

## Perimenopause

### Non-Hormonal Management of Vasomotor Symptoms: Evidence for Complementary or Alternative Treatments of Vasomotor Symptoms *Self-Study*

#### Contributor

Lindsay R. Standeven, MD

#### Recommended Reading

- Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. *Menopause*. 2015 Nov;22(11):1155-72; quiz 1173-4.

#### Learning Objectives

- Briefly discuss VMS and reasons women may elect or need alternative therapies.
- Gain a basic knowledge of the types of alternative therapies available and summarize the current research level, findings, and limitations.
- Learn to integrate knowledge of alternative treatments to guide and educate patients.

#### 1. What are vasomotor symptoms?

Vasomotor symptoms or “hot flashes” are the most common symptom of menopause affecting greater than three quarters of perimenopausal women. The etiology of the symptoms is not entirely clear but are believed to be caused by the decreasing levels of ovarian estrogen production on the thermoregulatory center of the hypothalamus. Hot flashes typically manifest as a sensation of heat that often starts on the chest or face and then spreads. The onset of symptoms is typically sudden, can last 2-4 minutes, and are associated with sweating, palpitation, chills, shivering and increased anxiety.

While many women use traditional therapies (discussed in module entitled, “Hormone Replacement Therapy”), approximately 50-75% of women opt for non-traditional treatment modalities. Women may elect for alternative treatments to hormone replacement therapy due to contraindications (e.g. current, past, or suspected breast cancer, estrogen-sensitive malignant conditions, endometrial hyperplasia, active liver disease, uncontrolled hypertension, and thrombophilia) and/or personal beliefs about taking prescription medications. Additionally, many women may use alternative treatment as an adjunct to traditional modalities. For this reason, it is important to have a general overview of the current treatment options and results of existing research to facilitate discussing the risk and benefits of varying treatment options with your patients.

#### 2. For a review of the levels of evidence: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3124652/>

*In summary*

Level I: Large RCTS with clear results

Level II: Small RCTs with unclear results

Level III: Cohort and Case Control Studies

Level IV: Historical cohort or case control studies

Level V: Case series, studies without controls

3. **Alternative Treatments:** (see summary tables below).

**LIFESTYLE INTERVENTION** (see table on next page)

<b>ALTERNATIVE TREATMENT</b>	<b>DESCRIPTION</b>	<b>LEVEL OF RESEARCH</b>	<b>SUMMARY OF RESEARCH</b>	<b>ADDITIONAL READING</b>
<b>COOLING TECHNIQUES</b>	Hot flashes can be triggered by increases in body temperature. Cooling techniques are used to prevent or alleviate symptoms. E.g. breathable clothing materials, dressing in layers, ice packs, fans.	Level V	No evidence to support that this either prevents nor alleviates symptoms.	None
<b>AVOIDING TRIGGERS</b>	Avoiding raising body temp, triggering foods (e.g. spicy food) and drinks (e.g. Alcohol)	Level V	No evidence to support that this either prevents nor alleviates symptoms.	Guthrie JR, Dennerstein L, Hopper JL, Burger HG. Hot flashes, menstrual status, and hormone levels in a population-based sample of midlife women. <i>Obstet Gynecol</i> 1996;88:437-442.
<b>EXERCISE</b>	Trials have included a variety of different exercises, intensities and techniques.	Level I	Multiple RCTs with insufficient evidence to show significant difference. But still of general health benefit.	Daley A, Stokes-Lampard H, Thomas A, MacArthur C. Exercise for vasomotor menopausal symptoms. <i>Cochrane Database Syst Rev</i> 2014;11:CD006108.
<b>YOGA</b>	Trials studied multiple modalities of Yoga (e.g. Iyengar, traditional Indian, Tibetan yoga) of varying length and intensities.	Level I	Multiple RCTs did not show any significant difference between peri and postmenopausal women randomized to yoga vs. control in reduction of VMS.	Newton KM, Reed SD, Guthrie KA, et al. Efficacy of yoga for VMS: a randomized controlled trial. <i>Menopause</i> 2014;21:339-346.
<b>WEIGHT LOSS</b>	Studies have varied in baseline BMI of women studied and amount of loss needed to see effect. So, the definition of “weight loss” is not consistent.	Level II	One RCT in overweight or Obese women had significant reduction in frequency of hot flashes compared to controls. Weight loss and VMS were correlated ( $r=0.47$ , $P=0.006$ ). No difference in severity of episodes.	

