REVIEW ARTICLE

Managing Hot Flushes in Menopausal Women: A Review

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ABSTRACT

Hot flushes during menopause are distressing for women and result in poor quality of life. Purpose of the current review was to evaluate the available treatment modalities that should be utilised for the management of hot flushes. Menopause refers to last menses of women life and can be declared after amenorrhea of 12 months. Vasomotor symptoms including hot flushes and night sweats are common after menopause, affecting almost 50 - 85% women older than 45 years. The mean increment in core body and skin temperature is 0.5°C and 0.25 - 3°C during a hot flush attack. Low level of estrogen during menopause and its association in triggering episodes of hot flushes, is still under debate. The most accepted hypothesis is a narrowing of the thermoneutral zone (TNZ) triggered by estrogen fluctuations. Although, hormone replacement therapy (HRT) remains the standard treatment for the alleviation of such symptoms, incidence of life threatening side effects restrained medical professionals from its use. Complications associated with the use of HRT can be avoided by appropriate evaluation of patients before initiating therapy. Several guidelines have also recommended HRT (estrogen and progesterone) to be safe for up to a period of seven years. Both hormonal and non-hormonal treatments are used for the management of hot flushes. Since hot flushes are the least appreciated and neglected complication of menopause, current review provides detailed information on its background, pathophysiology and management, and emphasises the need of its treatment.

Key Words: *Menopause. Hot flushes. Hormone replacement therapy. Vasomotor symptoms. Climacteric symptoms.*

INTRODUCTION

Menopause (*menos*: month, and *pausis*: cessation), a critical phase in women life, is defined as last menses and can be declared after 12 months of amenorrhea. The average age of menopause is 51 years, but symptoms usually occur 10 years prior to this age (peri-menopausal symptoms). The hallmark of menopause is vasomotor symptoms including hot flushes and night sweating.[1] Hot flushes are characterised by sudden onset of heat sensation that begins in chest and may progress to the whole chest and the neck.[2] In addition to the vasomotor symptoms, menopause is also characterised by dynamic changes in endocrinology of female's body such as cycle irregularities, reduced fertility, and psychological symptoms. Menopause can also be induced artificially by surgical procedures (hysterectomy or oophorectomy), either by chemotherapy or radiations.[3]

About 50-70% women of menopausal experience several episodes of hot flushes and night sweats. These symptoms are more severe in women with surgical menopause as compared to natural menopause. Hot flushes, the most common and troublesome problem associated with menopause, are associated with a sharp rise in circulating luteinising hormone and epinephrine (a potent stimulator of heart function that increases heart rate, cardiac output, and systolic blood pressure) with a simultaneous decline in the hormone norepinephrine (which increases blood pressure dramatically).[4]

Flushes vary in intensity, frequency, and duration from one person to another. SWAN (Study of Women`s Health Across the Nation, having data of 16000 women) demonstrated that many women experience hot flushes on daily basis, some as frequently as every hour while some have weekly or monthly episodes. Majority of the women experience hot flushes for 6 months to 2 years where symptoms are severe after 2 years of menopause. These symptoms include discomfort, embarrassment, restlessness and loss of sleep. Sometimes an aura precedes hot flush by several seconds. During this period, heart rate and blood flow towards finger increase followed by a sensation that the flush is about to occur. Immediately, there will be an increase in finger temperature (up to 6°C), while a simultaneous decrease in body temperature (0.1 to

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0.6°C) would be experience as a result of sweating on forehead and chest.[5]

Epidemiology: Prevalence of hot flushes largely depends upon the culture and ethnicity. Table I shows varying incidence of hot flushes among different ethnic groups. According to an estimate, 50-85% women older than 45 years embraced hot flushes during their life.[6] United State census bureau statistics shows the incidence of hot flushes as 75% among women older than 50 years.[5]

The Prevalence of hot flushes in different ethnic groups is 46% in African Americans, 34% in Hispanics, 31% in Whites, 21% in Chinese, and 18% in Japanese.

