Managing Vasomotor Symptoms Due to Menopause With Elinzanetant—Hypothetical Clinical Case Scenarios

Tara K. Iyer, MD, DABOM, MSCP; Alexa Fiffick, DO, MBS, NCMP

doi:10.12788/fp.0791

Sponsorship: This activity is sponsored by Primary Care Education Consortium and Primary Care Metabolic Group and supported by funding from Bayer.

FACULTY

Tara K. Iyer, MD, DABOM, MSCP
Medical Director
Menopause and Midlife Clinic
Division of Women's Health
Brigham and Women's Hospital
Chestnut Hill, MA

Alexa Fiffick, DO, MBS, NCMP
Founder
Concierge Medicine of Westlake
Associate Director of Education
Ms Medicine
Expert, The Menopause Mandate, US
Westlake, OH

DISCLOSURES

Dr. Iyer has served as a consultant and advisory board member to Bayer.

Dr. Fifflik is a member of the Bayer Advisory Board.

ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, at Primary Care Education Consortium.

INTRODUCTION

Vasomotor symptoms (VMS; also known as hot flashes) are among the most common and disruptive features of menopause, affecting 60% to 80% of women during menopause.[1] Hot flashes (or night sweats, if occurring at night) are sudden bursts of warmth, characterized by flushing and vasodilation, that are usually most intense over the face, neck, and chest and last for approximately 1 to 5 minutes. The experience of menopause and symptom severity can vary significantly among women of different races and nationalities.[2-7] On average, women experience hot flashes for more than 7 years, but up to one-third of women endure VMS for 10 years or longer.[2-4] Moderate hot flashes are defined as a sensation of heat with sweating and the ability to continue activity, whereas severe hot flashes are defined as the sensation of heat with sweating that causes cessation of activity.[8,9] The sensation of heat frequently is accompanied by a cascade of other disruptive symptoms such as anxiety, palpitations, dizziness, and nausea.[10]

When severe, these symptoms can significantly disrupt daily activities and diminish quality of life, leading to sleep disturbances in 40% to 60% of menopausal women (e.g., trouble falling asleep, nighttime awakenings), reduced energy, and mood changes.[11,12] The presence of VMS has been consistently associated with adverse health outcomes, including higher cardiovascular risk,[13-19] neurocognitive risk, and bone loss.[20-22]

Key takeaways

- For many women, VMS significantly disrupt daily activities, causing adverse workplace outcomes, negatively impacting interpersonal relationships, and diminishing quality of life.
- A limited number of therapies are approved for the management of VMS, and not all are suitable for every patient due to medical conditions, drug-drug interactions, side effects, or patient preferences. In addition, the strength of evidence supporting efficacy and safety varies across available options, and some treatments used in practice are not approved by the US Food and Drug Administration (FDA) for VMS, resulting in off-label use.
- Elinzanetant, the only approved dual neurokinin-targeted (NKT) therapy, is a neurokinin 1 (NK1) and neurokinin 3 (NK3) receptor antagonist that is FDA approved for moderate-to-severe VMS due to menopause.
- NKT therapies (elinzanetant and fezolinetant) offer a unique hormone-free option for women who seek effective VMS control.
- Patient education and shared decision-making are important aspects of VMS care to select the most appropriate treatment.

Despite the availability of therapeutic options for VMS, many women experiencing moderate-to-severe VMS remain untreated. A recent study showed that, of more than 100,000

women diagnosed with VMS, 79.5% had no treatment.[3] Prior to FDA approval of NKT therapies for moderate-to-severe VMS, the most commonly prescribed medications were menopausal hormone therapy (MHT) or selective serotonin/norepinephrine reuptake inhibitors (SSRIs/SNRIs).[23,24] With the exception of paroxetine 7.5 mg, SSRIs and SNRIs are not FDA approved for VMS.

