

Challenges in the Treatment of Vasomotor Symptoms: Update in Non-Hormonal Strategies

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Abstract

Perimenopause and menopause per se significantly impacts on women quality of life (QoL), especially due to vasomotor symptoms (VMS); their duration is uncertain, and often long. Although menopause hormone therapy (MHT) is the most effective treatment for climacteric symptoms as a whole, its use is contraindicated in some cases. Therefore, it is mandatory that different treatment approaches be offered to women for whom hormone therapy is contraindicated. As for treatment selection, there are a wide range of nonhormonal options, both pharmacological and nonpharmacological. These options include alternative or natural therapies (isoflavones and *Cimicifuga Racemosa*), lifestyle modifications and complementary therapies. Regarding pharmacological strategies the literature review shows that serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), antihypertensives and anticonvulsants, decrease the intensity and frequency of VMS, proving a clinically significant improvement.

Keywords: Hot flashes; Vasomotor symptoms; Nonhormonal treatment; Alternative therapies; Isoflavone; *Cimicifuga racemosa*; Breast cancer; Antidepressants; Antiepileptics

Abbreviations: VMS-Vasomotor Symptoms; QoL-Quality of Life; MHT-Menopause Hormone Therapy; SNRIs-Serotonin-Norepinephrine Reuptake Inhibitors; SSRIs-Selective Serotonin Reuptake Inhibitors; FMP-Final Menstrual Period; CBT-Cognitive-Behavioral Therapy; GABA-Gamma-Amino Butyric Acid; IMS-International Menopause Society; FDA-Food and Drug Administration; NAMS-North American Menopause Society

Introduction

Vasomotor symptoms (VMS) affect approximately 75% of menopausal women, of which 25% report a negative impact on quality of life (QoL). Its duration and frequency vary from one woman to another and can often be prolonged for many years. Hot flashes are described as a feeling of intense heat, with face and neck flushing, accompanied by perspiration and tachycardia, often followed by chills. The SWAN study (an observational study of the menopause transition), enrolled 3302 women and had a 17-year follow up, showed an average total mean duration of 7.4 years and a mean persistence after the final menstrual period (FMP) of 4.5 years [1]. Other studies, including the Melbourne Women's Midlife Health Project [2], found a total duration of 5.2 years; and the Penn

Ovarian Aging Study [3] showed a total duration of 8.8 to 10.2 years and a post-FMP duration of 4.6 years.

A special mention deserves the patients with personal history of breast cancer, since it has been reported that they experience a significantly greater amount of moderate to severe hot flashes due to the treatment of their underlying disease. Tamoxifen and aromatase inhibitors are usually part of the standard management in these patients after surgical treatment and may aggravate or induce hot flashes in these women [4] Although menopause hormone therapy (MHT) is the most effective treatment for climacteric symptoms, as a whole including hot flashes, in some cases, whether because hormonal treatment is contraindicated or due to the patient's

refusal to use it, non-hormonal treatments can be considered. Detecting habits and behaviors that pose a risk to health, which are fundamental pillars of the VMS' treatment, such as lifestyle modifications, counseling on healthy habits and stopping harmful behaviors (e.g. providing smoking cessation counseling), should be part of the usual gynecological consultation [5]. Currently there are pharmacological approaches and nonpharmacological approaches (lifestyle modifications, complementary therapies and alternative

therapies). On the one hand, nonhormonal treatments include the use of nonpharmacological alternatives and complementary therapies, such as acupuncture, relaxation techniques, Black Cohosh and ginseng, among others. On the other hand, pharmacological agents, include clonidine, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin and pregabalin. figure 1

