**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.

**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...
about herbal products, 64% had concerns or were not sure about herb-drug interactions, and 61% did not feel confident about herbal product dosing. In another survey, nearly half of 293 women reported feeling confused about menopausal symptom management treatment options. 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. 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 and Nelson and colleagues.) 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. 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, 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. 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. However, others have found no relationship between level of physical activity or exercise and VMS, and exercise may trigger VMS in symptomatic women. The numerous RCTs of the effects of exercise on VMS have been summarized in several Cochrane reviews. The first review included one study, the second review included five studies, and the third review added two studies. 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; supervised prescribed aerobic exercise versus yoga versus usual activity plus omega-3 or placebo pills in a 1:1 ratio with each group; thrice weekly supervised aerobic exercise class versus hormone therapy; 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. When three studies that compared exercise to no exercise were pooled, exercise had no effect on VMS frequency. 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. 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. A systematic review and meta-analysis of five RCTs found no evidence that yoga was an effective intervention for VMS or menopausal symptoms. 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 published after the systematic review also found no effect of yoga on VMS. Newton and colleagues 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 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. 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). 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). 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. 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, 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. 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 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 and the self-guided CBT manual 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. 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, 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. 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). Level I evidence

Relaxation

Current evidence is limited and inconsistent on relaxation for hot flashes. A 2014 Cochrane review and a 2008 systematic review 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). In all studies, results were inconsistent and quality was poor, primarily because of small sample sizes and lack of an appropriate attention control group. 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 and one RCT in women with at least seven hot flashes per day. 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. 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. Participants in the clinical hypnosis arm reported significantly lower hot flash frequency (74% vs 17%) and hot flash scores (frequency × 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 biochemistry 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

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aglycone</td>
<td>The actual isoflavone without a sugar attached</td>
</tr>
<tr>
<td>Daidzein</td>
<td>A diphenoic 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</td>
</tr>
<tr>
<td>Equol</td>
<td>A nonsteroidal isoflavone metabolite that is produced from daidzein by intestinal bacteria</td>
</tr>
<tr>
<td>Equol nonproducer</td>
<td>Some women and men cannot convert daidzein to equol</td>
</tr>
<tr>
<td>Equol producer</td>
<td>Some women and men can metabolize daidzein to equol, which enables them to benefit from soy and soy isoflavone products</td>
</tr>
<tr>
<td>Estrogen receptors</td>
<td>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</td>
</tr>
<tr>
<td>Genistein</td>
<td>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</td>
</tr>
<tr>
<td>Glycitein</td>
<td>Another isoflavone found in soy protein and the protein of other legumes in relatively minor amounts</td>
</tr>
<tr>
<td>Glycoside</td>
<td>A sugar attached to the aglycone portion of an isoflavone</td>
</tr>
<tr>
<td>Isoflavones</td>
<td>Plant-derived compounds, also known as phytoestrogens, with estrogen-like biologic activity and a chemical structure similar to that of estradiol</td>
</tr>
<tr>
<td>Phytoestrogens</td>
<td>Another term for isoflavones</td>
</tr>
<tr>
<td>S(-)-equol</td>
<td>An isomer in the plasma of equol producers that is thought to have biologic activity; a metabolite of daidzein</td>
</tr>
<tr>
<td>Soy</td>
<td>The most widely used isoflavone-containing food; usually refers to a product derived from the whole soybean (or soya bean).</td>
</tr>
<tr>
<td>Soy germ</td>
<td>Part of the soybean that has a high concentration of isoflavones, but with four times more daidzein than genistein, and high concentrations of glycitein</td>
</tr>
<tr>
<td>Soy isoflavones</td>
<td>Isoflavones derived from soy (as opposed to from red clover, kudzu, or groundnut)</td>
</tr>
<tr>
<td>Soy protein</td>
<td>A product derived by extracting the protein out of the whole bean; rich source of isoflavones</td>
</tr>
</tbody>
</table>

(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 colleagues63); systematic reviews (eg, Utian and colleagues64; Kronenberg and Fugh-Berman65); a NAMS Translational Science Symposium and publication66; and a Cochrane Collaboration analysis67—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 racemoseae), 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. More recent studies indicate activity similar to selective ER modulators or modulation of serotonergic pathways, as well as antioxidant and anti-inflammatory effects.

A 2012 Cochrane review 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. 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.”

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. The branded product, Crila, is sold for VMS. No studies of Crinum 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, mass spectrometry 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. The pathway for these hormonal effects may reside in metabolic alterations other than steroid 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. 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. 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 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. 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 enterolactone and enterodiol, 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 polysaturated 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 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, 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 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 senticosus), 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, 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. A second study from the same team 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. 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. 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, 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 phytoestrogen, 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. 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. 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 omega-3s, 270 mg. 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, 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. 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. 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 pistols 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.