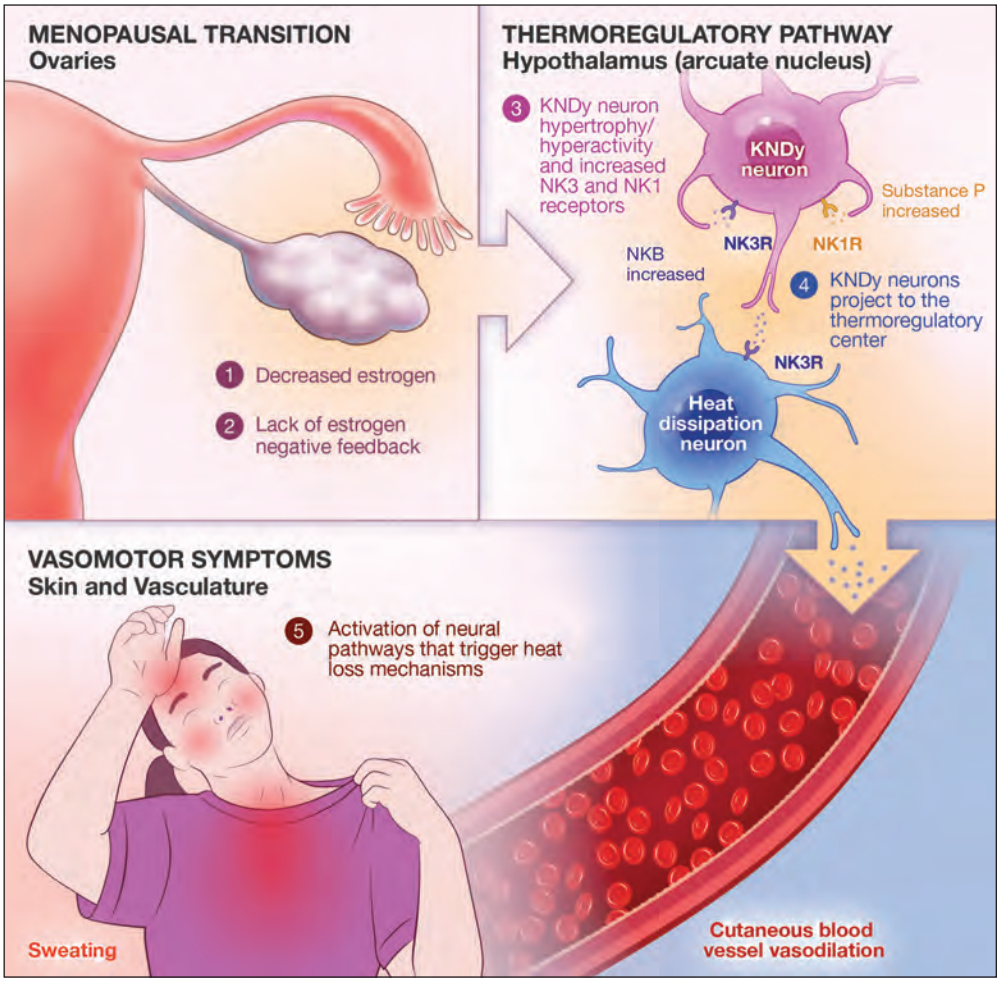
Discontinuation rates of MHT and SSRI/SNRI exceed 50% within about 7 months, reflecting wide variation in individual preferences, tolerability, and response to therapy.[25] Recent research has advanced our understanding of the underlying pathways involved in the etiology of hot flashes, leading to the development of NKT therapies. Considering the evolving therapeutic landscape with novel emerging options, treatment of VMS should be tailored to meet individual patient needs, medical history, tolerability, response, and preferences. This article aims to support clinicians in making informed decisions on treatment and in counseling women on the available options for menopausal VMS management.

MECHANISM OF ACTION, CLINICAL EVIDENCE, AND INDICATIONS FOR NKT THERAPIES

NKT therapies target the brain's thermoregulatory center within the hypothalamus, where kisspeptin/neurokinin B/dynorphin (KNDy) neurons are located. During menopause, KNDy neurons become hyperactive due to the decline of estrogen. Overexpression of substance P (SP) and neurokinin B (NKB) causes overstimulation of the thermoregulatory center, which disrupts normal temperature regulation, triggering hot flashes and night sweats. On KNDy neurons, SP binds and activates NK1 receptors, while NKB binds and activates NK3 receptors. Elinzanetant blocks NK1 and NK3 receptors, preventing SP and NKB from binding to KNDy neurons. Such antagonism reduces KNDy neuron hyperactivity, restoring thermoregulatory balance (**FIGURE 1**). Additionally, SP and NK1 receptors may further contribute to peripheral vasodilation, as well as primary insomnia.[20]

