

Pharmacologic Management of Vasomotor Menopausal Symptoms

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Most women experience menopause as a natural life-course event due to permanent loss of ovarian follicular activity and related estrogen production.¹ Menopause typically occurs between the age of 45 to 56 years in women with a mean age of onset around 51 years.¹ Perimenopause is characterized by cessation of the menstrual cycle and onset of vasomotor and genitourinary symptoms.² This newsletter will review current evidence for medications used to manage vasomotor symptoms associated with menopause and summarize Oregon Health Plan (OHP) fee-for-service (FFS) policies for these medications.

Frequency of Vasomotor Symptoms

During perimenopause, 60% to 80% of women experience vasomotor symptoms.³ Hot flashes and night sweats are the symptoms associated with sleep and mood disturbances, as well as decreased cognitive function.⁴ Hot flashes involve sudden sensations of heat in the upper body that usually last 1 to 5 minutes and are characterized by perspiration, flushing, chills, clamminess, anxiety, and occasionally heart palpitations.⁵ These symptoms may persist intermittently for an average of 7 to 10 years and have a substantial negative impact on quality of life, contributing to physical and psychosocial impairment that can affect work performance, social activities, and personal and social relationships.⁴

Prevalence of vasomotor symptoms varies between different ethnic groups.³ In the United States, the peak incidence of vasomotor symptoms is during late perimenopause with a higher incidence of frequent vasomotor symptoms and a longer duration of symptoms among Black women (median duration, 10 years) and non-Hispanic White women (median duration, 9 years) compared with Chinese or Hispanic women (median duration, 5 years).⁶ In all racial/ethnic groups, reports of vasomotor symptom increase as women progress from premenopause to early perimenopause and even more dramatically as they make the transition to late perimenopause.³ Other risk factors related to severity of vasomotor symptoms include older age, body mass index (BMI) greater than 30 kg/m², lower education level (college-educated versus less than a college education), smoking history longer than 40 pack-years, and high baseline anxiety or depression scores.³

Preferred Management of Vasomotor Symptoms: Hormone Therapy

2022 guidance from North American Menopause Society (NAMS) suggests estrogen products (oral tablets, transdermal patches, topical gel) are the most effective treatment for bothersome vasomotor symptoms. They should be considered

in women who need additional treatment for menopausal symptoms who do not have contraindications to estrogen therapy.⁷ Estrogen therapy is Food and Drug Administration (FDA)-approved for 4 indications: moderate to severe vasomotor symptoms due to menopause; prevention of osteoporosis in postmenopausal women; treatment of hypoestrogenism caused by hypogonadism; and treatment of moderate to severe vulvovaginal symptoms.⁷

Contraindications to oral and topical estrogen treatment include a history of breast cancer, hepatic disease, cardiovascular disease, stroke, or a venous thromboembolism event (VTE).⁷ In women with an intact uterus, estrogen is given in combination with a progestogen to prevent endometrial hyperplasia which increases the risk of developing endometrial cancer associated with unopposed estrogen use.⁷ Systemic estrogen alone or combined with a progestogen compared to placebo reduces the frequency of vasomotor symptoms by approximately 75%.¹ A reduction in 50% or more in the severity of vasomotor symptoms is considered a clinically meaningful effect.⁸ In clinical trials, a reduction of at least 2 moderate to severe hot flashes per day is considered a clinically significant reduction in frequency of symptoms.⁸

For women who cannot tolerate progestogen therapy due to side effects, bazedoxifene is an alternative treatment. Bazedoxifene is a selective estrogen-receptor modulator (SERM) and is combined with conjugated estrogen 0.45 mg to form a tissue selective estrogen complex to provide endometrial protection without the need for progestogens.⁷ The combination of bazedoxifene/conjugated estrogen (DUAVEE) is FDA-approved for managing vasomotor symptoms associated with menopause and to prevent postmenopausal osteoporosis.⁹ Like other SERMs, the risk of VTE is increased with bazedoxifene.⁹ The combination of conjugated estrogen 0.45 mg/bazedoxifene 20 mg in women with moderate to severe hot flashes decreases hot flash frequency by approximately 75% (versus 50% for placebo).¹⁰

Nonhormonal Options for Alleviating Vasomotor Symptoms

The selective serotonin reuptake inhibitor (SSRI) paroxetine at a dose of 7.5 mg, is a non-hormonal product FDA-approved to treat moderate-to-severe vasomotor symptoms associated with menopause.¹¹ Low-dose paroxetine reduced the frequency and severity of hot flashes by approximately 40% to 65% compared to placebo at 4 weeks, but it can

cause headache, lethargy, nausea, and vomiting.^{1,11} There are no comparative trials that have evaluated efficacy of other paroxetine formulations or other antidepressants for treatment of vasomotor symptoms. Paroxetine can interfere with conversion of tamoxifen to its active metabolite, so it should not be used in women who are taking tamoxifen.¹¹ This SSRI formulation is not indicated for treatment of any psychiatric condition, as the dosing of paroxetine in these conditions ranges from 10 to 60 mg.¹¹