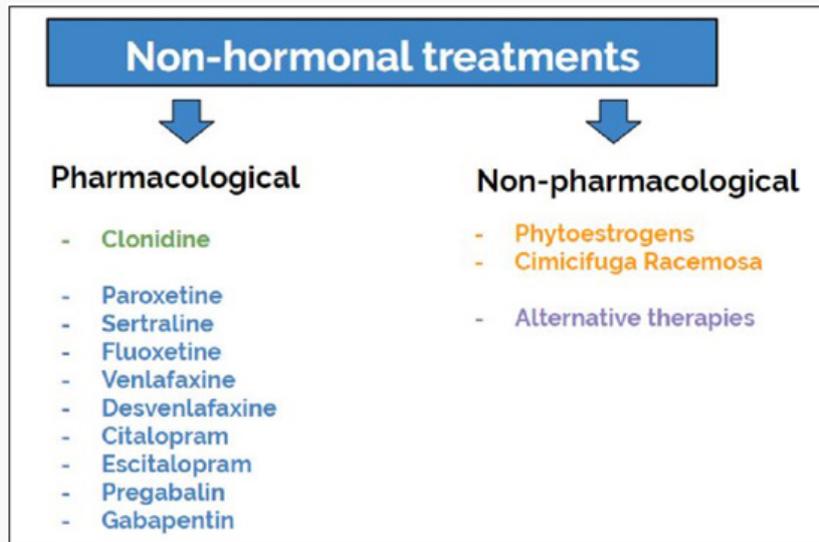


Figure 1: Non-hormonal treatments.

Non-Pharmacological Strategies

Lifestyle Interventions and Complementary Therapies

There are few large randomized clinical trials that recommend lifestyle interventions and complementary therapies as first line treatment. However, good eating habits, as well as physical exercise and multiple relaxation techniques, are necessary in order to enjoy a good QoL. The level 1 recommendations (proven by high quality randomized clinical trials) include only cognitive-behavioral therapy (CBT) and hypnosis [6]. Research conducted in the last decades consistently indicate that CBT is effective in the treatment of disorders such as depression or anxiety because it is based on the premise that one's thoughts and behaviors play a major role in determining emotional responses. CBT consists in a structured psychological treatment of limited duration which has been widely investigated and has shown to be highly effective in reducing symptoms in a variety of health and mental health conditions, including major depression [7]. Two randomized controlled double-blind clinical trials, *menos 1* [8] (which compared women who have had breast cancer and were treated with CBT vs population without intervention) and *menos 2* [9] (healthy women treated with CBT vs population without intervention), have shown a significant reduction in the intensity of VMS [6]. CBT positively impacts both the perception of VMS and stress control, improving patients' QoL, quality of sleep and VMS [10].

Hypnosis is a psycho-physical therapy which uses a state of deep relaxation, mental images and customized suggestions [6].

Hypnosis is studied for a wide variety of pathologies, such as anxiety and chronic pain. In regard to VMS, two clinical trials were performed: one randomized patients with a personal history of breast cancer [11] and the other one included women with over seven hot flashes per day [12]. Both studies concluded that patients in the group that used hypnosis therapy had approximately a 70% reduction in the intensity of hot flashes. Recommendations with inconclusive or insufficient evidence include weight loss, physical exercise, mindfulness therapy, multiple relaxation techniques, yoga [13], acupuncture [14,15], cooling techniques, avoidance of triggers and stellate ganglion block.

Phytoestrogens

Phytoestrogens are plant-derived non-steroidal compounds with weak estrogenic action. The most studied group consists of isoflavones, mostly the soy-derived ones: genistein and daidzein, which exhibit a structure similar to estradiol. They may be taken through diet modifications or as dietary supplements. Many foods are a source of phytoestrogens, such as legumes, mainly soy (isoflavones), flaxseed (lignans), alfalfa and soybean sprouts (coumestans) [5]. Phytoestrogens are taken orally and are metabolized by the intestinal bacteria. This intestinal metabolism seems key for optimizing their action, and fundamental for treatment response. The ability to metabolize phytoestrogens varies by ethnicity: 30% in North American women [6] and a much higher percentage in Asian women. As for their mechanism of action, phytoestrogen bind to estrogen receptors alpha (ERα)

and beta (ER β), with a higher binding affinity to ER β . It is believed that the biological function of isoflavones depends of endogenous levels of estradiol [6]. When endogenous estradiol levels are high, isoflavones have an anti-estrogenic action binding with ER α [6], but when levels are low (such as in post menopause), they have an estrogenic action by activating the ER β .