In 2025, the FDA approved elinzanetant, the first and only dual NK1 and NK3 receptor antagonist, for the treatment of moderate-to-severe VMS due to menopause. Elinzanetant is a hormone-free, dual NKT therapy that has also demonstrated benefit in improving sleep disturbances and menopause-related quality of life in clinical trials. The recommended dosage is 120 mg (two 60 mg capsules) administered orally once daily at bedtime.[26-31] In 2023, fezolinetant, a selective NK3 receptor antagonist,[32] was approved for moderate-to-severe VMS at a dose of 45 mg daily. In clinical trials of fezolinetant, a small percentage of patients experienced elevations in liver function tests, necessitating frequent hepatic laboratory testing during the first year of treatment,[33] which may be burdensome for patients. Aggregated phase 1 to 3 clinical trial data suggest there is a low risk of liver toxicity for elinzanetant.[34]

FIGURE 1. Thermoregulatory pathway.[20]



Elinzanetant clinical evidence

Elinzanetant's efficacy and safety at a 120 mg daily dose

have been evaluated in the phase 3 clinical trial program OASIS,[28-31] demonstrating VMS reduction as early as week 1, as well as improvements in sleep disturbances and menopause-related quality of life, with low risk of liver-related adverse events.

OASIS-1 and OASIS-2

OASIS-1 and OASIS-2 were multicenter, placebo-controlled, phase 3 trials. Participants included natural or surgical (bilateral oophorectomy with or without hysterectomy) postmenopausal women aged 40 to 65 years, experiencing ≥50 moderate-to-severe VMS per week. A total of 796 menopausal women were randomized 1:1 to receive elinzanetant 120 mg or placebo for 12 weeks, followed by 14 weeks of elinzanetant 120 mg.[29] Both trials demonstrated statistically significant reductions in VMS frequency and severity compared to placebo at weeks 4 and 12. Additionally, reduction in VMS frequency was statistically significant as early as week 1 in both trials. Clinically meaningful reductions in VMS frequency were observed as early as week 1 in OASIS-1 and at weeks 4 and 12 in both trials, with the effect maintained for 26 weeks. Elinzanetant also significantly improved sleep disturbances and menopause-related quality of life at week 12 (**TABLE 1**).[29]

Common adverse events included headache and fatigue; these were mild or moderate in severity. Participants taking elinzanetant reported a lower incidence of headache and fatigue between weeks 13 and 26 vs weeks 1 and 12. Reductions in VMS frequency and improvements in severity were maintained in the elinzanetant group, and benefits were consistently observed in participants switching from placebo to elinzanetant.[29]

OASIS-3

The OASIS-3 trial was a double-blind, placebo-controlled, randomized phase 3 study evaluating the long-term safety and efficacy of elinzanetant for moderate-to-severe VMS in postmenopausal women. More than 600 postmenopausal women aged 40 to 65 years with no minimum requirement of VMS events were randomized to receive 120 mg elinzanetant or placebo daily. The change in moderate-to-severe VMS frequency from baseline to week 12 showed a statistically significant reduction in VMS frequency (P <.001). Descriptive analyses demonstrated improvements for participants taking elinzanetant vs placebo in VMS frequency and severity over 50 weeks, as well as sleep disturbances and menopause-related quality of life over 52 weeks.[30]

Over 52 weeks, the safety profile remained consistent with prior studies. Treatment-emergent adverse events (TEAEs) were more frequent with elinzanetant vs placebo (70% vs 61.1%) but were mostly mild to moderate and included somnolence, fatigue, and headache. There were no serious TEAEs that were considered treatment related. Although a few liver enzyme level elevations were observed, there were no severe liver enzyme elevations or signs of hepatotoxicity.[35] Elinzanetant was not associated with an increased risk of endometrial hyperplasia or cancer.[30]