In 2023 NAMS issued guidance for nonhormonal therapy for management of vasomotor menopausal symptoms. The publication recommends SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin (strong recommendation for all 3 therapies), and oxybutynin (weak recommendation) to reduce vasomotor symptoms in symptomatic women (see **Table 2**).¹² Typically, the onset of action with these medications is within 2 weeks. There are limited trials comparing nonhormone therapies with hormone therapy to alleviate vasomotor symptoms.¹²

A pooled analysis from 3 randomized controlled trials (RCTs) showed that 10 mg to 20 mg of escitalopram, 0.5 mg of estradiol, or 75 mg of venlafaxine daily resulted in comparable reductions in vasomotor frequency.¹³ Hot flash reductions vary from 25% to 69% with these treatments, with improvements in composite hot flash severity and frequency from 27% to 61%.¹² Sertraline and fluoxetine have been studied, but results were not statistically different from placebo; therefore, they are not recommended.¹²

A meta-analysis of 7 RCTs studying gabapentin 900 mg (300 mg three times/day) showed gabapentin improved the frequency and severity of vasomotor symptoms.¹⁴ Possible adverse events with gabapentin include dizziness, unsteadiness, and drowsiness, typically seen during the first week, with improvement during the second week and resolution by week 4.¹⁴ In a placebo-controlled trial, higher doses of gabapentin (titrated to 2,400 mg/day) were as beneficial as conjugated estrogen (0.625 mg/day) in reducing hot flash severity scores.¹⁵ Adverse events of gabapentin at this dose included dizziness, headache, and disorientation, which limit its potential benefits.¹² Because drowsiness is an adverse effect, and the half-life is short, bedtime dosing of gabapentin may be preferable for women with disruptive sleep due to vasomotor symptoms.¹²

One prospective study and 2 double-blind RCTs 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 at bedtime significantly improved moderate to severe vasomotor symptoms compared to placebo.¹² 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 people.¹²

Table 2. Alternatives to Hormonal Therapy for Management of Vasomotor Symptoms

Drug	Dose
Selective Serotonin Reuptake Inhibitors (SSRIs)	
Paroxetine mesylate	7.5 mg once a day
Paroxetine HCl	10 mg-20 mg once a day
Citalopram	10 mg-20 mg once a day
Escitalopram	10 mg-20 mg once a day
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	
Venlafaxine	37.5 mg-150 mg once a day
Desvenlafaxine	100mg-150 mg once a day
Gamma-aminobutyric acid (GABA) analog	
Gabapentin	300 mg three times a day
Anticholinergic	
Oxybutynin	5mg-15 mg per day
Neurokinin 3 Receptor Antagonist	
Fezolinetant	45 mg once a day

Fezolinetant (VEOZAH), received FDA-approval in May 2023 for the treatment of moderate-to-severe vasomotor symptoms associated with menopause in people assigned female at birth.¹⁶ Fezolinetant acts as a selective neurokinin 3 receptor antagonist, resulting in reduced episodes of hot flashes.¹⁷ The recommended dose is 45 mg orally once daily with or without food.¹⁶

Two phase 3 clinical trials, Skylight 1 and Skylight 2, evaluated the efficacy of fezolinetant over 12 weeks.^{18,19} The 2 co-primary endpoints were mean change in vasomotor symptom frequency (a reduction of at least 2 events per day was considered clinically significant) and change in severity of moderate-to-severe vasomotor symptoms at Weeks 4 and 12.^{18,19} The mean baseline frequency of vasomotor symptoms in Skylight 1 ranged from 10.4 to 10.7 symptoms per day across the 3 treatment groups.¹⁸ In Skylight 2, the mean baseline frequency of vasomotor symptoms ranged from 11.23 to 11.79 vasomotor symptoms per day.¹⁹ Moderate-quality evidence showed a statistically and clinically significant reduction from baseline in vasomotor symptom frequency with fezolinetant 45 mg versus placebo in Skylight 1 and Skylight 2 at week 4 (least squares mean [LSM] difference: -2.07 and -2.55, respectively; p<0.01) and week 12 (LSM difference: -2.55 and -2.53, respectively; p<0.01).^{18,19}

Severity of vasomotor symptoms was defined as mild, moderate, or severe on a 3-point scale and recorded in a daily electronic diary by study participants.^{18,19} Mean symptom baseline severity scores in Skylight 1 ranged from 2.39 to 2.43.¹⁸ In Skylight 2, the mean baseline symptom

severity scores ranged from 2.41 to 2.44.¹⁹ Symptom severity was reduced in people taking fezolinetant 45 mg compared to placebo recipients at Week 4 (LSM difference -0.19 and -0.29; $p < 0.01$) and Week 12 (LSM difference: -0.20 and -0.29; $p < 0.01$; moderate-quality evidence for both endpoints).^{18,19} Although statistically significant, the clinical impact of a 0.2-to-0.3-point change on a 3-point scale is relatively small.

