modification followed by nonprescription and/or prescription therapies, when needed.

Most of the clinical recommendations in this section are based on medical evidence, and they represent areas in which the Editorial Board reached consensus. If the evidence was inconclusive, recommendations were made based on expert opinion and clinical judgments; readers should be aware that these opinions might not be shared by all healthcare clinicians. In some cases, an intervention is recommended, or not discouraged, if it seems to have a harmless side effect profile. In other cases, interventions are not recommended if they have the potential for adverse effects.

Lifestyle changes

In women who need relief from mild menopause-related hot flashes, NAMS recommends first considering lifestyle changes, which include environmental manipulations and behavioral changes, such as keeping the core body temperature as cool as possible, participating in regular exercise, and avoiding hot flash trig-

gers. Use of paced respiration is another option to consider, based on its effectiveness in studies, ease of use, and lack of side effects. Because both obesity and a sedentary lifestyle are linked to increased hot flashes, a strategy to maintain a healthy weight and to exercise regularly may be helpful.

Nonprescription remedies

When lifestyle changes are not adequate to achieve the desired level of relief from mild hot flashes, adding a nonprescription remedy may be considered. A trial of dietary isoflavones or supplements containing black cohosh or vitamin E may be an option, primarily because these remedies are not associated with serious side effects. However, because of inconclusive efficacy data, this is not a consensus recommendation.

Efficacy in clinical trials of both soy foods and isoflavone supplements (from either soy or red clover) has been mixed, possibly because it is limited to the subset of women who are equol producers. Nevertheless, for women with frequent hot flashes, clinicians may consider recommending soy foods or soy isoflavone supplements. Most hot flash studies used isoflavone amounts of 40 to 80 mg/day. Whole foods may be a better choice than isoflavone supplements or fortified foods, based on lack of potential isoflavone “overdose” with soy foods.¹⁶⁰ Effects, if any, may take several weeks. Isoflavones exhibit a low incidence of side effects, although caution is advised when estrogenicity is a concern. Whether these foods or supplements can treat hot flashes effectively and safely in women who have had or are at risk for breast cancer is unknown.

Additional studies are needed to determine whether there are differences among whole food, soy protein, and isoflavone extracts. Whole soy foods have been consumed for thousands of years and are presumed safe, but supplements and fortified foods may contain high levels of isolated isoflavones, the long-term effects of which are unknown.

In the most recent trials of black cohosh, the results have been negative. However, some older and smaller trials from Germany have shown some efficacy for hot flashes. With its low incidence of side effects, a black cohosh supplement (two 20-mg tablets daily of a 27-deoxyactein standardized preparation) taken for fewer than 6 months is likely to do no harm and may provide relief of mild hot flashes.

Vitamin E, 800 IU/day, is another nonprescription option to try for hot flash relief, although clinical evidence is mixed. A statistically significant but not clinically significant decrease in hot flashes among breast cancer survivors was noted in one clinical trial, al-

though older trials found no benefit for vitamin E over placebo. Because vitamin E seems to be nontoxic at low doses, inexpensive, and available without a prescription, it is a reasonable option for a trial. Effects, if any, may take weeks.

Scientific data are lacking regarding the efficacy and safety of topical progesterone creams for relief of hot flashes. Contents and concentrations vary widely in different brands of nonprescription progesterone creams. Additionally, safety concerns regarding systemic progestogen preparations may also apply to topical progesterone preparations. Therefore, NAMS does not recommend use of progesterone creams for hot flash relief.

Given the lack of efficacy data, NAMS also does not recommend dong quai, evening primrose oil, ginseng, licorice, Chinese herb mixtures, acupuncture, or magnet therapy for hot flash relief.

Prescription therapies: hormonal options

When lifestyle changes and nonprescription approaches do not provide the desired relief, prescription options are available. Hormonal approaches, primarily systemic ET/EPT, are most often prescribed and are the only government-approved therapies in the United States and Canada for treating moderate to severe hot flashes. During perimenopause, follicle-stimulating hormone and estradiol levels fluctuate. Dosing estrogen at this time provides uncertain results. After menopause is reached and ovarian activity ceases, response to estrogen therapy will be more predictable.

NAMS considers treatment for moderate to severe menopause-related hot flashes to be a primary indication for systemic ET and EPT. Use of ET and EPT should be limited to the shortest duration consistent with treatment goals, benefits, and risks for the individual woman.