There is only one small RCT of pollen extracts in meno-
pause.\(^{95}\) Sixty-four postmenopausal women were random-
ized, 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

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

Two small studies reported the effects of puerpura on
menopausal symptoms, but neither included specific
measures of VMS. In one study, 52 hysterectomized, symp-
tomatic 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 research-
ers 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 rhabonticum*)
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
hydroestilbenes found in rhubarb, rhapontigenin and desoxy-
rhaphontigenin, have very weak binding affinity for ER-\(\alpha\), with
higher affinity for ER-\(\beta\). In vitro and in vivo studies support
the hypothesis that the hydroestilbenes 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 intro-
duced 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 \((12.7\% \text{ retention rate})\) 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 recom-
ended 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, effec-
tively mitigates most, if not all, menopausal symptoms.

Botanical combinations, although proferring better symp-
tom relief, are difficult to assess, given the complexity of the
formulations, the potential for adverse events, and the diffi-
culty in predicting drug-herb interactions (Table 2).\(^{102-114}\)
(Mary Tagliaferri, MD, Founder, Dr. Tagliaferri Formulas,
email communication, 2015) The botanical combinations

(NAMS POSITION STATEMENT

Copyright @ 2015 The North American Menopause Society. Unauthorized reproduction of this article is prohibited.)
TABLE 2. Combination herbal therapies for menopause tested in clinical trials

<table>
<thead>
<tr>
<th>Traditional name/trade name</th>
<th>Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black cohosh plus Chinese herbal preparation</td>
<td>Zizyphus spinosa (Suan zao ren) 500 mg, Rehmannia glutinosa (Sheng di huang) 400 mg, Ageratum conyzoides (Zhi mu) 400 mg, Aparagus lucidus (Tian men ding) 400 mg, Epimedium sagittatum (Yin yang huo) 400 mg, Curculeo orchoides (Xian mao) 375 mg, Phellodendron amurense (Huang bai) 325 mg, Cimicifuga racemosa (Black cohosh) 350 mg, Angelica sinensis (dang quai) 100 mg, matricaria chamomilla (hamomile) 50 mg</td>
</tr>
<tr>
<td>Climex</td>
<td>125 mg soy extract daily (providing 50 mg isoflavones, including 24 mg genistein)</td>
</tr>
<tr>
<td>CuraTrial Research Group</td>
<td>1,500 mg evening primrose oil extract (providing 150 mg γ-linoleic acid)</td>
</tr>
<tr>
<td>Ding Gui Buxue Tang</td>
<td>200 mg calcium, 1.25 mg vitamin D, 10 IU vitamin E</td>
</tr>
<tr>
<td>Dr. Tagliaferri’s Formula (Mary Tagliaferri, MD, Founder, Dr. Tagliaferri Formulas, email communication, 2015)</td>
<td>125 mg soy extract daily (providing 50 mg isoflavones, including 24 mg genistein)</td>
</tr>
<tr>
<td>Er-Xian decoction, Er xian tang, Menofine</td>
<td>Rhizoma Curculiginis Orchioidis (Shi chang pu) with Qing Hao Bie Jia</td>
</tr>
<tr>
<td>Estro G-100</td>
<td>Cynanchum wilfordii, Phlomis umbrosa, Angelica gigas Kakai extracts</td>
</tr>
<tr>
<td>Jiawei Qing’e Fang (JQF)</td>
<td>Cortex Eucommiae, Fructus Poriae, Semen Juglandis, Rhizoma Garlic</td>
</tr>
<tr>
<td>Menoprogen</td>
<td>Chinese wolfberry, Safflower, Sea kelp, Hawthorne berry, Mulberry</td>
</tr>
</tbody>
</table>

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 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. 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. 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 improved, whereas only 15% of the gabapentin group improved.

TABLE 2. Continued

<table>
<thead>
<tr>
<th>Traditional name/trade name (HALT)</th>
<th>Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actaea racemosa (Black cohosh) 200 mg, Medicago sativa (Alfalfa) 400 mg, Vitex agnus-castus (Chaste tree) 200 mg, Angelica sinesis (Dong quai) 400 mg, Chamaeleire luteum (False unicorn) 200 mg, Glycyrrhiza glabra (Licorice) 200 mg, Panax gramineus (Pomegranate) 400 mg, Eleutherococcus senticosus (Siberian ginseng) 400 mg, Boron 4 mg, Er-Xian decoction, Er xian tang, Menofine, Phyto-Female Complex, Nutrafem, Zhi Mu 14 (with and without acupuncture)</td>
<td></td>
</tr>
</tbody>
</table>
completed the study. At 3 months, there was no significant difference in VMS between groups. 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. 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 non-hormonal 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. 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. One trial 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. Level II evidence

**Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors**

Meta-analyses, a pooled analysis, a Cochrane review, and a review focused on evidence in cancer survivors provide evidence that SSRIs and SNRIs are associated with mild to moderate improvements in symptomatic menopausal 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). 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), 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 per day; for venlafaxine, 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. 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. 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. 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 but less effective than SSRIs, SSNRIs, and gabapentin.
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 and a 2013 Cochrane review conclude that, although acupuncture is superior to no treatment or a wait-list control, acupuncture is not superior to sham acupuncture. 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. 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.

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 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. Generally, however, needing 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 II 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. 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. 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). 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
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. 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. 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 for nonpharmacologic, nonhormonal intervention trials.

- **Recommended nonpharmacaceuticals:** 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, concomitantly administered 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.

**TABLE 4. Summary levels of evidence and recommendations**

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

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

- **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, puwepura, 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.

**Acknowledgments and Disclosures:** NAMS appreciates the contributions of the Position Statement Advisory Panel and the work of the NAMS Board of Trustees, which conducted the final review and approval. Disclosures indicate financial relationships with relevant commercial interests in the past 12 months.

**Position Statement Advisory Panel**

Janet Carpenter, PhD, RN, FAAN, Chair
Indiana University School of Nursing, Indianapolis, IN
No relevant financial relationships

Margery L.S. Gass, MD, NCMP
The North American Menopause Society, Mayfield Heights, OH
No relevant financial relationships

Pauline M. Maki, PhD
University of Illinois at Chicago, Chicago, IL
Consultant/Advisory Board or Review Panel: Abbott, Pfizer, Noven

Katherine M. Newton, PhD
Group Health Research Institute, Seattle, WA
No relevant financial relationships

JoAnn V. Pinkerton, MD, NCMP
University of Virginia Health System, Charlottesville, VA
Consultant/Advisory Board or Review Panel: Pfizer, Noven, TherapeuticsMD
Grant/research support: TherapeuticsMD

Maida Taylor, MD, MPH
University of California San Francisco, San Francisco, CA
Consultant/Advisory Board or Review Panel: Chemo Spain
Speakers Bureau: Shionogi

Wulf H. Utian, MD, PhD, DSc(Med)
The North American Menopause Society, Mayfield Heights, OH Consultant/Advisory Board or Review Panel: Pharmavite, PulseNMore

**NAMS 2014-2015 Board of Trustees**

Pauline M. Maki, PhD (President)
University of Illinois at Chicago, Chicago, IL
Consultant/Advisory Board or Review Panel: Abbott, Noven, Pfizer

Peter F. Schnatz, DO, FACOG, FACP, NCMP (President-Elect)
The Reading Hospital, Reading, PA
No relevant financial relationships
NAMS POSITION STATEMENT

Andrew M. Kaunitz, MD, FACOG, NCMP (Treasurer)
University of Florida College of Medicine, Jacksonville, FL
Consultant/Advisory Board: Actavis, Bayer, Merck
Grant/Research Support: Bayer, TherapeuticsMD
Royalties/Patents: UpToDate

Marla Shapiro, MD, MDCM, CCFP, MHSc, FRCPC, FCFP, NCMP (Secretary)
University of Toronto, Toronto, ON
Consultant/Advisory Board: Actavis, Angen, GlaxoSmithKline, Merck, Novartis, Pfizer
Speaker’s Bureau: Angen, Merck, Novartis, Novo Nordisk, Pfizer
Other: healthhandbone.ca

Jan L. Shifren, MD, NCMP (Immediate Past President)
Harvard Medical School, Boston, MA
Royalties/Patents: UpToDate

Wulf H. Utian, MD, PhD, DSc(Med) (Medical Director)
The North American Menopause Society, Mayfield Heights, OH
Consultant/Advisory Board: Pharmavite, PulseNMOR

Howard N. Hodis, MD
University of Southern California, Los Angeles, CA
No relevant relationships

Sheryl A. Kingsberg, PhD
Case Western Reserve University School of Medicine, Cleveland, OH
Consultant/Advisory Board: Emotional Brain, Endoceutics, Novo Nordisk, Nueta, Palatin, Pfizer, Shionogi Sprout, SST, Teva, Trimel Biopharm, Viveve

James H. Liu, MD
Case Western Reserve University School of Medicine, Cleveland, OH
Consultant/Advisory Board or Honoraria: Ferring, Nora, Noven, Decile Ten, Huntsworth Health North America
Patent Litigation Consulting: Actavis

