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CME

Position Statement

Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society

Abstract

Objective: To update and expand The North American Menopause Society's evidence-based position on nonhormonal management of menopause-associated vasomotor symptoms (VMS), previously a portion of the position statement on the management of VMS.

Methods: NAMS enlisted clinical and research experts in the field and a reference librarian to identify and review available evidence. Five different electronic search engines were used to cull relevant literature. Using the literature, experts created a document for final approval by the NAMS Board of Trustees.

Results: Nonhormonal management of VMS is an important consideration when hormone therapy is not an option, either because of medical contraindications or a woman's personal choice. Nonhormonal therapies include lifestyle changes, mind-body techniques, dietary management and supplements, prescription therapies, and others. The costs, time, and effort involved as well as adverse effects, lack of long-term studies, and potential interactions with medications all need to be carefully weighed against potential effectiveness during decision making.

Conclusions: Clinicians need to be well informed about the level of evidence available for the wide array of nonhormonal management options currently available to midlife women to help prevent underuse of effective therapies or use of inappropriate or ineffective therapies. **Recommended:** Cognitive-behavioral therapy and, to a lesser extent, clinical hypnosis have been shown to be effective in reducing VMS. Paroxetine salt is the only nonhormonal medication approved by the US Food and Drug Administration for the management of VMS, although other selective serotonin reuptake/norepinephrine reuptake inhibitors, gabapentinoids, and clonidine show evidence of efficacy. **Recommend with caution:** Some therapies that may be beneficial for alleviating VMS are weight loss, mindfulness-based stress reduction, the S-equol derivatives of soy isoflavones, and stellate ganglion block, but additional studies of these therapies are warranted. **Do not recommend at this time:** There are negative, insufficient, or inconclusive data suggesting the following should not be recommended as proven therapies for managing VMS: cooling techniques, avoidance of triggers, exercise, yoga, paced respiration, relaxation, over-the-counter supplements and herbal therapies, acupuncture, calibration of neural oscillations, and chiropractic interventions. Incorporating the available evidence into clinical practice will help ensure that women receive evidence-based recommendations along with appropriate cautions for appropriate and timely management of VMS.

Key Words: Complementary therapies – Hot flashes/diet therapy – Hot flashes/drug therapy – Hot flashes/prevention and control – Menopause – Post-menopause.

INTRODUCTION

Vasomotor symptoms (VMS) are the cardinal symptom of menopause, affecting more than three-quarters of midlife women. Symptoms typically last 5 to 7 years, although some women continue to experience symptoms for longer than 10 or 15 years.[1,2] Hormone therapy (HT) was previously the mainstay of treatment, but other options are needed because HT may not be the treatment of choice because of personal preference or medical contraindications (eg, hormonally dependent cancers). As a result, surveys suggest that 50% to 80% of midlife women use nonhormonal therapies for VMS.[3-6]

Decisions about which nonhormonal options are best can be difficult. Most midlife women indicate that they do not feel fully informed or have concerns about various treatment options.[3,7] For example, a national survey of 781 midlife women revealed that 75% of them did not feel fully informed

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about herbal products, 64% had concerns or were not sure about herb-drug interactions, and 61% did not feel confident about herbal product dosing.[3] In another survey, nearly half of 293 women reported feeling confused about menopausal symptom management treatment options.[7] Because these challenges can lead to underuse of effective therapies or use of inappropriate or ineffective therapies, it is imperative that healthcare professionals be fully informed and prepared to assist women's decision making about nonhormonal VMS management.

Eleven years have passed since NAMS issued its last position statement on the management of VMS.[8] In that intervening time, the National Institutes of Health held a state-of-the-science conference on nonhormonal management of VMS, and a large amount of new evidence has been published in the form of reviews, meta-analyses, and original research. The current position statement updates and expands information on nonhormonal management of VMS that was contained in the previous NAMS position statement and is intended to provide direction to guide evidence-based use of nonhormonal management of menopausal VMS.

METHODOLOGY

For this position statement, an experienced reference librarian searched five multidisciplinary databases using appropriate keywords. The types of nonhormonal therapies included in the search were identified from the previous position statement as well as review articles. (For examples, see reviews by Nedrow and colleagues[9] and Nelson and colleagues.[10]) The databases searched were Academic Search Premier, Embase, Family and Society Studies Worldwide, PsychInfo, and PubMed. These databases were identified for searching on the basis of their medical, psychological, and sociological content, which were all pertinent to the subject. The searches were split into three sections to differentiate the results for easier review: pharmaceuticals, supplements, and nonprescription and nonsupplemental therapies.

After searching each treatment type, 2,919 results were returned from all five databases. After removing articles not in English, duplicate articles across databases, and consumer publications, 1,428 citations remained. Articles including men, hormonal therapy, or narrative reviews were eliminated. Further review by the position statement panel distilled the results for review to 340 original research articles and 105 systematic reviews. Of these, 83% of the research articles and 88% of the systematic reviews were published between 2005 and 2015, or after the previous NAMS position statement was published, illustrating the growth in the literature that needed to be incorporated into this new position statement.

Individual panel members reviewed the evidence on the different therapies for which they had special expertise and made treatment recommendations. Members evaluated the evidence for various nonhormonal therapies with the knowledge that nonhormonal VMS trials have a placebo improvement rate of 20% to 60%, with more anxious women showing higher response to placebo.[11]

Levels of evidence were assigned on the basis of the following categories: Level I—high-quality randomized trials; systematic reviews of level I studies. Level II—lesser-quality randomized, controlled trials (RCTs), systematic reviews of level II studies, or level I studies with inconsistent results. We included trials using poorly validated measures (eg, Kupperman Index) in this category. Level III—uncontrolled trials, case-control studies, systematic reviews of level III studies. Level IV—case series, case-control studies. Level V—expert opinion. Citations refer primarily to RCTs and higher-quality reviews (eg, meta-analyses, Cochrane reviews), with no attempts made to cite all available reviews.

NONPRESCRIPTION THERAPIES

Lifestyle changes

Cooling techniques

Because hot flashes can be triggered by small core body temperature elevations,[12-14] it is rational to propose lifestyle practices that lower core body temperature or that prevent it from rising to decrease VMS frequency. These include clothing adjustments (such as dressing in layers; wearing sleeveless blouses, natural fiber clothing that breathes, and light cotton night clothes; and avoiding pullover sweaters/tops and scarves) and environmental controls (keeping a hand fan, electric fan, or ice water nearby; putting a cold pack under the pillow and turning the pillow when feeling warm; using dual control electric blankets or a bed fan—a simple device that blows air under the top sheet; and lowering the room temperature). However, no clinical trial evidence supports the efficacy of cooling interventions as treatments for VMS. *Level V evidence*

Avoiding triggers

It is also often recommended that women avoid ''triggers'' such as alcohol, spicy foods, and hot foods or liquids. No clinical trials have studied the effect of presumed triggers, and the Melbourne Women's Midlife Health Project found no significant association between alcohol intake and VMS.[15] *Level V evidence*

Exercise

The hypothesis that regular aerobic exercise might be associated with a reduction in VMS arose from observational studies that found that women who exercise regularly report having fewer VMS.[16-18] However, others have found no relationship between level of physical activity or exercise and VMS,[19] and exercise may trigger VMS in symptomatic women.[13]

The numerous RCTs of the effects of exercise on VMS have been summarized in several Cochrane reviews.[20-22] The first review[20] included one study,[23] the second review[21] included five studies,[24-28] and the third review[22] added two studies.[29,30]

Across all three Cochrane reports, the authors concluded that the evidence was insufficient to determine whether exercise is an effective treatment for menopausal symptoms, and the overall evidence was viewed as poor. Methods and

exercise interventions varied widely across studies, for example: structured supervised walking versus yoga versus no intervention[26]; supervised prescribed aerobic exercise versus yoga versus usual activity plus omega-3 or placebo pills in a 1:1 ratio with each group[30]; thrice weekly supervised aerobic exercise class versus hormone therapy[23]; and unsupervised aerobic training four times weekly versus controls plus lectures once or twice per month on physical activity and general health in both groups.[29] When three studies that compared exercise to no exercise were pooled, exercise had no effect on VMS frequency.[22] No difference was found between yoga and exercise in the two studies that made this comparison. In the study comparing exercise and HT, HT was far more effective than exercise in reducing VMS.