**MIND/BODY  
THERAPEUTIC  
INTERVENTIONS**

<b>ALTERNATIVE TREATMENT</b>	<b>DESCRIPTION</b>	<b>LEVEL OF RESEARCH</b>	<b>SUMMARY OF RESEARCH</b>	<b>ADDITIONAL READING</b>
<b>COGNITIVE BEHAVIORAL THERAPY (CBT)</b>	Study completed among women with VMS following breast cancer treatment. Group based and self-guided therapy in which participants learned paced-breathing and relaxation techniques versus controls.	Level I	<p>Two RCTs -- Significant Reduction in “problematic” hot flashes and night sweats. Improvement in QOL and mood in both self-help and group-based format compared to controls.</p> <p>Self-guided CBT as effective as Group- based CBT.</p> <p>Therapeutic effect thought to come from sense of control over symptoms.</p>	<p>Mann E, Smith M, Hellier J, Hunter MS. A randomized controlled trial of a cognitive behavioral intervention for women who have menopausal symptoms following breast cancer treatment (MENOS 1): trial protocol. BMC Cancer 2011;11:44.</p> <p>Ayers B, Smith M, Hellier J, Mann E, Hunter MS. Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flashes and night sweats (MENOS 2): a randomized controlled trial. Menopause 2012;19:749-759.</p>
<b>MINDFULNESS-BASED STRESS REDUCTION (MBSR)</b>	8-week group-based program that combines practices of meditation, body scanning and yoga.	Level II	One RCT of N=110 comparing group who received MBSR versus control. Greater reduction in intensity and problematic VMS compared to controls, but did not reach significance.	Carmody JF, Crawford S, Salmoirago-Blotcher E, Leung K, Churchill L, Olendzki N. Mindfulness training for coping with hot flashes: results of a randomized trial. Menopause 2011;18:611-620.

<b>PACED RESPIRATION</b>	Slowing breathing to 6-8 per minute with inhalations through the nose and exhalations out of the mouth.	Level I	Two RCTs showed no difference in VMS.	<p>Carpenter JS, Burns DS, Wu J, et al. Paced respiration for vasomotor and other menopausal symptoms: a randomized, controlled trial. J Gen Intern Med 2013;28:193-200.</p> <p>Sood R, Sood A, Wolf SL, et al. Paced breathing compared with usual breathing for hot flashes. Menopause 2013;20:179-184.</p>
<b>RELAXATION</b>	Trials included a variety of relaxation techniques, including: progressive relaxation, release-only relaxation, and cue-controlled relaxation	Level II	Small RCTs and studies show no significant benefit between relaxation and placebo, acupuncture, superficial needle insertion or paced respiration. Two of main RCTs occurred in women with cancer and treatment-induced symptoms.	<p>Saensak S, Vutyavanich T, Somboonporn W, Srisurapanont M. Relaxation for perimenopausal and postmenopausal symptoms. Cochrane Database Syst Rev 2014;7:CD008582.</p> <p>Lindh-A °strand L, Nedstrand E. Effects of applied relaxation on VMS in postmenopausal women: a randomized controlled trial. Menopause 2013;20:401-408.</p>

<b>HYPNOSIS</b>	Clinical hypnosis involves induction of a deep relaxation state and altered state of awareness using imagery techniques that has been previously studied in pain and anxiety treatment.	Level I	Two RCTs – Elkins et al., (2013) N=187 showed significant reduction in VMS frequency (mean: 55.82 hot flashes/week for the clinical hypnosis intervention versus a 12.89 for the control -- $p < .001$ , 95% CI, 36.15–49.67) at study completion. Results maintained at 12-week follow-up.	Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ. Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. <i>Menopause</i> 2013;20:291-298.
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ALTERNATIVE TREATMENT	DESCRIPTION	LEVEL OF RESEARCH	SUMMARY OF RESEARCH	ADDITIONAL READING
<b>ISOFLAVONE-PHYTOESTROGEN CONTAINING FOODS</b>	Isoflavones and phytoestrogens are compounds naturally occurring in many plants, fruits and vegetables (most notably Soy) that possess estrogen agonist and antagonist properties.	Level II	RCTs and Studies have shown no significant difference between soy isoflavones and controls on VMS. Study designs and interpretation have been limited by manufacturing variability resulting in inconsistent levels of isoflavones and phytoestrogens across products.	Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for menopausal VMS. Cochrane Database Syst Rev 2013;12:CD001395.
	Genistein and daidzein are found in high amounts in soybeans and soy products (though quantity depends of processing). Daidzein can be converted to Equol (estrogen agonist) by 30% of US women.			Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. Ann Intern Med 2002;137:805-813.
<b>BLACK COHOSH (ACTAEA RACE- MOSA)</b>	Most commonly purchased herbal supplement for VMS. Unclear biological mechanism. Some evidence to support estrogen receptor	Level I	Cochrane review of 16 RCTs showed no significant different in patients taking Black Cohosh at average dose of 40mg compared to controls.	Chen MN, Lin CC, Liu CF. Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. Climacteric 2015;18:260-269.

modulation. Reports of  
Hepatotoxicity.

hormone replacement  
therapy? Maturitas  
2003;44 (suppl 1):S9-  
S20.

