

## NAMS POSITION STATEMENT

# The 2023 nonhormone therapy position statement of The North American Menopause Society

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### Abstract

**Objective:** To update the evidence-based Nonhormonal Management of Menopause-Associated Vasomotor Symptoms: 2015 Position Statement of The North American Menopause Society.

**Methods:** An advisory panel of clinicians and research experts in women's health were selected to review and evaluate the literature published since the Nonhormonal Management of Menopause-Associated Vasomotor Symptoms: 2015 Position Statement of The North American Menopause Society. Topics were divided into five sections for ease of review: lifestyle; mind-body techniques; prescription therapies; dietary supplements; and acupuncture, other treatments, and technologies. The panel assessed the most current and available literature to determine whether to recommend or not recommend use based on these levels of evidence: Level I, good and consistent scientific evidence; Level II, limited or inconsistent scientific evidence, and Level III, consensus and expert opinion.

**Results:** Evidence-based review of the literature resulted in several nonhormone options for the treatment of vasomotor symptoms. **Recommended:** Cognitive-behavioral therapy, clinical hypnosis, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, gabapentin, fezolinetant (Level I); oxybutynin (Levels I-II); weight loss, stellate ganglion block (Levels II-III). **Not recommended:** Paced respiration (Level I); supplements/herbal remedies (Levels I-II); cooling techniques, avoiding triggers, exercise, yoga, mindfulness-based intervention, relaxation, suvorexant, soy foods and soy extracts, soy metabolite equol, cannabinoids, acupuncture, calibration of neural oscillations (Level II); chiropractic interventions, clonidine; (Levels I-III); dietary modification and pregabalin (Level III).

**Conclusion:** Hormone therapy remains the most effective treatment for vasomotor symptoms and should be considered in menopausal women within 10 years of their final menstrual periods. For women who are not good candidates for hormone therapy because of contraindications (eg, estrogen-dependent cancers or cardiovascular disease) or personal preference, it is important for healthcare professionals to be well informed about nonhormone treatment options for reducing vasomotor symptoms that are supported by the evidence.

**Key Words:** Clinical hypnosis – Cognitive-behavioral therapy – Gabapentin – Hormone therapy – Menopause – Nonhormone therapy – Selective serotonin reuptake inhibitors – Serotonin-norepinephrine reuptake inhibitors – Stellate ganglion block – Vasomotor symptoms.

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Hot flashes and night sweats (vasomotor symptoms [VMS]) are the most common symptoms of menopause and occur in up to 80% of menopausal women.<sup>1</sup> Vasomotor

symptoms can be bothersome, lasting a mean duration of 7 to 9 years, and in one-third of women, can last more than 10 years.<sup>2</sup> Hormone therapy (HT) remains the most effective treatment and should be considered in menopausal women aged younger than 60 years, within 10 years of their final menstrual periods, and without contraindications. Despite this, the use of HT has declined substantially after the publication of the Women's Health Initiative (WHI).<sup>3-5</sup> Evidence suggests that contrary to guideline recommendations, younger women and those with more VMS were less likely to receive HT after the WHI than before.<sup>6</sup> Additionally, rates of continuation of HT have declined in women with more frequent VMS after the WHI, largely because of media reports and provider advice.

Despite the underuse of HT in symptomatic women, some may choose not to use HT or have contraindications to its use, such as a history of an estrogen-sensitive cancer (including breast cancer), coronary heart disease, myocardial infarction,

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stroke, venous thromboembolism, or inherited high risk of thromboembolic disease.<sup>7</sup> Nonhormone options are important considerations for women who are not good candidates for HT.

This Position Statement updates and expands information on the nonhormone management of VMS from the 2015 NAMS Position Statement on nonhormone therapies and is intended to provide direction to guide evidence-based nonhormone management of VMS.

## METHODS

An advisory panel of clinicians and research experts in the field of women's health was selected to review and evaluate the literature published after the Nonhormonal Management of Menopause-Associated Vasomotor Symptoms: 2015 Position Statement of The North American Menopause Society.

Topics were divided into five sections for ease of review: lifestyle; mind-body techniques; prescription therapies; dietary supplements; and acupuncture, other treatments, and technologies. Individual panel members reviewed and evaluated the evidence on the different therapies for which they had special expertise, with the knowledge that trials of nonhormone treatments of VMS have a placebo improvement rate of 20% to 66%, and women with more anxiety show higher response to placebo.<sup>8</sup>

The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society was written after an extensive review of the pertinent literature and includes key points identified during the review process. The resulting manuscript was submitted to and approved by the NAMS Board of Trustees.

The panel assessed the most current and available literature to recommend or not recommend use with the level of evidence assigned on the basis of these categories:

- Level I: Good and consistent scientific evidence.
- Level II: Limited or inconsistent scientific evidence.
- Level III: Consensus and expert opinion.

This Position Statement uses gender-specific language as reflected in the referenced publications. However, NAMS recognizes that some persons experiencing menopause may identify differently than with the gender and pronouns used in this statement.

## LIFESTYLE

### Cooling techniques

Hot flashes can be triggered by small, core-body-temperature elevations<sup>9-11</sup>; therefore, it is feasible that changing lifestyle practices that control core body temperature may decrease VMS frequency. These include clothing adjustments (ie, dressing in layers; wearing sleeveless blouses; using breathable clothing materials; avoiding pullover sweaters, tops, and scarves) and environmental controls (hand or electric fans; cold packs under the pillow; turning the pillow when feeling warm; dual control electric blankets or a bed fan; lower room temperature). One small (N = 20), uncontrolled trial of postmenopausal women showed benefits with the use of a forehead cooling device and sleep hygiene instructions for reduction in self-reports of sleep problems and VMS over a 4-week period.<sup>12</sup> Another small trial

(N = 39) of a nighttime thermal comfort intervention was studied in a 4-week randomized, crossover trial.<sup>13</sup> Women reported no objective changes in the number or duration of nighttime VMS with this device, despite some self-reported improvements in sleep compared with baseline (ie, no device). Overall, cooling interventions must be tested in larger randomized, placebo-/sham-controlled clinical trials for the treatment of VMS. (Level II; not recommended)

### Avoiding triggers

Women are often told to avoid “triggers” such as alcohol, caffeine, spicy foods, or hot foods or liquids. One cross-sectional study of 4,595 Chinese women found a positive association between alcohol intake and VMS<sup>14</sup>; however, this has not been reported in other studies (such as the Melbourne Women's Midlife Health Project).<sup>15</sup> There are no clinical trials assessing the effects of avoiding triggers for the alleviation of VMS. (Level II; not recommended)

### Exercise and yoga

Observational studies revealed that women who exercise regularly report fewer VMS.<sup>16-18</sup> However, others have found no relationship between level of physical activity or exercise and VMS,<sup>19</sup> and exercise may trigger VMS in symptomatic women.<sup>10</sup> Several *Cochrane* reviews concluded that there was insufficient or poor evidence to consider exercise as a treatment for VMS.<sup>20-22</sup> Among the challenges, methods and exercise interventions varied widely across studies. They included, for example, supervised walking versus yoga versus no intervention<sup>23</sup> and supervised aerobic exercise versus yoga versus usual activity plus omega-3 or placebo pills.<sup>24</sup> No difference was found between yoga and exercise. When study results comparing exercise to no exercise were pooled, exercise had no effect on VMS frequency.<sup>22</sup> One study in the *Cochrane* review comparing exercise and HT found that HT was far more effective than exercise in reducing VMS.