In a randomized trial published subsequent to the Cochrane reviews, 261 women were randomized to: 1) one-on-one consultation with a physical activity facilitator; 2) the same counseling plus a digital video disc, a booklet, and five study leaflets; or 3) a control group.[31] Women were followed for 6 months. The exercise goal was 30 minutes of moderate-intensity exercise 3 to 5 days per week. Neither intervention had an effect on total VMS frequency or night sweats that was greater than control.

Although there are many health benefits for recommending that midlife women exercise, randomized trials to date do not support any benefit of physical activity for VMS. *Level I evidence*

Yoga

Randomized trials to date do not support the case that regular yoga practice will reduce VMS.[32,33] A systematic review and meta-analysis of five RCTs[25,26,34-36] found no evidence that yoga was an effective intervention for VMS or menopausal symptoms.[32] Yoga varied from Iyengar yoga, to traditional Indian yoga, an ''integrated'' approach to yoga, and a combination of Yogasana and Tibetan yoga; some included only poses, whereas others included poses, breathing, and meditation. Doses varied from 1 to 2 hours per session, 1 to 5 sessions per week, and 8 to 12 weeks. Comparison groups included no treatment, exercise, or both.

Two trials[37,38] published after the systematic review also found no effect of yoga on VMS. Newton and colleagues[37] conducted an RCT in perimenopausal and postmenopausal women with at least two VMS per day randomized to yoga (n = 107), exercise (n = 106), or usual activity (n = 142). The yoga intervention used 12 weekly 90-minute yoga classes with daily home practice. There was no significant difference between groups in change in VMS frequency from baseline to 6 and to 12 weeks. Avis and colleagues[38] randomized 54 late perimenopausal and postmenopausal women aged 45 to 58 years with at least four VMS per day to one of three groups: yoga (n = 18), health and wellness education (n = 19, attention control group), or a wait-list control group (n = 19). Yoga and education consisted of weekly 90-minute classes for 10 weeks, and yoga included recommended home practice. VMS frequency declined similarly in all groups. At 10 weeks, the mean decrease in VMS per group was 6.5 (66%) in the yoga group, 5.9 (63%) in the health and wellness group, and 4.2 (36%) in the wait-list control group. *Level I evidence*

Weight loss

One RCT suggests weight loss may alleviate VMS. Forty overweight or obese women with at least four VMS per day were randomized to a 6-month behavioral weight loss intervention or wait-list control.[39] Women randomized to the weight loss intervention lost significantly more weight (−8.86 kg) than women randomized to control (+0.23 kg; $P < 0.0001$) and had a significantly greater reduction in questionnaire-reported hot flashes (−63.0 over 2 wk) than women in the control group (−28.0; $P = 0.03$). Reductions in weight and hot flashes were highly correlated ($r = 0.47$, $P = 0.006$). Changes in hot flash severity, bother, the number of physiologically measured hot flashes, and diary-reported hot flashes did not differ between groups.

Additional evidence comes from three studies in which weight loss was studied, but hot flashes were not a primary outcome. The first was a 6-month study of weight loss for urinary incontinence that included 154 women who reported hot flash bother (7.5-kg weight loss in intervention vs 2.0-kg loss in control).[40] The intervention was associated with significantly greater improvement in bothersome hot flashes versus control. Reductions in weight, body mass index, and abdominal circumference were related to significant decreases in hot-flash bother. The second analysis used data from the Women's Health Initiative Dietary Modification trial (n = 17,473).[41] Baseline presence and severity of hot flashes were identified via questionnaire: 65% of respondents reported no; 25% mild; 8% moderate; and 2% severe VMS. Compared with control, women randomized to the intensive intervention to promote healthy eating were more likely to lose weight and have VMS symptoms eliminated at 1 year (odds ratio, 1.14; 95% confidence interval, 1.01-1.28). Compared with women who maintained their weight, women who lost 10 lb or more were 23% more likely to eliminate VMS at 1 year, and those who lost 10% or more of their baseline body weight were 56% more likely to have this outcome. The third study was the Women's Healthy Eating and Living study, a dietary intervention trial for women with breast cancer.[42] In a secondary analysis, women were classified as having no/mild symptoms versus moderate/severe symptoms (36% at study entry). At 2 years, women who had gained at least 10% of their prediagnosis weight had a 33% ($P = 0.003$) greater risk of reporting moderate/severe VMS than those with stable weight; whereas those who lost at least 10% of their prediagnosis weight had a 28% ($P = 0.118$) lower risk of reporting moderate to severe VMS. Taken together, these studies suggest that weight loss might be associated with a decrease in or the elimination of VMS. *Level II evidence*

Mind-body techniques

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) was effective in reducing VMS problem ratings, but not VMS frequency, in two

randomized, double-blind, controlled trials. MENOS 1 showed efficacy of group CBT compared with usual care in 96 breast cancer survivors,[43] and MENOS 2 showed efficacy of self-guided and group CBT compared with usual care in 140 perimenopausal and postmenopausal women without a history of breast cancer.[44] A clinical psychologist administered the group CBT intervention, which involved psycho-education, paced breathing, and cognitive and behavioral strategies to manage VMS. Women were trained in relaxation and paced breathing. Discussion topics included the physiology of VMS, stress as a VMS trigger, negative beliefs about VMS, and sleep hygiene. The usual-care group received information about VMS, advice on treatment options and symptom management, and instructions for paced breathing and relaxation. In both studies, improvements were maintained at 26 weeks, and more women in the CBT group (65% to 78% across studies) reached a clinically significant threshold for improvement in VMS problem ratings than in the usual-care group. The self-guided CBT was identical to group CBT and included a self-help book completed during a 4-week period, two contacts with a clinical psychologist, weekly homework, and a CD for daily practice of relaxation and paced breathing. A follow-up study[45] revealed that beliefs about coping and control over VMS and belief about sleep and night sweats mediated the effect of CBT on VMS problem ratings. Both the group CBT manual[46] and the self-guided CBT manual[47] are available. CBT is an effective treatment for bothersome VMS for both breast cancer survivors and menopausal women. *Level I evidence*

Mindfulness-based stress reduction

Current evidence is limited for mindfulness-based stress reduction (MBSR) and hot flashes. MBSR emphasizes acceptance, mindfulness meditation, and yoga as coping mechanisms to handle stress.[48] Participants are taught to approach thoughts, feelings, and sensations in a nonreactive manner. An RCT of MBSR versus wait-list control was conducted with 110 women who had five or more moderate to severe hot flashes per day. The MBSR intervention was a standardized, widely used, 8-week program involving weekly 2.5-hour group classes, at-home practice (45 min × 6 d/wk), and an 8-hour in-person group retreat. After 20 weeks, the MBSR group showed greater reductions in hot flash intensity (21.62% vs 10.50%) and bother (44.56% vs 26.97%) than wait-list controls, but these differences were not statistically significant. *Level II evidence*

Paced respiration

Paced respiration is unlikely to provide any benefit for hot flashes. Paced respiration involves taking six to eight slow deep breaths per minute while inhaling through the nose and exhaling through the mouth. Paced respiration was shown to reduce hot flashes in small, laboratory-based studies,[49-51] but two larger studies did not show it to be more effective than other forms of breathing. In a randomized trial of 208 women, paced respiration was no better than shallow breathing or usual care for reducing hot flash frequency, severity, bother, or interference.[52] Similarly, in a randomized trial of 92 women, paced breathing practiced once or twice per day was no better than usual breathing for reducing hot flash scores (frequency × severity).[53] *Level I evidence*