Katherine M. Newton, PhD
Group Health Research Institute, Seattle, WA
Grant/Research Support: Integrated Diagnostics
Stock/Ownership: Microsoft

Gloria Richard-Davis, MD, FACOG
University of Arkansas Medical Sciences, Little Rock, AR
Consultant/Advisory Board: Pfizer

Nanette Santoro, MD
University of Colorado School of Medicine, Aurora, CO
Grant/Research Support: Bayer
Stock/Ownership: Menogenix

Lynnette Leidy Sievert, BSN, PhD
University of Massachusetts, Amherst, MA
No relevant financial relationships

Isaac Schiff, MD (Ex Officio)
Harvard Medical School, Boston, MA
No relevant financial relationships

Reference Librarian
Caitlin Pike, MLS, AHIP
Indiana University-Purdue University Library, Indianapolis, IN
No relevant financial relationships

NAMS Staff
Penny Allen
No relevant financial relationships

REFERENCES

1168 Menopause, Vol. 22, No. 11, 2015

© 2015 The North American Menopause Society


108. Xia Y, Zhao Y, Ren M, et al. A randomized double-blind placebo-controlled trial of a Chinese herbal medicine preparation (Jiawei Qing’e


NAMS CONTINUING MEDICAL EDUCATION ACTIVITY

Designated Article:

NAMS is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. NAMS designates this educational activity for a maximum of 2 AMA PRA Category 1 Credits™. Participants who are not physicians will be issued a certificate of participation. NAMS has determined that this activity includes 0.75 hours of pharmacotherapeutics education.

This activity is made possible by donations to the NAMS Education & Research Fund and has received no commercial support.

To participate in this activity, read the preceding position statement, reflect on how the information applies to your clinical practice, complete the CME post-test and evaluation, and follow the instructions after the evaluation to apply for CME credit or obtain your certificate of participation by November 1, 2016. Credit will be awarded to all who answer 5 of the 7 test questions correctly.

POST-TEST

1. Which lifestyle approach may alleviate menopausal VMS and can be recommended with caution?
   A. Yoga
   B. Weight loss
   C. Exercise

2. Which over-the-counter supplement can be recommended with caution for menopausal VMS?
   A. Dong quai
   B. Soy extract
   C. Vitamin E

3. Which mind-body technique is supported by level I evidence for managing menopausal VMS?
   A. Mindfulness-based stress reduction
   B. Paced respiration
   C. Clinical hypnosis

4. How long should isoflavone therapy continue in order to judge its effectiveness?
   A. 12 weeks
   B. 6 weeks
   C. 3 weeks

5. Which prescription therapy is FDA approved for menopausal VMS?
   A. Paroxetine
   B. Escitalopram
   C. Gabapentin

6. Which prescription therapy used off-label for menopausal VMS is supported by level I evidence?
   A. Gabapentin
   B. Venlafaxine
   C. Clonidine

7. To minimize adverse events with prescription therapies used off-label for menopausal VMS, clinicians should
   A. Titrate the dose
   B. Test for inflammation
   C. Test for drug allergy

EVALUATION

What changes will you make in your approach to counseling on and treatment of VMS as a result of reading and studying this position statement? (Check all that apply)

__ Ask all my menopausal patients if they are trying over-the-counter, herbal, or other nonhormonal therapies.

__ For patients who do not wish to take any medication or supplement, list which lifestyle, mind-body techniques, and alternative medical approaches are effective and which are not.

__ For patients interested in herbs and supplements, discuss use of soy isoflavones.
NAMS POSITION STATEMENT

Select the most appropriate prescription therapy for individual patients who cannot or do not wish to use hormonal therapy for VMS.

None. I already do these in my practice

What barriers do you face in implementing the Position Statement’s recommendations in your practice?

____________________________________________

____________________________________________

TO APPLY FOR CME CREDIT OR CERTIFICATE OF PARTICIPATION

To receive credit for this activity, the post-test and evaluation must be submitted to NAMS by November 1, 2016. NAMS members may read the position statement, complete the post-test and evaluation, and download their certificates online at www.menopause.org/for-professionals/member-center/cme-dashboard.

Participants may complete the test and evaluation on paper and mail or fax the completed form to:

The North American Menopause Society
5900 Landerbrook Drive, Suite 390
Mayfield Heights, OH 44124, USA
Fax: 440/442-2660

Keep a copy for your file. A certificate of credit will be sent to those who successfully complete the examination.

Name (please print) ____________________________________________________________
Address __________________________________________________________________________
City ___________________________ State/Province __________________________
Zip/CountryCode ___________________________ Country __________________________
Telephone ___________________________ Fax ___________________________ E-mail ___________________________