


A Review of Management of Perimenopausal Hot Flashes

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ABSTRACT

Vasomotor symptoms, also known as hot flashes, can be defined as a sensation of heat, intense sweating, and flushing, which are experienced episodically by many perimenopausal women. This sensation usually affects the face, neck, and chest. It is estimated that about 75% to 80% of women would suffer from hot flashes at some point during their perimenopausal years. A decline in oestrogen levels during menopause seems to be responsible for the appearance of hot flashes. This decline increases norepinephrine levels, leading to an up regulation of serotonin receptors in the hypothalamus, which are involved in temperature regulation. The outcome of the activation of this norepinephrine serotonin pathway is believed to be the narrower thermoregulation zone, which in turn results in a greater risk of crossing the upper and lower thresholds of the thermoregulatory zone. Thus, it causes sweats and chills in this group of women. The most known effective treatment of hot flashes is hormone replacement therapy (HRT); however, in recent years, other non-hormonal options have become available for those women who cannot or do not want to take HRT.

Keywords: Menopause, Hot flashes, Gabapentin

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Introduction

Context

Vasomotor symptoms (VMS), also known as hot flashes, are subjective feelings of heat accompanied with cutaneous vasodilation. It can be defined as a sensation of heat, intense sweating, and flushing, which are experienced episodically by many perimenopausal women. This sensation usually affects the face, neck, and chest. It is estimated that about 75% to 80% of women would suffer from hot flashes at some point during their perimenopausal years.

Hot flashes may be accompanied by palpitation and anxiety. On average, each episode of hot flashes can last 3–10 minutes and can relapse with fluctuating frequencies. Some women experience several episodes in an hour or per day, whereas other women may experience hot flashes occasionally (1).

Management of hot flashes is divided into three different areas: medications (hormonal and non-hormonal), complementary medicine, and lifestyle changes.

This paper aims to review the studies that have been carried out in recent years on the effectiveness of different treatment options of hot flashes.

Evidence Acquisition

Although much research has been and still being carried out to understand the mechanism of hot flashes, its pathophysiology is not completely understood yet. Vasomotor symptoms are thought to be a kind of temperature dysregulation resulted from fluctuations in gonadal hormones, which take place around perimenopause.

Oestrogens are believed to be powerful neuromodulators of many neuronal pathways. The appearance of vasomotor symptoms seems to be associated with impaired functioning of the thermoregulatory nucleus, which is located in the anterior hypothalamus. The thermoregulatory nucleus plays a vital role in adjusting the core body temperature. It helps to keep the core body temperature within a normal range called the thermoregulatory zone (2).

In a study, in 2005, it was shown that perimenopausal women have a narrower thermoregulatory zone, which in turn results in a greater risk of crossing the upper and lower thresholds of the thermoregulatory zone; hence causing sweats and chills in this group of women (Figure 1) (3).

Moreover, it has been shown that a decline in oestrogen levels during menopause increases norepinephrine levels, leading to an up regulation of serotonin receptors in the hypothalamus, which are involved in temperature

regulation. This activation of the noradrenergic and serotonin pathways may further narrow the upper threshold of the thermoregulatory zone, causing a greater tendency for hot flashes (4).

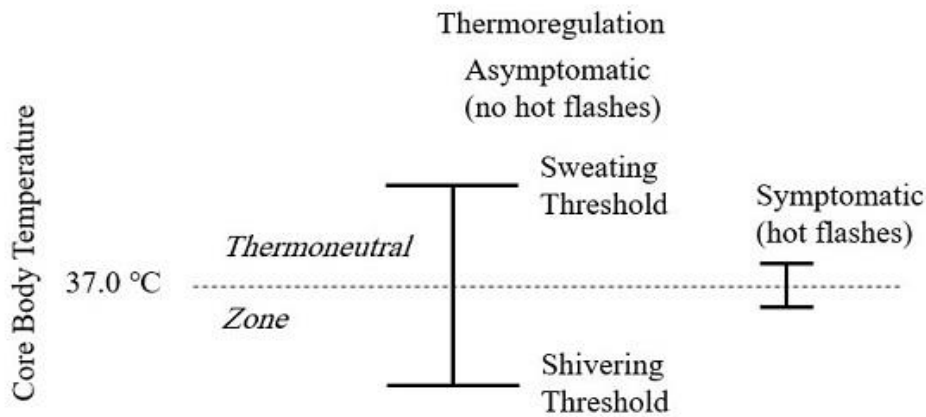


Figure 1. Shows changes in the thermoregulatory zone in perimenopausal women (5).