A pooled analysis of individual data from four MsFLASH trials (N = 1,005) assessed various interventions compared with placebo for the treatment of VMS, including estradiol, antidepressants, omega-3, cognitive-behavioral therapy (CBT) for insomnia, and yoga or aerobic exercise.<sup>25</sup> Women with more bothersome VMS benefited the most from estradiol, whereas those with VMS and insomnia improved with CBT for insomnia. Those with VMS and psychosocial complaints reported improvement with antidepressants or CBT for insomnia. Overall, exercise and yoga led to smaller improvements and were not recommended as single interventions for VMS.

A systematic review and meta-analysis of 12 randomized, controlled trials (RCTs; N = 1,306) assessed yoga against no treatment, health education, exercise, and auricular acupressure for the treatment of VMS.<sup>26</sup> Given that all outcomes were self-reported and that there was insufficient blinding of participants, there was a high risk for reporting and detection bias among the studies. Additionally, there was significant heterogeneity in yoga styles, intensity, and frequency, limiting the interpretability of the findings. Yoga had limited benefits compared

with exercise for the treatment of VMS, and there were no benefits compared with no treatment.

Although there are other health benefits associated with exercise or yoga, the evidence of those interventions for the treatment of VMS is sparse. (Level II; not recommended)

### Dietary modification

Research evaluating the relationship of diet and VMS is limited. A study in postmenopausal women with more than two VMS per day (N = 84) randomized to a low-fat, plant-based diet and a half-cup of cooked soybeans per day versus no dietary changes found an 88% reduction in moderate to severe VMS compared with a 34% reduction in those with no dietary changes after 12 weeks.<sup>27</sup> In surveys, more vegetable and fruit consumption was associated with fewer menopause symptoms,<sup>28</sup> and women who followed a vegan diet reported fewer bothersome VMS than those who ate meat. For both, increased vegetable consumption was associated with fewer bothersome symptoms.<sup>29</sup> One longitudinal cohort study showed high-fat and -sugar diets were associated with an increased risk of VMS.<sup>30</sup> One study found that women who had higher soy milk and vegetable consumption had fewer menopause symptoms, whereas those who ate poultry and skimmed dairy products had worse menopause symptoms overall, including more VMS.<sup>31</sup> There is limited evidence from clinical trials to support the use of dietary modification for improving VMS. (Level III; not recommended)

### Weight loss

Studies have found that women who are obese are more likely to report more frequent and severe hot flashes than women of normal weight.<sup>32</sup> Randomized, controlled trials have found that weight loss from behavioral interventions are associated with a decrease in VMS.<sup>33,34</sup> Additionally, reducing hot flashes was a major motivator for losing weight.<sup>33</sup> Evidence suggests that the role of adiposity and weight loss in VMS may vary depending on age or menopause stage and specifically that adiposity acts as a risk factor for VMS earlier in the transition (perimenopause and early postmenopause)<sup>35</sup> but not when women are older or later in the transition.<sup>36</sup> Weight loss may have greater effects in reducing VMS when women are earlier in the transition.<sup>33</sup> In an open-label single-arm pilot study of a weight-loss medication (selective serotonin 2C [5-HT<sub>2C</sub>] receptor agonist) tested in 20 women, after 12-weeks there were both a decrease in weight and significant improvement in VMS (decline, 5.4 hot flashes/d) from baseline to week 12.<sup>37</sup> The study also found that after the weight-loss medication was stopped, there was a rapid increase in VMS with a return to baseline weight, further supporting the notion that weight loss improved VMS. However, these studies are either small pilot studies, nonrandomized trials, or post hoc analyses of studies designed for a different purpose. Larger, rigorously designed RCTs are needed. The limited available evidence suggests that weight loss may be used to improve VMS for some women. (Levels II-III; recommended)

### Key points

- There is no strong evidence that lifestyle changes such as cooling techniques and avoiding triggers improve VMS.
- There is insufficient or poor evidence to consider exercise or yoga as a treatment for VMS.
- A healthy diet is important for health promotion and chronic disease prevention; however, there is limited evidence to support dietary modifications as a tool for improving VMS.
- Weight loss may be considered for improving VMS.

## MIND-BODY TECHNIQUES

### Cognitive-behavioral therapy

Cognitive-behavioral therapy (CBT) has been shown to reduce the degree to which VMS are rated as a problem. Initial evidence came from two double-blind RCTs: MENOS 1, which showed that group CBT compared with usual care reduced VMS problem ratings in 96 survivors of breast cancer,<sup>38</sup> and MENOS 2, which showed self-guided and group CBT compared with usual care reduced VMS problem ratings in 140 perimenopausal and postmenopausal women without a history of breast cancer.<sup>39</sup>

A clinical psychologist administered the group CBT intervention, which involved psychoeducation (physiology of VMS; how thoughts and emotions affect the perception of physical sensations), training in relaxation and paced breathing, and cognitive and behavioral strategies to manage VMS (identifying and challenging negative beliefs about VMS; monitoring and modifying triggers of VMS; relaxation exercises). The content of the self-guided CBT was identical to that of the group CBT and included a self-help book completed during a 4-week period, two contacts with a clinical psychologist, weekly homework, and a compact disc for daily practice of relaxation and paced breathing.

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 in VMS problem ratings were maintained at 26 weeks, and more women in the CBT group (65%-78% across studies) reached a clinically significant threshold for improvement in VMS that are rated as a problem than in the usual-care group. Beliefs about coping and control over VMS and beliefs about sleep and night sweats mediated the effect of CBT on VMS problem ratings.<sup>40</sup>

Since these initial trials, several studies have extended this intervention to other modes of delivery and in other populations. Two studies in survivors of breast cancer showed that CBT reduced 1) VMS rated as a problem, hot flash interference, and self-reported VMS frequency when delivered by trained nurses in MENOS 4 (N = 130),<sup>41</sup> or 2) VMS rated as a problem and self-reported VMS frequency when delivered via the internet (with or without therapist support; N = 254).<sup>42</sup>

A workplace study of 124 menopausal women with problematic VMS found that women who received CBT for VMS using a self-help book had significant reductions in their VMS problem ratings compared with a waitlist control.<sup>43</sup> Another study examined CBT in combination with physical exercise in



422 survivors of breast cancer, showing that CBT (with or without exercise), but not physical exercise alone, reduced VMS problem ratings but not VMS frequency compared with a waitlist control.<sup>44</sup>

Finally, a study of 72 perimenopausal and postmenopausal women with VMS and depressed mood found that women randomized to a 12-week group-based CBT intervention had greater reductions in VMS bother and interference<sup>45</sup> as well as improvements in depressive symptoms than women randomized to a waitlist control. A caveat to this body of work is that the studies largely employ waitlist or usual-care controls, which are less rigorous controls than active controls matched on time and attention. However, the body of literature as a whole supports that CBT alleviates bothersome VMS for both survivors of breast cancer and menopausal women. (Level I; recommended)

