REVIEW

CME MOC

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Nonhormone therapies for vasomotor symptom management

ABSTRACT

Vasomotor symptoms (VMS) are associated with adverse health consequences and can cause significant morbidity for postmenopausal women. Although hormone therapy remains the gold standard of VMS treatment in menopausal women, some women have contraindications to or may choose not to take hormone therapy. This article provides an up-to-date overview of the current evidence-based nonhormone therapies available for managing VMS. Evidence supporting various treatment options is reviewed, including lifestyle interventions, mind-body therapies, procedures, pharmacologic agents, and emerging therapies, such as neurokinin-receptor antagonists. The efficacy, safety, and clinical use of these treatments are detailed, offering insights for clinicians to make informed decisions in menopausal VMS management.

KEY POINTS

- VMS in menopausal women can lead to adverse health outcomes.
- Many complementary and alternative therapies for treating VMS lack strong scientific evidence.
- Nonhormone pharmacologic agents including some selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors, gabapentin, and oxybutynin are commonly used and effective for VMS treatment.
- Fezolinetant, a VMS medication newly approved by the US Food and Drug Administration, is a neurokinin-receptor antagonist that reduces hot flashes by modulating kisspeptin, neurokinin B, and dynorphin neurons in the hypothalamus.

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Vasomotor symptoms (VMS), more commonly known as hot flushes or flashes and night sweats, are the cardinal symptoms of menopause, occurring in up to 80% of postmenopausal women.[1,2] Apart from being disruptive and bothersome, VMS may independently have adverse health consequences associated with cardiovascular and metabolic changes, including increased carotid intima thickness, increased carotid and aortic calcifications, worsening lipid profiles, increased insulin resistance, and increased risk of hypertension.[3–6] Additionally, VMS have been linked to decreased bone mineral density and increased fracture incidence.[7,8]

Although hormone therapy is considered the gold standard of treatment of VMS in menopausal women, a woman may not want, or may not be a candidate (**Table 1**), to take hormone therapy for several reasons. Thus, it is important that nonhormone treatment options be made available to control symptoms, either alone or in combination with hormone therapy.

This review details various nonhormone therapies, both currently available and on the horizon, for menopausal VMS, with an emphasis on the appropriate clinical utilization, efficacy, and safety of pharmacologic agents.

NONPRESCRIPTION, COMPLEMENTARY, AND ALTERNATIVE THERAPIES

Use of complementary and alternative therapies for management of menopausal symptoms has increased over the past few decades, but concerns regarding their safety and effectiveness persist. Evidence regarding complementary and alternative therapies is often lacking, as

TABLE 1
Contraindications to hormone therapy

Contraindications	Pertinent considerations
Prior history of coronary heart disease, stroke, myocardial infarction, or unprovoked venous thromboembolism or inherited high risk of thromboembolic disease, or significantly high risk for cardiovascular disease	Relative contraindication: hormone therapy can be considered on a case-by-case basis
Unexplained vaginal bleeding	Relative contraindication: unexplained vaginal bleeding should be evaluated before hormone therapy is considered
End-stage liver disease	Relative contraindication: hormone therapy can be considered on a case-by-case basis
Prior history of estrogen-receptor-positive cancer	Absolute contraindication

many studies of these therapies have methodological deficiencies. Additionally, there are few randomized, sham, or placebo-controlled trials, which are critical in the appraisal of these therapies given the preponderance of data suggesting that placebo interventions improve VMS.[9]

The Menopause Society, formerly known as the North American Menopause Society, recommends certain evidence-based lifestyle interventions, mind-body therapies, and procedures for managing VMS.[10,11] Randomized controlled trials have demonstrated that weight loss may be effective for reducing VMS, particularly earlier in the menopause transition.[12,13] Cognitive behavioral therapy has been shown in various studies to effectively reduce the degree to which women perceive VMS as a problem.[11] Multiple studies have demonstrated that group and self-guided cognitive behavioral therapy, when compared with usual care or no active intervention, resulted in improvements in bothersome VMS, hot flash interference, and depressive symptoms.[11,14,15] Although the studies generally lacked rigorous controls, the overall body of evidence supports cognitive behavioral therapy as a recommended treatment for bothersome VMS.[11] Two separate 5-week-long randomized controlled trials demonstrated that when compared with controls, clinical hypnosis reduced the severity and frequency of VMS and also improved mood and sleep.[11,16,17]

