Treatment of Vasomotor Symptoms

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Vasomotor symptoms (VMS) related to the menopausal transition affect the majority of women and contribute to significant quality of life burden. Incidence, length, severity and report of symptoms vary by race, ethnicity, and coexisting health conditions. The pathophysiology of VMS is not fully understood and is likely multifactorial, involving changes in the hypothalamicpituitary-ovarian axis during the menopausal transition. Treatment approaches include lifestyle modifications, hormonal and non-hormonal therapies, including integrative and complementary medicine approaches. Systemic hormone therapy with estrogen is the most effective treatment. Emerging evidence suggests that treatment with SSRIs, SNRIs, and gabapentin is effective for many women who want to avoid hormone therapy. A shared decision approach to treatment decisions involves consideration of risks with treatment options and discussion of patient priorities. (J Am Board Fam Med 2024;37:923–932.)

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Epidemiology

Vasomotor symptoms (VMS), namely hot flashes and night sweats, are the hallmark symptoms of the menopausal transition. These symptoms, characterized by brief (1 to 5 minute) episodes of increased heat and flushing in the upper body, are often accompanied by elevations in heart rate and anxiety followed by a rapid descent of core body temperature and sweating. VMS impact up to 80% of perimenopausal and menopausal women, however fewer than 30% are treated.

The median duration of VMS is 7.4 years, while some women may experience moderate to severe symptoms for as many as 10 years.[1,2] Racial and ethnic variations in the duration of symptoms have been observed. African American women have the greatest prevalence of VMS, and experience a longer duration of symptoms (10.1 year) compared with White women (6.5 years).[1–4] The median duration of symptoms for other ethnic groups is as follows: Hispanic women 8.9 years, Chinese women 5.4 years, and Japanese women 4.8 years. The majority of women rate their VMS as moderate to severe.[5] Those who have had a hysterectomy, irrespective of ovarian preservation, are more likely to experience vasomotor symptoms. Symptoms are also more likely to be experienced by those undergoing breast cancer treatment and those who undergo oophorectomy.[5] Women who smoke, have low income and/or low educational attainment and those who experience mood disorders or obesity have a higher prevalence of VMS.[6]

The impact of VMS is significant and extends beyond quality of life or comfort issues. Accumulating evidence suggests that VMS may be associated with an increased future risk of several chronic diseases, including metabolic syndrome, increased biomarkers for cardiovascular disease, type 2 diabetes mellitus, nonalcoholic fatty liver disease, and osteoporosis in perimenopausal and postmenopausal women.[7–9] These findings suggest that VMS may be markers of impaired cardiometabolic conditions rather than just transient symptoms associated with menopause.[10] However, causal pathways have not been established. VMS are also associated with sleep and mood disturbances, impaired cognitive function, loss of work productivity and increase health care cost and utilization.[1,8]

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VMS are the primary driver for seeking medical attention for menopause-related symptoms.[11] Compared with non-Hispanic white women, Black and Hispanic women are more likely and Asian women are less likely to report symptoms. However, African American women are less likely to be treated for VMS.[12] While the reasons for reporting differences are not fully understood, they likely result from a combination of factors including lifestyle, genetics, psychosocial, cultural, and personal perceptions.[1,12]

Pathophysiology

The pathophysiology of VMS is not fully understood. The causes of symptoms are likely multifactorial and involve changes in the hypothalamic-pituitary-ovarian axis during the menopausal transition. Declining estrogen levels from the aging ovaries and a narrowing of the hypothalamic thermoregulatory zone that is more sensitive to changes in body temperatures, likely trigger hot flashes. Emerging evidence suggests that estrogen sensitive hypothalamic neurons containing estrogen-sensitive neuropeptides may contribute to the thermoregulatory dysfunction of VMS via their role in controlling the release of GnRH.[12–13] Deficient estrogen levels result in unopposed and increased activation of neurons that signal.[12,13] the hypothalamic thermoregulatory control center. This results in activation of heat dissipation mechanisms, vasodilation and sweating, experienced as VMS.

