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CORRESPONDENCE

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"Veozah (Fezolinetant): A Promising Non-Hormonal Treatment for Vasomotor Symptoms in Menopause"

Ayesha Shaukat[1] | Azka Mujeeb[2] | Syeda Shahnoor[1] | Nathalie Nasser[3] | Abdul Moiz Khan[4]

[1]Department of Internal Medicine, Dow University of Health Sciences, Karachi, Pakistan

[2]Department of Internal Medicine, Jinnah Sindh Medical University, Karachi, Pakistan

[3]Lebanese University Faculty of Medical Sciences, Dekwaneh, Lebanon

[4]Ayub Medical College, Abbottabad, Pakistan

Correspondence

Nathalie Nasser, Lebanese University Faculty of Medical Sciences, Dekwaneh, Lebanon.
Email: nathalienasser158@gmail.com

Abstract

Vasomotor symptoms (VMS) are a common and distressing experience during menopause, affecting a significant portion of women. Hormone therapy (HT) has been the traditional treatment, but its limitations and potential risks have led to the search foar non-hormonal alternatives. Recently, the FDA approved Veozah (Fezolinetant) as a promising nonhormonal solution for moderate to severe VMS in menopause. Veozah, an innovative neurokinin 3 (NK3) receptor antagonist, targets the disrupted thermoregulation underlying VMS. It modulates neural activity within the thermoregulatory center by crossing the blood-brain barrier, offering relief from hot flashes and night sweats. Clinical trials, including SKYLIGHT 1TM, SKYLIGHT 2TM, and SKYLIGHT 4TM, have established Fezolinemtant's efficacy and safety profile. The recommended dosage of one 45 mg tablet per day demonstrates proportional pharmacokinetics, with generally mild side effects that require regular monitoring. Fezolinetant's oral availability makes it a convenient and accessible option for women seeking relief from VMS, potentially improving their overall well-being.

KEYWORDS

obstetrics/gynecology, pharmacology and pharmacy

1 | BACKGROUND

Vasomotor symptoms (VMS), also known as hot flashes and night sweats, are a primary outcome associated with menopause experienced by a larger population of women from 40 to 64-year-old.[1] During the menopausal transition, the prevalence of vasomotor symptoms (VMS) in postmenopausal women is reported to be as high as 80%, according to a study conducted by Women's Health Across the Nation. An investigation involving data from 10 countries revealed that VMS affected approximately 30%–50% of women in their late 50 s. Similarly, a cross-sectional study carried out in Australia reported a rate of 33% among women aged 65–79 years.[2] VMS occur due to impaired estrogen feedback mechanism on the hypothalamus, resulting in disrupted thermoregulation. On average, VMS persists for approximately 7.4 years. The uncomfortable experiences of hot flashes and night sweats are associated with various effects on women's well-being, including decreased mood, disrupted sleep, impaired social interactions, difficulties at work, heightened anxiety, and fatigue. Ultimately, these symptoms have a detrimental impact on women's quality of life (QoL), leading them to seek treatment to alleviate the discomfort.[2,3] Hormone therapy (HT), consisting of either estrogen alone or a combination of estrogen and progesterone, is considered the established and successful treatment for VMS associated with menopause. This treatment approach is

particularly useful for women experiencing symptoms who are under the age of 60 and within 10 years of the onset of menopause.[3] Nevertheless, there is evidence suggesting that HT may be linked to an increased risk of hormone-dependent cancers (such as breast cancer), stroke, and venous thromboembolism. Therefore, despite its effectiveness in managing symptoms, HT has limitations due to factors such as individual risk factors, personal preferences, the timing of menopause onset, underlying medical conditions, and age. Regular monitoring and evaluation are necessary when undergoing HT to ensure its safety and appropriateness.[2,3] Selective serotonin reuptake inhibitors (SSRIs), gabapentin, cognitive behavioral therapy, and herbal therapies are among the nonhormonal treatments available for managing menopause-associated symptoms. However, their clinical effectiveness is limited, and they may be associated with adverse effects such as sedation and nausea.

2 | VEOZAH AS AN ALTERNATIVE NONHORMONE THERAPY (NHT)

In the quest for a safe and alternative, the FDA recently approved Veozah (fezolinetant) for the treatment of moderate to severe VMS caused by menopause. As one of the initial nonhormonal neurokinin 3 (NK3) receptor antagonists, Veozah offers a promising solution. Veozah, known as fezolinetant, is an innovative nonhormonal medication to treat moderate to severe VMS associated with menopause. VMS occurs due to disruptions in thermoregulation, which is influenced by altered signaling of kisspeptin, neurokinin B, and dynorphin (KNDy) within the body. Estrogen plays a role in regulating the neuropeptide Neurokinin B (NKB), which activates the Neurokinin 3 receptor (NK3R) found on KNDy neurons. Following menopause, decreased estrogen levels lead to increased NKB signaling and subsequent release of Gonadotropin-releasing hormone (GnRH) through KNDy neuron activity.[3] Fezolinetant, acting as an NK3R antagonist, modulates neural activity within the thermoregulatory center by crossing the blood-brain barrier. This mechanism helps to mitigate vasomotor symptoms and provide relief.

