

An Overview of Menopause Associated Vasomotor Symptoms and Options Available in its Management

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ABSTRACT

BACKGROUND: Vasomotor Symptoms are the most common and distressing menopausal complaint, for which women seek advice from their physician.

OBJECTIVE: To review menopausal associated vasomotor symptoms and options available in its management.

METHODS: Pertinent literature on menopause associated vasomotor symptoms, selected references, textbooks, journals and internet services using the PubMed and Medline databases were included in this review.

RESULTS: Hot flushes are the most common and distressing symptom, for which women seek advice from their physician. It occurs in more than 75% of postmenopausal women. Management of hot flushes is problematic because the most recognized effective option oestrogen, is often contraindicated. This has resulted in extensive research exploring different therapeutic options for treatment of hot flushes. Currently, various safe and efficacious nonhormonal options exist but further research is still needed to improve on the treatment of hot flushes.

CONCLUSION: The management of the most common and distressing vasomotor symptoms associated with menopause (hot flushes) is controversial. Regardless of the management strategy adopted, treatment options should be periodically reassessed as menopause-related vasomotor symptoms will abate with time even without any intervention in majority of postmenopausal women.

KEYWORDS: Menopause, Vasomotor symptoms, Hot flushes, oestrogen therapy.

Vasomotor symptoms are the most common and distressing menopausal complaint for which women seek advice from their physician². Hot flushes occur in 75% of menopausal women¹. Hot flushes are unpredictable in onset, may present with recurrent period of sudden, explosive, overwhelming uncomfortable sensation of intense heat or flushing that begins on the face or upper part of the neck and then to upper chest and may involve the whole body¹. However, no tests are currently available to help predict those women who will suffer from prolonged and frequent vasomotor disturbances. Hot flushes may be associated with palpitations, a feeling of anxiety and red blotching of the skin³. Hot flushes last for 2 - 5 minutes, varying in frequency with some women experiencing episodes multiple times in a day but decrease with the passage of time⁴. Hot flushes have a detrimental effect on a woman's functional ability and quality of life, however, they are not life threatening^{4,5}. Night sweats are hot flushes that occur with perspiration during sleep. The terms hot flush, hot flash and vasomotor symptoms are often used to describe the same condition⁵.

Vasomotor symptoms are more common and severe in surgical menopause, premature menopause, breast cancer survivors or breast cancer patients than women who undergo normal menopause^{6,7}.

Preventive and treatment measures for breast cancer may induce hot flushes such as antioestrogenic medications, oophorectomy and chemotherapy^{6,8}. Among the options for the treatment of hot flushes, simple hormone treatments are effective⁴. Non-hormonal treatments have also been employed for decades with varying degrees of success^{4,7}. However, only hormonal replacement therapy (HRT) is believed to address the root cause of vasomotor symptoms, and has proved effective for symptomatic relief of hot flushes^{2,7}. Hormone replacement therapy remains the reference standard for assessing the effectiveness of non-hormonal modalities^{5,7}. The aim of this review is to present an overview of menopause associated vasomotor symptoms and options available in its management.

METHODS

Pertinent literature on menopause associated vasomotor symptoms, selected references, journals, textbooks and internet services using the PubMed and Medline databases were reviewed. Comprehensive literature search on relevant publications related to menopause

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INTRODUCTION

Menopause is a physiological process associated with multiple symptoms such as vasomotor symptoms (hot flushes and night sweats), vaginal symptoms, urinary incontinence, sexual dysfunction and sleep disturbances. Menopause and the postmenopausal period are very important landmarks in a woman's life since she will spend more than a third of her life during these periods without significant endogenous oestrogen production, thus presenting with distressing vasomotor symptoms¹.

and associated vasomotor symptoms using the keywords “Menopause”, “Vasomotor Symptoms”, “Hot Flushes”, Oestrogen Therapy”, was conducted.

PATHOPHYSIOLOGY

The actual cause of hot flushes is not completely understood, but may be as a result of changing endogenous oestrogen concentrations associated with menopause⁵. The old tradition has been that hot flushes result from the decrease in oestrogen levels associated with menopause. The number of ovarian follicles and production of oestrogen decreases during menopause. Hot flushes seem to occur synchronously with these changes⁹. However, the exact role of oestrogens in the causation of hot flushes is still unclear. Some authors believe that it is the oestrogen withdrawal and not low levels of oestrogen that results to hot flushes¹⁰.

