

Nonhormonal medication treatment of VMS

For patients with bothersome vasomotor symptoms (VMS) who cannot or choose not to take estrogen, nonhormonal medication options include escitalopram, paroxetine, gabapentin, and fezolinetant



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VMS, also known as hot flashes, night sweats, or cold sweats, occur for the majority of perimenopausal and menopausal women.¹ In one study, the mean duration of clinically significant VMS was 5 years, and one-third of participants continued to have bothersome hot flashes 10 or more years after the onset of menopause.² VMS may contribute to disrupted sleep patterns and depressed mood.³

All obstetrician-gynecologists know that estradiol and other estrogens are highly effective in the treatment of bothersome VMS. A meta-analysis reported that the frequency of VMS was reduced by 60% to 80% with oral estradiol (1 mg/day), transdermal estradiol (0.05 mg/day), and conjugated estrogen (0.625 mg).⁴ Breast tenderness

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and irregular uterine bleeding are common side effects of estrogen treatment of VMS. Estrogen treatment is contraindicated in patients with estrogen-responsive cancers, coronary heart disease, myocardial infarction, stroke, venous thromboembolism, and some cases of inherited thrombophilia. For these patients, an important option is the nonhormonal treatment of VMS, and several nonhormonal medications have been demonstrated to be effective therapy (TABLE 1, page 6). In this editorial I will review the medication treatment of VMS with escitalopram, paroxetine, gabapentin, and fezolinetant.

Escitalopram and paroxetine

Escitalopram and paroxetine have been shown to reduce VMS more than placebo in multiple clinical trials.⁵⁻¹⁰ In addition, escitalopram and

paroxetine, at the doses tested, may be more effective for the treatment of VMS than sertraline, citalopram, or fluoxetine.¹¹ In one trial assessing the efficacy of escitalopram to treat VMS, 205 patients with VMS were randomly assigned to 8 weeks of treatment with placebo or escitalopram.⁵ The initial escitalopram dose was 10 mg daily. At week 4:

- if VMS frequency was reduced by $\geq 50\%$, the patient remained on the 10-mg dose
- if VMS frequency was reduced by $< 50\%$, the escitalopram dose was increased to 20 mg daily.

Following 8 weeks of treatment, the frequency of VMS decreased for patients in the placebo and escitalopram groups by 33% and 47%, respectively. Similar results have been reported in other studies.⁶

Paroxetine at a dose of 7.5 mg/day administered at bedtime is approved by the US Food and Drug Administration (FDA) for the treat-

TABLE Options for the nonhormonal medication treatment of vasomotor symptoms

Medication	Dose range	Starting daily dose	Dose titration
Off-label use of medications			
Escitalopram ^{5,6}	10–20 mg/day	10 mg	Following 4 weeks of treatment, if hot flash frequency has not decreased by at least 50%, increase dose to 20 mg daily
Paroxetine, immediate release ^{7,8}	10–20 mg/day	10 mg	Increase to 20 mg if needed
Gabapentin ¹⁵⁻¹⁷	300–900 mg/day in 3 divided doses	300 mg at bedtime. Some clinicians initiate treatment at a dose of 100 mg at bedtime.	Increase single bedtime dose at weekly intervals 300 mg, 600 mg, and 900 mg, if needed. Monitor for AEs of headache, dizziness, and morning drowsiness. Doses of 2,400 mg have been used to treat VMS but are associated with an increased frequency of AEs.
FDA approved medications			
Paroxetine 7.5 mg (Brisdelle) ^{9,10}	7.5 mg/day	7.5 mg/day at bedtime	No dose titration
Fezolinetant 45 mg (Veozah) ^{21,22}	45 mg/day	45 mg/day	No dose titration Perform LFTs prior to initiation; do not initiate therapy in patients with ALT, AST, and/or total bilirubin ≥2 times the upper limit of normal

Abbreviations: AE, adverse effect; ALT, alanine transaminase; AST, aspartate aminotransferase; LFTs, liver function tests.

ment of VMS. In a pivotal study, 1,112 patients with VMS were randomly assigned to receive a placebo or paroxetine 7.5 mg at bedtime.⁹ In the 12-week study the reported decrease in mean weekly frequency of VMS for patients in the placebo and paroxetine groups were -37 and -44, respectively.⁹ Paroxetine 7.5 mg also reduced awakenings per night attributed to VMS and increased nighttime sleep duration.¹⁰

Depressed mood is prevalent among perimenopausal and postmenopausal patients.¹² Prescribing escitalopram or paroxetine for VMS also may improve mood. Venlafaxine and desvenlafaxine are effective for the treatment of VMS;^{13,14} however, I seldom prescribe these medications for VMS because in my experience they are associated with more bothersome side effects, including dry mouth, decreased appetite, nausea,

and insomnia than escitalopram or low-dose paroxetine.