Case example: Barbara is a 52-year-old African American woman who presents with complaints of hot flashes up to 10 times a day and night sweats. She describes waking up 3 to 4 times at night and feels exhausted. She asks you whether there is anything to treat her symptoms. Her last menstrual period was 6 months ago.

Pharmacologic Treatment

Both hormonal and nonhormonal treatments are options for moderate or severe VMS symptoms.[15] Systemic hormonal therapy with estrogen is the most effective option available. For those with an intact uterus, progestogen should be added to prevent endometrial hyperplasia or cancer.[14] Despite increasing evidence of the safety of hormonal therapy for vasomotor symptoms over the past 20 years, utilization of this effective treatment option remains low following the release of the Women's Health Initiative (WHI) results.[16] Recent updates to recommendations demonstrate that used in the appropriate patients, hormone therapy can be effective and safe.[14] The North American Menopause Society's 2022 position statement on hormone therapy informed by recent evidence suggests that for women who are within 10 years of their final menstrual period and/or those under age 60 without contraindications, it is safe to initiate hormone therapy.[14] Follow up studies from the WHI found that women 50 to 59 years did not have an increase in all-cause, Cardiovascular Disease (CVD) or cancer mortality after 18 years of cumulative follow up.[16] Similarly, women treated with conjugate estrogen alone for a median of 7.2 years maintained a significantly reduced risk breast cancer mortality, while those treated with conjugated equine estrogen (CEE) and medroxyprogesterone acetate for 5.6 years only had a slightly increased, but not statistically significant increased breast cancer mortality risk after 18 years of follow up.[17]

Estrogen therapy should be prescribed at the lowest effective dose for an adequate time to relieve symptoms.[14] Oral and transdermal estrogens seem to be equally effective. FDA approved hormone formulations can be found in Tables 1 and 2. The table notes bioidentical options. Bioidentical hormones are synthetic formulations that exactly mimic the hormones found in the body. Conjugated equine estrogen is derived from the urine of pregnant mares and is a hormone not found in the human body. "Natural" hormones are derived from plants. The levonorgestrel Intrauterine Device (IUD) has been used in women who want to avoid systemic progestins.[14] A newer product that combines conjugated equine estrogen with bazedoxifene, a selective estrogen receptor modulator, is approved for the treatment of VMS and osteoporosis and can provide endometrial protection without systemic progestins.[17] Compounded hormonal preparations should be used with caution as they are not standardized or monitored for safety.[14] Although bioidentical hormone therapy is synthesized to be identical to hormones produced naturally, there is no evidence that it is safer or more effective than other hormone therapy.[14]

Case cont. Barbara is otherwise healthy. She has no history of HTN, CAD, VTE or breast cancer. She has no family history of breast cancer. You discuss options of hormone therapy and include potential risks and benefits. She elects to start on an estrogen patch and an oral progestin.

Table 1. Hormonal Treatments of Vasomotor Symptoms

Medication	Formulation	Dose (mg)
Estrogen		
Conjugated equine estrogen	Oral	0.3, 0.45, 0.625, 0.9, 1.25 (per day)
Estradiol*	Oral	
	Transdermal patch**	0.025, 0.0375, 0.05, 0.075, 0.1 (1 to 2 times per week
	Transdermal gel	0.25, 0.5, 0.75, 1.0 (per day)
	Transdermal spray	1.53 mg per spray (1 to 3 sprays per day)
Progestin		
Medroxyprogesterone acetate	Oral	2.5, 5, 10 mg (dosed once a day; can also be dosed for 10 to 15 days a month)
Norethindrone acetate	Oral (as part of a combination product)	
Levonorgestrel	Patch** (as part of a combination product)	
	Progestin IUD (not FDA approved for postmenopausal women)	
Micronized progesterone*	Oral	100 mg twice a day (may also be dosed at 100 mg or 200 mg daily; can also be dosed for 15 days a month; only FDA approved for cyclic use)

*Bioidentical (synthetic hormone that exactly mimics the hormones in the body).
**Patches can be nonadherent.
Abbreviations: IUD, Intrauterine Device; FDA, Food and Drug Administration.