### Mindfulness-based interventions

Evidence is limited for mindfulness-based interventions (MBI) for the management of VMS. Common features of MBI include instruction in meditation practices and how to approach thoughts, feelings, and bodily sensations in an accepting, nonjudgmental manner. A widely disseminated MBI is mindfulness-based stress reduction (MBSR), a multicomponent intervention that includes mindfulness meditation, body awareness, and yoga.<sup>46</sup> An RCT of MBSR versus waitlist control was conducted in 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. Vasomotor symptoms were assessed via a diary. After 20 weeks, the MBSR group showed greater reductions in hot flash bother (21.62% vs 10.50%;  $P = .07$ ) and intensity (44.56% vs 26.97%;  $P = .057$ ) than waitlist controls; these differences were marginally significant, reflecting the pilot nature of the study, variability in the outcome, and pronounced placebo effect.

Several additional studies have examined MBSR or other MBI for a constellation of menopause symptoms (eg, VMS, anxiety, depressive symptoms, sleep disturbance) in women transitioning through menopause<sup>47,48</sup> who were survivors of breast cancer<sup>49</sup> or who had undergone early bilateral oophorectomy.<sup>50</sup> A meta-analysis similarly examined MBI for quality of life or general menopause symptoms.<sup>51</sup> These studies have generally shown positive effects in reducing menopause symptoms broadly, with mixed effects for VMS specifically. Given that these studies were limited by their small sizes or limited control groups and that they were not designed to consider VMS (eg, women with VMS were not specifically enrolled), there are not enough data to recommend MBSR for the management of VMS. Future rigorously designed trials are needed to test the efficacy of MBI for VMS. (Level II; not recommended)

### Clinical hypnosis

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 survivors of breast cancer<sup>52</sup> and one RCT in women with at least seven hot flashes per day.<sup>53</sup> In both trials, clinical hypnosis involved 5 weekly in-person sessions of hypnotherapy with at-home self-hypnosis practice. In a 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.<sup>52</sup>

A 2013 single-blind RCT 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.<sup>53</sup> Both clinical hypnosis and structured-attention control included 5 weekly sessions that included discussion of symptoms, attentive listening, interpersonal exchange, avoidance of negative suggestions, monitoring, measurement, and encouragement provided in a therapeutic environment with a trained clinician. The hypnosis group additionally received hypnotic inductions and cooling suggestions. Participants in the clinical-hypnosis arm reported significantly lower hot flash frequency (74% vs 17%;  $P < .001$ ) and hot flash scores (frequency times severity, 80% vs 15%;  $P < .001$ ) 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%;  $P < .001$ ), indicating a clinically significant improvement. A follow-up analysis showed that effects were not related to women's expectations about whether hypnosis would work.<sup>54</sup> The program can be delivered via a trained provider or accessed via a smartphone application. (Level I; recommended)

### 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 several small studies that were done in a behavioral laboratory.<sup>55-57</sup> Two larger studies did not show any benefits over 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.<sup>58</sup> Similarly, in a randomized trial of 92 women, paced respiration practiced once or twice per day was no better than usual breathing for reducing hot flash scores (frequency times severity).<sup>59</sup> A third study showed that women who used a chest device to guide their slow, deep breathing practice at home for at least 15 minutes per day had significantly less benefit than a control group assigned to music listening.<sup>60</sup> (Level I; not recommended)

### Relaxation

Evidence is limited and inconsistent on relaxation for hot flashes. A 2014 *Cochrane* review<sup>61</sup> and a 2008 systematic review<sup>62</sup> both concluded that evidence from RCTs of relaxation was insufficient. There are two studies that were not included in either review. The first was a nonblinded, randomized trial showing a reduction in hot flash frequency with applied relaxation ( $n = 33$ ) compared with a waitlist control group ( $n = 27$ ).<sup>63,64</sup>

The second was a randomized trial comparing a nine-module, internet-delivered, applied relaxation program to an untreated control group. Of 46 women randomized in a 1:1 fashion, 66% dropped out early (no reasons provided), and the study had to be terminated. Limitations across studies included small sample sizes or lack of an appropriate attention-control group.<sup>55,56,63,65-68</sup> (Level II; not recommended)

### Key points

- CBT has been shown to reduce the bother and interference associated with VMS.
- Clinical hypnosis has been shown to reduce VMS frequency and severity.
- MBSR interventions for the management of VMS are limited by sample size and lack of control groups and are not designed to consider VMS; therefore, there are not enough data to recommend treatment.
- Paced breathing and relaxation techniques do not alleviate VMS and are not recommended.

### PRESCRIPTION THERAPIES

Many nonhormone prescription therapies have been evaluated and found to significantly reduce VMS in symptomatic menopausal women. However, there are only two FDA approved for this indication: paroxetine mesylate 7.5 mg daily and fezolinetant 45 mg daily. Other medications that reduce VMS include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, and oxybutynin. Typically, the onset of action is within 2 weeks. There are limited trials comparing nonhormone prescription therapies head-to-head with hormone therapy.

#### Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors

Evidence exists that SSRIs and SNRIs are associated with mild to moderate improvements in VMS, regardless of whether menopause is natural or surgical, as supported by meta-analyses,<sup>69-71</sup> a pooled analysis,<sup>72</sup> a *Cochrane* review,<sup>73</sup> and a review focused on evidence in survivors of cancer.<sup>74</sup> Limitations to these reviews include heterogeneity of the populations and variations in inclusion criteria, as well as variability in the population that was tested, dosing, length of treatment, and outcomes evaluated.

Paroxetine,<sup>75</sup> escitalopram,<sup>76</sup> citalopram,<sup>77</sup> venlafaxine,<sup>78,79</sup> and desvenlafaxine<sup>80</sup> have been shown to significantly reduce VMS in large, double-blind RCTs of symptomatic women. Duloxetine has been found to reduce VMS in smaller studies.<sup>81,82</sup> Hot flash reductions vary from 25% to 69% with these treatments, with improvements in composite hot flash severity and frequency from 27% to 61%. Trends toward improvement have been seen with sertraline and fluoxetine, but these were statistically insignificant; therefore, they are not recommended.<sup>69,79,83-86</sup>

A pooled analysis from three RCTs showed that 10 mg to 20 mg of escitalopram, 0.5 mg of oral 17 $\beta$ -estradiol, and 75 mg of venlafaxine daily resulted in comparable reductions in VMS frequency. A trial reported that 75 mg per day of venlafaxine was similar to low-dose oral estradiol 0.5 mg per day.<sup>79,87</sup> Oral estradiol reduced the frequency of hot flashes

by 2.3 more per day than placebo ( $P < .001$ ), whereas venlafaxine reduced the frequency of hot flashes by 1.8 more per day than placebo ( $P = .005$ ). However, neither of these trials allowed dose escalation, in which case estradiol would be expected to provide 77% improvement in hot flashes on average.<sup>88</sup>

A low-dose paroxetine salt (7.5 mg/d) was the first nonhormone pharmaceutical FDA approved for the treatment of moderate to severe VMS, with improvements found in VMS severity and frequency for up to 24 months, along with improvements in sleep disruption, without weight gain or negative effects on libido.<sup>89,90</sup>

Prior neuroleptic syndrome, serotonin syndrome, and concurrent use of monoamine oxidase inhibitors are contraindications to SSRIs and SNRIs. Caution should be taken in prescribing in patients with uncontrolled seizures, bipolar disorder, kidney or liver insufficiency, uncontrolled hyponatremia, and poorly controlled hypertension, as well as concurrent use of other SSRIs or SNRIs and pertinent polymorphisms in cytochrome P450 enzyme pathways. Black box warnings include uncommon suicidal thoughts in adolescents and children within the first few months.