Stellate ganglion blockade, a widely used treatment for pain management that involves injecting an anesthetic agent in the lower cervical or upper thoracic region to target the stellate ganglion, has shown potential for alleviating VMS in menopausal women. A randomized sham-controlled trial (N = 40) demonstrated a reduction in VMS intensity and frequency with stellate ganglion block, measured subjectively by patient report and objectively with ambulatory skin conductance monitors, when compared with sham controls.[18] Multiple studies have additionally reported reductions in VMS with stellate ganglion block.[19–21]

Moreover, a study in patients with breast cancer (N = 40) demonstrated comparable efficacy between stellate ganglion blockade and paroxetine 7.5 mg daily for VMS reduction.[22] While adverse events (bleeding, transient seizures) are rare and minimized with imaging guidance, they can be serious.[11] As such, larger randomized controlled trials are warranted to provide more conclusive evidence regarding the risk-benefit ratio of stellate ganglion block in VMS management.

Though complementary and alternative therapies such as trigger avoidance, cooling techniques, dietary modification, exercise, mindfulness-based interventions, acupuncture and electroacupuncture, and yoga have shown potential benefit, additional research is needed to confirm their effectiveness.[10,11] Chiropractic treatments and paced respiration have not been shown to be effective.[11] Additionally, there is currently negative, inconclusive, or insufficient evidence regarding the use of soy foods, S-equol, other soy extracts and derivatives, cannabinoids, and herbal supplements (eg, black cohosh, ashwagandha, evening primrose oil) for the reduction of VMS.[10,11] While black cohosh is not currently recommended, women who choose to take it should be counseled about its potential hepatotoxicity.

NONHORMONE PHARMACOLOGIC AGENTS

Although not as efficacious as hormone therapy, nonhormone medications remain a valuable tool for VMS relief. Pharmacologic agents found to be effective

compared with placebo for VMS treatment include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, oxybutynin, clonidine, and a newer class of medications known as neurokinin-receptor antagonists. It is essential to note that these medications are not mutually exclusive and may be judiciously combined, while considering tolerability and effectiveness, to improve control of VMS frequency and severity. Apart from neurokinin-receptor antagonists, the precise mechanism of how each of the listed nonhormone medications reduces the burden of VMS has not yet been clearly elucidated.

SSRIs and SNRIs

SSRIs and SNRIs demonstrate mild to moderate improvement of VMS.[10,11,23,24] While limited by variability in criteria, dosing, and outcomes, large randomized, double-blind, placebo-controlled trials have found that paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, and duloxetine reduced hot flashes by 24% to 69% compared with placebo, with composite hot flash frequency and severity improving by 19% to 61%.[10,11,23–25] Sertraline and fluoxetine do not consistently demonstrate reductions in VMS.[24,26,27]

Given these medications are first-line treatments for a variety of mood disorders, SSRIs and SNRIs may be beneficial for patients with concurrent mood issues, such as worsening or new-onset depression or anxiety, both of which are common in peri- and postmenopausal patients.[10] As noted in **Table 2**, low doses of SSRIs and SNRIs typically control VMS compared with the higher doses that may be needed for management of mood symptoms.[10,11,23–35]

SNRIs, especially duloxetine, which is approved by the US Food and Drug Administration for the treatment of fibromyalgia and chronic musculoskeletal pain, are frequently used to treat chronic somatic pain conditions.[36–38] As such, they could be considered a good option for the treatment of VMS in patients with prominent menopause-related arthralgia. Because nonhormone medications are often used to treat VMS in breast cancer survivors, it is important to note that paroxetine and fluoxetine are potent cytochrome P450 CYP2D6 (the enzyme that converts tamoxifen to its most active metabolite) inhibitors and should not be used with tamoxifen, as they would reduce tamoxifen's bioavailability and efficacy.[10]

Although low doses of SSRIs and SNRIs are generally well-tolerated and effective in the management of hot flashes, the possible side-effect profile of these medications must be considered. The most commonly reported bothersome side effects of SSRIs and SNRIs are nausea, gastrointestinal disturbances, sleep disturbances, weight changes, sexual dysfunction, and headache.[39,40] Particularly with regard to weight and sexual dysfunction, these side effects may be dose-dependent, as a randomized placebo-controlled trial found that low-dose paroxetine (7.5 mg) did not cause weight gain or negative libido changes for up to 24 weeks.[41] Given that weight gain, sexual dysfunction, and sleep disturbances are frequently reported menopausal symptoms, it is imperative that clinicians counsel patients on these possibilities before initiating treatment.