NAMS recommends considering lower-than-standard doses of ET and EPT (ie, daily doses of 0.3-mg conjugated estrogens tablet, 0.25-0.5-mg 17 β -estradiol tablet, 0.025-mg 17 β -estradiol patch, or the equivalent). Many studies have demonstrated that these doses provide similar vasomotor symptom relief. Lower EPT doses are better tolerated and may or may not have a more positive safety profile than standard doses; however, lower doses have not been tested for outcomes (including endometrial safety) in long-term trials.

For all women with an intact uterus who are using estrogen therapy, NAMS recommends that they receive adequate progestogen, either in a continuous-combined or continuous-sequential EPT regimen.

However, there is insufficient evidence regarding long-term endometrial safety to recommend use of long-cycle progestogen (ie, progestogen every 3-6 months for 12-14 days), a progestin-containing intrauterine device, or low-dose estrogen without progestogen as an alternative to standard EPT regimens. If utilizing any of these approaches, close surveillance of the endometrium is recommended, pending more definitive research.¹⁰⁹ Some women with an intact uterus who choose EPT may experience undesirable side effects from the progestogen component.

If the initial ET/EPT dose is not effective, it may be increased. For women who are not obtaining symptom relief with once-daily dosing of oral ET due to the possibility of their metabolizing the hormone more rapidly, twice-daily dosing with half doses may be advised or they may be switched to transdermal ET. There is often no need to increase the total daily oral dose in women suspected of having rapid or irregular metabolism of exogenous estrogen. In such women, stability of the circulating estrogen level may be more important than attainment of an absolute level. The route of administration can also be switched. Transdermal ET may provide more stable levels of circulating estrogen than oral therapies. Another option is the vaginal estrogen ring (Femring) that is FDA-approved for treating hot flashes.

There are few clinical trial data on custom hormone preparations. For most women, NAMS does not recommend these preparations for hot flash relief, due to lack of efficacy and safety data on the specific compounded prescriptions.

With cyclic ET regimens (ie, estrogen-only for 3 weeks followed by 1 week off therapy), hot flashes may return by the end of the hormone-free week. This is especially true with 17 β -estradiol, due to its rapid clearance from the body. Thus, NAMS recommends using continuous ET regimens before cyclic regimens when treating hot flashes.

If hot flashes persist after an adequate trial (ie, 2-3 months) of HT, other conditions associated with hot flashes should be considered in the differential diagnosis.

When ET/EPT is discontinued abruptly, hot flashes often return within several days, depending on the type and route of estrogen therapy. No specific protocols can be recommended for discontinuing therapy to avoid rebound hot flashes. Some clinicians gradually decrease the dose, whereas others lengthen the time between doses. There are no data to suggest that one method is better than the other. If hot flashes recur, ET/EPT may be reinstated then discontinued at a later time.

Prescription progestogen alone can be used to treat hot flashes of varying severity. In clinical trials, DMPA, MPA, and megestrol acetate have demonstrated efficacy. Short-term use of these drugs seems reasonable in women without contraindications who do not wish to try estrogen but who are not opposed to trying another hormone, although progestogens have been linked to breast cancer risk in some studies.

Perimenopausal women who need both hot flash relief and contraception may achieve both goals with low-dose, combined estrogen-progestin OCs. NAMS supports this use for otherwise healthy women who do not smoke or have other contraindications. The potential side effects of nausea, mood swings, and headaches can usually be decreased or eliminated by altering the regimen or dose. Relief of hot flashes should be achieved within 2 to 3 months of starting therapy. If hot flashes occur during the placebo week, adding a low dose of supplemental estrogen or shortening or eliminating the placebo interval may provide relief. DMPA offers another option for hot flash relief and contraception, although adverse effects are greater than with OCs. Standard menopausal doses of ET/EPT have not been well studied with respect to protection from an unwanted pregnancy and, thus, should not be relied on for contraception.

If EPT is needed postmenopause, transitioning from a combination OC to EPT should be done as soon as appropriate. Even OCs with very low hormone doses still provide significantly more hormone than in standard EPT, which may increase exposure to unnecessary risks from long-term use.

Prescription therapies: nonhormonal options

In women with hot flashes for whom hormones are not an option, nonhormonal prescription drugs have shown some effectiveness in relieving hot flashes. However, there are no comparative trials in similar patient populations to guide clinicians in selecting a particular option.