Coadministration of SSRIs may lead to inhibition of CYP2D6 (the enzyme that converts tamoxifen to its most active metabolite, endoxifen) in women using tamoxifen, particularly with paroxetine and fluoxetine. Safer choices for those on tamoxifen include venlafaxine, desvenlafaxine, escitalopram, or citalopram because they have less of an effect on the CYP2D6 enzyme. There is a possible reported risk of bone fracture with SSRIs because serotonin alters signaling on bone metabolism,<sup>91,92</sup> although this has not been seen with short-term use.<sup>93</sup> They may produce nausea or dizziness, which typically improves after 1 to 2 weeks. (Level I; recommended)

#### Gabapentinoids

Gabapentin is FDA approved as an antiepileptic drug that is commonly used to treat diabetic neuropathy and postherpetic neuralgia. However, several trials studying the dose of 900 mg (300 mg three times/d) show that this has improved the frequency and severity of VMS.<sup>94-96</sup> Possible adverse events (AEs) include dizziness, unsteadiness, and drowsiness, typically seen during the first week, with improvement during the second week and resolution by week 4. In a placebo-controlled trial, higher doses of gabapentin (titrated to 2,400 mg/d) were as beneficial as estrogen (conjugated equine estrogens 0.625 mg/d) in reducing hot flash severity scores.<sup>97</sup> Adverse events of gabapentin at this dose included dizziness, headache, and disorientation, which limited its potential benefits. Because drowsiness is an AE, and the half-life is short, bedtime dosing of gabapentin may be a good choice for women with disruptive sleep from VMS. Black box warnings for all antiepileptic agents, including gabapentin, include uncommon suicidal thoughts or behaviors. Adverse events include drowsiness, dizziness, and impaired balance or coordination. The suggested dosing (Table 1) for gabapentin is 900 mg to 2,400 mg per day in divided doses. (Level I; recommended)

**TABLE 1.** Suggested dosing ranges for nonhormone prescription therapies

<b>SSRIs</b>		
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 evaluated for efficacy)
<b>SNRIs</b>		
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
<b>Gabapentinoids</b>		
Gabapentin	900-2,400 mg/d	Start with 100-300 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)
<b>Neurokinin B antagonists</b>		
Fezolinetant	45 mg/d	Single dose, no titration needed

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

### Pregabalin

Pregabalin is a gamma-aminobutyric acid analog structurally related to gabapentin FDA approved for the management of neuropathic pain and seizures. There has been one phase 3 RCT in 163 women (40% with a history of cancer) evaluating pregabalin for VMS.<sup>98</sup> After 6 weeks of treatment, pregabalin at a dose of 75 mg twice a day or 150 mg twice a day decreased VMS frequency by 59% and 61%, respectively, whereas placebo decreased symptoms by 35%. There were more dizziness and cognitive difficulties reported in those taking pregabalin. Because of limited studies, AEs, including weight gain, and because pregabalin is listed as a Schedule V controlled substance (because of the potential for abuse), pregabalin is not recommended. (Level III; not recommended)

### Clonidine

Clonidine is a centrally active  $\alpha$ -2 adrenergic agonist that has been shown to be modestly more beneficial than placebo<sup>69</sup> but less beneficial than SSRIs, SNRIs, and gabapentin in reducing VMS.<sup>69,73</sup> It is used infrequently because of AEs, including hypotension, lightheadedness, headache, dry mouth, dizziness, sedation, and constipation. Sudden cessation can lead to significant elevations in blood pressure. Because there are other more effective therapies with fewer AEs, clonidine is not recommended. (Levels I-III, not recommended)

### Oxybutynin

Oxybutynin is an antimuscarinic, anticholinergic therapy that is used for the treatment of overactive bladder and urinary urge incontinence. One prospective study<sup>99</sup> and two randomized, double-blind studies<sup>100,101</sup> in postmenopausal women demonstrated that oxybutynin at doses ranging from 2.5 mg or 5 mg twice daily up to 15 mg extended-release daily significantly improved moderate to severe VMS. Adverse events of oxybutynin are usually dose-dependent and most commonly include a dry mouth and urinary difficulties. Long-term use of anticholinergics may be associated with cognitive decline, particularly in older persons.<sup>102-104</sup> (Levels I-II; recommended)

### Suvorexant

Suvorexant is a dual orexin-receptor antagonist that blocks the effects of the hypothalamic neuropeptide orexin-A, which promotes wakefulness and may be involved in the occurrences

of hot flashes. Postmenopausal women have plasma levels that are three times higher than premenopausal women, which may contribute to sleep disruption and impaired thermoregulation.<sup>105</sup> Suvorexant has been shown to reduce insomnia severity,<sup>106-108</sup> and findings in a small study of menopausal women showed that it led to reductions in nighttime VMS frequency compared with placebo and was well tolerated.<sup>109</sup> Suvorexant did not improve daytime VMS. Given limited data to support its use, suvorexant is not recommended. (Level II; not recommended)

### Neurokinin B antagonists

New nonhormone therapies, only one of which (fezolinetant) is FDA approved, are important because their development was founded on the burgeoning understanding of VMS physiology. It is recognized that pulsatile gonadotrophin-releasing hormone (GnRH) secretion is itself driven by an ensemble of pacemaker cells that produce kisspeptin, neurokinin B, and dynorphin, leading to the coined acronym *KNDy* (pronounced *candy*) to describe this unique subset of hypothalamic neurons. These *KNDy* neurons are surrounded by a dense plexus of interconnected fibers to ensure that all *KNDy* neurons fire in concert and together constitute the GnRH pulse generator.<sup>110</sup>

Neurokinin B stimulates and dynorphin inhibits sustained pulsatile kisspeptin secretion. In turn, kisspeptin acts directly on GnRH neurons to stimulate GnRH secretion, thereby driving luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release. In parallel with the effect of *KNDy* neurons on GnRH in the hypothalamus, the *KNDy* neuronal plexus has direct effects on the adjacent hypothalamic thermoregulatory center.<sup>111</sup> After declines in circulating levels of estradiol across the menopause transition, VMS are triggered by hyperactivity of the *KNDy* neuron plexus, resulting in hypersecretion of neurokinin B.<sup>112</sup> Hypersecretion of neurokinin B from the *KNDy* neurons onto the adjacent thermoregulatory center in the hypothalamus<sup>111</sup> causes disruption of temperature control and the occurrence of VMS.<sup>112,113</sup>

Therapeutic development of neurokinin B antagonists was initiated as a novel strategy to target VMS. This nonhormone approach directly targets the neural mechanism underlying VMS. Published results of RCTs are available for three distinct agents, with fezolinetant, which is FDA approved, and elinzanetant<sup>114-116</sup> in development. A third agent, antagonist (MLE4901),<sup>117,118,121</sup> is no longer being pursued as a VMS treatment.