Evaluation of Vasomotor Symptoms: Women presenting with classic hot flushes between the ages of 40 - 50 year do not require laboratory examination. However, other causes of hot flushes, if suspected, must be ruled out. These causes include alcohol consumption, carcinoid, the dumping syndrome, hyperthyroidism, narcotic withdrawal, pheochromocytoma, and medications including nitrates, niacin, gonadotropin-releasing hormone agonists, and anti-estrogens. Usually, the levels of FSH and LH fall in normal range in menopausal transition.[7] Temperature changes can be assessed with thermography as temperatures of finger and toes increase about 20 to 33°C during hot flushes.[8] The increment in core body temperature and mean skin temperature is 0.05°C and 0.25-0.3°C, respectively during hot flushes.[9]

Pathophysiology of hot flushes: The underlying mechanism of hot flushes is debatable to date. Studies on animals (monkeys and rats) with surgically induced menopause suggest that decline in estrogen levels as a result of menopause is the main cause of hot flushes.[10] Contrary to this, low and high levels of estrogen are observed among pre-pubertal and pregnant women, respectively; but low level of estrogen during pre-puberty does not lead to hot flushes among young girls. Pregnant women may incur hot flushes despite high levels of estrogen. Although hot flushes are first symptom of menopause transition; but they subside after menopause, when estrogen levels are markedly low. Despite these contrary findings, most of the investigators believe a relationship between estrogen levels and hot flushes.[8]

Many investigators have proposed different hypothesis to explain underlying mechanism of flushes; but recently, Robert Freedman presented an attractive explanation based on thermoregulation. Thermoregulation in human body is controlled by hypothalamus *via* neurotransmitters (serotonin, nor-epinephrine) and neuromodulators (estrogen). There is a thermo-neutral zone of about 0.4°C in normal and asymptomatic women. Within this zone, fluctuations in core body temperature do not result in initiation of compensatory mechanisms including

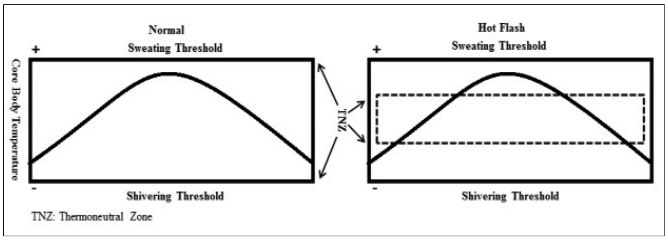

Figure 1: Thermoneutral zone in asymptomatic (normal) and symptomatic (hot flush) women.

flushing and sweating. On the other hand, in symptomatic women, thermo-neutral zone becomes narrow as a result of increased central noradrenergic activation caused by changes in estrogen level as shown in Figure 1.[11] Due to narrow thermo-neutral zone, fluctuations in core body temperature causes hot flushes and sweat.[12]

The relationship between estrogen and hot flushes can also be explained with Hemmie`s hypothesis, which states that estrogen enhances synthesis of 5HT and endorphins, which in turn, inhibit the production of noradrenaline. As menopause results in deficiency of estrogen, it results in decrease level of 5HT and endorphins, followed by an increase in noradrenaline level. This increase in noradrenaline causes narrowing of thermal neutral zone and results hot flushes.[13] Other theories, explaining pathophysiology of hot flushes, state the altered sensitivity of cutaneous vessels and changes in level of circulating gonadotropic hormones might contribute to exaggerated response, i.e. hot flushes.[14,15]

Treatment options: As far as treatment of menopause and its associated symptoms are concerned, there are two schools of thought, one in favour of treatment considering the fact that menopause is a result of hormone deficit and should be treated; while other not in favor of treatment considering menopause as a natural process that subsides with the passage of time.[16] Women having hot flushes due to menopause face significantly lower quality of life that is inexplicably associated with loss of productivity. Such women bear disruption in family relationship, social isolation, anxiety, embarrassment, fatigue, osteoporosis, bone fragility and sleep disturbance.[17,18] These symptoms should be addressed to improve the quality of life during peri- and post-menopausal phase.[6,19] There are several approaches to manage vasomotor symptoms during peri-menopausal and post-menopausal women. Depending on the severity of symptoms (mild, moderate, severe) treatment approach is selected as shown in Figure 2.

