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Menopause and Vasomotor Symptoms: Narrative Review of Evidence and Therapeutic Perspectives

Pedro Augusto Júnior Zaiats[1,2]

[1]Brazilian Medical Association (SBCM), São Paulo, Brazil
[2]Brazilian Institute of Medical Sciences, São Paulo, Brazil
Email: pedroazj@gmail.com

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Abstract

Menopause is a physiological process characterized by ovarian failure and consequent hypoestrogenism, often accompanied by vasomotor symptoms (VMSs), such as hot flashes and night sweats. These manifestations affect up to 80% of women, may persist for more than a decade, and significantly impact quality of life, occupational performance, and psychosocial well-being. Hormone therapy (HT) remains the gold standard for managing VMS; however, it is not risk-free and is contraindicated in specific subgroups, such as women with a history of breast cancer or thromboembolic events. In this context, non-hormonal alternatives have been increasingly studied, including antidepressants, gabapentin, neurokinin-3 receptor (NK3R) antagonists such as fezolinetant, as well as complementary therapies and behavioral interventions. This article aims to provide a narrative review of the most relevant evidence published between 2014 and 2024 regarding the pathophysiology, clinical impact, and hormonal and non-hormonal therapies for menopausal vasomotor symptoms, highlighting recent advances and future perspectives.

Keywords

Menopause, Vasomotor Symptoms, Hot Flashes, Hormone Therapy, Fezolinetant

1. Introduction

Menopause, retrospectively defined after 12 consecutive months of amenorrhoea, occurs on average at the age of 51 and represents the end of a woman's reproductive life [1]. This natural process is marked by progressive ovarian failure and con-

sequent decline in circulating estrogen and progesterone levels [2].

Among the most prevalent clinical manifestations are vasomotor symptoms (VMSs), characterized by hot flashes (sudden heat waves) and night sweats [3]. It is estimated that 60% - 80% of women experience such symptoms at some stage of the menopausal transition, with up to 25% reporting severe and disabling manifestations [4]. The average duration is 7 to 10 years, and symptoms may persist beyond this period in a significant portion of women [5].

In addition to physical discomfort, VMSs are associated with reduced quality of life, sleep disturbances, irritability, fatigue, subjective cognitive decline, and even increased cardiovascular risk, especially in women who develop early and intense symptoms [6] [7].

The clinical management of these symptoms remains one of the main challenges in women's health care during the climacteric period. Hormone therapy (HT), when not contraindicated, is considered the most effective treatment, providing up to a 75% reduction in frequency and an 87% in intensity of hot flashes [8]. However, contraindications such as hormone-dependent breast cancer, previous thrombolytic events, and cardiovascular disease limit its use in a significant portion of patients [9].

Over the past two decades, there has been increasing interest in safe and effective non-hormonal strategies. Among them are well-established pharmacological agents such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, and clonidine [10]. More recently, new pharmacological agents have emerged as promising alternatives, including neurokinin-3 receptor (NK3R) antagonists, especially fezolinetant, which demonstrated efficacy comparable to HT in phase III clinical trials [11].

In parallel, complementary therapies and lifestyle modifications have also been investigated, such as weight loss, cognitive behavioral therapy (CBT), hypnosis, physical exercise, and acupuncture, although with varying levels of evidence [12]-[14].

2. Objective

This narrative review aims to compile and critically discuss current evidence regarding the pathophysiology, clinical impact, and treatment strategies for VMS, with an emphasis on emerging non-hormonal approaches.

3. Methodology

This is a narrative literature review designed to synthesize and critically discuss the main available evidence on menopause and vasomotor symptoms (VMSs).

The literature search was conducted between June and August 2025 in electronic databases such as PubMed/MEDLINE, SciELO, Embase, and Cochrane Library. The following keywords were used in both Portuguese and English: menopausa, climatério, vasomotor symptoms, hot flashes, night sweats, hormone therapy, non-hormonal therapy, NK3 receptor antagonist, fezolinetant, and cognitive behavioral

therapy.

3.1. Inclusion Criteria

- Original articles, narrative or systematic reviews, guidelines, and consensus statements published between 2014 - 2024;
- Studies in humans, published in English, Portuguese, or Spanish;
- Works addressing the pathophysiology, epidemiology, or pharmacological/non-pharmacological management of VMS.

3.2. Exclusion Criteria

- Isolated case reports;
- Articles focusing exclusively on other menopausal manifestations (such as urogenital or osteoarticular changes);
- Publications without the full text available.

A qualitative analysis of the selected articles was performed, extracting the most relevant data related to the pathophysiology, prevalence, impact on quality of life, therapeutic indications, and adverse effects of different treatment modalities.