Leach MJ, Moore V.  
Black cohosh  
(Cimicifuga spp.) for  
menopausal symptoms.  
Cochrane Database Syst  
Rev 2012;9:CD007244.

**DONG QUAI**

**(AKA: *ANGELICA SINENSIS*)**

Used to balance female  
hormones and for  
gynecologic complaints in  
traditional Chinese medicine.  
Human studies have not  
found any evidence  
supporting any estrogenic  
properties.

Level I

Cochrane review of 22 RCTs showed  
no significant difference in Chinese  
herbal medicines compared to control.  
Effects on safety were inconclusive,  
but prior studies raised concern for  
photosensitization, anticoagulation,  
and carcinogenicity. Adverse effects  
reported include: diarrhea, breast  
tenderness, GI upset and bad taste.

Zhu X, Liew Y, Liu ZL.  
Chinese herbal medicine  
for menopausal  
symptoms. Cochrane  
Database Syst Rev.  
2016;3:CD009023. Epub  
2016 Mar 15.

**DIETARY SUPPLEMENTS AND (SELECTED) HERBAL THERAPIES:**

**\*\* For a more comprehensive list of herbal remedies used by women for treatment of VMS, see recommended reading**



## PHARMACOLOGICAL INTERVENTIONS

ALTERNATIVE TREATMENT	DESCRIPTION	LEVEL OF RESEARCH	SUMMARY OF RESEARCH	ADDITIONAL READING
<b>GABAPENTIN</b>	Anti-epileptic medication -- FDA approved for peripheral neuropathy and postherpetic neuralgia.	Level I	RCTs using Gabapentin at 900mg (300mg TID) significant improved frequency of VMS. One-time dose of 300mg PO QHS used to treat night sweats. At higher doses (2,400mg) was found to be equivalent to HRT in reduction of VMS, but poor tolerability.	<p>Hayes LP, Carroll DG, Kelley KW. Use of gabapentin for the management of natural or surgical menopausal hot flashes. <i>Ann Pharmacother</i> 2011;45:388-394.</p> <p>Guttuso T Jr, Kurlan R, McDermott MP, Kieburtz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. <i>Obstet Gynecol.</i> 2003 Feb;101(2):337-45. PubMed PMID: 12576259.</p>
<b>PREGABALIN</b>	Gabapentinoid and used to treat seizures, neuropathic pain, and fibromyalgia.	Level II	One RCT showed significant decreases in VMS and tolerated at target doses of 75mg BID.	Loprinzi CL, Qin R, Balcueva EP, Flynn KA, Rowland KM Jr, Graham DL, Erwin NK, Dakhil SR, Jurgens DJ, Burger KN. Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for alleviating hot flashes, N07C1. <i>J Clin</i>

Oncol. 2010;28(4):641.  
Epub 2009 Nov 9.

**CLONIDINE**

$\alpha$ 2 adrenergic agonists.

Level II

Moderate improvement in VMS, but not as effective as SSRIs, SNRIs and Gabapentin. Not used as frequently due to adverse side effects.

Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, Nicolaidis C, Walker M, Humphrey L. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA. 2006;295(17):2057.

**OTHER THERAPIES**

ALTERNATIVE TREATMENT	DESCRIPTION	LEVEL OF RESEARCH	SUMMARY OF RESEARCH	ADDITIONAL READING
<b>ACUPUNCTURE</b>	Among the most frequently used alternative therapies. Based on Chinese tradition of inserting thin needles superficially into select areas to balance energy or <i>chi</i> .	Level I	Systematic and Cochrane Reviews are mixed – some evidence that acupuncture reduced VMS compared to wait-list controls. However, when acupuncture is compared to sham acupuncture (insertion of needles at non-therapeutic sites), there is no significant difference.	<p>Dodin S, Blanchet C, Marc I, et al. Acupuncture for menopausal hot flushes. <i>Cochrane Database Syst Rev</i> 2013;7:CD007410.</p> <p>Ee C, Xue C, Chondros P, Myers SP, French SD, Teede H, Pirotta M. Acupuncture for Menopausal Hot Flashes: A Randomized Trial. <i>Ann Intern Med.</i> 2016;164(3):146. Epub 2016 Jan 19.</p>
<b>STELLATE GANGLION BLOCK</b>	Injection of local anesthetic at the C6 level to block nerves of the stellate ganglion (bilateral nerve group from C6-T2). Exact utility in reducing VMS is unknown.	Level II	Four uncontrolled, open label studies showed reduction in symptoms ranging from 45-90% after blockade. One randomized sham-control study, showed significant reduction in frequency of moderate to severe VMS symptoms, but no significant overall change between groups.	<p>Walega DR, Rubin LH, Banuvar S, Shulman LP, Maki PM. Effects of stellate ganglion block on VMS: findings from a randomized controlled clinical trial in postmenopausal women. <i>Menopause</i> 2014;21: 807-814.</p> <p>Lipov EG, Joshi JR, Xie H, Slavin KV. Updated findings on the effects of stellate-ganglion block on hot flushes and night awakenings. <i>Lancet Oncol</i> 2008;9:819-820.</p>