Hormonal Treatments (HT): It includes treatment with estrogen alone (in case of hysterectomy) or in combination with progesterone (in case of intact uterus) to protect from endometrial hyperplasia.[21] International Menopause Society and America Association of Endocrinologists guidelines recommend HRT therapy as most effective treatment for vasomotor symptoms and

Table I: Hormone replace therapy (HRT) side effects and contraindications.[27,28]

Agents	Side Effects	Contraindication
Estrogen	Breast tenderness, nausea, headache, bloating; may resolve by continuous use, decrease dose or substitution with other agents	Unexplained vaginal bleeding, acute liver disease, acute thromboembolic disease, known or suspected breast cancer, caution should also be taken in cardio vascular disease and hypertriglyceridemia
Progesterone	Alteration in mood, breast tenderness, bloating; can be alleviated by switching to another progestogenic agent.	Known or suspected breast cancer, pregnancy and undiagnosed vaginal bleeding.

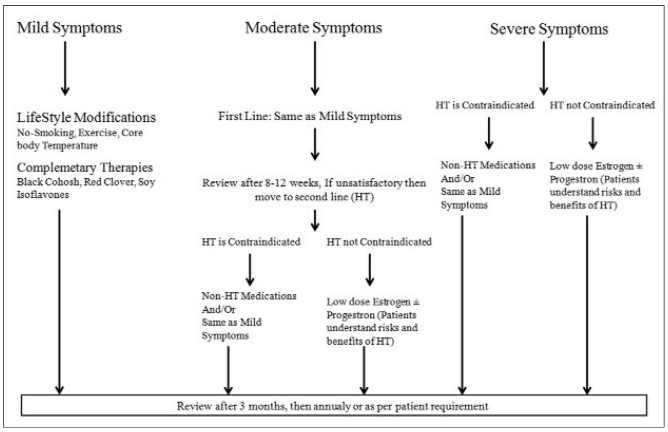

Figure 2: Severity-based management strategies for patients having hot flushes.[20]

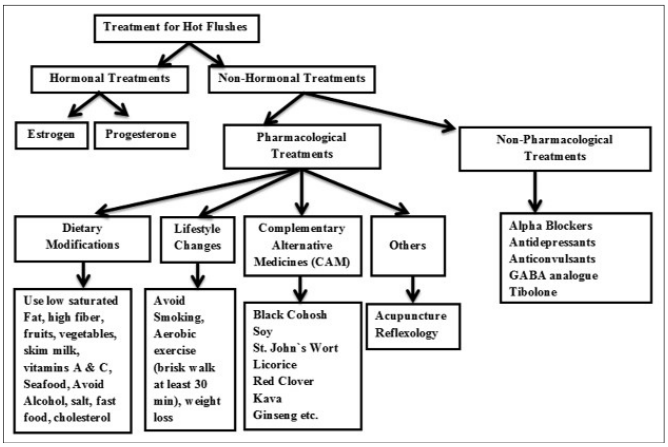

Figure 3: Treatment summary for hot flushes.[22,30,33]

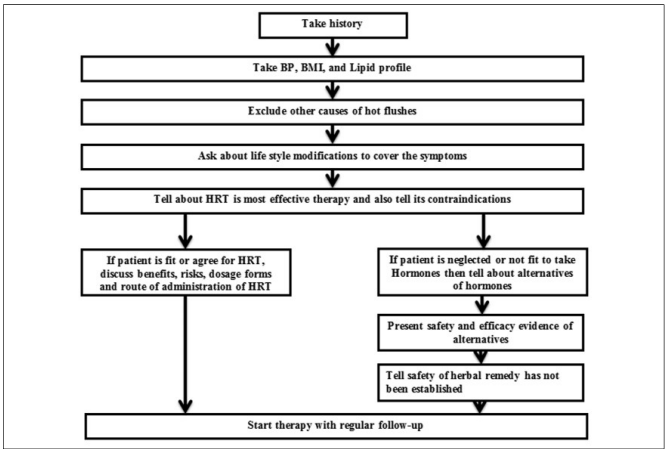

Figure 4: Clinical approach to manage hot flushes.

for maintaining the improved quality of life.[21,22] On the contrary, studies have shown that HRT may cause coronary heart disease, strokes, venous thrombo-embolism and invasive breast cancer.[23] These findings left both the healthcare professionals and the patients ambiguous regarding HRT use.