Of note, at the comparatively higher doses of SSRIs and SNRIs used to alleviate mood symptoms, these agents can increase VMS or diaphoresis, which is often more pronounced with SNRIs than with SSRIs because of their specific norepinephrine binding and stimulation.[39,40,42] Additionally, it is crucial to counsel patients that SSRIs and SNRIs should not be abruptly discontinued, as this may lead to severe withdrawal side effects.

Gabapentinoids (gabapentin and pregabalin)

Multiple randomized controlled trials have shown that when compared with placebo, gabapentin is effective at reducing hot flash frequency by 54% and hot flash composite score (combined hot flash frequency and severity score) by 31% to 51%.[28–30]

Gabapentin is helpful in patients with a history of neuropathic pain issues, and when dosed before bedtime, can be an effective sleep aid.[10,11] The most pertinent side effects of gabapentin to consider before initiation include dizziness or coordination difficulties (thus, possible increase in fall risk), edema, drowsiness, lethargy, weight gain, nausea, and gastrointestinal disturbances.[10,11,28–31] Because fatigue and weight gain are often experienced by menopausal women, a commonly used strategy to minimize negative or compounding side effects of gabapentin is to use the lowest effective dose or nightly dosing.[11]

Current recommendations from the Menopause Society no longer support pregabalin as a treatment for reducing VMS owing to limited evidence.[11]

Oxybutynin

Evidence from several randomized controlled trials supports the effectiveness of oxybutynin in treating hot flashes, showing reduction in hot flash frequency by up to 70% to 86%.[23,24,43] Oxybutynin is an effective treatment for overactive bladder symptoms, which can increase in hypoestrogenic states. As such, it may be an ideal choice for women with prominent urinary

TABLE 2
Nonhormone pharmacologic agents currently available for management of vasomotor symptoms

Class	Medication	Dosing for VMS[a]	Clinical pearls
SSRIs	Paroxetine salt[10,11,23,24]	7.5 mg daily at bedtime	Potent cytochrome P450 CYP2D6 enzyme inhibitors; do not use with tamoxifen as SSRIs reduce tamoxifen bioavailability and efficacy
	Paroxetine[10,11,23,24]	10–25 mg daily	
	Fluoxetine[11,23,24,26]	10–30 mg daily	Paroxetine mesylate 7.5 mg was the first and only US Food and Drug Administration–approved nonhormone medication for moderate to severe menopausal VMS until the development of neurokinin-receptor antagonists
	Sertraline[11,23,24,27]	25–100 mg daily	
	Citalopram[10,11,23,24]	10–20 mg daily	Fluoxetine and sertraline are not recommended for VMS reduction owing to inconsistent data regarding efficacy in hot flash frequency and severity reduction
	Escitalopram[10,11,23–25]	10–20 mg daily	
			Sertraline has a moderate effect on the CYP2D6 enzyme
			Citalopram and escitalopram may cause QT prolongation
SNRIs	Desvenlafaxine[10,11,23,24]	100–150 mg daily	SNRIs may increase blood pressure, use with caution in patients with hypertension
	Venlafaxine[10,11,23,24]	37.5–75 mg daily	Venlafaxine is the most well studied SNRI in combination with tamoxifen
	Duloxetine[11,23,25]	30–60 mg daily	Duloxetine has a moderate effect on the CYP2D6 enzyme
Gabapentinoid	Gabapentin[10,11,28–31]	300–2,400 mg daily (divided doses)	Consider for patients with a history of neuropathic pain or sleep concerns
			Consider nightly dosing (starting dose of 100–300 mg at bedtime) to minimize any adverse effects of daytime fatigue
Antimuscarinic	Oxybutynin[11,24,31,32]	2.5–5 mg twice a day (immediate release), up to 15 mg/day (extended release)	Consider for patients with concurrent overactive bladder or hyperhidrosis
			Use caution in older adults (≥ 65 years); avoid altogether in patients ≥ 65 years taking concomitant anticholinergic medications
Alpha-2 adrenergic agonist	Clonidine[11,32,33]	0.05–0.1 mg once or twice a day	Consider for patients with hypertension, especially if improved blood pressure control is desired
			Avoid in older adult patients (≥ 65 years)
			Less often used and no longer recommended by the Menopause Society owing to modest efficacy vs placebo and side-effect profile
Neurokinin-receptor antagonist	Fezolinetant[11,34,35]	45 mg daily	Exercise caution in patients taking concomitant CYP1A2 enzyme inhibitors, which increase potency of fezolinetant
			Check transaminase levels at baseline, 3 months, 6 months, and 9 months