Published trial results include demonstration of efficacy of fezolinetant<sup>116,119,120</sup> and elinzanetant<sup>116,121</sup> relative to placebo. Fezolinetant is a selective neurokinin B receptor-3 antagonist found to be more beneficial than placebo within and up to 12 weeks of use. Elinzanetant is a dual neurokinin B receptor-3 and receptor-1 antagonist found to be more beneficial than placebo within 2 weeks of use. Phase 3 trials have demonstrated safety, with headache as the most common AE.<sup>120</sup> Elevation of hepatic enzymes was rare and resolved either during continued treatment or with treatment discontinuation.

The effect of neurokinin B antagonists on other symptoms that commonly co-occur with VMS or are frequently experienced during the menopause transition has received less attention. Early evidence suggests benefit for quality of life- and VMS-related distress, nocturnal awakenings, and sleep quality.<sup>114-116,119,121-123</sup> Further effect on VMS-related mood and genitourinary, sexual, cardiovascular, metabolic, and bone health are lacking. Higher doses appear to suppress LH but not estradiol in postmenopausal women with VMS.<sup>114</sup> However, potentially advantageous and detrimental effects on other physiologic processes have yet to be fully investigated in larger populations.

### Key points

- SSRIs and SNRIs are associated with mild to moderate improvements in VMS.
- Gabapentin is associated with improvements in the frequency and severity of VMS.
- Pregabalin is not recommended for VMS because of AEs and controlled-substance prescribing restrictions.
- Because of significant AEs and no recent studies showing greater benefit than placebo, clonidine is not recommended.
- Oxybutynin has been shown to reduce moderate to severe VMS, although in older adults, long-term use may be associated with cognitive decline.
- Given limited data, suvorexant is not recommended.
- Fezolinetant is a first-in-class neurokinin B antagonist that is FDA approved for management of vasomotor symptoms.

## DIETARY SUPPLEMENTS

Managing VMS with dietary supplements is complex and challenging because there are limited rigorous randomized, clinical trial data from which to evaluate supplements and a lack of government regulation to ensure their purity and safety. These over-the-counter products remain widely marketed through direct-to-consumer marketing. They are permitted to market toward specific claims of alleviating symptoms despite limited evidence as long as there is no claim to provide disease benefit.

### Dietary supplements with limited or inconsistent evidence of benefit

#### *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 a greater affinity for ER- $\beta$  than for ER- $\alpha$  and possess

both estrogen-agonist and estrogen-antagonist properties.<sup>124</sup> Soy is among the eight most common food allergens,<sup>125</sup> and reactions can range from mild (eg, bloating, flatulence, loose stools) to severe (eg, anaphylaxis).

“The Nonhormonal Management of Menopause-Associated Vasomotor Symptoms: 2015 Position Statement of The North American Menopause Society” noted mixed evidence for use of soy for VMS.<sup>126</sup> Soy trials published since 2015 are difficult to summarize because of the wide variation in interventions tested (eg, soy-based drinks,<sup>127,128</sup> soy isoflavone derivatives in tablets only<sup>129</sup> or combined with exercise,<sup>130</sup> or mixed with other supplements [herbals, vitamins, or minerals]), with widely varying dosages tested.<sup>131-135</sup> These studies also have significant limitations, including small sample sizes,<sup>129-131,133,134</sup> use of symptom checklists<sup>126-131,133,135</sup> rather than VMS diaries,<sup>134</sup> and relatively short-term assessment of outcomes. For example, most participants reported VMS after 12 weeks of treatment,<sup>127-129,131,133-135</sup> yet meta-analyses suggest more than 13 weeks are needed to demonstrate half of the expected maximal effects,<sup>136</sup> and more than 16 weeks are needed for optimal effects.<sup>137</sup> As a result of these study differences and limitations, the findings are mixed, with some studies showing soy to be beneficial for reducing VMS or severity,<sup>131,132,135</sup> and others showing no benefit of soy over placebo<sup>127,128,130,133</sup> or finding soy to be less beneficial than other treatments.<sup>129</sup> (Level II; not recommended)

#### *Soy metabolite equol*

Equol is a nonsteroidal estrogen that binds to ER- $\alpha$  and ER- $\beta$ , but because of its high affinity for ER- $\beta$ , it is often designated as an ER- $\beta$  agonist. Few studies have considered whether study participants can metabolize soy, which is critical for soy’s potential estrogenic effects. Only 35% of North American women can metabolize the soy isoflavone daidzein to equol.<sup>138</sup> Women who are able to metabolize soy into equol would be expected to experience relief from VMS with soy products or equol. Women who cannot produce equol after ingesting soy do not benefit from soy but would be expected to benefit from equol. Tests to ascertain whether women are equol producers are not commercially available to the public or healthcare professionals.

A 2019 systematic review and meta-analysis found positive effects of equol supplementation over placebo for reducing VMS frequency in three of five trials.<sup>139</sup> Null findings in the remaining two trials were hypothesized to have been because of large differences in VMS at baseline in one trial and inclusion of only equol-producing women in the largest trial. A limitation in most studies (4 of the 6) was inclusion of fewer than 50 participants per group.

There is currently mixed evidence for soy foods, soy extracts, and the soy metabolite equol from widely diverse studies, with some significant limitations. (Level II; not recommended)

#### *Pollen extract*

A proprietary extract made from flower pollen has been available under the brand names Relizen, Serelys, Femal, and Femalen. One RCT (N = 53) found that women randomized to receive pollen extract showed significant reductions in VMS on the Menopause

Rating Scale (MRS; 65% VMS reduction with pollen extract vs 38% with placebo,  $P < .006$ ) and daily diaries (27% greater reduction with treatment than placebo,  $P < .026$ ) after 3 months of use.<sup>140</sup> A single-arm multicenter study (N = 104) found a significant decrease in menopause symptoms after 12 weeks' use of pollen extract.<sup>141</sup> An additional observational, single-arm study (N = 108) that included perimenopausal and menopausal women found reduction in hot flashes after 3 months' use of pollen extract.<sup>142</sup> However, based on expert opinion and limited scientific research for the management of VMS, pollen extract is not recommended. (Level III; not recommended)