Furthermore, hot flushes are often more prevalent at the beginning of menopause and do not usually continue throughout the postmenopausal period when circulating oestrogens are low¹⁰. It is equally not associated with prepuberty, hypophysectomized women, or those with primary ovarian failure, although some antioestrogenic drugs are associated with flushing (e.g. Clomiphene).

The vascular changes (vasodilatation) and perspiration associated with hot flushes seem to be controlled by the thermoregulatory nucleus in the preoptic area of the hypothalamus. Hot flushes are triggered if body temperatures are elevated or sweating thresholds are lowered^{2,11,12}. Women who suffer from hot flushes appear to have a thermoregulatory zone that is narrower and with a little increase in core body temperature can trigger hot flushes¹³. Norepinephrine and serotonin may be involved in the complex neuroendocrine pathway controlling the thermoregulatory zone⁹. It is thought that elevated brain norepinephrine narrows the thermoregulatory zone^{12,13}. Furthermore, there has been increased interest in the role of serotonin in the hot flush mechanism. Activation of specific serotonin receptors can cause hypothermia or hyperthermia^{13,14}. Oestrogen withdrawal is associated with decreasing levels of serotonin and an increase in serotonin receptors in the hypothalamus^{9,10}.

Some authors are of the opinion that in the pathogenesis of hot flushes, oestrogen withdrawal leads to a decrease in endorphin and catecholestrogen levels. This in turn leads to increased norepinephrine and serotonin release, which lowers the set point in the thermoregulatory nucleus, thus increasing the likelihood of hot flushes⁹. Hot flushes have also been observed in women with pituitary insufficiency and in patients with Kallman's syndrome after discontinuation of oestrogen treatment, but they do not occur in women with gonadal dysgenesis who have not been exposed to exogenous

oestrogen¹⁵.

TREATMENT OF VASOMOTOR SYMPTOMS

All the available options do not cure hot flushes, however, they can only provide significant relief^{2,5}. In most women, hot flushes will abate overtime without intervention⁵. The most widely studied and most effective treatment option for relief of menopause associated vasomotor symptoms is oestrogen. Oestrogen is considered the standard of care for women with moderate-to-severe vasomotor symptoms^{2,5,7}.

HORMONAL THERAPIES

Relatively, simple hormone treatments are effective for vasomotor symptoms. Hormone replacement therapy remains the reference standard for assessing the effectiveness of non-hormonal interventions^{4,5,7}. Hormone replacement therapy should be used at the lowest effective dose and for the shortest duration possible (preferably < 5 years) in women in whom the potential benefits outweigh the potential risks^{4,5,7}. Oestrogen is used alone or with progestogen for women with intact uterus. Other hormones used include progestogens alone, oral contraceptives, androgen-oestrogen and custom hormonal preparations.

OESTROGEN THERAPY

Oestrogen is the most effective option for reducing hot flushes with reductions of more than 75% in frequency¹⁶¹⁷. However, there are some conditions in which oestrogen therapy is contraindicated such as venothrombotic disease, breast cancer, stroke and coronary artery disease¹⁸. In spite of this, hormone therapy is still recommended for the treatment of moderate to severe vasomotor symptoms¹⁷. Treatment of hot flushes with hormonal therapy involves the use of lowest dose and for the shortest effective length of time^{5,17}. Oestrogen shows a significant reduction in the frequency of hot flushes and these reductions were dose dependent¹⁹. Low dose oestrogen may be less likely to cause many of the serious complications associated with higher dose oestrogen²⁰. The risks associated with long term use of low dose oestrogens are still unknown since this has not been evaluated in clinical trials²¹. However, HRT is still considered justifiable and indeed recommended for symptomatic relief of severe vasomotor symptoms although it is no longer recommended for long-term prophylaxis^{16,20-21}. The use of oestrogen therapy in breast cancer survivors is controversial. Some authors suggest that oestrogen therapy might be safe in breast cancer survivors⁸, but most clinicians are of the opinion that oestrogen therapy should be avoided in breast cancer survivors²².