[a]Based on clinical efficacy demonstrated in randomized controlled trials and the Menopause Society recommendations.[10,11]

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitors; VMS = vasomotor symptoms

conditions and VMS. Common side effects include dry mouth and eyes, urinary retention, dizziness, drowsiness, constipation, vision changes, and nausea.[43,44]

Anticholinergics, including oxybutynin, are noted on the American Geriatrics Society Beers Criteria list as potentially inappropriate medications in adults ages 65 and older owing to an association with impaired cognitive and physical functioning, risk of dementia, and risk of delirium.[32] Multiple case-control studies have linked oxybutynin to an increased incidence of cognitive impairment, consistent with mounting evidence indicating that a high anticholinergic burden elevates the risk of cognitive decline and potentially worsens long-term neurocognitive outcomes.[45–47] While caution should be exercised in the use of oxybutynin in the general population, the use of more than 1 medication with anticholinergic properties should be avoided in older adults.[32]

Of note, extended-release oxybutynin, though potentially more tolerable than immediate-release formulations and effective for VMS management, has been predominantly investigated at a 15-mg daily dose for reducing hot flashes and night sweats.[48] Considering the efficacy of lower doses of immediate-release oxybutynin, ranging from 2.5 to 5 mg twice daily, it is reasonable to contemplate lower-dose, extended-release formulations for VMS reduction.

Clonidine

Multiple studies demonstrate modest improvement in hot flashes with clonidine.[10,11,23,24,33] One randomized, double-blind, placebo-controlled trial demonstrated a 26% decrease in hot flash frequency (P = .045 clonidine vs placebo) in patients with breast cancer. One randomized, double-blind, placebo-controlled trial demonstrated a 38% decrease in hot flash frequency in postmenopausal patients with breast cancer using tamoxifen.[49]

Common side effects of clonidine include fatigue and weakness, headache, dry eyes and mouth, hypotension, dizziness or lightheadedness, and sedation.[11,24] Rebound hypertension and withdrawal symptoms may also occur with abrupt discontinuation of clonidine.[11,23,50] Given the high risk of adverse effects, such as depression of the central nervous system, bradycardia, and orthostatic hypotension, clonidine is included in the 2015 American Geriatrics Society Beers Criteria and it is generally not recommended in patients 65 or older.[32] Additionally, given the significant side-effect burden and lower comparative efficacy with this medication, the Menopause Society has removed it as a recommended nonhormone treatment for menopause.[11]

Neurokinin-receptor antagonists

It has been postulated that VMS are directly caused by estrogen decline or deficiency given that estrogen therapy often eliminates VMS.[51,52] However, this is not the case for all women,[53] and unconjugated serum estrogen levels do not differ between symptomatic and asymptomatic women.[54] Kisspeptin, neurokinin B, and dynorphin (KNDy) neurons are present in the thermoregulatory zone of the hypothalamus, and are noted to be hypertrophied in postmenopausal women.[11,34,54,55] Evidence shows that these neurons play a role in VMS etiology.[55] KNDy neurons are inhibited by estrogen and activated by neurokinin.[55] Therefore, blockade of KNDy neurons is a proposed target for VMS treatment.

Neurokinin-receptor antagonists are a novel group of medications that directly target the thermoregulatory center in the hypothalamus through modulation of KNDy neurons and are currently being studied for VMS relief.