#### ***Ammonium succinate***

An ammonium succinate-based supplement (Amberen) was studied for the management of menopause symptoms in a manufacturer-sponsored clinical trial, with an initial study published in 2016,<sup>143</sup> and later a pooled analysis including this study and a second additional study was published in 2019.<sup>144</sup> The studies were identical multicenter, double-blind, 90-day RCTs including women aged 42 to 60 years with mild to moderate menopause symptoms (n = 227). Both studies showed improvement in menopause symptoms such as sleep, fatigue, loss of interest in sex, joint and muscle pain, VMS, and a decrease in anxiety compared with the placebo group. Women in the ammonium succinate-supplement group also showed an increase in serum estradiol levels and a decrease in leptin. The authors concluded that the pooled analysis of the two studies found that the ammonium succinate-based supplement improved menopause symptoms, including VMS, compared with placebo. Because of limited studies and the results being based on manufacturer-sponsored clinical trials, ammonium succinate is not recommended. (Level II; not recommended)

#### ***Lactobacillus acidophilus***

*Lactobacillus acidophilus* YTI was studied for managing menopause symptoms.<sup>145</sup> One 12-week, multicenter, double blind, RCTI (N = 67) involved women with menopause symptoms including VMS. After 12 weeks, total Kupperman Index (KI) scores decreased, and quality of life was improved (Menopause-Specific Quality of Life [MSQOL] questionnaire) in all four symptom domains (physical, psychological, vasomotor, and sexual). There were no reported changes in hormone levels or endometrial lining. Given that this data is limited to one small study, based on global menopause symptom ratings, and has not been replicated, it is not recommended at this time. (Level II; not recommended)

#### ***Rhubarb***

Siberian rhubarb (*Rheum raphaniticum*) is used as a food and as a medicinal plant for constipation, diarrhea, and other gastrointestinal complaints. A single commercial preparation of rhubarb extract, which has been used in Germany for more than 20 years, was introduced in the United States (Estrovera). The product contains a proprietary extract called *rhaponticin* or extract ERr 731 and contains estrogenic properties but is not estrogen. One study randomized 109 symptomatic perimenopausal women to ERr 731 (n = 54) or placebo (n = 55) daily for 12 weeks.<sup>146</sup> Only

7 of 55 women randomized to placebo completed the trial (12.7% retention rate), and 39 of 54 women randomized to active treatment completed the trial. The researchers reported that at 12 weeks, the MRS total score and each symptom within the scale (including VMS) significantly improved in the active-treatment group versus placebo. Human safety data were drawn from a group of 23 women followed for 48 weeks, 20 of whom completed a 96-week observation period. Few AEs were reported.<sup>147</sup> Another open-label, single-arm study in Indian perimenopausal women over 12 weeks reported improved menopause symptoms.<sup>148</sup> Given the extremely low retention rate in clinical trials and the open-label study design in one study, the conclusions are limited. (Level II; not recommended)

### **Dietary supplements without demonstrated evidence of benefit**

#### ***Black cohosh***

Black cohosh, scientific name *Actaea racemosa* L. (previously *Cimicifugae racemosae*), is the most purchased botanical for menopause symptoms. The active ingredients in black cohosh extract are unknown, and its 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.<sup>149</sup> Other studies indicate activity similar to selective estrogen-receptor modulators<sup>150</sup> or modulation of serotonergic pathways, as well as antioxidant and anti-inflammatory effects.

Reports of possible hepatotoxicity started to appear after 2000. After examining all reported cases, the US Pharmacopeial Convention Dietary Supplements-Botanicals Expert Committee found 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 health-care practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice."<sup>151</sup>

A 2012 *Cochrane* review<sup>152</sup> 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 VMS. Data on safety were inconclusive. Other literature compared black cohosh to HT in a randomized trial of three groups: group A, 1 mg estradiol plus cyclic 4 mg medroxyprogesterone acetate; group B, 1 mg estradiol daily plus cyclic 100 mg micronized progesterone; and group C, 100 mg *Cimicifuga foetida* extract daily.<sup>153</sup> The study was limited by sample size because only 81 women (84%) completed the study, and although the KI scores were reduced in each group, there were no significant differences between groups. Despite this, the authors concluded that *C foetida* extract could alleviate VMS after 12 weeks. Another large systematic review (35 studies and one meta-analysis) noted that the effects of *C foetida* was possibly dose-dependent as well as augmented when combined with other products such as St. John's wort.<sup>154</sup> At this time, there is insufficient evidence to support the use of black cohosh for VMS. (Level I; not recommended)



### Other supplements

**Wild yam.** *Dioscorea barbasco*, *D mexicana*, and *D villosa* are the varieties of wild yam 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. Evidence for *Dioscorea* for VMS is limited. One clinical trial employing a yam cream to treat VMS reported no significant benefit.<sup>155</sup> Tested yam creams often do not contain any yam extract, and many have been adulterated with undisclosed steroids, including estrogens, progesterone, and medroxyprogesterone acetate. Because of the potential harm that may result from adulterants and lack of efficacy data, yam creams are not recommended for VMS. (Level II; not recommended)

**Dong quai**, also known as *Angelica sinensis*, dang gui, and tang kuei, is the root of the *Angelica polymorpha* Maxim var *sinensis* (Oliv). Researchers enrolled 71 women in an RCT of 4.5 g dong quai per day or placebo.<sup>156</sup> After 24 weeks, there were no differences in VMS frequency; KI scores; levels of FSH, LH, or estradiol; vaginal maturation index; or endometrial thickness. Dong quai does not appear to alleviate VMS, and there are a number of safety concerns, including possible photosensitization, anticoagulation, and carcinogenicity. (Level II; not recommended)

**Evening primrose**, *Oenothera biennis* L, is a flowering plant rich in linolenic acid and  $\gamma$ -linolenic acid. There is a single trial of evening primrose oil for menopause symptoms in which 56 women were randomized to evening primrose oil 500 mg per day or placebo for 6 months.<sup>157</sup> Evening primrose oil did not show benefit over placebo, with VMS declining by 1.0 per day with evening primrose oil and by 2.6 per day with placebo. (Level II; not recommended)

**Maca** (*Lepidium Meyenii* Walp, *Lepidium peruvianum* Chacon), a traditional foodstuff from South America, contains a weak phytoestrogen ( $\beta$ -sitosterol) also found in several other botanicals such as saw palmetto. 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, four studies showed improvements in Greene Climacteric Scale or KI scores. However, because of quality, design, sample sizes, or limited reporting of study data,<sup>158</sup> existing evidence is not strong enough to support the use of maca for VMS. (Level II; not recommended)

**Ginseng.** There are two distinct true ginsengs in common use; *Panax ginseng* and *Panax quinquefolius*, as well as a third substance, Siberian ginseng (*Acanthopanax senticosus* or *Eleutherococcus senticosus*), a member of a closely related family of plants (Araliaceae). In a study of a specific proprietary product, G115 (Ginsana in the United States), 384 postmenopausal women were randomized to G115 or placebo.<sup>159</sup> After 16 weeks, women taking G115 did not show greater VMS reductions than with placebo. Similarly, researchers found no significant effect of Korean red ginseng on VMS frequency versus placebo.<sup>160</sup> A second study similarly found that ginseng failed to affect VMS when measured by the KI and the MRS.<sup>161</sup> Thus,

ginseng does not appear to be beneficial for VMS. (Level I; not recommended)