<b>CALIBRATION OF NEURAL OSCILLATIONS</b>	High resolution, relational, resonance-based electro-encephalic mirroring (HIRREM) is a non-invasive technique in which electroencephalic data is collected and a series of musical tones are delivered to permit auto-calibration and “greater hemispheric symmetry”.	Level III	Insufficient data to recommend.	Gerdes L, Gerdes P, Lee SW, H Tegeler C. HIRREM™: a noninvasive, allostatic methodology for relaxation and auto-calibration of neural oscillations. Brain Behav. 2013 Mar;3(2):193-205.
<b>CHIROPRACTIC INTERVENTION</b>		Level III	No studies to date.	None

#### 4. Case Study

Ms. M is a 48-year-old woman who presents to your office reporting hot flashes and night sweats that are interfering with her ability to complete work projects and wake her from sleep. Her gynecologist referred her to you for concern of depressed mood. On evaluation, she denies mood symptoms, does not have any psychiatric history and does not currently meet criteria for an affective disorder. She is not a candidate for HRT as her mother died of breast cancer and she herself had a double mastectomy for suspected estrogen-sensitive mass found in breast. Ms. M is not interested in “taking pills” because she has “always disliked medications”. She wants to know if there are alternative treatments the doctor would recommend to help alleviate the hot flashes during the day and at night? In particular she is interested in learning whether it is true that exercise, weight loss, and Black Cohosh could be helpful in alleviating her VMS. Her current BMI is 33.

*How would you respond to the patient regarding the currently guidelines for Exercise and the evidence that it can reduce VMS?*

ANS: Will not discourage exercise but there is no evidence that exercise itself reduces VMS. There are many other good reasons to recommend exercise including sleep regulation, appetite regulation and mood treatment.

*How would you respond to the patient regarding the current guidelines for weight loss and the evidence that it can reduce VMS?*

ANS: The data on the efficacy of weight loss for relief of VMS have been mixed and have included women with different BMIs. The only study to date that shower a reduction in the number of vasomotor symptoms was among obese women. It is not known whether women with normal to overweight BMIs will have significant reductions. However, there are may be other health related reasons that the patient

can consider weight loss, but a detailed discussion about proper nutrition (ensuring sufficient calcium) will be important. Recommended with caution, some evidence to support.

*How would you respond to the patient regarding the currently guidelines for Black Cohosh? Herbal Supplements in general?*

ANS: There have been very detailed and well controlled studies evaluating Black Cohosh for the relief of VMS. None of the studies have found any significant reduction in symptoms among women taking Black Cohosh. Additionally, because Black Cohosh and other herbal supplements are not FDA regulated, the doses and compositions of the pills sold can vary widely – risks include spending money on essentially unknown product and/or serious side effects. In the case of Black Cohosh, there is some evidence suggesting it may cause hepatotoxicity.

*What might you recommend for this patient who is not interested in medications?*

ANS: CBT or Clinical Hypnosis have shown the most robust and clinically significant effects.

### Summary of Current Recommendations

(\*adopted from NAMS 2015 Position Statement)

<b>Recommend</b> (Evidence to support and low risk)	<b>Recommend with Caution</b> (some evidence to support)	<b>Do not Recommend</b> (no evidence to support efficacy in relieving or preventing VMS)
Cognitive Behavioral Therapy	Weight loss	Cooling Techniques
Hypnosis	Mindfulness	Avoiding Triggers
SSRIs/SNRIs	S-equol/Soy derivatives	Exercise
Gabapentin	Stellate ganglion Block	Yoga
Pregabalin		Paced Breathing

Clonidine		Relaxation
		Herbal Supplements
		Acupuncture
		Neural Oscillation Calibration
		Chiropractic work