OASIS-4

The phase 3, placebo-controlled OASIS-4 trial included women experiencing at least 35 moderate-to-severe VMS per week associated with endocrine therapy for treatment or prevention of hormone receptor–positive (HR+) breast cancer. Participants were randomized 2:1 to receive either once-daily elinzanetant 120 mg for 52 weeks or once daily placebo

TABLE 1. Efficacy of elinzanetant across primary and secondary endpoints vs placebo in women with moderate-to-severe VMS due to menopause.[29a]

	OASIS-1			OASIS-2		
Endpoints	**Week 1**	**Week 4**	**Week 12**	**Week 1**	**Week 4**	**Week 12**
VMS frequency	LS: –2.5 [95% CI: –3.4, –1.6] P <.001	LS: –3.3 [95% CI: –4.5, –2.1] P <.001	LS: –3.2 [95% CI: –4.8, –1.6] P <.001	LS: –1.7 [95% CI: –2.7, –0.6] P <.001	LS: –3.0 [95% CI: –4.4, –1.7] P <.001	LS: –3.2 [95% CI: –4.6, –1.9] P <.001
VMS severity		LS: –0.3 [95% CI: –0.4, –0.2] P <.001	LS: –0.4 [95% CI: –0.5, –0.3] P <.001		LS: –0.2 [95% CI: –0.3, –0.1] P <.001	LS: –0.3 [95% CI: –0.4, –0.1] P <.001
Sleep disturbance (PROMIS-SD-SF 8b)			LS: –5.6 [95% CI: –7.2, –4.0] P <.001			LS: –4.3 [95% CI: –5.8, –2.9] P <.001
Menopause-related quality of life			LS: –0.4 [95% CI: –0.6, –0.2] P <.001			LS: –0.3 [95% CI: –0.5, –0.1] P =.0059

Abbreviations: CI, confidence interval; LS, least squares; PROMIS-SD-SF 8b, Patient-Reported Outcomes Measurement Information System Sleep Disturbance-Short Form 8b.

[a]Mean daily change from baseline.

for 12 weeks followed by once daily elinzanetant 120 mg for 40 weeks. Participants who completed 52 weeks of the trial regimen were offered the opportunity to continue treatment with elinzanetant for an additional 2 years. Elinzanetant significantly reduced VMS frequency at weeks 4 and 12 vs placebo (P <.001); improvements were noted as early as week 1. Improvements were observed in sleep disturbances, menopause-related quality of life, and VMS severity (weeks 4 and 12).[31]

Improvements in VMS frequency were sustained for up to 50 weeks, and participants switching from placebo to elinzanetant showed improvements across all endpoints. Somnolence, fatigue, and headache were the most reported adverse events during weeks 1 through 12; adverse events were mostly mild or moderate. Based on the available 52-week data for participants who received elinzanetant, the liver safety monitoring board concluded there was no substantive hepatotoxicity signal.[31]

Fezolinetant clinical evidence

SKYLIGHT 1 and SKYLIGHT 2

In 2 pivotal randomized, double-blind, placebo-controlled trials, women with an average of ≥7 moderate-to-severe hot flashes per day were randomized to daily fezolinetant 45 mg, fezolinetant 30 mg, or placebo for 12 weeks, with a 40-week extension.[36,37] Fezolinetant 45 mg reduced daily VMS frequency and severity vs placebo at weeks 4 and 12 (**TABLE 2**); improvements were observed by week 1 and were maintained through week 52 of the extension.[36,37]

SKYLIGHT 4

The phase 3 SKYLIGHT 4 trial was a double-blind, 52-week safety study that randomized postmenopausal women experiencing VMS to fezolinetant or placebo.[34] TEAEs occurred in 67.9% and 63.9% of the fezolinetant 30 mg and 45 mg groups, respectively, compared to 64.1% of the placebo group. Liver enzyme elevations more than 3 times the upper limit of normal occurred in 1% of the placebo group, 1.4% of the fezolinetant 30 mg group, and 2% of the fezolinetant 45 mg group.[34] Of note, there are limitations in comparing elinzanetant and fezolinetant clinical evidence, as no head-to-head trials have been conducted, and cross-trial comparisons have inherent limitations.