PROGESTATIONAL AGENTS

Women with an intact uterus requiring hormonal therapy for menopausal symptoms require progesterone²³.

However, progestational agents have been shown recently to be a reasonable alternative to oestrogen for the treatment of vasomotor symptoms^{24,25}. Both megestrol acetate and depomedroxy progesterone acetate (DMPA) are efficacious in reducing hot flushes^{24,26}. Both agents have similar efficacy in reduction of hot flushes among post-menopausal women with a history of breast cancer²⁷. The role of progesterone cream for the treatment of hot flushes is controversial. Some authors report reduction of hot flushes²⁸, while others found no significant difference in hot flushes reduction²⁹. Progestogens are associated with similar side effects as oestrogen, and thus contraindicated in women with thrombo-embolic disorders, impaired liver function and undiagnosed uterine bleeding²³. The role of progestational agents in women with a history of breast cancer is still unclear. This is controversial because it has been proposed that progestational agents may stimulate tumour growth^{23,30}.

TIBOLONE

This is a synthetic steroid that has both a weak oestrogenic, progestogenic and androgenic properties³¹. Tibolone has been used for the treatment of vasomotor symptoms in Europe but is not available in the USA³². The use of tibolone in treatment of hot flushes is comparable to oestrogen therapy³³. The most common side effects are weight gain and bloating³¹. Tibolone increased the risk and recurrence of breast cancer^{34,35}. Tibolone should not be used in breast cancer patients and should be used with caution in postmenopausal women with vasomotor symptoms.

DEHYDROEPIANDROSTERONE (DHEA)

This is a proandrogen produced by the adrenal glands and liver. DHEA supplementation in postmenopausal women resulted in a decrease in vasomotor symptoms³⁶. This finding still need to be further evaluated in a large randomized placebo-controlled trial^{36,37}.

NON HORMONAL THERAPY

Some authors feel that the risks associated with hormonal therapy outweigh the therapeutic benefit. Non-hormonal therapies for hot flushes have received a lot of attention over the past 20 years. Among the non-hormonal agents are antidepressants, anticonvulsants, and antihypertensives. These agents may be appropriate alternatives in women who cannot use HRT for vasomotor symptoms relief, such as those with a history of or at risk of breast cancer^{1,5}. These nonhormonal therapies are less effective than HRT¹. The mechanisms by which nonhormonal therapies reduce hot flushes remain unknown.

BELLERGA

This is a combination product of Belladonna alkaloids and Phenobarbital. It was used in 1970's and 1980's as a

treatment for hot flushes. The adverse effects associated with Bellergal (dry mouth, dizziness, rash and sleepiness) limited its use in the treatment for hot flushes³⁸. Bellergal is not recommended for treatment of hot flushes.

CLONIDINE

This is a central acting alpha-adrenergic agonist, first proposed as a treatment for hot flushes in the 1970's³⁹. The use of clonidine for hot flushes treatment is not recommended because of significant side effects⁴⁰ (dry mouth, dizziness, drowsiness, constipation and sedation).

METHYLDOPA

This is an antihypertensive agent that was investigated for hot flushes treatment. The adverse effects of methyldopa dizziness, sedation, headache, nausea, and fatigue occurred in 50% of the patients⁴¹, because of this, methyldopa is not recommended as a therapy for hot flushes.

VERALIPRIDE

This is a benzamide derivative with antidopaminergic effects which has been studied as a treatment for hot flushes. Adverse effects of veralipride included breast tenderness, galactorrhoea, gastrointestinal complaints and dyspnoea⁴². Due to toxicity of veralipride, it is not recommended for the treatment of hot flushes.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI)

These are newer antidepressants. Trials on SSRI are promising.

VENLAFAXINE

Selectively inhibits reuptake of serotonin, norepinephrine and dopamine. Because of venlafaxine toxicities its use in treatment for hot flushes is not recommended⁴³.

DESVENLAFAXINE

This is a new serotonin norepinephrine reuptake inhibitor (SNRI), and is the succinate salt form of the major active metabolite of venlafaxine⁴⁴. The most common side effect is nausea, which is dose-dependent.