Fezolinetant, a neurokinin-3–receptor antagonist, was found to be safe, well-tolerated, and efficacious for the treatment of moderate to severe VMS and was approved by the US Food and Drug Administration at a dose of 45 mg daily in May 2023.[35] SKYLIGHT 2 was a randomized, double-blind, placebo-controlled, 12-week, phase 3 trial with re-randomization for a 40-week active treatment extension in women ages 40 to 65 experiencing a minimum average of 7 moderate to severe VMS episodes per day.[34] Fezolinetant 45 mg reduced VMS frequency by more than 50% compared with placebo (average 2 to 3 fewer VMS episodes per day) with rapid onset of effect by week 1 and full effect by week 4 that was sustained through week 52.[34] At week 12, VMS frequency was reduced by 93% with fezolinetant and 46% with placebo.[34,56] The 45-mg dose of fezolinetant also demonstrated clinically meaningful improvements in sleep measures.[34]

The most common side effects of fezolinetant in clinical studies included abdominal pain, diarrhea, headache, nausea, and gastrointestinal disturbances.[34,35] Pooled clinical trial data found that approximately 2.3% of patients exposed to fezolinetant 45 mg experienced transaminase elevations.[35] As such, checking alanine aminotransferase and aspartate aminotransferase levels is recommended at baseline, 3 months, 6 months, and 9 months when using this medication.[35]

Contraindications for use of this medication, listed on the package insert, include known cirrhosis, severe renal impairment, and concurrent use with CYP1A2 inhibitors.[35] Given that CYP1A2 inhibitors can significantly increase the potency of fezolinetant, it is

important to assess whether patients are using these pharmacologic agents before starting concomitant medications. Pertinent drugs to consider include caffeine, certain SSRIs (such as fluvoxamine), fluoroquinolone antibiotics, and some estradiol formulations. Of note, although caffeine is considered a weak to moderate CYP1A2 inhibitor, caffeine consumption was not limited in participants of fezolinetant clinical studies and thus caffeine can be used judiciously.[34] Additionally, smoking (a moderate CYP1A2 inducer) does not seem to significantly impact clinical exposure of fezolinetant in concomitant users.[34,35]

Elinzanetant, which acts as an antagonist in both the neurokinin-1 and neurokinin-3 receptors, is not yet commercially available. SWITCH-1 was a multicenter, multicountry, double-blind, phase 2b, adaptive, dose-range–finding study evaluating the safety and efficacy of elinzanetant for VMS management. It found that elinzanetant 120 mg yielded statistically significant reductions vs placebo in VMS frequency and severity at 4 weeks (difference in least square means [SE] −3.93 [1.02]; $P < .001$) and 12 weeks (−2.95 [1.15]; $P = .01$).[57] Clinically meaningful improvements in sleep and quality-of-life measures were also seen.[57] Pending further study, this medication is expected to be available sometime after 2025.

CONCLUSION

Menopausal VMS are often overlooked and undertreated. It is imperative for healthcare professionals to evaluate for and manage VMS in women, ensuring that all available options are presented as viable choices for those experiencing distressing symptoms. Although menopausal hormone therapy remains the gold standard of care for VMS in women under age 60 or within 10 years of menopause without contraindications, clinicians have many nonhormone options to use in conjunction with or instead of menopausal hormone therapy.[58]

The existing literature provides compelling evidence for the efficacy of nonhormone therapies in managing VMS when hormone-based options are not an option or are undesired. Given the wide range of symptoms resulting from ovarian hormone cessation in menopause, clinicians must consider the possible exacerbating ramifications of each pharmacologic agent on other menopausal symptoms when selecting a treatment for VMS. Recently, emerging therapies such as neurokinin-receptor antagonists have shown promise in reducing VMS with few adverse effects. Clinicians should individualize treatment based on patient needs, history, response, and preferences.

Despite the availability of numerous nonhormone and nonpharmacologic options for VMS treatment, many patients still face significant symptom burden owing to limitations in treatment tolerability, efficacy, and access. As such, there remains a pressing need for more effective and safe treatment options for menopausal VMS management.