Relaxation

Current evidence is limited and inconsistent on relaxation for hot flashes. A 2014 Cochrane review[54] and a 2008 systematic review[55] both concluded that evidence from RCTs of relaxation was insufficient. Not included in either review was a nonblinded randomized trial showing a reduction in hot flash frequency with applied relaxation (n = 33) compared with a wait-list control group (n = 27).[56] In all studies, results were inconsistent and quality was poor, primarily because of small sample sizes and lack of an appropriate attention control group.[49,50,56-60] *Level II evidence*

Clinical hypnosis

Current evidence for clinical hypnosis is limited but suggests it may be a promising strategy for managing hot flashes. Clinical hypnosis is a mind-body therapy that involves a deeply relaxed state and individualized mental imagery and suggestion. It has been widely used to manage other chronic symptoms, such as pain and anxiety. Hypnosis has been studied for the treatment of hot flashes in two trials—one randomized trial in breast cancer survivors[61] and one RCT in women with at least seven hot flashes per day.[62] In both trials, clinical hypnosis involved 5 weekly in-person sessions of hypnotherapy with at-home self-hypnosis practice. In the study of 60 women with a history of breast cancer, clinical hypnosis was significantly better at reducing hot flashes and improving mood and sleep than no treatment.[61] The more recent trial, the randomized, single-blind, controlled clinical trial of 187 postmenopausal women reporting at least 50 hot flashes a week at baseline, evaluated clinical hypnosis over 12 weeks against an active structured attention control.[62] Participants in the clinical hypnosis arm reported significantly lower hot flash frequency (74% vs 17%) and hot flash scores (frequency x severity, 80% vs 15%) than controls. In addition, physiologically monitored hot flashes were reduced significantly more in the hypnosis group than in the attention control group (57% vs 10%). *Level I evidence*

Dietary management and supplements

Soy foods and soy extracts

Soy is the most widely used isoflavone-containing food. Isoflavones are a class of phytochemicals, a broad group of nonsteroidal compounds of diverse structure that bind to estrogen receptors (ERs) in animals and human beings. Isoflavones have greater affinity for ER-β than for ER-α and possess both estrogen-agonist and estrogen-antagonist properties. The isoflavones include the biochemicals genistein, daidzein, glycitein, biochanin A, and formononetin. Genistein and daidzein are found in high amounts in soybeans and soy products as well as in red clover, kudzu, and groundnut

TABLE 1. *Isoflavone terminology*

Aglycone	The actual isoflavone without a sugar attached
Daidzein	A diphenolic biochemical, designated as an isoflavone, found in high amounts in soy and red clover; the relative amounts of genistein and daidzein are thought to be determinants of therapeutic efficacy of soy supplementation
Equol	A nonsteroidal isoflavone metabolite that is produced from daidzein by intestinal bacteria
Equol nonproducer	Some women and men cannot convert daidzein to equol
Equol producer	Some women and men can metabolize daidzein to equol, which enables them to benefit from soy and soy isoflavone products
Estrogen receptors	A group of receptors within cells activated by the hormone 17β-estradiol and other structurally similar compounds such as the isoflavones; generally, the isoflavones have more binding affinity for ER-β than for ER-α
Genistein	A biochemical, also designated as an isoflavone, found in high amounts in soy and red clover; the relative amounts of genistein and daidzein are thought to be determinants of therapeutic efficacy of soy supplementation
Glycitein	Another isoflavone found in soy protein and the protein of other legumes in relatively minor amounts
Glycoside	A sugar attached to the aglycone portion of an isoflavone
Isoflavones	Plant-derived compounds, also known as *phytoestrogens*, with estrogen-like biologic activity and a chemical structure similar to that of estradiol
Phytoestrogens	Another term for isoflavones
S(-)-equol	An isomer in the plasma of equol producers that is thought to have biologic activity; a metabolite of daidzein
Soy	The most widely used isoflavone-containing food; usually refers to a product derived from the whole soybean (or soya bean).
Soy germ	Part of the soybean that has a high concentration of isoflavones, but with four times more daidzein than genistein, and high concentrations of glycitein
Soy isoflavones	Isoflavones derived from soy (as opposed to from red clover, kudzu, or groundnut)
Soy protein	A product derived by extracting the protein out of the whole bean; rich source of isoflavones

(Table 1). The relative amounts of isoflavones vary, depending on the portion of the soybean from which the material is obtained. The whole soybean contains about equal amounts of genistein and daidzein, with smaller amounts of glycitein. Some soy supplements are made from soy germ, which is higher in daidzein than genistein. Therapeutic efficacy of soy supplementation may vary based on the relative amounts of genistein and daidzein. Individual isoflavones, such as genistein, may have different therapeutic outcomes when administered alone than when the same amounts are administered with all three isoflavones (genistein, daidzein, and glycitein) in the supplement.

Although soy protein is low in potential adverse effects, prevalence data for soy protein intolerance are scarce. Common symptoms of use include bloating, flatulence, and loose stools. Soy protein is on the list of primary allergens in the United States and Canada.

About 30% of North American women have the ability to metabolize daidzein to equol. Equol is a nonsteroidal estrogen that binds to both estrogen receptors but with a high affinity for ER-β; thus, it is often designated as an ER-β agonist. Equol is produced from daidzein by intestinal bacteria and is thought to be a stable characteristic that is best revealed after a soy challenge of just a few days. Equol has two isomers, *S(-)-equol* and *R(+)-equol*. Only S(-)-equol is detected in the plasma of equol-producing women and thought to have any biologic activity. By far the most exciting research opportunities in the area of soy isoflavone menopausal health concern the potential benefits of equol and the unanswered issue of whether equol is merely a marker for some beneficial effect of gut bacteria on steroid metabolism. More research is needed that compares equol producers with equol nonproducers.

Efficacy. The literature on soy foods and extracts, including derivatives and metabolites, has been the subject of intense scrutiny through meta-analyses (eg, Chen and coleagues[63]); systematic reviews (eg, Utian and colleagues[64]; Kronenberg and Fugh-Berman[65]); a NAMS Translational Science Symposium and publication[66]; and a Cochrane Collaboration analysis[67]—all within the last 2 to 4 years.

The most recent randomized, blinded, comparative clinical trials on soy isoflavonoids reviewed in the analyses have found them to be no more effective than a placebo. Most studies have been criticized for numerous study design defects. Other limitations are that manufacturing processes are multiple and largely uncontrolled, with resulting composition and batch-to-batch variation that may differ significantly, and that any benefits associated with isoflavones may occur more slowly and to a lesser extent than those achieved with traditional medications. In addition, there may be a difference between women who can convert the isoflavone daidzein to equol—and hence show efficacy of a supplement—and nonconverters, who would be unlikely to respond. A deficiency in most studies has been the fact that the study population has not been so defined. A supplement containing natural S-equol has been developed for women who do not have the capacity to produce equol,[64,66,67] but additional research is needed to determine whether the supplement may be effective for these women. *Level II evidence*

Over-the-counter supplements and herbal therapies

Black cohosh. Black cohosh, scientific name *Actaea racemosa* L (previously *Cimicifugae racemosae*), has been used by Native Americans as a medicinal plant but was not used in traditional folk medicine as a menopause remedy. Nonetheless, it is the most commonly purchased botanical for

menopausal symptoms. The active ingredients in black cohosh extract are unknown, and mechanism of action is unclear. At one time it was thought to be estrogenic, with in vitro and in vivo assays indicating estrogen-like activity.[68] More recent studies indicate activity similar to selective ER modulators[69] or modulation of serotonergic pathways, as well as antioxidant and anti-inflammatory effects.