PAROXETINE

This is SSRI. The most frequently reported side effects are headache, nausea and insomnia⁴⁵. Dose of paroxetine is 12.5 to 25mg per day.

FLUOXETINE

The use of fluxetine in the treatment of hot flushes is promising but trials are still on going. The adverse effects associated with fluoxetine use in treatment for hot flushes are not significant⁴⁶. Dose of fluoxetine is

20mg per day.

CITALOPRAM

The use of citalopram in the treatment for hot flushes is promising and has provoked further research, including randomized, placebo-controlled trials. It was found that its beneficial effect was increased with adjuvant hormonal therapy⁴⁷.

CYP2D6

This is a cytochrome p450 enzyme. Newer antidepressants have shown to be promising therapy for hot flushes, but some of them are contra-indicated in breast cancer patients such as Tamoxifen (selective oestrogen receptor modulator) which is widely used for both treatment and prevention of breast cancer⁴⁸. Tamoxifen is metabolized into its active metabolite, endoxifen by a cytochrome p450 enzyme CYP2D6⁴⁸. Some newer antidepressants such as paroxetine and fluoxetine, can inhibit this enzyme resulting in lower levels of endoxifen. Venlafaxine has less of an inhibitory effect on plasma levels of endoxifen⁴⁹.

GABAPENTIN

This is structurally related to the neurotransmitter gamma-aminobutyric acid and is currently used as an anticonvulsant and for neuropathic pain. Patients on gabapentin experienced a decrease in hot flushes frequency of 66%⁵⁰. The recommended dose for treatment of hot flushes is 900mg/day⁵¹.

PREGABALIN

This is a newer generation compound with a mechanism of action similar to gabapentin. The adverse effects are sleepiness, dizziness, cognitive troubles that are marked with higher doses⁵².

COMPLEMENTARY AND ALTERNATIVE THERAPIES

These therapies refer to herbal remedies such as isoflavones (soy, red clover), black cohosh, Vitamin E, Dong quai, evening primrose oil, ginseng, licorice, Chinese herb mixtures, wild yam extract. Herbal remedies are commonly used for the treatment of vasomotor symptoms, however, the mechanism by which they reduce the frequency of vasomotor symptoms remains unknown and clinical trial efficacy data are inconsistent and inconclusive¹.

PHYTOESTROGENS

Soy beans and soy-based dishes are potent source of phyto-estrogens which are naturally occurring compounds with both oestrogenic and anti-oestrogenic properties⁵³. Phytoestrogens can be classified into two main classes: Isoflavones and Lignans. Various forms of phytoestrogens have been investigated on hot flushes. However, there is currently no evidence that

phytoestrogens supplementations reduce either the frequency or severity of hot flushes⁵⁴. Currently, phytoestrogens are not recommended for the treatment of hot flushes because their role is unclear, poorly understood, as clinical trial efficacy data are inconsistent and inconclusive^{1,55}.

BLACK COHOSH

This is a plant native to the Eastern United States and Canada. It is also known as *Cimicifuga racemosa*. It was originally used for menstrual and menopausal conditions⁵⁶. Neither red clover nor black cohosh significantly reduced hot flushes⁵⁷, and there is some concern regarding possible adverse effects of black cohosh on the liver and its overall long-term safety⁵⁸. Therefore, black cohosh is not recommended as a treatment for hot flushes.

VITAMINE

Vitamin E was first used as a possible treatment for hot flushes in the 1940's⁵⁹. In recent years, there has been concern about carcinogenicity of vitamin E, however, there is reported evidence that vitamin E does not increase cancer risk⁶⁰. Currently, vitamin E cannot be strongly recommended as an effective treatment for hot flushes.

OTHER HERBAL REMEDIES

These include evening primrose oil (*oenothera biennis*) rich in linoleic acid, Dong quai (*Angelica Sinensis*), licorice, Ginseng (*panax ginseng*), and wild yam (*Dioscorea villosa*). Currently, these herbal remedies (evening primrose oil, dong quai, ginseng or wild yam) are not associated with any sound evidence that they are effective in treating hot flushes, and therefore should not be used as a therapy for vasomotor symptoms⁶¹⁻⁶⁴. Their role remains unclear, as clinical trial efficacy data are inconsistent and inconclusive.