**Labisia pumila/Eurycoma longifolia** was studied in a double-blind, 24-week RCT of women aged 41 to 55 years (N = 119) experiencing menopause symptoms (MRS and MSQOL questionnaire used for assessment of symptoms).<sup>162</sup> At week 12, the group randomized to active treatment experienced improvement in symptoms (65%) compared with placebo (60%;  $P < .01$ ). However, at weeks 12 to 24, significant improvement in the MRS and MSQOL questionnaire scores were noted in both treatment and placebo groups ( $P < .001$ ). Overall, the authors concluded that there were no significant differences in menopause symptoms between treatment and placebo groups. (Level I; not recommended)

**Chasteberry.** Vitex species have estrogenic properties, and compounds such as apigenin and penduletin are their ER- $\beta$ -selective compounds, whereas rotundifuran and agnuside activate ER- $\alpha$ -dependent responses.<sup>163</sup> Four double-blind RCTs have tested supplements containing varying amounts of Vitex agnus-castus (an amount equivalent to 1,000 mg dried vitex fruit,<sup>164,165</sup> 50 mg of vitex fruit extract,<sup>166</sup> or 125 mg vitex fruit<sup>167</sup>) in combination with various other supplements<sup>165-167</sup> or combined with *Nigella satvia* and citalopram 20 mg per day.<sup>164</sup> All trials included perimenopausal or postmenopausal women with VMS and included methods to assess compliance. The largest and most rigorous trial (n = 100) compared a mixed supplement to placebo and found no group differences in daily diary VMS frequency or questionnaire VMS intensity after 16 weeks of treatment.<sup>165</sup> The remaining three smaller (<50 women/group) trials used less rigorous questionnaire-only measures of VMS (rather than diaries) and found significant reductions in VMS frequency, bother, or intensity ratings after 8 to 12 weeks of treatment.<sup>164,166,167</sup> Few AEs were reported in any of the trials. Because of differences in the compounds that were tested, it is not possible to conclude that Vitex alone improves VMS. (Level II; not recommended)

**Milk thistle** is a member of the Asteraceae family, a therapeutic herb used for fever and kidney and spleen disease. One previous study evaluated its effect in polyherbal formulations that included black cohosh, dong quai, and other herbs. It has been evaluated in a small RCT of 40 women receiving *Silybum marianum* extract and 40 women receiving placebo over a 12-week period and reported improvement in hot flashes and night sweats severity over placebo.<sup>168</sup> Because of the limitations of one study, there is not enough evidence to make a recommendation. (Level II; not recommended)

**Omega-3 fatty acid** supplements contain polyunsaturated fatty acids, including eicosapentaenoic acid, docosahexaenoic acid, and  $\alpha$ -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, 1,100 mg eicosapentaenoic acid plus 50 mg docosahexaenoic acid), VMS frequency and intensity were significantly improved with omega-3 compared with placebo.<sup>169</sup> 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.<sup>170</sup> Therefore, there is mixed and inconclusive evidence for the use of omega-3s for the management of VMS. (Levels I-II; not recommended)

**Vitamin E.** Previous studies investigating the effects of vitamin E for VMS treatment included two crossover trials (N = 120; N = 50) that showed limited reduction in VMS frequency with vitamin E compared with placebo.<sup>171,172</sup> There is very little evidence for vitamin E having significant benefit in reducing VMS. A study from Iran with a total of 93 participants evaluated the use of curcumin alone and vitamin E alone in reducing VMS as well as other symptoms of menopause versus placebo (30 women/group).<sup>173</sup> There was some improvement seen at 4 weeks for curcumin and at 8 weeks for vitamin E compared with placebo. Results were significant at 4 weeks for curcumin and at 8 weeks for vitamin E, but sample sizes were small, limiting conclusions. Therefore, vitamin E is not recommended for the management of VMS. (Level I; not recommended)

### **Cannabinoids**

The data evaluating the relationship between cannabinoids and menopause symptoms is very limited. This lack of evidence is particularly notable because more than one-quarter of women have used or are using marijuana to treat their menopause symptoms.<sup>174</sup> A systematic review found only three small studies that evaluated cannabis use and its associations with menopause symptoms, including VMS, insomnia, mood, and depression/anxiety.<sup>175</sup> Based on the lack of available evidence, cannabinoids cannot be recommended for the treatment of VMS. (Level II; not recommended)

### **Key points**

- Given mixed evidence of benefit for VMS, soy foods, soy extracts, and the soy metabolite equol are not recommended.
- Given the lack of rigorous, evidence-based scientific research supporting the use of any over-the-counter supplements and herbal therapies for the management of VMS, these remedies are not recommended.
- Cannabinoids are not recommended for the treatment of VMS.

## **ACUPUNCTURE, OTHER TREATMENTS, AND TECHNOLOGIES**

### **Acupuncture**

Acupuncture is a component of the ancient practice of traditional Chinese medicine in which thin needles are inserted into the skin at key points in the body and activated through specific movements (manual acupuncture) or with electrical stimulation (electroacupuncture) to create an energy flow, or *Qi*, which is believed to improve overall health. Sham acupuncture is a placebo-equivalent treatment involving needles inserted at unrelated points or needles that do not pierce the skin.

Over the last decade, several systematic reviews and meta-analyses examined acupuncture versus no treatment or sham intervention for the treatment of VMS. In most systematic

reviews,<sup>176-178</sup> as well as in RCTs,<sup>179</sup> acupuncture was deemed to alleviate some menopause-related symptoms (eg, mood, sleep, pain) as reflected in the reduction in menopause-related total scores (eg, KI, Greene Climacteric Scale) or the improvement in quality-of-life measurements (eg, MSQOL questionnaire); it had, however, little to no clinical benefit for the improvement of VMS compared with sham interventions, either for symptomatic midlife women or for survivors of breast cancer.

Consistent with this conclusion, a 2018 study (umbrella meta-analysis) that included three systematic reviews and four RCTs found modest benefits of acupuncture for the alleviation of menopause-related symptoms, quality of life, and VMS severity or frequency when treatments were compared with no treatment.<sup>180</sup> Results, however, were no longer clinically significant when acupuncture was compared with sham intervention.

There has been a considerable debate regarding the use of appropriate comparisons or control groups in acupuncture studies; some have argued, for example, that sham interventions may not be physiologically inert and therefore would not be the most appropriate comparison for studies or trials that aim to inform clinical practice. It is important to note that although most studies that compared traditional acupuncture with sham interventions found no significant difference in VMS frequency or severity, trials with electroacupuncture showed some benefits with this intervention and even stronger results for electroacupuncture when compared with manual acupuncture.<sup>181</sup>

In a 2021 model-based meta-analysis, Li and colleagues assessed 17 studies (1,123 participants), including manual acupuncture, electroacupuncture, and sham acupuncture.<sup>178</sup> The authors found that after 8 weeks of treatment, both electroacupuncture and a combination of both acupuncture modalities (traditional acupuncture and electroacupuncture) led to significant reduction of VMS per day compared with sham intervention. Moreover, the benefits of electroacupuncture for VMS were comparable to those reported in previous studies using nonhormone, pharmacologic treatments such as SSRIs, SNRIs, gabapentin, and escitalopram.