A 2012 Cochrane review[70] analyzed 16 RCTs of 2,027 perimenopausal or postmenopausal women treated with black cohosh using a median daily dose of 40 mg for a mean duration of 23 weeks. There was no significant difference between black cohosh and placebo in the frequency of hot flashes. Data on safety were also inconclusive. The authors concluded that, at this time, there is insufficient evidence to support the use of black cohosh for menopausal symptoms. *Level I evidence*

Black cohosh appears to have no effect on circulating luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, or estradiol. A 52-week study reassuringly demonstrated that black cohosh does not increase endometrial thickness on ultrasound.[71] Reports of possible hepatotoxicity started to appear after 2000. After examining all reported cases, the US Pharmacopeial Convention's Dietary Supplements-Botanicals Expert Committee found only 30 reports possibly related to black cohosh. The committee issued a directive that black cohosh products carry a warning statement: ''Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice.''[72]

Crinum. Crinums (genus *Crinum*) are members of the amaryllis family (Amaryllidaceae) and are widely used in folk medicine in South Asia. Extracts are said to exert antitumor, immune-modulating, analgesic, and antimicrobial effects.[73] The branded product, Crila, is sold for VMS. No studies of Crila can be found in the available medical research literature. *Level V evidence*

Dioscorea (wild yam). Dioscorea barbasco, *D mexicana*, and *D villosa* are the varieties most commonly used. *D villosa,* also known as Mexican yam or wild yam root, contains diosgenin, a steroid precursor used in the manufacture of synthetic steroids. Diosgenin is converted in vitro to progesterone, but there is no biochemical pathway for this conversion in vivo. Alternative medicine practitioners suggest that yams have dehydroepiandrosterone-like activity and serve as precursors for the endogenous production of sex hormones, including estrogen and progesterone. When *D alata* was substituted for other carbohydrates twice daily for 30 days in the diets of 24 Japanese women, they showed significant increases in serum concentrations of estrone (26%) and sex hormone-binding globulin (9.5%) and a near-significant increase in estradiol (27%), unlike 19 women fed plain sweet potatoes.[74] The pathway for these hormonal effects may reside in metabolic alterations other than steroidal conversion, perhaps modification of the enterohepatic circulation.

Evidence for efficacy of *Dioscorea* on VMS is limited. One clinical trial employing a yam cream to treat menopausal symptoms reported no significant benefit.[75] Yam creams that have been tested often do not contain any yam extract, and many have been adulterated with undisclosed steroids, including estrogens, progesterone, and medroxyprogesterone acetate (MPA). Because of the potential harm that might result from adulterants and lack of efficacy data, yam creams are not recommended for VMS. *Level II evidence*

Dong quai. Dong quai, also known as *Angelica sinensis*, dang gui, and tang kuei, is the root of the *Angelica polymorpha* Maxim var *sinesis* Oliv. It has been used as a female balancing agent in traditional Chinese medicine and as a panacea for gynecologic complaints. Dong quai is reputed to be estrogenic, based on reports of uterine bleeding with use and uterotropic effects in ovariectomized rats.[76] Human studies, however, have not found any evidence of estrogenic activity.

Dong quai does not appear to be effective for VMS, and there are a number of safety concerns, including possible photosensitization, anticoagulation, and possible carcinogenicity. Hirata and colleagues[77] enrolled 71 women in an RCT of 4.5 g dong quai per day or placebo. After 24 weeks, there were no differences in the VMS frequency; Kupperman Index scores; levels of FSH, LH, and estradiol; vaginal maturation index; or endometrial thickness. Critics have stated that the dose was much lower than in traditional Chinese medicine formulations and that dong quai is not used alone but rather must be given in concert with other botanicals to promote the synergies needed for therapeutic effect. (See the information on combination botanical products.) *Level II evidence*

Evening primrose. Evening primrose, *Oenothera biennis* L, is a flowering plant rich in linolenic acid and γ-linolenic acid. Evening primrose oil (EPO) is recommended for a wide array of inflammatory and autoimmune disorders including allergies, eczema, arthritis, diabetic neuropathy, mastalgia/mastodynia, and inflammatory or irritable bowel disease. There is a single trial of EPO for menopause in which 56 women were randomized to EPO 500 mg per day or placebo for 6 months. Only 18 women taking EPO and 17 taking placebo completed the trial. EPO proved ineffective, with hot flashes declining by 1.0 per day with EPO and by 2.6 per day with placebo.[78] *Level II evidence*

Flaxseed. Flaxseed or linseed (*Linum usitatissimum*) is a rich source of lignans, polyphenolic sterols that, when acted on by microbiota in the gut, produce enterodiol and enterolactone, both weakly estrogenic sterols. The lignans in flaxseed reside in cell walls and are not bioavailable without extensive crushing. Highly milled flax flour and flax meal, but not flaxseeds, are sources of lignans in the human diet. Flaxseed oil, a good source of polyunsaturated fatty acids such as α-linolenic acid, provides no lignans. Flaxseed meal, flour, and oil are safe as foods.

To date, the accumulated evidence for flaxseed does not support its use for VMS. Dew and Williamson[79] reviewed flaxseed as a menopausal remedy and found a total of five relevant studies consisting of (at least) 437 flax and placebo volunteers, but none reported a benefit for VMS frequency/severity beyond placebo. Within their review, they mentioned Pruthi and colleagues,[80] who enrolled 188 women in a

randomized trial using a flaxseed nutritional bar with 410 mg of lignans or a placebo bar for 6 weeks. Although the mean hot flash severity score change was not significant, 4.9 in the flaxseed group and 3.5 in the placebo group ($P = 0.29$), the authors noted a significant improvement in VMS interference with leisure activities. LeMay[81] reported flax as an effective remedy because it appeared to have comparable efficacy to 0.625 mg conjugated equine estrogens (CEE) as a positive control. Kupperman Index scores decreased from baseline by 24.2% ($P < 0.001$) and 32.7% ($P < 0.01$) for flax and HT, respectively. No placebo arm was included in the study. *Level I evidence*

Ginseng. There are two distinct true ginsengs in common use, *Panax ginseng*, also known as Asian, Korean, or Chinese red ginseng, and American ginseng (*Panax quinquefolius*), sometimes called white ginseng. A third substance, Siberian ginseng (*Acanthopanax senticosus* or *Eleutherococcus senticosis*), is not a true ginseng but a member of a closely related family of plants, Araliacea, which also includes sarsaparilla. Some safety issues have been raised, particularly when ginseng is used in energy drinks with other stimulants.

Ginseng does not appear to be effective for VMS. In a study of a specific proprietary product, G115, sold in the United States as Ginsana,[82] 384 postmenopausal women were randomized to G115 or placebo. After 16 weeks, women taking G115 showed slightly better overall symptom relief, but changes were not statistically significant ($P < 0.1$) and accrued only from improvements in depression, well-being, and health scores, not VMS. Ginseng had no effect on FSH, estradiol, endometrial thickness, vaginal maturation index, and vaginal pH. Kim and colleagues measured hot flash frequency with Korean red ginseng versus placebo and found no statistically significant difference between groups.[83] A second study from the same team[84] found that ginseng improved both Kupperman Index ($P = 0.032$) and Menopause Rating Scale scores ($P = 0.035$) but failed to specifically affect hot flash scores within either scale ($P = 0.046$ and $P = 0.121$, respectively). These findings were later summarized in a review by Kim and colleagues.[85] *Level I evidence*

Hops. The female flowers of hops (*Humulus lupulus*), also called the seed cones or strobiles, are used in beer, often to add a bitter, tart flavor to other grains. The plant makes a flavonoid, 8-prenylnaringenin, which is said to have greater estrogenic activity than soy-derived isoflavones.