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REFERENCES

1. **Gold EB, Colvin A, Avis N, et al.** Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: Study of Women's Health Across the Nation. Am J Public Health 2006; 96(7):1226–1235. doi:10.2105/AJPH.2005.066936
2. **Nappi RE, Kroll R, Siddiqui E, et al.** Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. Menopause 2021; 28(8): 875–882. doi:10.1097/GME.0000000000001793
3. **Thurston RC, El Khoudary SR, Sutton-Tyrrell K, et al.** Vasomotor symptoms and lipid profiles in women transitioning through menopause. Obstet Gynecol 2012; 119(4):753–761. doi:10.1097/AOG.0b013e31824a09ec
4. **Jackson EA, El Khoudary SR, Crawford SL, et al.** Hot flash frequency and blood pressure: data from the Study of Women's Health Across the Nation. J Womens Health (Larchmt) 2016; 25(12):1204–1209. doi:10.1089/jwh.2015.5670
5. **Thurston RC, Chang Y, Barinas-Mitchell E, et al.** Menopausal hot flashes and carotid intima media thickness among midlife women. Stroke 2016; 47(12):2910–2915. doi:10.1161/STROKEAHA.116.014674
6. **Thurston RC, El Khoudary SR, Sutton-Tyrrell K, et al.** Vasomotor symptoms and insulin resistance in the Study of Women's Health Across the Nation. J Clin Endocrinol Metab 2012; 97(10):3487–3494. doi:10.1210/jc.2012-1410
7. **Gast GC, Grobbee DE, Pop VJ, et al.** Vasomotor symptoms are associated with a lower bone mineral density. Menopause 2009; 16(2):231–238. doi:10.1097/gme.0b013e318185e25b
8. **Crandall CJ, Aragaki A, Cauley JA, et al.** Associations of menopausal vasomotor symptoms with fracture incidence. J Clin Endocrinol Metab 2015; 100(2):524–534. doi:10.1210/jc.2014-3062
9. **Li L, Xu L, Wu J, Dong L, Lv Y, Zheng Q.** Quantitative analysis of placebo response and factors associated with menopausal hot flashes. Menopause 2017; 24(8):932–937. doi:10.1097/GME.0000000000000858
10. **The North American Menopause Society Position Statement Advisory Panel.** Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. Menopause 2015; 22(11):1155–1174. doi:10.1097/GME.0000000000000546
11. **The North American Menopause Society Position Statement Advisory Panel.** The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society Advisory Panel. The 2023 nonhormone therapy position statement of The North American Menopause Society. Menopause 2023; 30(6):573–590. doi:10.1097/GME.0000000000002200