Existing evidence does not support the use of traditional acupuncture for the treatment of VMS, neither for midlife women nor for VMS in survivors of breast cancer. (Level I; not recommended). The use of electroacupuncture, although more promising, still warrants further investigation. (Level II; not recommended)

### **Stellate ganglion block**

Stellate ganglion blockade is a widely used treatment for pain management, including for migraine and complex regional pain syndrome. The treatment is accomplished through the injection of an anesthetic agent at the lower cervical or upper thoracic region because the stellate ganglion is located bilaterally in the C6-T2 region of the anterior cervical spine. Adverse events, such as transient seizures or a bleeding complication, are extremely rare and minimized using imaging guidance during the procedure.<sup>182</sup>

Stellate ganglion blockade has emerged as a potential treatment option for VMS in both midlife women and those with breast cancer, although the exact mechanism of action of stellate ganglion blockade on VMS remains unclear.

One randomized, sham-controlled trial assessed active stellate ganglion blockade with bupivacaine versus a sham procedure (subcutaneous saline injection) for VMS in women with natural or surgical menopause (N = 40).<sup>183</sup> Over a 6-month follow-up, there was a reduction in subjectively reported VMS intensity and frequency (moderate to very severe) in the stellate ganglion blockade group compared with the sham-control group. Moreover, there was a reduction (21%,  $P < .05$ ) of physiologic VMS measured with ambulatory skin conductance monitors from baseline to 3 months in the stellate ganglion blockade group, whereas the sham-control group showed no reduction. Four uncontrolled, open-label studies showed that stellate ganglion blockade reduced VMS, with effects ranging from a 45% to a 90% reduction 6 weeks to several months after blockade.<sup>184-187</sup>

In a study of patients with breast cancer (N = 40), stellate ganglion blockade (10 mL 0.5% bupivacaine injected bilaterally) was compared with paroxetine 7.5 mg per day over a 6-week period.<sup>188</sup> Both treatments had a positive effect on an index comprising both VMS frequency and severity, with no significant differences between treatments.

Overall, stellate ganglion blockade might help alleviate moderate to very severe VMS in select women. Results from ongoing larger RCTs are needed to provide more definitive evidence. Given that stellate ganglion blockade is a procedure that involves potential risks and AEs, its potential use for VMS should be carefully evaluated. (Levels II-III; recommended)

### Calibration of neural oscillations

High-resolution, relational, resonance-based electroencephalic mirroring is a closed-loop acoustic stimulation neurotechnology based on the principle of allostasis. Essentially, scalp sensors and software algorithms translate specific brain frequencies into audible tones of varying pitch in real time, and these tones are immediately mirrored back via ear buds, allowing the brain to “listen to itself” in an acoustic mirror. High-resolution, relational, resonance-based electroencephalic mirroring has shown some preliminary benefits for the management of insomnia<sup>189</sup> and for military-related stress.<sup>190</sup>

In an uncontrolled study, 14 women showed a significant reduction in VMS frequency and severity after administration with high-resolution, relational, resonance-based electroencephalic mirroring aimed at autocalibration of neural oscillations.<sup>191</sup> Given the lack of controlled trials, high-resolution, relational, resonance-based electroencephalic mirroring is not recommended for treatment of VMS. (Level II; not recommended)

### Chiropractic intervention

There have been no clinical trials of chiropractic interventions for VMS, and epidemiologic survey data show no association between use of such interventions and VMS.<sup>192</sup> Chiropractic interventions are not recommended for treatment of VMS. (Level II; not recommended)

### Key points

- Existing evidence does not support the use of traditional acupuncture for the treatment of VMS; electroacupuncture requires more rigorous study before it can be recommended.

- Stellate ganglion blockade might alleviate moderate to very severe VMS in select women but is associated with potential risk.
- Calibration of neural oscillations and chiropractic interventions are not recommended for treatment of VMS.

## RECOMMENDATIONS

Vasomotor symptoms are common in midlife women and remain undertreated. These symptoms can disrupt a women’s overall quality of life and last a mean duration of 7 to 9 years, longer in some women. Hormone therapy remains the first-line recommended treatment to ameliorate VMS in healthy women at or around the time of menopause. However, it is important to recognize that not all women are candidates for HT because of contraindications or personal preference. This Position Statement supports the use of and recommends CBT, clinical hypnosis, SSRIs, SNRIs, gabapentin, fezolinetant (Level I); oxybutynin (Levels I-II); weight loss, stellate ganglion block (Levels II-III). There is negative or insufficient evidence for these, so they are not recommended: paced respiration (Level I); supplements/herbal remedies (Levels I-II); cooling techniques, avoiding triggers, exercise, yoga, MBI, relaxation, suvorexant, soy foods and soy extracts, soy metabolite equol, cannabinoids, acupuncture, calibration of neural oscillations (Level II), chiropractic interventions, clonidine; (Levels I-III); dietary modification and pregabalin (Level III). Clinicians should be knowledgeable of the nonhormone options supported by evidence that are available to offer to women (Table 2).

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**TABLE 2.** Treatment recommendations for nonhormone therapies for vasomotor symptoms with levels of evidence

Category	Treatment	Recommended	Not recommended
<b>Lifestyle</b>	Cooling techniques		Level II
	Avoiding triggers		Level II
	Exercise		Level II
	Yoga		Level II
	Dietary modifications		Level III
	Weight loss	Levels II-III	
<b>Mind-body techniques</b>	Cognitive-behavioral therapy	Level I	
	Mindfulness-based interventions		Level II
	Clinical hypnosis	Level I	
	Paced respiration		Level I
	Relaxation		Level II
<b>Prescription therapies</b>	SSRIs/SNRIs	Level I	
	Gabapentin	Level I	
	Pregabalin		Level III
	Clonidine		Levels I-III
	Oxybutynin	Levels I-II	
	Suvorexant		Level II
	Fezolinetant	Level I	
<b>Dietary supplements</b>	Soy foods and soy extracts		Level II
	Soy metabolites equol		Level II
	Supplements/Herbal remedies <sup>a</sup>		Levels I-III
	Cannabinoids		Level II
<b>Acupuncture, other treatments, and technologies</b>	Acupuncture		Level II
	Stellate ganglion block	Levels II-III	
	Calibration of neural oscillations		Level II
	Chiropractic intervention		Level II

Level I, good and consistent scientific evidence; Level II, limited or inconsistent scientific evidence; Level III, consensus and expert opinion.

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

<sup>a</sup>Pollen extract, ammonium succinate, *Lactobacillus acidophilus*, rhubarb, black cohosh, wild yam, dong quai, evening primrose oil, maca, ginseng, *labisia pumila/eurycoma longifolia*, chasteberry, milk thistle, omega-3 fatty acids, vitamin E.

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The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society has been designated a CME activity for all NAMS members. NAMS members should log in to the NAMS website, [www.menopause.org](http://www.menopause.org), and then select Online CME in the Member Center. CME credit will be available from June 1, 2023, to June 1, 2024.