Evidence for hops is limited and inconsistent. There are two trials using hops to treat symptoms of menopause. The first included 67 women randomized to two standardized doses of hops extract (100 μg or 250 μg) or placebo.[86] Hops 100 μg was better than placebo at 6 weeks ($P = 0.023$) but not at 12 weeks ($P = 0.086$). The 250-μg dose offered no therapeutic efficacy over placebo. In the second study,[87] 36 women were randomized to either hops or placebo for 8 weeks and then crossed over for 8 additional weeks of the alternate treatment. Outcome measures included scores on the Kupperman Index, the Menopause Rating Scale, and a multifactorial visual analog scale at baseline, 8, and 16 weeks. The researchers reported no significant reduction ($P = 0.06$) on the Menopause Rating Scale after 16 weeks. *Level II evidence*

Maca. Maca (*Lepidium Meyennii* Walp, *Lepidium peruvianum* Chacon), a traditional foodstuff from South America, is a cruciferous root grown exclusively in the central Peruvian Andes at 12,000 to 14,000 feet altitude. It is recommended as a tonic and adaptogen, characterized as ''Peruvian ginseng,'' and used for strength and stamina, athletic performance, anemia, and fertility and as an aphrodisiac.

The mechanism of action of maca on male and female hormones remains to be elucidated but is postulated to be modulation of sex steroid-receptor dynamics. Maca contains a weak phytosterol, β-sitosterol, also found in several other botanicals, such as saw palmetto, which is often recommended as a treatment for prostate problems. Both methanolic and aqueous extracts of maca exhibit estrogenic activity in vitro, but studies have found no in vivo estrogenic effects.

In a systematic review, only four maca studies were evaluable. All showed improvements in Greene Climacteric Scale or Kupperman Index scores, but all were poor quality with poor trial design, very small sample sizes, or limited reporting of study data.[88] Thus, these studies are not strong enough to support the use of maca for VMS. *Level II evidence*

Omega-3 fatty acids. Omega-3 supplements contain polyunsaturated fatty acids, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linolenic acid. Phospholipids, a major component of neuronal cells, contain a high prevalence of fatty acids. Two trials have evaluated omega-3s for VMS. In an 8-week trial of 91 women randomized to placebo or omega-3 supplement (total daily dose: EPA 1,100 mg + DHA 150 mg), VMS frequency and intensity were significantly improved with omega-3 compared with placebo.[89] In a 12-week trial, women were randomized in a 1:1 ratio to omega-3s (n = 177) or placebo (n = 178) and simultaneously in a 3:3:4 ratio to yoga (n = 107), aerobic exercise (n = 106), or their usual physical activity (n = 142). There were no significant differences in VMS frequency or bother with omega-3s or placebo. The total daily dose of omega-3 was EPA, 1,275 mg; DHA, 300 mg; and other assorted omega-3s, 270 mg.[90] *Level II evidence*

Pine bark. Pine bark from the Mediterranean pine (*Pinus pinaster*) serves as a source of proanthocyanidins, the same group of compounds found in grape seeds. Proanthocyanidins derived from pine bark are promoted as antioxidants and are sold under the registered trademark name Pycnogenol.

Three trials evaluated Pycnogenol for menopausal symptoms, but none included detailed measures of VMS. The first randomized 200 women to 200 mg or placebo,[91] with 175 completers and 155 providing complete data. Using the Women's Health Questionnaire, the researchers reported significant improvements in all scale domains, including one pertaining to VMS symptoms. In another trial, 38 women given 100 mg Pycnogenol daily for 8 weeks showed greater improvement in VMS compared with a parallel (nonrandomized) group of 32 untreated women.[92] Third, 170 perimenopausal women were randomized to 30 mg Pycnogenol twice

daily or placebo with 156 women—78 women in each arm—completing the study.[93] After 12 weeks, symptoms were significantly more improved with treatment than placebo, based on Women's Health Questionnaire vasomotor scores ($P < 0.05$) and total Kupperman Index scores ($P < 0.05$). These studies suggest Pycnogenol might offer some benefits in relieving symptoms, but data to date are not of sufficient quality to document the degree of therapeutic benefit, and the effective dose has yet to be determined. Pycnogenol is possibly safe, but the safety of other pine bark preparations cannot be assured. *Level II evidence*

Pollen extract. A proprietary extract made from flower pollen, Relizen, has been recently introduced in the United States. This product has been available in the European Union (EU) since 1999 and sold under the brand names Serelys, Femal, and Femalen. Its constituents are pollen cytoplasmic extract (GC Fem) and pistil extract (PI 82), and the proposed mechanism of action is said to be antioxidant and anti-inflammatory. The current product contains 40 mg of GC Fem and 120 mg of PI 82. Older formulations sold in the EU also contained vitamin E. The manufacturer states that there is no pollen in the product and that it is safe for persons with pollen allergies. In vitro and animal studies found pollen extract does not specifically bind to estrogen receptors and has no estrogenic activity[94] (Prof. Dr. Eduardo Muñoz, Department of Cell Biology, Physiology and Immunology, University of Córdoba, VivaCell Biotechnology GmbH. Unpublished data, 2012).

There is only one small RCT of pollen extracts in menopause.[95] Sixty-four postmenopausal women were randomized, with data reported for 53 completers. After 3 months and compared with placebo, significant reductions in VMS were seen on the Menopause Rating Scale (65% vs 38% reporting reductions) and daily diaries (27% greater reduction with treatment). The Menopause Rating Scale evidenced significant improvements in other quality-of-life parameters in the pollen extract group ($P < 0.031$). More studies are needed. *Level II evidence*

Puerpuria. Pueraria mirifica, also known as kwao krua, is a plant found in northern and northeastern Thailand and Myanmar. The plant is estimated to contain 8% to 10% isoflavone by dry weight.

Two small studies reported the effects of puerpuria on menopausal symptoms, but neither included specific measures of VMS. In one study, 52 hysterectomized, symptomatic women were randomized to *P mirifica* 25 mg or 50 mg per day and followed for 6 months. No placebo was included. On the Greene Climacteric Scale, the baseline scores were 24.19 ± 9.11 and 23.19 ± 7.89, respectively. After 3 months of treatment, scores were 17.92 ± 10.40 for the low dose and 15.35 ± 8.44 ($P = 0.332$) for the high dose. After 6 months, the scores were 14.08 ± 10.30 for the low dose and 12.46 ± 6.38 ($P = 0.500$) for the high dose.[96] No significant adverse effects were seen at either dose. In a second study, 71 women were randomized to 50 mg raw *P mirifica* or 0.625 mg CEE, with or without 2.5 mg MPA, depending on whether they had an intact uterus.[97] Data from 60 completers were reported but lacked detail. The researchers claimed that both treatments performed equally well and that measures of estradiol, FSH, and LH were also similar in both the *P mirifica* and CEE groups. The lack of a placebo arm and poor reporting of data in both studies are limitations. *Level II evidence*

Siberian rhubarb. Siberian rhubarb (*Rheum rhaponticum*) is used as a food and as a medicinal plant for constipation, diarrhea, and other gastrointestinal complaints. It has laxative qualities that are similar to extracts from senna plants. Two hydrostilbenes found in rhubarb, rhapontigenin and desoxyrhapontigenin, have very weak binding affinity for ER-α, with higher affinity for ER-β. In vitro and in vivo studies support the hypothesis that the hydrostilbenes in rhubarb act as selective estrogen receptor modulators (SERMs) with mixed agonist/antagonist activity.[98]

A single commercial preparation of rhubarb extract, which has been used Germany for more than 20 years, was introduced in the United States and sold as Estrovera. The product contains a proprietary extract called ''rhaponticin'' or ''extract ERr 731.''

One study evaluated this product for menopausal symptoms but did not include detailed measures of VMS. Heger and colleagues[99] randomized 109 symptomatic perimenopausal women to one enteric-coated tablet of ERr 731 ($n = 54$) or placebo ($n = 55$) daily for 12 weeks. Only 7 of 55 women randomized to placebo (12.7% retention rate) and 39 of 54 women randomized to active treatment completed the trial. Given the small number of completers, the study is probably underpowered. Nonetheless, the researchers reported that at 12 weeks, the Menopause Rating Scale II total score, and each symptom within the scale, significantly improved in the active-treatment group versus placebo ($P < 0.0001$).