This methodology allowed the construction of a broad, updated, and critical overview of the topic, aiming to support evidence-based clinical practice and shared decision-making between healthcare professionals and patients.

4. Pathophysiology and Vasomotor Symptoms

Vasomotor symptoms (VMSs) are the most characteristic clinical manifestation of the menopausal transition. Although widely described, their pathophysiology is not yet fully understood.

4.1. Role of Hypoestrogenism

The decline in estradiol levels is considered the main trigger for the development of hot flashes. Estrogen plays a crucial role in modulating hypothalamic thermoregulation, acting on neurons in the preoptic nucleus of the hypothalamus [1]. Estrogen deficiency promotes instability in the thermoregulatory "set-point", reducing the thermoneutral zone. As a result, small increases in core body temperature trigger exaggerated vasodilatory responses, clinically manifested as hot flashes [2].

4.2. KNDy Neurons and Neurokinin-3 Receptors

Recent studies highlight the importance of KNDy neurons (kisspeptin, neurokinin B, and dynorphin), located in the arcuate nucleus of the hypothalamus [3]. These neurons have estrogen receptors and are highly sensitive to hypoestrogenism.

Estrogen reduction leads to hyperactivity of KNDy neurons, with increased release of neurokinin B (NKB), which acts on NK3 receptors in the medial preoptic

nucleus. This overstimulation promotes central thermoregulatory dysregulation, triggering VMS [4].

The reduction of estrogen levels during menopause leads to hyperactivity of KNDy neurons, resulting in increased release of neurokinin B (NKB). NKB acts on NK3 receptors located in the medial preoptic nucleus, a region crucial for body temperature regulation. This overstimulation causes dysregulation of the thermoregulatory center, which manifests in peripheral responses characteristic of hot flashes, such as cutaneous vasodilation, increased sweating, and a sudden sensation of heat.

Recognition of this pathophysiological mechanism has supported the development of NK3 receptor antagonists, such as fezolinetant, which has demonstrated robust clinical efficacy in reducing hot flashes in phase III clinical trials [5].

4.3. Alterations in the Autonomic Nervous System

Evidence suggests that hypoestrogenism is also associated with increased sympathetic activation and altered cutaneous blood flow [6]. This autonomic dysfunction contributes to hot flashes and night sweats, reinforcing the multifactorial nature of VMS.

4.4. Modulating Factors

Several factors influence the frequency and intensity of symptoms, including:

- **Obesity and insulin resistance** are associated with a higher prevalence of hot flashes [7].
- **Family history and genetic factors**: Certain polymorphisms in genes related to estrogen metabolism and serotonin receptors have been linked to increased risk of severe symptoms [8].
- **Psychological stress and cultural factors**: Modulate perception and intensity of symptoms, explaining variations between different populations [9].

5. Hormone Therapy (HT)

Hormone therapy (HT) remains the gold standard for the treatment of menopausal vasomotor symptoms (VMSs). Several randomized trials and systematic reviews demonstrate its superior efficacy compared to any other available therapeutic modality [1]-[3].

5.1. Mechanism of Action

HT involves the administration of estrogen alone (in hysterectomized women) or in combination with a progestogen (in women with an intact uterus) to partially replace the hormonal deficiency characteristic of menopause [4].

- **Estrogen**: Restores hypothalamic modulation of thermoregulation, expanding the thermoneutral zone reduced by hypoestrogenism.
- **Progestogen**: Prevents endometrial hyperplasia and cancer in women with an intact uterus.

This mechanism results in a rapid decrease in the frequency and intensity of hot flashes, which is often observed within the first 2 to 4 weeks of treatment [5].

5.2. Clinical Efficacy

- Controlled clinical trials show that HT reduces the frequency of VMS by up to 75% and intensity by up to 87% [6] [7].
- Improvements in quality of life, sleep, and sexual health are also consistently documented [8].
- In comparison, non-hormonal therapies rarely achieve reductions greater than 50%, underscoring the superiority of HT [9].

5.3. Indications

- Women with moderate to severe vasomotor symptoms affecting quality of life;
- Patients up to 60 years old or within 10 years since menopause;
- Absence of absolute contraindications [10] [11].

5.4. Contraindications

HT should not be used in patients with:

- Current or past history of hormone-dependent breast cancer;
- Endometrial cancer;
- Previous venous thromboembolic disease;
- Established atherosclerotic cardiovascular disease (heart attack, stroke, unstable angina);
- Unexplained genital bleeding;
- Severe active liver disease [12].