3 | CLINICAL TRIALS

The approval of Veozah was supported by the results obtained from the BRIGHT SKY™ program, which included three phase 3 clinical trials: SKYLIGHT 1TM (NCT04003155), SKYLIGHT 2TM (NCT04003142), and SKYLIGHT 4TM (NCT04003389).[4] Both SKYLIGHT 1TM and SKYLIGHT 2TM trials demonstrated the efficacy of fezolinetant in reducing the frequency and severity of hot flashes associated with menopause. Importantly, no significant Treatment-Emergent Adverse Events (TEAEs) were observed during the trials, ensuring the safety of the drug.[2,5] In the clinical trial SKYLIGHT 4TM (NCT04003389), the objective was to assess the safety and tolerability of fezolinetant as a long-term treatment for menopause-associated moderate-to-severe VMS. The study focused on evaluating the frequency and severity of adverse effects related to the drug. The results of the trial provided additional evidence supporting the ongoing use of fezolinetant as an innovative nonhormonal approach to treat menopause-associated VMS.[1]

4 | RECOMMENDED DOSAGE AND SIDE EFFECTS

To achieve optimal effectiveness, it is advised to take one 45 mg Veozah tablet orally per day, either with or without food. In studies conducted with healthy women, it was observed that Fezolinetant's maximum concentration (Cmax) and overall exposure (AUC) increased in a proportional manner when doses ranging from 20 to 60 mg were administered once daily. These doses correspond to approximately 0.44–1.33 times the recommended dosage.[6] Surprisingly, the drug treatment did not show any noticeable patterns in the levels of steroid hormones, except for a temporary decrease in luteinizing hormone (LH) levels when Fezolinetant reached its highest concentrations. Remarkably, even when taken at 20 times the recommended dosage, the drug does not have a prolonged effect on the QT interval. According to the findings of clinical trial 3, a minimum of 2% of the participants who were administered Veozah 45 mg encountered more severe side effects compared to those who were given a placebo.[6] The primary manifestation of the drug's side effects consisted of various undesirable symptoms such as abdominal pain, diarrhea, insomnia, backache, hot flushes, and increased hepatic transaminases. In the combined laboratory data from Trials 1, 2, and 3, 2.3% of patients exposed to VEOZAH 45 mg experienced elevated hepatic transaminases, with an incidence rate of 2.7 per 100 person-years. In comparison, the placebo group exhibited elevated hepatic transaminases in 0.9% of patients, with an incidence rate of 1.5 per 100 person-years.[6] These observations underscore the importance of regularly monitoring patients who are undergoing treatment by analyzing their blood samples. Additionally, it is crucial to avoid administering Fezolinetant in cases where severe renal impairment or end-stage renal disease has been confirmed, as well as in combination with CYP1A2 inhibitors. The reasoning behind this precaution is that in women with severe renal impairment, the AUC (area under the curve) of ES259564, a significant metabolite of Fezolinetant, increases by approximately 380%. Since VEOZAH is a CYP1A2 substrate, co-administration with CYP1A2 inhibitors elevates its plasma Cmax (maximum concentration) and AUC. The drug exhibits a half-life of 9.6 h and a clearance rate of 10.8 L/h in patients, with 79.6% of the oral dose being eliminated in urine and 14.7% in feces.[6]

5 | CONCLUSION

Fezolinetant represents a significant breakthrough in the treatment of menopause-associated VMS and offers a nonhormonal alternative that meets the needs of countless women worldwide. The FDA's approval of Fezolinetant confirms its unique mechanism of action and

its potential to revolutionize the treatment of VMS. By effectively addressing the imbalance between estrogen and NKB that occurs during the cessation of the menstrual cycle, the drug tackles the disruption in the brain's thermoregulatory center, which leads to the development of VMS. Notably, as an NK3R antagonist, Fezolinetant is the first nonhormonal therapy that can cross the blood-brain barrier to inhibit NKB and alleviate hot flashes in the body. Furthermore, the oral availability of Fezolinetant provides a convenient option for menopausal women seeking relief from VMS, contributing to their overall well-being and quality of life. The availability of an oral medication like Fezolinetant expands its reach to a broader range of patients and promotes self-management. It eliminates the necessity for specialized medical facilities or healthcare professionals, making it more accessible to women regardless of their location or proximity to healthcare centers.

AUTHOR CONTRIBUTIONS

Ayesha Shaukat: Conceptualization; investigation; writing—original draft. **Azka Mujeeb**: Conceptualization; investigation; writing—original draft. **Syeda Shahnoor**: Conceptualization; project administration; supervision; visualization; writing—review & editing. **Nathalie Nasser**: Conceptualization; supervision; writing—review & editing. **Abdul Moiz Khan**: Conceptualization; project administration; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

TRANSPARENCY STATEMENT

The lead author Nathalie Nasser affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Ayesha Shaukat http://orcid.org/0009-0006-1541-3037
Syeda Shahnoor http://orcid.org/0000-0001-9049-3109
Nathalie Nasser https://orcid.org/0000-0001-9435-291X
Abdul Moiz Khan http://orcid.org/0000-0001-9796-8867

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