Vasomotor Symptoms: Clinical Management

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Vasomotor symptoms (VMS) or "hot flashes" are the most common complaint during the menopausal transition, occurring in up to 80% of women, with approximately 33% experiencing more than ten episodes per day [1, 2]. Despite the high prevalence, only a minor seek medical attention for treatment.

The pathophysiology of the hot flash is not fully understood and is likely related to multiple factors. Changes in reproductive hormones and in thermoregulatory mechanisms are involved. The thermoregulatory zone is narrowed and becomes more sensitive to subtle changes in core body temperature. Small increases in temperature trigger thermoregulatory mechanisms causing the sensation of a hot flash (vasodilatation, sweating, and decreased skin resistance) [1, 3]. They affect quality of life (QoL) and appear to be associated with adverse health outcomes including cardiovascular, bone, and brain health [4]. VMS may also interfere with sleep and cause chronic sleep disruption [1, 5].

Symptoms are progressive during the menopausal transition until early postmenopausal stage and can last 7.4 years. Women who experience early VMS have the longer total duration: 11.8 years being that 9.4 years is after the final menstrual period (FMP) [6].

Frequency, duration, and severity of symptoms appear to vary by culture and ethnicity. African American women reported the most vasomotor symptoms, and Asian women reported the fewest symptoms compared with other groups in a study that assessed menopause symptoms in a large sample of women with diverse ethnic backgrounds [6].

The management of VMS is based on the symptoms' intensity and frequency and the women's medical history and personal choice. Usually, the

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pharmacological treatments are used for women with moderate to severe hot flashes (symptoms that interfere with usual activities or usual activities cannot be performed).

19.1 Non-pharmacological Treatments

19.1.1 Behavioral Measures

Besides the lack of data from well-structured clinical trials, these behavioral measures are recommended. These measures help the core body temperature not to increase and not to initiate mechanisms to dissipate heat [7].

Higher temperatures are triggers for vasomotor symptoms, and identifying that is recommended [8, 9]. Also it is recommended avoiding spicy foods and stressful situations, alcohol intake, hot foods, or liquids [8].

Although other lifestyle changes, like performing aerobic physical exercises, yoga practice, or weight loss, have beneficial effects on several aspects of the physical and psychological health of the individual, they are not yet supported by high-quality evidence for improving VMS [8, 10, 11].

19.1.2 Other Techniques

Other potential options may include cognitive behavioral therapy (CBT), mindfulness-based stress reduction (MBSR), relaxation, paced respiration, hypnosis, and vitamin E.

CBT effectively reduced the impact of VMS by an average of 50% after 8 h of group CBT or self-help CBT with benefits maintained at 6 months. Improvements in QoL are more expressive in individuals who experienced group CBT. The frequency of night sweats reduced subjectively and objectively in healthy women who underwent CBT [12, 13]. This technique is recommended for management of hot flashes [8].

Current evidence does not support the efficacy of MBSR for VMS [9, 14]. There is insufficient evidence to recommend relaxation techniques [14, 15]. Paced breathing was previously recommended but has been found to be ineffective [9].

Hypnosis is recommended for treatment supported by randomized controlled trials [8, 16]. The mean reduction in hot flash score was 18.83 (80.32%) for the clinical hypnosis intervention compared with 3.53 (15.38%) for controls ($P < 0.001$; 95% CI 12.60–17.54) [8, 16].

The improvement superior to placebo for VMS in some pilot studies using vitamin E has been suggested. It was tested in a study with women treated for breast cancer, with a marginal reduction when compared with placebo (mean of 1 less

episode/day). At the dose of 800 international units (IU)/day, it is well tolerated and not associated with toxicity [17].

Some preliminary data suggest that stellate ganglion blockade (SGB), by local injection of anesthetic into the sympathetic nerve fibers of the neck, may reduce vasomotor symptoms in women with contraindications to HT. This is an invasive and costly procedure, and more evidence is needed [7, 8].

Initial evidence suggests that transcranial direct current stimulation (tDCS) showed a trend in VMS improvement. Complementary data are needed [18].

19.1.3 Alternative Techniques

19.1.3.1 Acupuncture

Several studies have been conducted to assess the effectiveness of acupuncture for the management of VMS with contradictory results [8, 19–23]. A systematic review published in 2017 concluded that acupuncture was more effective than no treatment [21]. Comparison with hormonal therapy with estrogen (HT) found that acupuncture was less effective than HT for hot flash frequency [8, 20].