Indications, contraindications, interactions, and testing

Elinzanetant is indicated for the treatment of moderate-to-severe VMS due to menopause. Although no human data are available, based on animal data, it is contraindicated in pregnancy; exposure to elinzanetant may cause pregnancy loss or stillbirth (but not fetal malformations). Pregnancy should be excluded in females of reproductive potential before initiating treatment. Elinzanetant is a substrate and a weak inhibitor of cytochrome P450 (CYP) 3A4. It is primarily metabolized by the CYP3A4 enzyme via the liver. Concomitant use of strong CYP3A4 inhibitors should be avoided as this may increase elinzanetant exposure, which may increase risk of adverse events. When moderate CYP3A4 inhibitors must be used concomitantly, the daily dose of elinzanetant should be reduced to 60 mg. Its use with strong or moderate CYP3A4 inducers is discouraged, as these may lower elinzanetant exposure and reduce its effectiveness.[8] The FDA recommends evaluations of liver enzymes at baseline and 3 months post treatment initiation to assess hepatic function and injury.[26]

Fezolinetant is indicated for the treatment of moderate-to-severe VMS due to menopause.[32] It is contraindicated in patients with known cirrhosis and severe, end-stage kidney disease, and it should not be used concomitantly with CYP1A2 inhibitors. Cases of serious drug-induced hepatotoxicity have led to a boxed warning and recommendations for baseline hepatic testing, monthly testing for the first 3 months, and repeated testing at 6 and 9 months.[32,35-44]

CHALLENGES IN VMS MANAGEMENT

Managing VMS in primary care presents numerous challenges. Treatment options are expanding, but many are unsuitable for some women due to medical history, age, time elapsed since menopausal onset, tolerability, contraindications, or personal preference.[38]

Furthermore, women of racial and ethnic minorities (such as Black and Hispanic populations) may experience menopause earlier, experience more severe symptoms for longer durations, and have worse health outcomes, highlighting the need for clinicians to consider race and ethnicity when evaluating women with VMS.[23,39] Accordingly, addressing VMS in varying patient presentations requires an individualized, shared decision-making approach.[21,40]

The following hypothetical clinical case studies high-

TABLE 2. Efficacy of fezolinetant 45 mg vs placebo in SKYLIGHT 1 and SKYLIGHT 2 phase 3 trials.[36,37]

	SKYLIGHT 1		SKYLIGHT 2	
Endpoints	**Week 4**	**Week 12**	**Week 4**	**Week 12**
VMS frequency[a]	–2.07 [SE, 0.42] *P* <.001	–2.55 [SE, 0.43] *P* <.001	–2.55 [SE, 0.46] *P* <.001	–2.53 [SE, 0.55] *P* <.001
VMS severity[a]	–0.19 [SE, 0.06] *P* =.002	–0.20 [SE, 0.08] *P* =.007	–0.29 [SE, 0.06] *P* <.001	–0.29 [SE, 0.08] *P* <.001

Abbreviation: SE, standard error.

[a]Difference in change in least squares mean.

light distinct challenges and opportunities for managing VMS due to menopause, illustrating scenarios in which elinzanetant could be considered.

CASE STUDY 1

A 46-year-old Black woman, who is a high school teacher, with natural menopause presents with severe, persistent VMS, including up to 20 hot flashes daily and sleep disturbances that markedly impair her quality of life. As a result, she experiences reduced self-confidence, frequent clothing changes, and day and night tiredness, which interfere with her job. Lifestyle modifications, including caffeine reduction, produce minimal benefits. She has an elevated body mass index (BMI) and takes medication for hyperlipidemia. She has tried MHT and despite trying several dosages, she is frustrated by adverse effects, including edema and severe breast tenderness.