Relief of symptoms is expected in 8 to 12 weeks with hormone therapy.[14] Patients should be advised that breast tenderness or vaginal bleeding may be expected after the initiation of hormone therapy. If symptoms persist beyond 3 months further evaluation should be considered. Patients should be evaluated for the presence of symptoms and treatment effectiveness at least annually once a stable regimen is achieved.[15]

Case (cont). Barbara's sister Betty comes to see you for the same complaint as Barbara. Her VMS are quite bothersome, having severe hot flashes up to 10 times a day. Betty was recently diagnosed with hormone receptor positive breast cancer so cannot take systemic hormone therapy. How would you treat Betty?

Discontinuation of Hormone Therapy

The decision to continue or discontinue hormone therapy should be a shared decision made between the patient and the clinician with consideration of ongoing symptoms, benefits of treatment, and risks of ongoing therapy.[18]

There is no absolute age or length of treatment at which hormone therapy should be stopped,[14] despite Beers Criteria suggesting that hormone therapy should be discontinued at age 65. As many as 10% of women in their 60 seconds and 2 to 5% of 70-year-olds continue to experience bothersome vasomotor symptoms.[19,20] There is no recommendation as to how to discontinue hormone therapy as studies have not shown a difference in recurrence of symptoms in patients who abruptly discontinue versus gradually taper hormone therapy.[18] Patients should be counseled that 50% of women will experience a temporary recurrence of vasomotor symptoms regardless of the discontinuation method chosen.[18]

Contraindications to Hormone Therapy and Approach to the High-Risk Patient

When considering treatment of VMS, clinicians must consider a patient's medical and family history to best determine treatment options.[14,18,21] Clinicians should consider nonhormonal treatment options for patients who have absolute contraindications to hormone therapy. Hormone therapy increases the risk of cardiovascular events and breast cancer.[14]

Breast Cancer and Other Hormone-Sensitive Malignancies

Systemic hormone therapy is almost always contraindicated in patients with a personal history of breast cancer, although 2022 North American Menopause Society (NAMS) position statement offers that for patients with severe VMS refractory to nonhormonal options, one can consider hormone therapy after consultation with the oncology team.[14] Hormone

Table 2. Combination Hormonal Products

	Estrogen Component	Progestin Component
Oral		
	Conjugated equine estrogen (0.3, 0.45, 0.625 mg)	Medroxyprogesterone acetate (1.5, 2.5, 5 mg)
	Ethinyl estradiol (2.5, 5 mcg)	Norethindrone (0.5, 1 mg)
	17 Beta Estradiol (0.5, 1 mg)	Norethindrone (0.5 mg)
	17 Beta Estradiol (0.25, 0.5 mg)	Drosperinone (0.5, 1.0 mg)
Transdermal		
	17 Beta estradiol (0.045, 0.05 mcg)	Levonorgestrel (0.014, 0.015 mcg)
	Conjugated equine estrogen (0.45 mg)	Bazedoxifene (20 mg)*

*Systemic estrogen reuptake inhibitor.

therapy may be considered for patients with a history of some gynecologic cancers such as low-grade endometrial cancer following surgical treatment, however it should be noted that hormone therapy is contraindicated in all endometrial cancers before surgical treatment. Hormone therapy should be avoided in patients with histories of high grade or advanced stage endometrial cancers or other estrogen-dependent tumors.[21,23,24]

Patients with known Breast Cancer gene (BRCA) ½ mutations who experience premature or early menopause as a result of bilateral oophorectomy can also be safely treated with hormone therapy.[15,26] Women who are at high risk, but without a personal history of breast cancer, may consider Hormone Therapy (HT). Risk assessment tools such as the National Cancer Institute Breast Cancer Risk Assessment Tool (Gail model) or the International Breast Intervention Study Calculator (Tyrer-Cuzick model) may be used to establish a patient's 5 or 10-year risk of invasive breast cancer and stratify their overall risk.[18] Clinical guidelines support shared-decision making with consideration of an individual's prognostic indicators, benefits, and risks of estrogen therapy.[21] Family history of breast cancer alone is not a contraindication to hormone therapy as observational studies have not demonstrated increased incidence of breast cancer with hormone therapy in these patients.[15]