Results

Treatment

The treatment of hot flashes can be divided into three different areas:

1. Medications: hormonal and non-hormonal
2. Complementary and alternative medicine
3. Lifestyle changes

Medications: Hormone Replacement Therapy

Hormone replacement therapy (HRT) is the most effective treatment of hot flashes in perimenopausal women.

In a study, a number of randomized healthy postmenopausal women, who were experiencing hot flashes, were allocated to three different groups: the first group received low-dose transdermal oestrogen, the second group received micro-dose transdermal estradiol, and the third group received placebo. They found that even those patients who received a low dose or even the micro-dose oestrogen had a 75% lower hot flash frequency compared to the placebo group (6).

Oestrogen is mainly used for women who have undergone a hysterectomy. In contrast, combined oestrogen-progestin therapy has been recommended for those with an intact uterus in order to prevent oestrogen-associated endometrial hyperplasia.

However, in 2002, results of the Women's Health Initiative (WHI) study (a set of two large randomized trials) raised concerns regarding the long term effects of HRT (7).

They found that combined oestrogen-progestin HRT was associated with a higher incidence of breast cancers, many of which were higher stage.

In the following years after the initial report of findings of the WHI study, a significant drop in breast cancer incidence was noted in the USA, which was assumed to be the result of a decrease in HRT intake (8).

Furthermore, data from a meta-analysis of 16 studies, assessing the use of oestrogen therapy alone, revealed that long-term oestrogen intake may be associated with a 30% greater risk of breast cancer (9).

Thus, the use of any type of HRT, following a diagnosis of breast cancer, has been discouraged in recent years.

Patients who suffer from high levels of triglycerides should not be given oral oestrogen, as it can cause an increase in very low-density lipoproteins (VLDL) secretion and a decrease in the activity of hepatic lipase, which leads to exacerbation hypertriglyceridemia.

The vast majority of women, who seek treatment for vasomotor symptoms, are in their late 40s or early to mid-50s. This group of women can be reassured regarding the safety of HRT, and the fact that the risk of complications for a young and healthy postmenopausal woman is very low.

Overall, HRT should be avoided in those with contraindications such as a history of breast cancer, history of migraine headaches, Deep vein thrombosis (DVT), stroke, high triglycerides levels, and endometrial hyperplasia (10).

Medications: Non-hormonal

The main non-hormonal medications that have been recommended for the management of perimenopausal hot flashes include selective serotonin reuptake inhibitors (SSRIs), Gabapentin, and Clonidine.

SSRIs

Paroxetine, with the brand name of Brisdelle, is the only non-hormonal therapy that is specifically approved for the management of hot flashes in the United States. Brisdelle contains 7.5 mg of paroxetine and is taken at bedtime. It offered the first non-hormonal option for those patients who cannot or do not want to take HRT.

The efficacy of Brisdelle was established in two randomized, double-blind, and placebo-controlled clinical trials. Among a total of 1,184 menopausal women, who had a median of 10 moderate-to-severe hot flashes per day, Brisdelle provided modest relief in comparison to placebo (11).

There are some concerns regarding the increased risk of suicidal behaviour associated with paroxetine; however, some believe that this risk mainly targets the children and adolescents but not the adults. A meta-analysis study found no evidence that SSRIs increased the risk of suicide. This study, however, could not exclude important protective or hazardous effects of this medicine (12).

In contrast to other paroxetine-containing products, Brisdelle doses do not have to be tapered before the use is discontinued (11).

Paroxetine should be avoided in breast cancer patients who are receiving tamoxifen. A study showed that the co-administration of paroxetine (10 mg per day for 4 weeks) in women, who use tamoxifen, can decrease plasma levels of endoxifen by 64%. Paroxetine is an inhibitor of the cytochrome P-450 enzyme; hence it can diminish the effect of tamoxifen (13).