The manufacturer has long-term safety data collected from beagle dogs and states that no abnormal hematologic or metabolic trends have been seen, even at high doses.[100] Human safety data were drawn from a group of 23 women followed up for 48 weeks, 20 of whom completed a 96-week observation period. Few adverse events were reported.[101] Additional evidence is needed on both efficacy and safety for use in VMS. *Level II evidence*

Combination botanical remedies. Combination botanicals are frequently used by herbal medicine practitioners, most often some variation on a multiple botanical formulation recommended in traditional Chinese medicine. Combinations are said to offer better outcomes because of the complexity and variety of menopause-related symptoms. Whether this is sound or logical is open to question because one agent, estrogen, effectively mitigates most, if not all, menopausal symptoms.

Botanical combinations, although proffering better symptom relief, are difficult to assess, given the complexity of the formulations, the potential for adverse events, and the difficulty in predicting drug-herb interactions (Table 2).[102-114] (Mary Tagliaferri, MD, Founder, Dr. Tagliaferri Formulas, email communication, 2015) The botanical combinations

TABLE 2. *Combination herbal therapies for menopause tested in clinical trials*

Traditional name/trade name	Constituents
Black cohosh plus Chinese herbal preparation[102]	Zizyphus spinosa (Suan zeo ren) 500 mg Rehmannia glutinosa (Sheng di huang) 400 mg Amerarrhena asphodeloides (Zhi mu) 400 mg Aparagus lucidus (Tian men dong) 400 mg Epimedium sagittata (Yin yang huo) 400 mg Curculigo orchioides (Xian mao) 375 mg Phellodendron amurense (Huang bai) 325 mg Cimicifuga racemosa (Black cohosh) 350 mg
Climex[103]	Angelica sinensis (dong quai) +matricaria chamomilla (chamomile)
CuraTrial Research Group[104]	125 mg soy extract daily (providing 50 mg isoflavones, including 24 mg genistein and 21.5 mg daidzein) 1,500 mg evening primrose oil extract (providing 150 mg γ-linoleic acid) 100 mg *Actaea racemosa* Linnaeus extract (providing 8 mg deoxyacetein) 200 mg calcium 1.25 mg vitamin D 10 IU vitamin E
Dang Gui Buxue Tang[105]	Angelica sinensis (Dong quai) 1:5 + Astragalus membranaceus (huang qi)
Dr. Tagliaferri's Formula (Mary Tagliaferri, MD, Founder, Dr. Tagliaferri Formulas, email communication, 2015)	Radix Rehnmanniae (Shu di huang) Fructus Corni Officinalis (Shan zhu yu) Radix Dioscoreae Oppositae (Shan Yao) Sclerotium Poriae Cocos (Fu ling) Cortex Moutan Radicis (Mu dan pi) Rhizoma Alismatis Orientalis (Ze xie) Anemarrhena rhizome (Zhi mu) Glycyrrhiza uralensis (Gan cao) Radix astragali (Mu dan pi) Atractylodis Macrocephalae Rhizoma (Bai zhu)
Er-Xian decoction, Er xian tang, Menofine[106]	Rhizoma Curculiginis Orchioidis (Xian Mao) Herba Epimedii Grandiflori (Yin Yang Huo) Radix Morindae Officinalis (Yin Yang Huo) Radix Angelicae Sinensis (Dang Gui) Cortex Phellodendri Chinensis (Huang Bo) Rhizoma Anemarrhenae Asphodeloidis (Zhi Mu)
Estro G-100[107]	Cynanchum wilfordii Phlomis umbrosa Angelica gigas Kakai extracts
Jiawei Qing'e Fang (JQF)[108]	Cortex Eucommiae Fructus Psoraleae Semen Juglandis Rhizoma Garlic
Menoprogen[109]	Chinese wolfberry Safflower Sea kelp
Naturopathic remedy (HALT)[110]	Actaea racemosa (Black cohosh) 200 mg Medicago sativa (Alfalfa) 400 mg Vitex agnus-castus (Chaste tree) 200 mg Angelica sinesis (Dong quai) 400 mg Chamaelire luteum (False unicorn) 200 mg Glycyrrhiza glabra (Licorice) 200 mg Punica granatum (Pomegranate) 400 mg Eleutherococcus senticosus (Siberian ginseng) 400 mg Boron 4 mg
Nutrafem[111]	Eucommia ulmoides bark extract 75 mg Vigna radiata beans 150 mg
Phytoestrogen blend[112]	Isoflavones (soy germ extracts, Glycine max, no GMO-SoyLife: 150 mg, titrated in isoflavones [40%] = 60 mg) Lignans (flaxseed extracts, Linum usitatissimum, no GMO-LinumLife: 100 mg, titrated in lignans [20%] = 20 mg) C racemosa (50 mg, titrated in triterpene [2.5%] = 1.25 mg)
Phyto-Female Complex[113]	Actaea racemosa (black cohosh) Angelica sinesis (gong quai) Milk thistle Red clover American ginseng Chastetree berry
Zhi Mu 14 (with and without acupuncture)[114]	*Zhi Mu14 is based on modification of Gan Mai Da Zao tang:* Radix Glycyrrhizae Uralensis (Gan Cao) Semen Tritici Levis (Xiao Mai) Fructus Jujubae (Da Zao) Radix Curcumae (Yu Jin) Radix Polygalae Tenuifoliae (Yuan Zhi) Rhizoma Acori Tatarinowii (Shi Chang Pu) with Qing Hao Bie Jia Tang (*Artemisia annua* and softshell turtle shell decoction)

This list is informational and is by no means exhaustive. The botanical combinations have been tested in at least one published clinical trial. Most of the trials referenced suffer from the same types of methodologic problems noted for single-agent botanicals.
van der Slujis CP, et al[102]; Kupfersztain C, et al[103]; Verhoeven MO, et al[104]; Haines CJ, et al[105]; Margit Tagliaferri, MD, Chief Medical Officer, Dr. Tagliaferri Formulas, email communication, 2015; Zhong LL, et al[106]; Lee KH, et al[107]; Xia Y, et al[108]; Liu D, et al[109]; Reed SD, et al[110]; Garcia JT, et al[111]; Sammartino A, et al[112]; Rotem C, et al[113]; Nedelijkovic M, et al.[114]

listed in Table 2 have been tested in at least one published clinical trial. Most of the trials referenced suffer from the same types of methodological problems noted above for single-agent botanicals. *Level II evidence*

Vitamins. Three trials show varying evidence for vitamin E on VMS. In one crossover trial, 120 women were randomized to 4 weeks of vitamin E (800 IU) followed by placebo or vice versa.[115] Although there was a subjective decrease in VMS with vitamin E, the reduction was only by about one hot flash per day; the authors concluded this was not clinically meaningful. However, another crossover trial of 50 postmenopausal women comparing 4 weeks of vitamin E (400 IU) followed by placebo or vice versa found a greater reduction in hot flash frequency of about 2 hot flashes per day ($P < 0.0001$) and hot flash severity ($P < 0.0001$) with vitamin E.[116] In a third trial, 115 women were randomized to vitamin E or gabapentin with significantly greater reduction in VMS with gabapentin. Thirty-five percent of the vitamin E group dropped out because of lack of efficacy.[117] *Level I evidence*

Evidence for other vitamin supplements is mixed. A multivitamin and mineral supplement was studied in a double-blind, randomized, placebo-controlled trial of 99 women, 70 of whom

completed the study. At 3 months, there was no significant difference in VMS between groups.[118] In another study of 46 women, vitamin B9 (folic acid) 5 mg daily for 4 weeks was found to reduce VMS significantly more than placebo.[119] Further trials are needed to attempt to replicate these findings in larger, more diverse samples. *Level II evidence*

PRESCRIPTION THERAPIES

A low-dose paroxetine salt (7.5 mg/d) is the only nonhormonal pharmaceutical approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe menopausal VMS, with improvements found in VMS frequency and severity up to 24 months and improvements in sleep disruption without negative effects on libido or weight gain.[120] *Level I evidence*