LIFESTYLE MODIFICATION

Lifestyle modification includes regulation of core body temperature techniques, regular physical activity, weight loss and smoking cessation.

Lifestyle modification is recommended as the first line therapy for patients suffering from mild vasomotor symptoms by the North American Menopause Society⁶⁵. Lifestyle modification involves keeping the core body temperature cool using techniques such as loose clothing, dressing in layers, using fans or air conditioning, sipping cold drinks, avoiding spicy food, or hot food and keeping a lower room temperature^{65,66}.

EXERCISE

Regular physical activity, weight loss and cessation of smoking may also reduce the risk of vasomotor symptoms.

A lot of researches are still ongoing on the effect of exercise on hot flushes. However, exercise has not been proven as an effective treatment for hot flushes⁶⁷.

YOGA

Yoga is a combination of exercise and meditation, which involves gentle stretching and breath control. A recent review of the literature on yoga and hot flushes concluded that current evidence does not support the use of yoga for menopausal related vasomotor symptoms⁶⁸.

RELAXATION TRAINING

This is a method of reducing stress and anxiety. Different forms of relaxation training have been investigated for the treatment of menopausal symptoms. Paced respiration is a good example of relaxation training, which involves slow controlled, diaphragmatic breathing. Researches are ongoing on the effects of relaxation training on hot flushes but only paced respiration has demonstrated efficacy in reducing hot flushes^{5,69}.

Mindfulness-based stress reduction (MBSR) is a form of trained relaxation. It is a program that teaches mindfulness meditation and yoga as a way to cope with stress⁷⁰. The result of mindfulness-based stress reduction on hot flushes is still inconclusive, further evaluations are needed on various forms of relaxation on hot flushes⁷¹.

HYPNOSIS

Hypnosis is a mind-body therapy that uses mental imagery to induce a state of deep relaxation and heightened focus. Hypnosis has been applied in the management of multiple medical conditions such as pain, anxiety and insomnia⁷². The effect of hypnosis on hot flushes is still inconclusive, trials are currently underway⁷³.

ACUPUNCTURE

Acupuncture is the use of thin needles inserted into specific points of the body. It is used as a treatment for multiple conditions. Currently, there is no evidence that acupuncture is an effective treatment for hot flushes⁷⁴.

STELLATE GANGLION BLOCK

Stellate ganglion block (SGB) is used to treat a variety of pain syndromes and vascular insufficiency⁷⁵. The mechanism by which SGB reduce hot flushes is unclear. However, Lipov and colleagues⁷⁶ proposed that the stellate ganglion has links with the areas of the central nervous system that control body temperature. A SGB may interrupt these connections and allow the body temperature regulating mechanisms to reset⁷⁷. Trials are still ongoing on the effects of stellate ganglion block on hot flushes.

PROBLEMS WITH VASOMOTOR TREATMENT

Management of hot flushes is controversial and problematic because the most recognized effective treatment option is often contraindicated.

Clinical trials for hot flushes are effected by the fluctuations in symptoms among peri-menopausal women and by the cessation of hot flushes over time⁶⁵. The placebo effect is higher in trials of hot flushes than for many other conditions.

Various treatment options have been used to relieve hot flushes but there were no cure established because there is no consensus on the pathophysiology of menopause-associated vasomotor symptoms^{2,5}. Efficacy and safety data from ongoing clinical trials are eagerly awaited. Additional studies are warranted to determine the efficacy and safety of nonhormonal therapy in the treatment of menopause-associated vasomotor symptoms. Comparative clinical trials and cost effectiveness analyses will be needed to determine if any of these investigational therapies are capable of replacing HRT as the standard of care in women with moderate to severe vasomotor symptoms.

CONCLUSION

Hot flushes are the most common vasomotor symptom associated with menopause. Management of hot flushes poses a lot of problems because the most recognized effective option oestrogen is often contraindicated. In view of this, an extensive amount of research has been ongoing exploring different therapeutic options for the treatment of hot flushes. Currently, various safe and efficacious non-hormonal options exist but further research is still needed to improve on the treatment of hot flushes.

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