5.5. Risks and Safety

The Women's Health Initiative (WHI) study, published in 2002, raised concerns about increased cardiovascular and breast cancer risks associated with hormone therapy (HT), leading to a significant global decline in its prescription [13].

However, subsequent analyses have shown that:

- Cardiovascular risk depends on age and time since menopause. In younger women (<60 years or <10 years since menopause), HT may even have a neutral or protective cardiovascular effect [14].
- Breast cancer risk is mainly associated with combined estrogen + progestogen therapy [15].
- The use of estrogen alone (in hysterectomized women) did not show a significant increase in breast cancer risk in the WHI [16].

Therefore, the current consensus is that the window of opportunity is associated with greater benefit and lower risk [17].

5.6. Routes of Administration

- **Oral**: Estradiol, estradiol valerate, conjugated estrogens;
- **Transdermal**: Estradiol patches or gels, associated with a lower thromboembolic risk;
- **Vaginal (low dose)**: Primarily indicated for genitourinary symptoms, with no significant effect on VMS [18].

The regimen should be individualized, considering the risk profile, patient preferences, and therapeutic availability.

6. Non-Hormonal Therapies

The search for alternatives to hormone therapy (HT) stems from the presence of absolute or relative contraindications in some women, as well as the refusal of certain patients to use hormones. In such cases, non-hormonal therapies play a crucial role.

They can be classified into:

1) Established non-hormonal drugs: Antidepressants, gabapentin, clonidine;

2) New pharmacological agents: Neurokinin-3 receptor (NK3R) antagonists, notably fezolinetant;

3) Herbal and complementary therapies.

6.1. Antidepressants (SSRIs and SNRIs)

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are the most studied non-hormonal drugs for VMS.

Mechanism: They modulate serotonergic and noradrenergic circuits involved in hypothalamic thermoregulation [1].

Efficacy: They reduce hot flash frequency by 40–65%; less effective than HT but superior to placebo [2].

Main options:

- **Venlafaxine (SNRI)**: Significant reduction of moderate to severe hot flashes by **50% - 60%** [3].
- **Desvenlafaxine**: Consistent improvement in frequency and intensity, with rapid onset [4].
- **Paroxetine (SSRI)**: The first drug approved by the FDA (at low dose, 7.5 mg/day) for moderate to severe hot flashes [5].
- **Escitalopram and sertraline**: Also demonstrated efficacy, although less than venlafaxine [6].

Adverse effects: Nausea, dry mouth, sexual dysfunction, and insomnia [7].

6.2. Gabapentin

Mechanism: Modulates voltage-gated calcium channels, reducing neuronal excitability [8].

Efficacy: Reduces hot flash frequency by 45% - 60%, especially effective in women

with nighttime symptoms and sleep disturbances [9].

Advantages: Useful in patients with contraindications to HRT and with predominantly nocturnal symptoms.

Adverse effects: Dizziness, drowsiness, fatigue, and peripheral edema [10].

6.3. Clonidine

- **Mechanism**: *α*2-adrenergic agonist, reduces central sympathetic activity [11].
- **Efficacy**: Modest benefit, with VMS reduction of 20% - 40%, lower than SSRIs/SNRIs and gabapentin [12].
- **Clinical use**: An option in refractory cases or when other therapies are contraindicated.

Adverse effects: Dry mouth, constipation, drowsiness, and hypotension [13].

6.4. NK3 Receptor Antagonists (Fezolinetant and Similar Agents)

In recent years, a new class of drugs targeting the pathophysiological mechanism of VMS has emerged: neurokinin-3 receptor (NK3R) antagonists.

- **Mechanism**: They block the action of neurokinin B in KNDy neurons in the arcuate nucleus, reducing hypothalamic hyperexcitability induced by hypoestrogenism [14].
- **Fezolinetant**:
- Phase III trials (SKYLIGHT 1 and 2) showed a significant reduction in hot flash frequency and intensity within the first 4 weeks, with sustained effect up to 52 weeks [15].
- Demonstrated comparable efficacy to HT in some outcomes, without hormone-related risks [16].
- Well tolerated; main adverse events: transient elevation of liver enzymes, headache, and insomnia [17].
- Approved by the FDA in 2023 for treatment of moderate to severe menopausal VMS [18].

6.5. Herbal and Complementary Therapies

Interest in natural products remains high, though the evidence is inconsistent.