As for hot flashes, isoflavones and derivatives are more effective than placebo [16] and should be prescribed to women with moderate to severe hot flashes [17]; however, a review by Cochrane in 2013 concluded that there is no consistent evidence to prove that phytoestrogen supplements effectively reduce the frequency or severity of VMS in perimenopausal and postmenopausal women [18]. There are controversial results regarding phytoestrogens and breast cancer. Prepubertal exposition of breast acini to phytoestrogens may cause them to mature early and, therefore, offer protection. In contrast, post pubertal exposition without breast maturity may potentially increase the risk of cancer through their estrogen agonist action. In turn, it was suggested that genistein appears to have a proliferative action on in vivo breast epithelium. Consequently, the use of isoflavones is currently not recommended in women with a history of breast cancer [19].

Cimicifuga Racemosa

Cimicifuga Racemosa (actaea racemosa, black cohosh, black bugbane, black snakeroot, fairy candle) is a perennial herb of the Ranunculaceae family, native of the USA and Canada. Cimicifuga extracts include triterpene glycoside and phenolic acids [6]. Its active metabolite is unknown, and its mechanism of action is unclear [5,6]. Current studies show that it seems to act as a partial agonist of serotonin receptors and opioid receptors, and that it seems to have a dopaminergic effect as well [17]. In 2012, a review by Cochrane analyzed 16 randomized controlled clinical trials on 2027 perimenopausal and postmenopausal women who were treated with 40mg of cimicifuga racemosa for 23 weeks. No significant differences were found in the decrease of hot flashes between the women who received treatment and the placebo group [20]. No drug interactions are known, although it may interfere with tamoxifen [10]; however, since its mechanism of action is unknown, its concomitant use with hormone therapies is not recommended in women with a personal history of hormone-dependent cancers.

Pharmacological Strategies

Clonidine, a central action alpha 2-adrenergic agonist, acts by decreasing the secretion of noradrenaline in the synaptic space [21]. A 10-study meta-analysis showed that clonidine is slightly more efficient than placebo in reducing vasomotor symptoms with a 46% efficacy in the reduction of hot flashes. Its use has been associated with several significant adverse effects, such as dry mouth, dizziness, hypotension, constipation and sedation, therefore its current clinical use has been limited [22]. Gabapentin, a gamma-aminobutyric acid, regularly used as treatment for epilepsy and chronic neuropathic pain, has shown to be efficient in reducing hot flashes in breast cancer patients [23]. It has no

drug interactions, does not cause sexual dysfunction and seems to be well tolerated. The recommended dose for the treatment of hot flashes is 900mg/day [24]. As for adverse events, patients report drowsiness, dizziness and some anhedonia, which appear following the first week of treatment and resolve without treatment by week four of use [25].

Pregabalin is a gamma-aminobutyric acid (GABA) analogue with the same indications as gabapentin. A randomized, double-blind, placebo-controlled study comparing 75mg twice daily or 150mg twice daily of pregabalin and placebo found, after 6 weeks, a 65% and 71% improvement in the reduction of hot flashes with pregabalin, depending on dose. As for adverse effects, insomnia, dizziness and weight gain were observed; it is important to note that some women experienced cognitive dysfunction at higher doses [26]. SSRIs and SNRIs are groups of drugs that have been widely studied for the treatment of VMS, especially in patients who have had breast cancer. Although their mechanism of action is unclear, it has been proposed to enhance serotonergic neurotransmission by its selective inhibition of serotonin reuptake, as well as its concentration at the hypothalamic level, through the activation of the 5HT₂ receptor. Their benefit on VMS appears independently of their antidepressant effect and much earlier than with other therapies [27]. They have proved to reduce hot flashes with a variability between 25-69%. Although patients inform some adverse effects, such as headaches, nausea, loss of appetite, gastrointestinal intolerance and sleep disorders among others, they are not usually observed at low doses, being a well-tolerated alternative. [28,29]