19.1.3.2 Phytoestrogens

Phytoestrogens are found naturally in foods. Its chemical structure is compared with intrinsic estradiol, acting as an estrogen agonist or antagonist. This occurs with respect to the type of estrogen receptor present in various tissues [24].

Isoflavone components genistein and daidzein are found in soy products that bind to estrogen receptors and have both estrogen agonist and antagonist properties. Soy supplementation with soy foods or soy extracts, including derivatives and metabolites, has been extensively studied, and there's no conclusive evidence to be more effective than placebo for VMS treatment [25–27]. Their safety are not established. Some limitations are the uncontrolled manufacturing process with resulting variability in composition and poor quality studies [8].

Black cohosh (*Actaea racemosa* L.—previously *Cimicifuga racemosa*) active compounds are unknown, as well as the mechanisms of action. After 23 weeks of black cohosh or placebo use, there was no significant difference in VMS treatment in perimenopausal or postmenopausal women [28]. There is insufficient evidence to support its use—and safety—for menopausal symptoms [8].

Other herbal treatments that have been studied for VMS include ginseng, St. John's wort, *Ginkgo biloba*, *Trifolium pratense* (red clover), maca, and dong quai (*Angelica polymorpha*). However, the overall quality of evidence for these therapies is poor. Despite the "natural" appeal, there is no data that phytoestrogens are proven to be superior to placebo in most well-designed studies, and, little is known about their safety, particularly in women with contraindication to hormone therapy (HT). Current evidence from randomized controlled trials does not support specific diet regimens such as plant-based diets or supplementations for the management of VMS [7–9, 24].

19.2 Pharmacological Treatments

19.2.1 Hormonal Treatment

19.2.1.1 Hormone Therapy

Systemic HT, with estrogen alone or in combination with progestogen, is the most effective therapy for vasomotor symptoms related to menopause [4, 29]. HT was found to reduce VMS frequency in 75% (IC: 64%–82%) and symptom severity in 87% (RR: 0.13; IC95%: 0.27) [30].

The candidates for HT are symptomatic women, younger than 60 years or who are within 10 years of FMP. The therapy should be individualized, taking into account the potential benefits and risks. The lowest dose that offers relief should be used, since it may have lower risks and may reduce the adverse events such as breast tenderness and vaginal bleeding [4, 29].

The association of estrogen and progestogen is required for the endometrial protection in women with a uterus [4, 29].

19.2.1.2 Combination of Selective Estrogen-Receptor Modulator (SERM)/Estrogen: TSEC

Bazedoxifene is a SERM that in combination with an estrogen results in a tissue-selective estrogen complex (TSEC). This class of drug is available for the treatment of VMS and osteoporosis prevention [4]. The association of bazedoxifene and conjugated equine estrogen (CEE) has estrogen agonist effects on bone, antagonist effects on the endometrium, and apparently neutral effects on breast. It promotes a decrease in the incidence of hot flashes with no increased risk of endometrial hyperplasia, without the need for a progestogen. It has also been associated with a lower incidence of breast pain and tenderness than other therapies. In addition, breast density does not increase [31, 32].

The combination of bazedoxifene with CEE is indicated for women with moderate to severe VMS who have breast tenderness with estrogen-progestin therapy or for women who cannot tolerate oral progestin therapy [4].

19.2.1.3 Tibolone

Tibolone is a synthetic steroid with tissue-specific estrogenic and progestogenic effects and appears to have a beneficial effect on bone density, vasomotor symptoms, and vaginal symptoms without estrogenic effects on the uterus [33, 34].

Tibolone is not FDA-approved and is not available in the United States.

19.2.1.4 Compounded Bioidentical Hormones

Bioidentical hormones are substances that are chemically similar or structurally identical to those produced by the body. Most compounded preparations have not undergone any rigorous clinical testing for either safety or efficacy, so the purity, potency, and quality of compounded preparations are a concern. There are no controlled trials which support claims for better efficacy and safety concerns.

Data do not support the use of progestin-only medications, testosterone, or compounded bioidentical hormones for the treatment of vasomotor symptoms [4, 7, 24, 29].

19.2.2 Nonhormonal Treatments

There are some options for women with moderate to severe VMS who are not candidates or don't want to use hormone therapy. It also can be tried in women who experience recurrent hot flashes after stopping HT.