- **Phytoestrogens** (soy isoflavones, red clover): Some studies suggest modest reduction of SVM, but meta-analyses show heterogeneous results [14].
- **Cimicifuga racemosa** (*black cohosh*): May reduce hot flash frequency by 25% - 30%, but poses hepatotoxicity risk and lacks standardized extracts [15].
- **Vitamin E**: Slight benefit, not superior to placebo in several studies [16].
- **Acupuncture**: Some clinical trials have shown an effect similar to placebo, but other analyses suggest modest reduction and subjective improvement [17].
- **Hypnosis and cognitive behavioral therapy (CBT)**: Do not directly reduce VMS, but improve symptom perception, sleep quality, and psychological well-being [18] (**Table 1**).

Table 1. Comparative summary of non-hormonal therapies.

Therapeutic Class	Average VMS Reduction	Onset Time	Main Side Effects
SSRIs/SNRIs	40% - 65%	1 - 2 weeks	Nausea, dry mouth, insomnia, sexual dysfunction
Gabapentin	45% - 60%	1 – 2 weeks	Drowsiness, dizziness, fatigue
Clonidine	20% - 40%	2% - 4% weeks	Hypotension, dry mouth, sedation
Fezolinetant (NK3R ant.)	50% - 70%	<4 weeks	Headache, insomnia, mild liver enzyme elevation
Herbal Therapies	10% - 30% (variable)	4% - 8% weeks	Hepatotoxicity (black cohosh), mild gastrointestinal effects

7. Behavioral Interventions and Lifestyle

Although pharmacological therapies—both hormonal and non-hormonal—are the most effective for managing vasomotor symptoms (VMSs), non-pharmacological interventions play an important complementary role, especially for women with contraindications to medications or those who prefer natural approaches.

7.1. Weight Loss and Physical Activity

Observational studies have shown an association between high body mass index (BMI) and increased frequency and intensity of hot flashes [1].

- Central adiposity appears to intensify hypothalamic thermoregulatory instability.
- Interventions promoting weight loss, such as dietary and exercise programs, have shown a significant reduction in VMS in some cohorts [2].

Regular physical activity:

- Improves cardiovascular fitness, sleep quality, and mood.
- Direct effects on VMS remain inconsistent, but indirect benefits contribute to symptom perception improvement [3].

7.2. Cognitive Behavioral Therapy (CBT)

CBT is one of the most well-studied behavioral interventions for VMS.

- It works by reinterpreting the experience of hot flashes, reducing perceived intensity and the impact on quality of life [4].
- Randomized clinical trials have shown significant improvements in how VMSs interfere with daily life, even without reducing their actual frequency [5].
- It is recommended by guidelines as an adjunct for women who cannot or do not want to use pharmacological therapies [6].

7.3. Relaxation Techniques and Mindfulness

- Progressive muscle relaxation, diaphragmatic breathing, and mindfulness have shown modest benefits in some studies, mainly by reducing anxiety associated

with VMS [7].

- Although not very effective at directly reducing hot flashes, they may be useful as complementary approaches [8].

7.4. Hypnosis

Clinical hypnosis has been evaluated in controlled trials for VMS.

- Studies show up to 50% reduction in hot flash frequency compared to control groups [9].
- Likely mechanism: altered cortical perception of thermal stimuli and reduced anxiety [10].
- Despite promising results, it still lacks standardization and wide clinical availability.

7.5. Acupuncture

Acupuncture is widely used, though evidence remains controversial.

- Some studies report 20% - 30% reductions in hot flash frequency, but placebo-controlled trials (sham needles) show similar results [11].
- It is believed that the positive effects are more related to the placebo effect and subjective well-being than to direct physiological modulation [12].

7.6. Sleep Hygiene and Stress Management

Nighttime VMS contributes to insomnia and daytime fatigue.

- Sleep hygiene strategies (avoiding caffeine, lowering room temperature, and wearing light clothing) can help alleviate nighttime discomfort [13].
- Stress management techniques, such as yoga and meditation, have a positive impact on quality of life, although they have only a modest effect on the frequency of hot flashes [14]

7.7. Health Education and Social Support

Health education programs for menopausal women and support groups help reduce anxiety and the stigma associated with menopause.

- Adequate social support contributes to improved subjective experience of VMS, even if it has no direct effect on symptom physiology [15].

8. General Comparison of Efficacy and Safety

Therapeutic options for managing vasomotor symptoms (VMSs) vary widely in terms of efficacy, safety profiles, availability, and cost.

8.1. Comparison between Hormonal and Non-Hormonal Therapy

Hormone Therapy (HT): Remains the most effective treatment, reducing VMS by 70% - 90%. It has a rapid onset (1% - 2% weeks) and significantly improves quality of life. Limitation: increased risks in some populations (e.g., breast cancer, thromboembolic events, cardiovascular disease).