The most common adverse effects reported with fezolinetant include abdominal pain, diarrhea, insomnia, back pain and hepatic transaminase elevations.¹⁶ The hepatic transaminase elevations were elevated approximately 2-fold greater the upper limit of normal in some of the 45 mg fezolinetant-treated patients compared with placebo-treated patients.⁸ These hepatic transaminase elevations were generally transient, and resolved while on fezolinetant 45 mg or shortly after discontinuation.⁸

In these studies, the frequency and severity of vasomotor symptoms were also reduced in the placebo group indicating a placebo effect.¹⁸ A strong placebo effect is widely reported in studies investigating potential treatments for vasomotor symptoms.¹⁸ Trials comparing the efficacy of SSRI's or hormone replacement therapy to neurokinin 3 receptor antagonists have not been conducted. Evidence from comparative trials would provide context for the place in therapy of fezolinetant to manage bothersome vasomotor symptoms associated with menopause.

In September 2024 the FDA issued a drug safety report that fezolinetant can cause rare but serious liver injury based on a post-marketing case in a patient who developed symptomatic acute mixed hepatocellular cholestatic liver injury with elevated liver function tests within 40 days of starting fezolinetant.²⁰ Liver injury resolved upon drug discontinuation.²⁰ The FDA added new recommendations for patients and health care professionals to increase the frequency of liver blood testing, adding monthly testing for 3 months after starting fezolinetant, and then at months 6 and 9 of treatment as already recommended.²⁰ In December 2024 the FDA added a black boxed warning to highlight the known risk of rare but serious liver injury associated with the use of fezolinetant.⁵

Oregon Health Plan Policy

In the Oregon fee-for-service program, claims for preferred estrogen therapies do not require prior authorization due to high-quality evidence of efficacy, safety and cost-effectiveness. Prior authorization (PA) is required before claims can be processed for fezolinetant. The PA requires a diagnosis of moderate-to-severe vasomotor symptoms due to menopause. Inadequate effect, intolerance or contraindication to a 30-day trial of menopausal hormone therapy (e.g., estrogen/progestin) is required. In addition, intolerance or contraindication to a 30-

day trial of paroxetine, citalopram, venlafaxine, desvenlafaxine, or gabapentin is also required. The PA criteria require documentation of baseline hepatic function and continued monitoring to ensure safety precautions are in place. **Figure 1** summarizes the preferred and nonpreferred therapies on the Oregon Health Plan Preferred Drug List.

Figure 1. Oregon Health Plan Therapies for Management of Menopausal Vasomotor Symptoms

Preferred Hormonal Therapies: Estradiol (oral, topical, vaginal tablets), Estropipate (oral), Conjugated Estrogens (oral)

Nonpreferred Hormonal Therapies: Estradiol/Norethindrone (oral, topical), Estradiol/Levonorgestrel (topical), Estradiol (vaginal cream and ring), Estrogen/Bazedoxifene (oral)

Preferred Estrogen Alternatives: Citalopram, Desvenlafaxine, Duloxetine, Escitalopram, Gabapentin, Oxybutynin, Paroxetine, Venlafaxine

Nonpreferred Estrogen Alternatives: Fezolinetant, Paroxetine 7.5 mg

Conclusion

Hot flashes and night sweats can disrupt sleep and cause mood disturbance in women experiencing vasomotor symptoms associated with menopause.⁴ Estrogen therapies (oral, topical, or vaginal) are the most effective treatment for bothersome vasomotor symptoms and should be considered in women who need treatment for vasomotor symptoms who do not have contraindications to estrogen therapy.⁷ In women with an intact uterus, estrogen is given in combination with a progestogen to prevent endometrial hyperplasia or carcinoma associated with unopposed estrogen use.⁷ Nonhormonal pharmacologic therapies to alleviate vasomotor symptoms associated with menopause include paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, gabapentin and oxybutynin.¹² Fezolinetant is also included in the NAMS position statement as an alternative to hormonal therapy for management of vasomotor symptoms.¹²

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