Depression and mood alterations are common after a breast cancer diagnosis. The use of a low dose of these pharmacological agents may notably improve the quality of life for these women [30]. In a double-blind, placebo-controlled, randomized trial [20] with venlafaxine, an SNRI, in increasing doses of 37.5, 75, and 150mg/day in patients with breast cancer who took tamoxifen, it was observed that, after four weeks, hot flashes scores had a rapid and significant 37% and 61% decrease, depending on dose. There was no drug interaction in the metabolism of tamoxifen [32]. The International Menopause Society (IMS) does not recommend the use of fluoxetine or sertraline due to the fact that no significant reduction in vasomotor symptoms was found in placebo-controlled studies [33]. Some drugs may interfere with the transformation of tamoxifen into its active metabolite, 4-hydroxy-desmethyl-tamoxifen (endoxifen), by inhibiting cytochrome P450 2D6 (CYP2D6) [34].

The US Food and Drug Administration (FDA) classifies these psychiatric drugs into strong, moderate and weak inhibitors, according to their interaction with cytochrome P450. Both paroxetine and fluoxetine have been classified as strong inhibitors; sertraline as a moderate inhibitor; and citalopram, escitalopram, venlafaxine and desvenlafaxine as weak inhibitors [35]. The American Clinical Oncology Society recommends avoiding the use

of antidepressants classified as strong inhibitors [35], considering venlafaxine and escitalopram as the best option for the treatment of vasomotor symptoms in these patients [36]. Escitalopram, an SSRI with weak effect on noradrenaline and dopamine reuptake, at increasing doses has shown a 55% reduction in hot flashes in menopausal women or women in the menopause transition, with 4% of side effects and a 70% satisfaction rate [37]. Our experience in the Climacteric Section of the Hospital Italiano de Buenos Aires with the use of escitalopram at 5mg and 10mg doses in patients with severe hot flashes, a history of breast cancer, or with a contraindication for MHT, was similar or even superior to the percentages of most published studies. Our results have indicated a 60% reduction by week 1, which is progressively maintained after one year of use, with good compliance and few side effects.

In the year 2013, the FDA approved the use of paroxetine at 7.5mg doses as treatment for hot flashes. The efficacy of paroxetine was established in two randomized, double-blind, placebo-controlled, multicenter clinical trials. Among a total of 1184 menopausal women who had a median of 10 moderate-to-severe hot flashes per day, paroxetine 7.5mg was shown to provide significant relief in comparison to placebo [38]. In the summarized literature, in fact, in breast cancer survivors paroxetine was associated with a 40%–67% reduction in hot flashes frequency [39]. The benefits were observed in 1-2 weeks of treatment, persisting for 6 weeks. Regarding sleep, paroxetine significantly reduces hot flashes in weekly frequency and severity and the number of nighttime awakenings attributed to vasomotor symptoms, increasing sleep duration. These improvements occur without increased sedation, suggesting that paroxetine has a selective therapeutic effect on sleep parameters related to VMS [40,41]. In the year 2015, the North American Menopause Society (NAMS) [42] published their position statement on the nonhormonal management of vasomotor symptoms associated with menopause. The NAMS panel concluded that the recommended therapies for menopausal and postmenopausal hot flashes are paroxetine 7.5-10-25mg/day; escitalopram 10-20mg/day; citalopram 10-20mg/day; desvenlafaxine 50-150mg/day; and venlafaxine XR 37.5-150mg/day.

Conclusion

Vasomotor symptoms significantly affect the quality of life; therefore, offer alternative strategies in women with a need for non-hormonal treatment resulting mandatory, since the ultimate goal is to improve our patient's quality of life.

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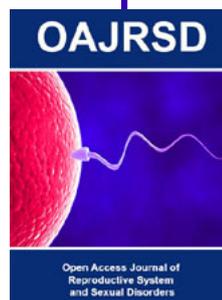
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