The choice will depend whether the patient is taking tamoxifen, the pattern of hot flashes, and the presence of a mood disorder or sleep problem.

19.2.2.1 Selective Serotonin Reuptake Inhibitors (SSRIs)/ Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Although paroxetine 7.5 mg/day is the only nonhormonal medication approved by the FDA for treatment of moderate to severe VMS of menopause, other SSRIs, SNRIs, and others show evidence of efficacy. SSRIs and SNRIs are the most effective nonhormonal pharmacologic alternatives, demonstrated in placebo-controlled trials and meta-analysis [8, 9, 35, 36].

Some drugs have been tested and have shown some degree of efficacy in symptomatic women. Although no head-to-head trials have been performed, indirect comparisons suggest that paroxetine [35, 37, 38], venlafaxine [39–41], desvenlafaxine [42–45], citalopram [46], and escitalopram [47, 48] have a similar benefit for hot flashes. These drugs appear to be equally effective [36].

These medications increases the levels of serotonin and norepinephrine, both implicated in the origin of hot flashes. The clinical response is rapidly observed, usually in 2 weeks, and is associated with mild to moderate improvements in symptomatic postmenopausal women. Reduction in hot flash frequency varies from 25 to 69% and severity from 27 to 61%. There's no difference between the responses in women with surgical or natural menopause [8]. Suggested dose of SSRI and SNRI for hot flash treatment is expressed in Table 19.1.

There's no consistent evidence to use fluoxetine and sertraline to hot flash treatment [35, 49–53].

Besides that, the use of paroxetine or fluoxetine is not recommended to treat hot flashes in women who use tamoxifen. These drugs may interfere with the

Table 19.1 Suggested dosing of SSRI and SNRI for hot flash therapy

Drug	Suggested dose (mg/day)
Paroxetine salt	7.5
Paroxetine	10–25
Escitalopram	10–20
Citalopram	10–20
Desvenlafaxine	100–150
Venlafaxine	37.5–150

Modified from the North American Menopause Society [8]

Table 19.2 Suggested gabapentin and pregabalin doses for hot flash therapy

Drug	Suggested dose (mg/day)
Gabapentin	900–2400
Pregabalin	150–300

Modified from the North American Menopause Society [8]

metabolism of tamoxifen by inhibiting cytochrome CYP 3A and CYP 2D6 reducing the effect of treatment of breast cancer [54].

19.2.2.2 Gabapentin and Pregabalin

Gabapentin is an antiepileptic drug whose action seems to involve a direct effect on the hypothalamus. Although it's used for neuropathy and neuralgia, some evidences have shown improvement in frequency and severity of hot flashes at 900 mg/day [8, 9, 35, 36, 55–57].

Gabapentin, SSRIs, and SNRIs have similar effects to reduce the VMS [58]. Gabapentin may be an option in some women whose hot flashes are primarily at night, interrupting sleep (because drowsiness can be an adverse event). Other adverse events include dizziness and unsteadiness, mainly at first week. Higher doses seem to be as effective as estrogen, but adverse events limit the use [8]. Suggested dose of gabapentin and pregabalin for hot flash treatment is expressed in Table 19.2.

Also there's evidence that pregabalin is effective for treatment of hot flashes [59].

19.2.2.3 Clonidine

Clonidine is an alfa-adrenergic agonist, with antihypertensive action. The decrease of VMS occurs by the reduction of central and peripheral vascular reactivity but is less effective than SSRIs, SNRIs, gabapentin, and pregabalin [9, 35].

The use is limited by security and adverse events of hypotension, dry mouth, sedation, dizziness, and constipation.

19.2.2.4 Sulpiride

Sulpiride is an atypical neuroleptic that can act on serotonin receptors in low doses. Originally, it is known that this drug has clinical positive effects on schizophrenia and for mood spectrum disorder treatment.

One pilot clinical trial comparing sulpiride 50 mg/day versus placebo results in improvement of frequency of hot flashes after 4–8 weeks, with minimal adverse events [60].

19.3 Conclusions

VMS are the most common complaint during the menopausal transition and postmenopausal women.

The management of hot flashes is individualized and based on symptom's intensity and frequency and women's medical history and personal choice. The aim is to promote QoL offering evidence-based information and safety and effective treatments, when needed.

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