Venous Thromboembolism (VTE)

Hormone therapy is generally contraindicated and should be avoided in patients with a personal history of VTE.[21,26,27] Transdermal estrogens have the advantage of avoiding the first pass effect in the liver, and in observational studies are associated with less risk of venous thromboemboli.[28] A meta-analysis of 5 observational studies demonstrated a RR of 1.9 for VTE in women on oral estrogen as compared with a RR of 1.0 in women using transdermal estrogen.[28] Another meta-analysis confirmed these results.[29] Personal and familial risk of VTE should be considered when initiating hormone therapy.[14] There is no consensus recommendation for treatment of patients who are considered at increased risk of VTE (patients with a clotting disorder, family history of VTE, etc), though presence of underlying thrombophilia should be considered a relative contraindication.[18,30,31] Nonhormonal therapies are generally preferred in patients with increased risk of VTE, however for refractory symptoms, transdermal or intravaginal preparations of estrogen and coagulation-neutral progestogens and adequate anticoagulation may mitigate VTE risk.[30]

Coronary Artery Disease, Hypertension, Stroke

For healthy women who initiate hormone therapy before the age of 60 and are within 10 years of

Table 3. Hormone Therapy and Risk of Co-morbidities[22]

	No HT	HT
Risk of MI	2/1000	3 to 7/1000 (after 1 year of HT use)
Risk of VTE	2/1000	4 to 11/1000 (after 1 year of use)
Risk of CVA	6/1000	6 to 12/1000 (after 3 years of use)
Risk of breast cancer	19/1000	20 to 30/1000 (after 5.6 years of use)

*Based on data from 43,637 post-menopausal American women.
**Data may vary based on type of formulation and mode of delivery of HT.
Abbreviations: VTE, Venous Thromboembolism; MI, Myocardial Infarction; CVA, Cerebrovascular Accident

menopause, the benefits of hormone therapy outweigh the risks of cardiovascular disease.[14] For women older than age 60 or who are greater than 10 years from menopause, the absolute risk of cardiovascular disease is higher.[19] The Endocrine Society recommends evaluating a patient's 10-year CVD risk using the ACC/AHA calculator and age since menopause to determine an individual patient's appropriateness for hormone therapy.[19] Transdermal options are preferred for women at moderate (5 to 10%) risk of CVD and nonhormonal options are recommended for those at high risk (>10%).[18] Diabetes, smoking, hypertension, obesity, limited mobility, autoimmune disease, hyperlipidemia, and metabolic syndrome confer intermediate risk for hormone therapy.[30] Due to an increased risk of stroke, uncontrolled hypertension (>180/110) is a relative contraindication to initiating hormone therapy and blood pressure should be under control before consideration for hormone therapy.[31] Ischemic stroke is a contraindication to hormone therapy.[30]

Resources for Assessing Risk Factors

- ASCVD Risk Estimator Plus: Available at: https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/
- IBIS Breast Cancer Risk Evaluation Tool: Available at: https://ibis-risk-calculator.magview.com
- Breast Cancer Risk Assessment Tool (Gail model): Available at: https://bcrisktool.cancer.gov/calculator.html

Nonhormonal Treatments of Vasomotor Symptoms

For women with contraindications to hormone therapy or who prefer to try nonhormonal treatment, many options are available (Table 4).[32–34] Vasomotor symptoms are thought to be due to central thermoregulatory dysfunction in the hypothalamus.[12] Norepinephrine is a neurotransmitter that is involved in adjusting the thermoregulatory set point. SSRIs and SNRIs may be effective in treatment of VMS due to their effect on norepinephrine.[25] Paroxetine was the first FDA approved, nonhormonal treatment of vasomotor symptoms but should not be used in people taking tamoxifen.[36] Gabapentin binds to calcium channels in the hypothalamus and can potentially widen the thermoregulatory zone.[37] Gabapentin has been shown to be effective for treatment of hot flashes, but data on pregabalin is not as robust.[38,39] Some data suggests that not all SSRIs or SNRIs are equally effective.[35,39] Systematic reviews demonstrate that escitalopram, paroxetine, and fluoxetine are most effective.[35,39] Fezolinetant is the first neurokinin 3 Receptor Antagonists that is FDA approved for the treatment of vasomotor symptoms.[40] Fezolinetant was