Although the Food and Drug Administration (FDA) considers Brisdelle to be a useful and reasonably safe non-hormonal option for treating moderate-to-severe vasomotor symptoms in menopausal women, the label on the box warns prescribers to weigh the likely benefit of this medicine against the risk of possible reduced effectiveness of tamoxifen. The Brisdelle label also recommends monitoring patients for suicidal thoughts and behaviours and recommends discontinuing the treatment if there is a worsening of depression or increased risk of suicidality (11).

Other SSRIs that have been used to treat hot flashes include:

- Venlafaxine (Effexor XR, Pristiq)
- Paroxetine (other brands, e.g., Paxil, Pexeva)
- Fluoxetine (Prozac, Sarafem) (14).

Gabapentin

Gabapentin is an anti-convulsion medication. According to a clinical trial in 2012 (known as BREEZE 3), extended-release (ER) gabapentin has shown to improve sleep and reduce hot flashes in menopausal women, (15). A dose of 300–900 mg, taken prior to bedtime, has been recommended for the management of vasomotor symptoms.

In a study, gabapentin was proved to be effective in the control of hot flashes in breast cancer patients at a dose of 900 mg/day, but not at a dose of 300 mg/day (16).

In a randomized, double-blind, placebo-controlled trial, 60 women were randomly allocated to three different groups: 20 women received gabapentin, 20 received oestrogen at 0.625 mg per day, and 20 received placebo. After 12 weeks of treatment, there was a reduction in hot flashes for both the gabapentin group (71%, P-values of 0.004) and the oestrogen group (72%, P-values of 0.016) compared to only 54% reduction of symptoms in the placebo group (17).

Common side effects of gabapentin are sleepiness, dizziness, increased risk of suicide, aggressive behaviour, and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. A gradual increase in the dose of gabapentin and taking it at mealtime seem to minimise the side effects (18).

Another problem of gabapentin is its price; gabapentin is a relatively expensive medicine. It costs about \$100-200/month in the USA and about £50-60/month in the UK (19, 20).

Clonidine

Clonidine is a centrally acting α_2 adrenergic agonist, which is mainly used as an anti-hypertensive medication. As explained above, the thermoregulatory zone is narrowed during menopause. Clonidine reduces central sympathetic activation, widens the thermoregulation zone, and decreases the frequency and severity of hot flashes. This medicine has shown to reduce vasomotor symptoms in some patients but may be completely ineffective in others. It is available in the form of a pill or dermal patch (21).

Its main side effects are dry mouth, constipation, drowsiness, and sleep disturbances.

Clonidine reduces blood pressure by inhibiting sympathetic discharge. Its sudden discontinuation, therefore, can cause hypertension to bounce back because of a rebound in sympathetic outflow. Thus, it is strongly recommended to slowly taper this medicine before stopping it completely (22).

Complementary and Alternative Medicine

Complementary medicine such as herbal, Chinese, and homeopathy medicine have become increasingly popular among Western societies in recent years. Black Cohosh, Agnus Castus, and Evening Primrose oil are only a few examples (23).

Phytoestrogens, which are plant-derived oestrogens, have been marketed as Isoflavone supplements. Phytoestrogens are found in many foods, such as soybeans and red clover (24).

Many women believe that because phytoestrogens are natural, they are safer than HRT; however, their safety has never been proven scientifically. On the contrary, some studies have shown that long-term use of phytoestrogens

in postmenopausal women can increase endometrial hyperplasia, which can lead to endometrial cancer (25).

Acupuncture has also shown to be very effective in easing the perimenopausal symptoms, especially in relief of vasomotor symptoms.

A placebo double blind-controlled trial, which was conducted to determine the effect of vitamin E supplements, showed a reduction in the frequency and severity of hot flashes by taking 400 IU of vitamin E daily for 4 weeks (26,27).

Relaxing techniques, such as yoga, meditation, and relaxing exercises, have also been recommended to menopausal women in order to ease the vasomotor symptoms (28,29).

Lifestyle Changes

According to the National Health Service (in the United Kingdom) and the North American Menopause Society, some lifestyle changes could ease the vasomotor symptoms. In this regard, wearing light and cool clothing could maintain the environment temperature within a reasonable range. Meditation, yoga, and regular exercise could decrease stress and anxiety; and avoiding anything that can trigger hot flashes, e.g., caffeine, alcohol, smoking, and spicy or chilli foods (30).