In this case scenario, the challenges of life-disruptive VMS, comorbidities, and concomitant medications are further compounded by the earlier onset and more severe VMS experienced by Black women. An alternative to MHT should be considered for this patient, given the adverse effects noted. While paroxetine 7.5 mg is an approved option, it may inadequately address her severe symptoms and cause problematic adverse effects such as weight gain and fatigue. An NKT therapy such as elinzanetant or fezolinetant may be more appropriate. While both fezolinetant and elinzanetant are effective in reducing the frequency and severity of VMS, elinzanetant has additionally demonstrated consistent sleep benefits and requires less frequent liver safety monitoring.[28-32] Importantly, clinical studies have demonstrated efficacy of elinzanetant in Black women and in women with higher BMIs, achieving clinically meaningful reductions in daily VMS frequency observed as early as week 1.[41]

CASE STUDY 2

A 50-year-old professional Asian woman presents with severe hot flashes and night sweats up to 4 times an hour, leading to significant trouble sleeping and impaired quality of life. The patient describes her hot flashes as lasting more than 10 minutes, accompanied by sweating and a rapid heartbeat. Her medical history includes HR+ breast cancer, now in remission, for which she takes endocrine therapy. The patient discontinued an SSRI after 4 months due to several intolerable side effects.

MHT is typically considered contraindicated in patients with a history of breast cancer, and the patient noted prior intolerance of an SSRI; thus, an NKT therapy such as elinzanetant or fezolinetant should be considered. Notably, in OASIS-4, women with VMS associated with adjuvant endocrine therapy for treatment or prevention of HR+ breast cancer experienced a reduction in symptom frequency, as well as improvements in sleep disturbances and menopause-related quality of life, while taking elinzanetant.[31] Based on OASIS-4 results, the National Comprehensive Cancer Network® Survivorship Guidelines now list elinzanetant as a preferred NKT option for the management of VMS in female breast cancer survivors, offering a safe and effective, hormone-free option to help improve VMS and quality of life.[42] To date, there are no data on fezolinetant in the breast cancer population.

POINTS TO CONSIDER AND SHARED DECISION-MAKING

Before prescribing therapy for VMS, clinicians should assess a patient's potential risks and consider individual characteristics and preferences, which may include choosing to avoid hormones and the burden of monitoring. Patients may also base decisions on potential for sleep improvement, route of administration, cost, and prior treatment experiences. Because menopause affects each person differently, it is important that women receive care from a clinician committed to understanding symptoms and improving quality of life, while also limiting potential health risks. Treatment decisions should be made collaboratively between the patient and clinician and should be revisited over time based on outcomes and changes in health status.

Shared decision-making should begin with proactive symptom inquiry, as many women normalize VMS as an unavoidable part of aging, may feel embarrassed discussing menopause, are unaware that newer hormone-free treatments are available, or may assume that treatment options are limited to MHT or over-the-counter products. Clinicians may also fail to address VMS because of limited menopause-specific training, competing priorities during brief visits, uncertainty about treatment guidance, or concerns about treatment safety.[40,43-45]

A practical approach might involve an ask-assess-align-adjust framework: ask routinely about hot flashes, night sweats, sleep disruption, mood changes, concentration, work impairment, and relationship burden; assess symptom severity, medical history, contraindications, concurrent medications, and prior treatment experiences; align treatment selection with the patient's goals and tolerance for monitoring or adverse events; and adjust the plan through scheduled follow-up based on symptom response, tolerability, adherence, and changes in health status.[38,43,45]

SUMMARY

VMS remain among the most common and disruptive features of menopause and can significantly impact daily activities and diminish quality of life. Increased understanding of the underlying pathways in the etiology of VMS has led to the development of NKT therapies that have been shown to treat menopausal VMS effectively.

Elinzanetant exerts an early, sustained effect on VMS due

to menopause and provides additional benefits in sleep quality and quality of life. By antagonizing 2 key receptors within the KNDy neuronal pathway (the central driver of thermoregulatory dysfunction), it offers a mechanism of action distinct from MHT and other hormone-free treatment options. In contrast, fezolinetant is an NK3 receptor–targeted therapy that, while effective for reducing frequency and severity of VMS, requires frequent monitoring of hepatic enzymes.

NKT therapies offer a unique option for women who are not candidates for, or who wish to avoid, MHT and seek effective and safe symptom control beyond over-the-counter treatments or lifestyle changes. Incorporating patient education on all available treatment options and aligning treatment with patients' preferences and characteristics through shared decision-making can help optimize VMS care. ●

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