Many selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine uptake inhibitors (SNRIs), along with gabapentin and clonidine, have been tested and have shown some degree of efficacy in symptomatic menopausal women. Onset of action is rapid, usually within 2 weeks. Clinical trials performed for FDA approval are evaluated for significance over placebo at 4 weeks and 12 weeks, and persistence is evaluated at 12 to 24 weeks. *Level I to II evidence*

Limited evidence suggests that menopausal HT is more effective than nonhormonal agents in reducing the frequency and severity of hot flashes. Head-to-head RCTs are limited, with comparisons including varying types, doses, and routes of administration with nonhormonal agents.[10,121-124] One trial[121] reported that 75 mg per day of venlafaxine was as effective as a low-dose oral estradiol 0.5 mg per day. In this RCT, oral estradiol reduced the frequency of hot flashes by 2.3 more per day than placebo ($P < 0.001$), whereas venlafaxine reduced the frequency of hot flashes by 1.8 more per day than placebo ($P = 0.005$) However, this trial did not allow dose escalation, in which case estradiol would be expected to provide 77% improvement in hot flashes on average.[125] *Level II evidence*

Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors

Meta-analyses,[10,126,127] a pooled analysis,[128] a Cochrane review,[124] and a review focused on evidence in cancer survivors[129] provide evidence that SSRIs and SNRIs are associated with mild to moderate improvements in symptomatic postmenopausal women, regardless of whether menopause is natural or surgical. The reviews are limited by variability in inclusion criteria, population tested, dosing, length of treatment, and outcomes tested. Those with statistically significant reductions in hot flashes in large, randomized, double-blind, placebo-controlled trials of symptomatic women include paroxetine, escitalopram, citalopram, venlafaxine, and desvenlafaxine. Reduction in hot flashes varies from 25% to 69%, with improvements in composite hot flash frequency and severity from 27% to 61%. Less consistent results have been seen with sertraline and fluoxetine (statistically insignificant trend toward improvement in hot flashes).[10,130-134] *Level I to II evidence*

Contraindications to SSRIs and SNRIs include prior neuroleptic syndrome, serotonin syndrome (beware of possible synergy with other medications), and concurrent use of monoamine oxidase inhibitors. Exercise caution for patients with bipolar disease, uncontrolled seizures, liver or kidney insufficiency, uncontrolled hyponatremia or poorly controlled hypertension, concurrent use of other SSRIs or SNRIs, or relevant polymorphisms in cytochrome P450 enzyme pathways. For women using tamoxifen, coadministration of SSRIs may lead to inhibition of CYP2D6 (the enzyme that converts tamoxifen to its most active metabolite, endoxifen). The most potent inhibition of CYP2D6 occurs with paroxetine and fluoxetine, so these should be avoided in tamoxifen users. Safer choices include venlafaxine or desvenlafaxine (SNRIs) or escitalopram or citalopram (SSRIs). Black box warnings include uncommon suicidal thoughts within first few months. Possible reported risks include increased risk of bone fracture (mixed reports of bone loss and fracture)[135,136]; SNRIs may produce significant nausea or dizziness, which improves after 1 to 2 weeks.

Suggested dosing for paroxetine salt is 7.5 mg per day; for paroxetine, 10 to 25 mg per day; for escitalopram, 10 to 20 mg per day; for citalopram, 10 to 20 mg perday; for desvenlafaxine, 100 to 150 mg per day; and for venlafaxine, 37.5 to 150 mg per day (Table 3).

Gabapentinoids

Gabapentin is an FDA-approved antiepileptic drug used for diabetic neuropathy and postherpetic neuralgia. In multiple trials at 900 mg (300 mg 3×/d), it improved the frequency and severity of VMS.[137,138] Adverse events include dizziness, unsteadiness, and drowsiness at week 1 (compared with placebo), which improves by week 2 and is back to baseline by week 4. Gabapentin extended release at asymmetric dosing of 1,800 mg per day was shown to be effective but was not approved by FDA for VMS. Higher doses of gabapentin (titrated to 2,400 mg/d) were as effective as estrogen (CEE 0.625/d) at reducing hot flash severity scores in a placebo-controlled trial. However, adverse events of gabapentin at this dose included dizziness, headache, and disorientation, so the effectiveness was limited by these.[123] Gabapentin may be a good choice for women with disruptive sleep from VMS because drowsiness is an adverse event. Pregabalin is effective in relieving hot flashes but is less well studied.[139] *Level I evidence*

Black box warnings for gabapentin and pregabalin include uncommon suicidal thoughts or behaviors. Adverse events include drowsiness, dizziness, and impaired balance or coordination. Pregabalin may impair memory or concentration.

Suggested dosing for gabapentin is 900 mg per day to 2,400 mg per day, and for pregabalin, 150 to 300 mg per day (Table 3).

Clonidine

Clonidine is a centrally active α-2 adrenergic agonist that has been shown to be modestly more effective than placebo[10] but less effective than SSRIs, SSNRIs, and gabapentin.[10,124]

TABLE 3. *Suggested dosing ranges for nonhormonal prescription therapies*

SSRIs		
Paroxetine salt	7.5 mg	Single dose, no titration needed
Paroxetine	10-25 mg/d	Start with 10 mg/d
Citalopram	10-20 mg/d	Start with 10 mg/d
Escitalopram	10-20 mg/d	Start with 10 mg/d (for sensitive or older women, start with 5 mg/d for titration, but this dose has not been tested for efficacy)
SNRIs		
Desvenlafaxine	100-150 mg/d	Start with 25-50 mg/d and titrate up by that amount each day
Venlafaxine	37.5-150 mg/d	Start with 37.5 mg/d
Gabapentinoids		
Gabapentin	900-2,400 mg/d	Start with 300 mg at night, then add 300 mg at night, then a separate dose of 300 mg in the morning (start 100 mg if concerned about sensitivity)
Pregabalin	150-300 mg/d	

Abbreviations: SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

However, it is used infrequently because of adverse events, including hypotension, lightheadedness, headache, dry mouth, dizziness, sedation, and constipation. Sudden cessation can lead to significant elevations in blood pressure. *Level II evidence*

OTHER TREATMENTS

Acupuncture

Acupuncture is a traditional component of Chinese medicine in which thin needles are inserted into the skin at key points in the body to balance the flow of energy or *chi*. Sham acupuncture is a placebo treatment involving needles inserted at unrelated points on the body or use of special needles that do not pierce the skin.

Drawing on a sizeable body of clinical trials, most systematic reviews[140,141] and a 2013 Cochrane review[142] conclude that, although acupuncture is superior to no treatment or a wait-list control,[143-147] acupuncture is not superior to sham acupuncture.[148-154] A 2015 review and meta-analysis concluded that acupuncture is effective in reducing VMS frequency and severity as well as in improving quality of life and psychiatric, somatic, and urogenital aspects of the Menopause Rating Scale.[155] However, the 2015 meta-analysis combined trials comparing acupuncture to sham acupuncture with trials comparing acupuncture to wait-list controls and also included a 2014 trial in which the effect size for reduction in VMS frequency was the largest among all studies comparing acupuncture to sham control.[114]

Most trials comparing acupuncture to sham acupuncture find no significant difference in VMS frequency or severity between the two treatments, whereas most trials using a wait-list control find that acupuncture reduces VMS frequency and severity. There is considerable debate about what the appropriate control group should be in studies of acupuncture. Some[155] have suggested that the light touch of the skin during sham acupuncture might induce a ''limbic touch response'' that can induce release of beta endorphins, a mechanism that has been implicated in VMS.[156] Generally, however, needling at acupuncture points does not appear to reduce VMS frequency or intensity independently of the superficial touch of a sham needle.