Table 1 has summarised the most important studies that have been carried out in recent years on the effect of different treatments on the reduction of hot flashes.

Table 1. A summary of recent randomized trials for the treatment of hot flashes (10).

Agent/Technique	N of Patients	Results	P-value
Megestrol acetate versus placebo	163	Effective treatment for men and women	$P<.001$
MPA versus oral megestrol acetate versus placebo	71	MPA is a long-lasting effective alternative to prolonged use of oral megestrol acetate	$P=.03$
Transdermal progesterone cream versus placebo	102	Effective treatment for vasomotor symptoms	$P<.001$
Progestelle progesterone cream versus placebo	223	Progesterone cream was no more effective than placebo	No significant differences
Clonidine	11	Effective treatment for hot flashes	$P<.001$
Clonidine versus placebo	86	Moderate reduction in hot flashes	(a) Clonidine before placebo, $P<.05$; (b) clonidine after placebo, $P<.0001$
Clonidine versus placebo	10	Modest improvement with toxicities	$P<.005$
Clonidine versus placebo	110	Moderate improvement with toxicities	$P<.0001$
Fluoxetine versus placebo	81	Moderate decrease in hot flashes	$P=.02$
Venlafaxine versus placebo	191	Moderate reduction in hot flashes	$P<.0001$
Citalopram versus placebo	254	Effective, well-tolerated treatment for hot flashes	$P<.002$
Gabapentin versus placebo	59	Effective treatment for hot flashes	$P=0.01$
Gabapentin versus placebo	420	Effective treatment for hot flashes	$P=0.007$
Gabapentin versus estrogen	60	Gabapentin as effective as estrogen	(a) Estrogen versus

Agent/Technique	N of Patients	Results	P-value
versus placebo			placebo, $P = 0.016$; (b)
			gabapentin versus placebo, $P = .004$
Venlafaxine versus gabapentin	66	Venlafaxine preferred over gabapentin	$P = .01$
MPA versus venlafaxine	227	MPA more effective than venlafaxine	$P < .0001$
Gabapentin versus gabapentin and antidepressant	113	The combination of gabapentin and an antidepressant was not significantly better than gabapentin alone	$P = .37$
Vitamin E versus placebo	105	Minimal reduction in hot flashes	$P < .05$
Soy phytoestrogen versus placebo	149	Soy phytoestrogen is not effective in alleviating hot flashes	No significant differences
Acupuncture versus venlafaxine	50	Both groups had similar changes in hot flash frequency	$P < .036$
Hatha yoga	11	Effective for less severe hot flashes	$P = .02$
Yoga versus physical exercises (control)	120	Yoga effective in decreasing vasomotor symptoms	$P < .05$
Exercise versus oral estradiol	30	Exercise may decrease hot flashes	No significant differences
Structured education and exercise versus no exercise	35	Structured education and exercise had significant effects in terms of Kupperman index	$P < .05$
Moderate-intensity exercise versus stretching (control)	173	Exercise patients had a greater risk for moderate/severe hot flashes over time than controls	$P = .02$
Paced respiration versus muscle relaxation versus a-wave ECG biofeedback (control)	23	Hot flush frequency decreased significantly for the paced respiration group	$P < .02$
Applied relaxation and oral estradiol	30	Applied relaxation patients had a moderate reduction in hot flashes	$P < .001$

Abbreviations: ECG, electrocardiogram; MPA, medroxyprogesterone acetate.

Conclusion

Considering all studies that have been carried out so far, it seems that there is no single fixed treatment for hot flashes. Each woman is unique and must be treated individually. A proper history and examination of each patient are essential to assess the potential risk factors. Many factors could be part of doctor's decision to use a particular treatment, such as woman's age, her risk factors (e.g., a history of breast cancer, hypertriglyceridemia, Deep vein thrombosis, stroke, etc.), her preferences, available treatment options, and the cost of different treatments.

As a woman's body changes over time and as more treatment options become available, re-evaluation of her symptoms is essential in order to adjust the treatment.

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Conflict of Interest

Authors declared no conflict of interests.

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