Table 4. Nonhormonal Treatments of Vasomotor Symptoms

Medication	SOR	Comments
SSRIs[36,37]	A (Systematic review and meta-analysis)	• Paroxetine is the only nonhormonal medication approved by the FDA for hot flashes. • Paroxetine should not be used in people taking tamoxifen • Systematic review suggests that escitalopram is superior to other SSRIs[36] • Another systematic review documented the benefit of escitalopram, paroxetine, and fluoxetine over other SSRIs[40] • May be limited by side effects
SNRIs[40]	A (systematic review and meta-analysis)	• Good evidence for the benefit of venlafaxine and desvenlafaxine. Not enough studies to evaluate benefit of duloxetine.[40,44]
Fezolinetant[41] (Neurokinin receptor antagonist)	A (systematic review and meta-analysis)	Fair evidence for benefit over placebo. Most studies were small but showed no significant adverse effects.
Gabapentin[38]	A (systematic review)	• Good evidence for gabapentin, but not enough studies on pregabalin.[35,38] • May be limited by side effects • Effective dose not clear
Clonidine[34,35]	B (randomized controlled trials)	• Limited by side effects

Abbreviations: SSRIs, Selective Serotonin Reuptake Inhibitors; SNRIs, Serotonin-Norepinephrine Reuptake Inhibitors; FDA, Food and Drug Administration

Table 5. Complementary Treatments for Vasomotor Symptoms

Intervention	Efficacy	Precautions	Notes
Black Cohosh *Cimicifuga acemose*	Possibly effective[49,50,51]	Rare but potential liver toxicity; consider monitoring liver enzymes or avoiding in liver disease; Estrogen receptor stimulation seems unlikely,[52,53] but not definitively safe in high risk hormone responsive cancers	Common dose is 20-40 mg twice daily of a standardized extract; Possible SERM-like activity; also thought to have anti-inflammatory and SSRI activity leading to potential to also help with aches/pains and mood related to perimenopause[54]
Soy *Glycine max*	Possibly effective[59,60]	Phytoestrogen	Products that contain at 15 mg-30 mg of the soy isoflavone genistein more consistently effective[61]; Genistein content in foods: ½ c miso—32 mg 3 oz uncooked tempeh: 30.7 mg 3 oz cooked tempeh: 18 mg 1 oz dry roasted soybeans: 21.2 mg 3 oz soft tofu: 10.1 mg ½ cup edamame: 6.3 mg 1 cup low fat soy milk: 3.7mg[62]
Siberian Rhubarb *Rheum rhaponticum*	Possibly effective[55]	Use root; leaf can be toxic May activate estrogen receptor beta, but not alpha	Studied dose is 4 mg of a dried extract, once daily. May also help with anxiety, sleep, mood, quality of life, fatigue
Sage *Salvia officinalis*	Possibly effective[56,57]	Recognized as a food In very high doses may be toxic due to thujone constituent[58]; alcohol extracts have higher thujone content than water infusions (tea); Possibly weak estrogen activity	Consider 1tsp of dried sage 2 to 3 x daily steeped in 1 cup near-boiling water for 7 to 10 minutes then strained
Red Clover *Trifolium pratense*	Insufficient reliable evidence[63,64]	Phytoestrogen	80 mg of dried leaves and 80 mg of standardized extract have both been studied
Yoga	Possibly effective[65,66]	Caution in patients with hypermobility syndromes or osteoporosis	May also help with psychological symptoms; practices that include meditation and breathwork may be better than hot yoga
Acupuncture	Insufficient reliable evidence[67,68]		Improves VMS over no treatment, but not over sham acupuncture (debate over "sham" acupuncture as true control is problematic in acupuncture literature in general) May be an appropriate adjunct to improve overall quality of life
Hypnosis	Likely effective[69]	Use with caution or avoid in those with history of trauma or abuse and with active psychosis	Professionals trained in clinical hypnosis can be found at: Available at: https://www.asch.net/aws/ASCH/pt/sp/find-member
Mindfulness, CBT, behavior therapies	Possibly effective[70,71]		Therapies may decrease negative experience or interference of hot flashes but not necessarily frequency. A specific protocol CBT for menopausal symptoms (CBT-Meno) may be more efficacious (study compared to waitlist).