12. **Thurston RC, Ewing LJ, Low CA, Christie AJ, Levine MD.** Behavioral weight loss for the management of menopausal hot flashes: a pilot study. Menopause 2015; 22(1):59–65. doi:10.1097/GME.0000000000000274
13. **Huang AJ, Subak LL, Wing R, et al.** An intensive behavioral weight loss intervention and hot flushes in women [published correction appears in Arch Intern Med 2010; 170(17):1601]. Arch Intern Med 2010; 170(13):1161–1167. doi:10.1001/archinternmed.2010.162
14. **Green SM, Donegan E, Frey BN, et al.** Cognitive behavior therapy for menopausal symptoms (CBT-Meno): a randomized controlled trial. Menopause 2019; 26(9):972–980. doi:10.1097/GME.0000000000001363
15. **Hardy C, Griffiths A, Norton S, Hunter MS.** Self help cognitive behavior therapy for working women with problematic hot flushes and night sweats (MENOS@Work): a multicenter randomized controlled trial. Menopause 2018; 25(5):508–519. doi:10.1097/GME.0000000000001048
16. **Elkins G, Marcus J, Stearns V, et al.** Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. J Clin Oncol 2008; 26(31):5022–5026. doi:10.1200/JCO.2008.16.6389
17. **Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ.** Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. Menopause 2013; 20(3):291–298. doi:10.1097/gme.0b013e31826ce3ed
18. **Walega DR, Rubin LH, Banuvar S, Shulman LP, Maki PM.** Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women. Menopause 2014; 21(8):807–814. doi:10.1097/GME.0000000000000194
19. **Pachman DR, Barton D, Carns PE, et al.** Pilot evaluation of a stellate ganglion block for the treatment of hot flashes. Support Care Cancer 2011; 19(7):941–947. doi:10.1007/s00520-010-0907-9
20. **Haest K, Kumar A, Van Calster B, et al.** Stellate ganglion block for the management of hot flashes and sleep disturbances in breast cancer survivors: an uncontrolled experimental study with 24 weeks of follow-up. Ann Oncol 2012; 23(6):1449–1454. doi:10.1093/annonc/mdr478
21. **van Gastel P, Kallewaard J-W, van der Zanden M, de Boer H.** Stellate-ganglion block as a treatment for severe postmenopausal flushing. Climacteric 2013; 16(1):41–47. doi:10.3109/13697137.2012.709889
22. **Rahimzadeh P, Imani F, Nafissi N, Ebrahimi B, Faiz SHR.** Comparison of the effects of stellate ganglion block and paroxetine on hot flashes and sleep disturbance in breast cancer survivors. Cancer Manag Res 2018; 10:4831–4837. doi:10.2147/CMAR.S173511
23. **Biglia N, Bounous VE, De Seta F, Lello S, Nappi RE, Paoletti AM.** Non-hormonal strategies for managing menopausal symptoms in cancer survivors: an update. Ecancermedicalscience 2019; 13:909. doi:10.3332/ecancer.2019.909
24. **Sahni S, Lobo-Romero A, Smith T.** Contemporary non-hormonal therapies for the management of vasomotor symptoms associated with menopause: a literature review. touchREV Endocrinol 2021; 17(2):133–137. doi:10.17925/EE.2021.17.2.133
25. **Biglia N, Bounous VE, Susini T, et al.** Duloxetine and escitalopram for hot flushes: efficacy and compliance in breast cancer survivors. Eur J Cancer Care (Engl) 2018; 27(1):10.1111/ecc.12484. doi:10.1111/ecc.12484
26. **Loprinzi CL, Sloan JA, Perez EA, et al.** Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 2002; 20(6): 1578–1583. doi:10.1200/JCO.2002.20.6.1578
27. **Grady D, Cohen B, Tice J, Kristof M, Olyaie A, Sawaya GF.** Ineffectiveness of sertraline for treatment of menopausal hot flushes: a randomized controlled trial. Obstet Gynecol 2007; 109(4):823–830. doi:10.1097/01.AOG.0000258278.73505.fa
28. **Guttuso T Jr, Kurlan R, McDermott MP, Kieburtz K.** Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. Obstet Gynecol 2003; 101(2):337–345. doi:10.1016/s0029-7844(02)02712-6
29. **Butt DA, Lock M, Lewis JE, Ross S, Moineddin R.** Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. Menopause 2008; 15(2):310–318. doi:10.1097/gme.0b013e3180dca175
30. **Pandya KJ, Morrow GR, Roscoe JA, et al.** Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. Lancet 2005; 366(9488):818–824. doi:10.1016/S0140-6736(05)67215-7
31. **Biglia N, Sgandurra P, Peano E, et al.** Non-hormonal treatment of hot flushes in breast cancer survivors: gabapentin vs. vitamin E. Climacteric 2009; 12(4):310–318. doi:10.1080/13697130902736921
32. **American Geriatrics Society 2015 Beers Criteria Update Expert Panel.** American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015; 63(11):2227–2246. doi:10.1111/jgs.13702
33. **Pandya KJ, Raubertas RF, Flynn PJ, et al.** Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. Ann Intern Med 2000; 132(10):788–793. doi:10.7326/0003-4819-132-10-200005160-00004
34. **Johnson KA, Martin N, Nappi RE, et al.** Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. J Clin Endocrinol Metab 2023; 108(8):1981–1997. doi:10.1210/clinem/dgad058
35. **Astellas Pharma US, Inc.** VEOZAH (fezolinetant) tablets, for oral use (package insert). https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216578s000lbl.pdf. Accessed March 6, 2024.
36. **Okifuji A, Gao J, Bokat C, Hare BD.** Management of fibromyalgia syndrome in 2016. Pain Manag 2016; 6(4):383–400. doi:10.2217/pmt-2016-006
37. **Ma X, Zhou S, Sun W, et al.** Efficacy and safety of duloxetine in chronic musculoskeletal pain: a systematic review and meta-analysis. BMC Musculoskelet Disord 2023; 24(1):394. doi:10.1186/s12891-023-06488-6
38. **Smith HS, Smith EJ, Smith BR.** Duloxetine in the management of chronic musculoskeletal pain. Ther Clin Risk Manag 2012; 8:267–277. doi:10.2147/TCRM.S17428
39. **Cascade E, Kalali AH, Kennedy SH.** Real-world data on SSRI antidepressant side effects. Psychiatry (Edgmont) 2009; 6(2):16–18. pmid:19724743
40. **Santarsieri D, Schwartz TL.** Antidepressant efficacy and side-effect burden: a quick guide for clinicians. Drugs Context 2015; 4:212290. doi:10.7573/dic.212290
41. **Portman DJ, Kaunitz AM, Kazempour K, Mekonnen H, Bhaskar S, Lippman J.** Effects of low-dose paroxetine 7.5 mg on weight and sexual function during treatment of vasomotor symptoms associated with menopause. Menopause 2014; 21(10):1082–1090. doi:10.1097/GME.0000000000000210
42. **Thompson SR, Compton LE, Fang ML, Chen J-L.** Pharmacologic treatment of antidepressant-induced excessive sweating: a systematic review. Arch Clin Psych 2021; 48(1):57–65. doi:10.15761/0101-60830000000279
43. **Leon-Ferre RA, Novotny PJ, Wolfe EG, et al.** Oxybutynin vs placebo for hot flashes in women with or without breast cancer: a randomized, double-blind clinical trial (ACCRU SC-1603). JNCI Cancer Spectr 2019; 4(1):pkz088. doi:10.1093/jncics/pkz088
44. **Jannsen Pharmaceutical.** DITROPAN XL® (oxybutynin chloride) Extended release tablets for oral use (package insert). https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DITROPAN+XL-pi.pdf. Accessed March 13, 2024.
45. **Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J.** Anticholinergic drug exposure and the risk of dementia: a nested case-control study. JAMA Intern Med 2019; 179(8):1084–1093. doi:10.1001/jamainternmed.2019.0677
46. **Malcher MF, Droupy S, Berr C, et al.** Dementia associated with anticholinergic drugs used for overactive bladder: a nested case-control study using the French National Medical-Administrative Database. J Urol 2022; 208(4):863–871. doi:10.1097/JU.0000000000002804