Acupuncture cannot be recommended for the treatment of VMS. *Level I evidence*

Stellate ganglion block

Emerging evidence suggests that stellate ganglion blockade (SGB), a widely used anesthesia treatment for pain management, is a promising treatment for VMS, but larger trials are needed. The stellate ganglion is a bilateral neural structure located in the C6-T2 region of the anterior cervical spine and can be safely blocked via the image-guided injection of local anesthetic (eg, bupivacaine) at the C6 level. The exact mechanism of action of SGB on VMS is unclear. Adverse events, such as transient seizures or a bleeding complication, occur extremely rarely.[157] The adverse events include pain with injection and transient bruising at the injection site. Four uncontrolled, open-label studies showed that SGB reduced VMS, with effects ranging from a 45% to 90% reduction 6 weeks to several months after blockade.[158-161] There has been one randomized, sham-controlled trial of active SGB with bupivacaine versus a sham procedure involving subcutaneous saline injection in women with natural or surgical menopause ($n = 40$).[162] Over a 6-month follow-up, there was no significant effect of SGB on overall VMS frequency. However, frequency of moderate to very severe subjective VMS and intensity of VMS was significantly reduced among SGB-treated women compared with the sham-control group. The frequency of physiologic VMS, measured with ambulatory skin conductance monitors, was reduced by 21% from baseline to 3 months in the SGB group, whereas the sham-control group showed no reduction. None of the study participants experienced adverse events.

Findings suggest that SGB might be an effective nonhormonal treatment for moderate to very severe VMS, but larger studies are needed. *Level II evidence*

TABLE 4. *Summary levels of evidence and recommendations*

Category	Therapy	Recommend	Recommend with caution	Do not recommend
Lifestyle changes	Cooling techniques			Level V
	Avoiding triggers			Level V
	Exercise			Level I
	Yoga			Level I
	Weight loss		Level II	
Mind-body techniques	Cognitive-behavioral therapy	Level I		
	Mindfulness-based stress reduction		Level II	
	Paced respiration			Level I
	Relaxation			Level II
	Clinical hypnosis	Level I		
Dietary/supplements	S-equol derivatives of soy isoflavones		Level II	
	Supplements, herbal therapies			Level I to V
SSRIs/SNRIs	Paroxetine	Level I		
	Escitalopram	Level II		
	Citalopram	Level II		
	Venlafaxine	Level II		
	Desvenlafaxine	Level II		
Other medications	Gabapentin	Level I		
	Pregabalin	Level II		
	Clonidine	Level II		
Other therapies	Acupuncture			Level I
	Stellate ganglion block		Level II	
	Calibration of neural oscillations			Level III
	Chiropractic intervention			Level III

Abbreviations: SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

Calibration of neural oscillations

In an uncontrolled study, 14 women showed a significant reduction in VMS frequency and severity after administration of an intervention aimed at autocalibration of neural oscillations.[163] The technique, called high-resolution, relational, resonance-based electroencephalic mirroring (HIRREM), aims to reduce VMS-related increases in amplitudes in high-frequency brain electrical activity. HIRREM is not recommended for treatment for VMS because of the lack of controlled trials. *Level III evidence*

Chiropractic intervention

To date, there have been no clinical trials of chiropractic interventions for VMS, and available studies from epidemiologic survey data show no association between use of such interventions and VMS.[164] Chiropractic interventions are not recommended for treatment of VMS. *Level III evidence*

RECOMMENDATIONS

These recommendations are based on the evidence reviewed (Table 4). Because most trials were between 8 and 24 weeks' duration, data on long-term use are limited.

- *Considerations when stopping or switching therapies:* Evidence from relatively short-term pharmaceutical trials (eg, 8-12 wk) suggests that there is a return of VMS when treatment is stopped. However, there are no available data on potential effects of withdrawing SSRIs or SNRIs after a period of 2 to 3 years when used for VMS in nondepressed women. Similar evidence is not available from nonpharmacologic, nonhormonal intervention trials.
- *Recommended nonpharmaceuticals:* Two mind-body therapies have level I evidence showing efficacy in alleviating VMS: cognitive-behavioral therapy according to the MENOS 1 and MENOS 2 protocols and clinical hypnosis according to the Elkins protocol. These are relatively risk-free therapies. Women may need education and help in weighing potential benefits against barriers, such as time commitment and difficulties in finding appropriately credentialed providers.
- *Recommended pharmaceuticals:* Nonhormonal effective pharmacologic therapies include the FDA-approved low-dose paroxetine salt at 7.5 mg/d and off-label use of other antidepressants (SSRIs and SNRIs), gabapentin or pregabalin, and clonidine.
  - For all therapies, the lowest dose should be tried first and then titrated up as needed to avoid or minimize adverse events. Onset of action is rapid, usually within 2 weeks.
  - With titration, these agents are usually well tolerated. Contraindications include hypersensitivity or prior adverse drug reactions. VMS often improve over time, and limited evidence from clinical trials suggests that nonhormonal therapy should be gradually tapered over 1 to 2 weeks to avoid drug withdrawal symptoms.
  - No clear recommendations can be given for efficacy of one nonhormonal prescription therapy over another because there are few head-to-head comparison efficacy trials, and trials have a varying number and severity of hot flashes.
  - Choice of therapy depends on prior effective and tolerated therapy, patient history, adverse events profile, coadministered medications or benefit of drowsiness as an adverse effect (gabapentin), coexistence of a mood disorder, whether hot flashes are more bothersome during day or night, sensitivity to medications, patient tolerance of potential adverse effects, pharmacogenetic testing, and patient preference.
  - Therapy should be carefully re-evaluated on a regular basis (eg, every 6-12 mo) because data on long-term use are limited.

- *Recommend with caution:* Some therapies have level II evidence suggesting that they may be beneficial for alleviating VMS: weight loss, mindfulness-based stress reduction, the S-equol derivatives of soy isoflavones and extracts, and stellate ganglion block. Additional studies of these therapies are warranted.
  - Women are likely to be able to access weight loss programs and mindfulness-based stress reduction programs within their communities. Women may need education and help weighing barriers of time and cost in relation to potential benefits. These therapies may not be best for women with severe VMS or those seeking immediate relief.
  - In postmenopausal women with mildly to moderately distressing hot flashes, the S-equol derivatives of the isoflavones may be a reasonable option, providing there is no history of soy intolerance or allergy. If a woman responds to S-equol supplementation, treatment can continue with monitoring for adverse events; if a woman does not respond after 12 weeks, other treatment options should be discussed. Severely distressing hot flashes will be relieved more effectively with prescription therapies. Shared decision making is valuable in this setting.
  - Overall, although benefits were reported from single trials investigating a phytoestrogen extract from the rhubarb plant (ERr 731) and an equol supplement (SE5-OH), data were insufficient to permit determination of whether any other type of phytoestrogen product had significant effects on VMS.[67]
  - Stellate ganglion block may be an option for some women.

- *Do not recommend at this time:* Several therapies have level II or lower evidence showing that they are *unlikely* to be beneficial in alleviating VMS: over-the-counter supplements and herbal therapies (including black cohosh, crinum, dioscorea, dong quai, evening primrose, flaxseed, ginseng, hops, maca, omega-3s, pine bark, pollen extract, puerperia, Siberian ginseng, and vitamin supplementation), as well as relaxation, calibration of neural oscillations, and chiropractic intervention. Until additional evidence from well-controlled trials is available, these therapies should not be recommended for VMS.
- *Do not recommend at this time:* Some therapies appear risk free but do not have any evidence testing their effects on VMS, and their use may lead to delay in receipt of more appropriate and efficacious treatment. These include cooling techniques and avoidance of ''triggers.'' Research testing these recommendations is warranted.
- *Do not recommend:* Several therapies have level I evidence that shows that they are unlikely to alleviate menopausal VMS: exercise, yoga, paced respiration, and acupuncture. Although there are many health benefits associated with these, attempts to use these therapies are likely to delay receipt of more appropriate and effective therapies. In symptomatic women, such delays should be avoided given the association of VMS with other symptoms and overall quality of life. Exercise, yoga, and paced respiration should not be recommended for relief of VMS.

The NAMS Position Statement Advisory Panel strongly encourages readers to ensure that printed and electronic educational materials and websites are updated to be consistent with these recommendations.

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