Gabapentin

Numerous randomized clinical trials have reported that gabapentin is superior to placebo for the treatment of VMS.¹⁵ In one trial, 420 patients with breast cancer and VMS were randomly assigned to 8 weeks of treatment with placebo, gabapentin 300 mg/day (G300), or gabapentin 900 mg/day (G900) in 3 divided doses.¹⁶ Following 8 weeks of treatment, reduction in hot-flash severity score among patients receiving placebo, G300, or G900 was 15%, 31%, and 46%, respectively. Fatigue and somnolence were reported more frequently among patients taking gabapentin 900 mg/day. In a small trial, 60 patients with VMS were

randomized to receive placebo, conjugated estrogen (0.2625 mg/day), or gabapentin (target dose of 2,400 mg/day in 3 divided doses).¹⁷ Following 12 weeks of treatment, the patient-reported decrease in VMS for those taking placebo, estrogen, or gabapentin was 54%, 72%, and 71%, respectively.

High-dose gabapentin treatment was associated with side effects of headache and dizziness more often than placebo or estrogen. Although gabapentin is not a treatment for insomnia, in my practice if a menopausal patient has prominent and bothersome symptoms of sleep disturbance and mild VMS symptoms, I will consider a trial of low-dose gabapentin. Some experts recommend initiating gabapentin at a dose of 100 mg daily before bedtime to assess the effectiveness of a low dose that seldom causes significant side effects.

Fezolinetant

In a study of genetic variation associated with VMS, investigators discovered that nucleic acid variation in the neurokinin 3 (NK3) receptor was strongly associated with the prevalence of VMS, suggesting that this receptor is in the causal pathway to menopausal VMS.¹⁸ Additional research demonstrated that the kisspeptin/neurokinin B/dynorphin (KNDy) neurons, which are involved in the control of hypothalamic thermoregulation, are stimulated by neurokinin B, acting through the NK3 receptor, and suppressed by estradiol. A reduction in hypothalamic estrogen results in unopposed neurokinin B activity, which stimulates KNDy neurons, destabilizing the hypothalamic thermoregulatory center, causing vasodilation, which is perceived as hot flashes and sweating followed by chills.¹⁹

Fezolinetant is a high-affinity NK3 receptor antagonist that blocks the activity of neurokinin B, stabilizing the hypothalamic thermoregulatory center, thereby suppressing hot flashes. It is approved by the FDA for the treatment of moderate to severe VMS due to menopause using a fixed dose of 45 mg daily.²⁰ In one clinical trial, 500 menopausal patients with bothersome VMS were randomly assigned to 12 weeks of treatment with placebo, fezolinetant 30 mg/day, or fezolinetant 45 mg/day. Following 12 weeks of treatment, the reported frequency rates of VMS among patients in the placebo, F30, and F45 groups were reduced by 43%, 61%, and 64%, respectively.²¹ In addition, following 12 weeks of treatment, the severity of VMS rates among patients in the placebo, F30, and F45 groups were reduced by 20%, 26%, and 32%, respectively.

Fezolinetant improved the quality of sleep and was associated with



an improvement in patient-reported quality of life. Following 12 weeks of treatment, sleep quality among patients in the placebo, F30, and F45 groups was reported to be “much or moderately better” in 34%, 45%, and 54% of the patients, respectively.²¹ Similar results were reported in a companion study.²²

Fezolinetant is contraindicated for patients with liver cirrhosis or severe renal impairment (estimated glomerular filtration rate of < 30 mL/min/1.73 m²). Before initiating treatment, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin (total and direct). Fezolinetant should not be prescribed if any of these tests are greater than twice the upper limit of normal. These tests should be repeated at 3, 6, and 9 months, and if the patient reports symptoms or signs of liver injury (nausea, vomiting, jaundice). Fezolinetant is metabolized by CYP1A2 and should not be

prescribed to patients taking strong CYP1A2 inhibitors. The most common side effects associated with fezolinetant treatment are abdominal pain (4.3%), diarrhea (3.9%), insomnia (3.9%), back pain (3.0%), and hepatic transaminase elevation (2.3%). Fezolinetant has not been thoroughly evaluated in patients older than age 65. Following an oral dose of the medication, the median maximum concentration is reached in 1.5 hours, and the half-life is estimated to be 10 hours.²⁰ Of all the medications discussed in this editorial, fezolinetant is the most expensive.

Effective VMS treatment improves overall health

Estrogen therapy is the gold standard treatment of VMS. However, many menopausal patients with bothersome VMS prefer not to take estrogen, and some have a medical condition that is a contraindication

to estrogen treatment. The non-hormonal medication options for the treatment of VMS include escitalopram, paroxetine, gabapentin, and fezolinetant. Patients value the ability to choose the treatment they prefer, among all available hormonal and nonhormonal medication options. For mid-life women, effectively treating bothersome VMS is

only one of many interventions that improves health. Optimal health is best achieved with²³:

- high-quality diet
- daily physical activity
- appropriate body mass index
- nicotine avoidance
- a healthy sleep schedule
- normal blood pressure, lipid, and glucose levels.

Women who have a high-quality diet; daily physical activity; an appropriate body mass index; and normal blood pressure, cholesterol, and glucose levels are estimated to live 9 disease-free years longer than other women.²⁴ ●


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