47. **Richardson K, Fox C, Maidment I, et al.** Anticholinergic drugs and risk of dementia: case-control study. BMJ (Clin Res Ed) 2018; 361:k1315. doi:10.1136/bmj.k1315
48. **Simon JA, Gaines T, LaGuardia KD; Extended-Release Oxybutynin Therapy for VMS Study Group.** Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. Menopause 2016; 23(11):1214–1221. doi:10.1097/GME.0000000000000773
49. **Boekhout AH, Vincent AD, Dalesio OB, et al.** Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2011; 29(29):3862–3868. doi:10.1200/JCO.2010.33.1298
50. **Shionogi Pharma, Inc.** KAPVAY (clonidine hydrochloride) extended-release tablets, oral (package insert). https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022331s001s002lbl.pdf. Accessed March 13, 2024.
51. **Kenemans P, Barentsen R, Van de Weijer P.** Practical HRT. 2nd ed. Zeist, The Netherlands: Medical Forum International; 1996.
52. **Johnson SR.** Menopause and hormone replacement therapy. Med Clin North Am 1998; 82(2):297–320. doi:10.1016/s0025-7125(05)70608-8
53. **Thurston RC, Joffe H.** Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. Obstet Gynecol Clin North Am 2011; 38(3):489–501. doi:10.1016/j.ogc.2011.05.006
54. **Hutton JD, Jacobs HS, Murray MA, James VH.** Relation between plasma oestrone and oestradiol and climacteric symptoms. Lancet 1978; 1(8066):678–681. doi:10.1016/s0140-6736(78)90796-1
55. **Trower M, Anderson RA, Ballantyne E, Joffe H, Kerr M, Pawsey S.** Effects of NT-814, a dual neurokinin 1 and 3 receptor antagonist, on vasomotor symptoms in postmenopausal women: a placebo-controlled, randomized trial. Menopause 2020; 27(5):498–505. doi:10.1097/GME.0000000000001500
56. **Depypere H, Timmerman D, Donders G, et al.** Treatment of menopausal vasomotor symptoms with fezolinetant, a neurokinin 3 receptor antagonist: a phase 2a trial. J Clin Endocrinol Metab 2019; 104(12):5893–5905. doi:10.1210/jc.2019-00677
57. **Simon JA, Anderson RA, Ballantyne E, et al.** Efficacy and safety of elinzanetant, a selective neurokinin-1,3 receptor antagonist for vasomotor symptoms: a dose-finding clinical trial (SWITCH-1). Menopause 2023; 30(3):239–246. doi:10.1097/GME.0000000000002138
58. **The North American Menopause Society 2022 Hormone Therapy Position Statement Advisory Panel.** The 2022 hormone therapy position statement of the North American Menopause Society. Menopause 2022; 29(7):767–794. doi:10.1097/GME.0000000000002028

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