Abbreviations: SERM, Selective Estrogen Receptor Modulator; SSRI, Selective Serotonin Reuptake Inhibitor; VMS, Vasomotor Symptoms; CBT, Cognitive Behavioral Therapy.

Table 6. Practice Recommendations

	SORT
Estrogen containing hormone therapy is the most effective treatment for vasomotor symptoms (VMS).	A
Paroxetine and fezolinetant are the only FDA approved nonhormonal medications for the treatment of VMS and are better than placebo	A
Shared Decision Making that considers the benefits and risks of further hormone therapy should be utilized when considering discontinuation of hormone therapy for treatment of VMS.	C
SSRIs, SNRIs, and gabapentin are effective therapies for VMS.	A

Abbreviations: SSRI, Selective Serotonin Reuptake Inhibitor; VMS, Vasomotor Symptoms; SNRI, Serotonin-Norepinephrine Reuptake Inhibitor; FDA, Food and Drug Administration

better than placebo at 2 doses (30 and 45 mg) in the treatment of VMS.[42,43] (Table 3)

Integrative Approach to Managing VMS

For many women who do not have significant discomfort with VMS, simple lifestyle modifications may improve symptoms. Wearing layers, avoiding individual triggers such as hot and spicy foods, alcohol, hot tubs or saunas may decrease frequency or severity of symptoms.[42] There is insufficient evidence to recommend exercise for treatment of VMS.[45]

A number of herbs and complementary modalities have been studied for treatment of vasomotor symptoms, though data to support these methods is limited (Table 5). The strongest evidence of benefit is for hypnosis, black cohosh and soy. Hypnosis is initially facilitated by a trained professional followed by independent hypnosis with personalized guided recordings. Many black cohosh products use a standardized extract, but capsules of the crude herb in doses of 40 to 200 mg daily have also been used. A Cochrane review found insufficient evidence to support the use of phytoestrogens in treatment of VMS.[47] However, use of soy products is very common and can be a part of a healthy diet. Soy is best consumed in whole foods but if supplements are used, content of the isoflavone genistein should be at least 15 to 30 mg daily. When using herbs or supplements, it is always a good practice to find a high-quality product.[47]

An integrative approach to health and wellness during the menopausal transition does not isolate individual interventions but looks at the entirety of individual's life and health goals. For perimenopausal women, this would include conversation not just about an isolated herb, but also larger discussions about nutrition, exercise, stress management, sleep, and attitudes about entering the next phase of life (Table 6).

Case (cont.): Betty decides to start with some integrative approaches to treat her vasomotor symptoms. She starts with CBT and hypnosis and adds black cohosh. You discuss the use of an SSRI (other than paroxetine since she is on tamoxifen) if these interventions do not help with her symptoms.

Betty comes back to see you 3 months later and reports that CBT, hypnosis and black cohosh have been partially effective for her VMS, but she is still not sleeping well and has increased anxiety. You start her on venlafaxine and suggest that she discontinue black cohosh, but continue with CBT and hypnosis. You see her back in 2 months and she states that the venlafaxine is working very well. You continue on the same dose and schedule a follow up in 6 months.

Conclusion

VMS are common in perimenopausal and menopausal women. Estrogen containing hormone therapy is the most effective treatment of VMS, but other prescription medications and complementary therapies may be helpful. A shared decision making approach to treatment decisions involves risks of the treatment option and discussion of patient priorities.

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