8.2. Non-Hormonal Pharmacologic Therapies

- **SSRIs/SNRIs**: Reduce hot flashes by 40% - 65%, and are a good option for women with HT contraindications or associated depressive symptoms.
- **Gabapentin**: Moderate efficacy, especially useful for nighttime hot flashes.
- **Clonidine**: Modest efficacy, considered a second- or third-line option.
- **Fezolinetant (NK3 antagonist)**: Efficacy is comparable to HT in some studies, has a favorable safety profile, and represents the greatest innovation in recent years.

8.3. Behavioral and Herbal Interventions

- Generally less effective in objectively reducing VMS, but contributing to subjective symptom relief, sleep quality, and psychological well-being.
- Can be recommended as complementary strategies.

9. Future Perspectives

VMS treatment is evolving, driven by the need for effective and safe options for women who cannot or do not wish to use hormones.

9.1. Emerging Pharmacological Targets for the Management of Vasomotor Symptoms

NK3 Receptor Antagonists: These drugs act by blocking neurokinin 3 (NK3) receptors in hypothalamic KNDy neurons, which play a central role in body temperature regulation. Fezolinetant, currently approved by the FDA, has been shown to significantly reduce the frequency and severity of hot flashes in menopausal women. Other NK3 antagonists under investigation, such as elinzanetant and pavinetant, demonstrate promising clinical efficacy and may expand non-hormonal therapeutic options, particularly for women with contraindications to hormone therapy.

Endocannabinoid System Modulation: Emerging research suggests that the endocannabinoid system—involved in regulating physiological processes such as sleep, mood, and thermoregulation—could be a valuable target for managing hot flashes. Compounds modulating CB1 and CB2 receptors may stabilize hypothalamic thermoregulatory centers, reducing the intensity and frequency of vasomotor responses. However, most studies are still in preclinical or early clinical stages.

Digital Neurotherapies: Wearable technologies and AI-based digital platforms are being developed to monitor real-time physiological signals, including heart rate, body temperature fluctuations, and sleep patterns. Based on these data, personalized interventions such as biofeedback exercises, relaxation techniques, and behavioral adjustments can be applied to modulate autonomic responses associated with hot flashes and improve quality of life. This represents an innovative, non-pharmacological approach with potential for integration with conventional treatments.

9.2. Personalized Therapies

- Advances in pharmacogenomics may allow for selecting the best treatment based on genetic profile, cardiovascular risk, and cancer predisposition.
- The future points toward precision medicine, integrating clinical, genetic, and lifestyle data.

9.3. Multidisciplinary Integration

- Combined strategies (e.g., pharmacotherapy + CBT + physical activity) appear to offer greater overall impact.
- VMS management is shifting toward a multidisciplinary model, involving gynecologists, endocrinologists, psychiatrists, nutritionists, and psychologists.

10. Conclusions

Vasomotor symptoms (VMSs) represent the most prevalent and impactful clinical manifestation of the menopausal transition, significantly impairing women's quality of life. Their pathophysiology is closely related to estrogen deficiency and instability of the hypothalamic thermoneutral zone, modulated by neurotransmitters such as norepinephrine, serotonin, and neurokinins.

Hormone therapy (HT) remains the most effective treatment option, promoting reductions of up to 90% in VMS. However, its use must be carefully individualized, taking into account factors such as age, time since menopause, and contraindications.

Non-hormonal therapies, including SSRIs/SNRIs, gabapentin, clonidine, and more recently, fezolinetant, expand the therapeutic arsenal and are essential for women who cannot or do not wish to use hormones.

Behavioral interventions—such as cognitive-behavioral therapy, hypnosis, and lifestyle changes—play an important adjunctive role, especially in subjective improvement and quality of life, although their efficacy in objectively reducing hot flashes is limited.

From a practical standpoint, the management of VMS should be individualized, evidence-based, and multidisciplinary, combining pharmacological and non-pharmacological strategies according to the clinical profile, preferences, and expectations of the patient.

On the horizon, the arrival of neurokinin-3 receptor (NK3) antagonists and the advancement of personalized medicine promise to inaugurate a new era in menopause treatment, with greater efficacy, safety, and individualized profiles.

The ideal management of vasomotor symptoms should be multidisciplinary and evidence-based, incorporating the shared decision-making model, which values the patient's preferences and expectations and promotes safer and more appropriate therapeutic choices. Advances such as NK3 receptor antagonists and personalized medicine promise to further enhance treatment efficacy and safety, reaffirming that woman-centered care is key to preserving well-being, mental health, and quality of life during the climacteric and postmenopause.

Thus, understanding and appropriately managing VMS is essential not only to relieve symptoms but also to promote overall well-being, mental health, and quality of life for women in the climacteric and postmenopausal phases.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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