If there are no contraindications, NAMS recommends the antidepressants venlafaxine (at dosages of 37.5-75 mg/day), paroxetine (12.5-25 mg/day), or fluoxetine (20 mg/day) as options for women with hot flashes who are not candidates for HT, including breast cancer survivors. The additional antidepressant effect may benefit some women who suffer from mood disorders.

Hot flash relief, if any, is almost immediate with these therapies, whereas for depression, effects often are not observed for 6 to 8 weeks. This rapid onset of

action can be a powerful reinforcement for women who do not find relief from other, simpler methods. A brief trial of 1 week may determine if these agents are going to be effective.

Side effects, especially nausea and sexual dysfunction, should be monitored. Women who experience drowsiness should take the drug at night. Venlafaxine is the most likely in its class to promote weight loss (by causing anorexia), and may be preferred by overweight women. Paroxetine has similar side effects, although less nausea and anorexia. It can also cause blurred vision, although this is rare. Fluoxetine is less likely to cause acute withdrawal side effects because of its longer half-life.

To minimize side effects, very low doses of these antidepressants can be used when starting therapy. If not effective, the dose can be increased after 1 week. Higher doses than those used in trials do not seem appropriate, given the lack of additional efficacy and the potential for increased toxicity. Taking the drugs with food may lessen nausea.

These antidepressant medications should not be stopped abruptly, as sudden withdrawal has been associated with headaches and anxiety. Women who have been using an antidepressant for at least 1 week should taper off the drug. Tapering may require up to 2 weeks, depending on the initial dosage.

Gabapentin is another nonhormonal option recommended by NAMS for treating hot flashes. Therapy can be initiated at a daily dose of 300 mg (although starting at 100 mg/day may be advisable in women older than age 65). Bedtime administration is advised, given the initial side effect of dizziness. In women who continue to have hot flashes, the dose can be increased to 300 mg twice daily and then to three times daily, at 3- to 4-day intervals. Increased efficacy may be seen at even higher doses, although this has not been well studied. Antacids may reduce the bioavailability of gabapentin; the drug should be taken at least 2 h after antacid use.

Clonidine is sometimes used to treat mild hot flashes, although it is less effective than the newer antidepressants or gabapentin. In addition, clonidine has a side effect profile that limits its use in many women. The initial oral dose for hot flash treatment is 0.05 mg twice daily, but women may require at least 0.1 mg twice daily. The clonidine patch, delivering 0.1 mg/day, can also be considered. When discontinuing higher-dose therapy, the dose should be gradually tapered to avoid adverse side effects, including nervousness, headache, agitation, confusion, and a rapid rise in blood pressure.

Given their toxicity, NAMS does not recommend methyldopa or Bellergeral as hot flash treatments for most women.

Any hot flash treatment may need to change over time because of gradually lowering levels of ovarian hormones through perimenopause and the possible appearance of medical conditions unrelated to menopause or menopause treatments. New research and changing ideas about treatments may have an impact on health decisions. Before switching from one therapy to another, a wash-out period may be required.

SUMMARY

For mild vasomotor symptoms, lifestyle changes alone or combined with a nonprescription remedy, such as dietary isoflavones, black cohosh, or vitamin E, can be considered. Although there is insufficient clinical trial evidence to support the efficacy of these options, they are reasonable approaches to consider given their lack of potential short-term adverse effects. It is not known whether isoflavone supplements can be safely consumed by women with breast cancer.

Prescription systemic ET/EPT remains the gold standard for treating moderate to severe menopause-related hot flashes in women without contraindications. Oral contraceptives are an option for perimenopausal women, especially those needing contraception.

Options for women with concerns relating to estrogen-containing treatments include lifestyle modification combined with one of the following, provided there are no contraindications: the antidepressants venlafaxine, paroxetine, or fluoxetine, or gabapentin. Progestogens may be considered, although no definitive data are available on long-term safety in women with a history of breast cancer. Clonidine and methyldopa may be an option for some women, but they are limited by only moderate efficacy combined with a relatively high rate of adverse events.

Regardless of the management option utilized, treatment should be periodically evaluated to determine if it is still necessary, as in almost all women, menopause-related vasomotor symptoms will abate over time without any intervention.

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