Recent recommendations from International Menopausal Society on the use of HRT state that estrogen-progesterone combination or estrogen alone can be safely used for five and seven years respectively, in first time users. Review of 45 studies (1975-2000) showed that there is no significant risk of breast cancer with HRT and short duration therapy does not elevate the risk of breast cancer.[22] Besides all these controversies and recommendations, lifestyle modifications and OTC remedies should be approached for mild symptoms before considering HRT.[20]

Before initiation of HRT, evaluation of patient`s medical history should be done carefully to check for family history of breast, ovary and endometrium carcinoma, deep venous thrombosis, gall stone, migraine and epilepsy. Screening for blood sugar and lipid profile tests should be mandatory during HRT.[24]

HRT is effective for the prevention of hot flushes as well as fracture associated with menopausal osteoporosis. It may be cardio protective if started at the time of menopause.[25] HRT can also be used in breast cancer survivors and debate is still present, as some data show increase in recurrence of breast cancer with HRT, while few studies contravene it. Complementary therapies are still less effective as compared to HRT.[26] The benefits, side effects and contraindications are described in Table I.[27,28]

Non-hormonal treatment: Undoubtedly, hormonal treatment has potential benefits, but it is also associated with risks including breast cancer and endometrial hyperplasia.[27,28] Such risks have shifted attention of healthcare professionals towards non-pharmacological treatment options, resulting in wide use of them. According to a survey, 76% women use alternative therapies for the management of symptoms associated with menopause.[29] A brief overview of these interventions is shown in Table II. Non-hormonal pharmacological therapy includes alpha adrenoceptors agonist (methyldopa, colinidine and lofexidine), antidepressants and anticonvulsants, GABA analogue (Gabapentin).[30]

Tibolone is an alternative of HRT being used in current practice. It is a synthetic steroid developed for the treatment of climacteric complaints. Tibolone has estrogenic, progestogenic and androgenic effects. Its effects are comparable with estrogen-based HRT.[31] It is metabolised in liver to its metabolites, which bind on estrogen, progesterone and androgens receptors. However, Tibolone has a tendency to induce greater vaginal bleeding as compared to conventional HRT and is associated with increase relative risk of breast cancer and endometrial hyperplasia.[32-34]

Table II: Non-pharmacological treatment of hot flushes.[24]

Lifestyle modification	Measures
Lifestyle measures advices	Avoid smoking
	Aerobic exercise
	Weight loss measures
Dietary modifications advices	Use diet having low saturated fat and high fiber
	Use fruits and vegetables
	Use seafood and skinless chicken
	Use skimmed milk and its products
	Avoid high cholesterol and fast food
	More than 5 servings of fruits and vegetables per day
	Diet having antioxidant vitamins would be preferred over vitamin supplements
	Use salt up to 6 g/day
	Supplements of vitamin A and C (vitamin E: 800 iu/day)

Complementary alternative medicines (CAM): Various herbs and food supplements have made their place for the alleviation of vasomotor symptoms in menopausal women. Phytoestrogens are structurally related to estrogen (estradiol) and are present in several plant species including red clover, flax seed and soy.[35] Soy isoflavones have estrogenic properties and are mostly used by Asian women for the treatment of hot flushes. A comparative study among Western and Chinese women shows the incidence of hot flushes of 80% and 20%, respectively. This difference between incidences is attributed to dietary soy intake among Chinese population.[36,37] Table III summarises commonly used botanical products for the management of menopausal symptoms.[38]

Traditional acupuncture is beneficial for the treatment of vasomotor symptoms in breast cancer patients in conjunction with HRT.[39,40] Reflexology is also used for the treatment of menopausal symptoms and referred to

Table III: Complementary and alternative medicines for the treatment of menopausal symptoms.[35,38]

Herb	Proposed mechanism	Usual dose	Side effects
Black Cohosh *(Cimifuga Racemosa)*	Estrogenic and progestogenic effects	20 mg twice daily	GIT complaints, hypotension, dizziness, nausea, allergic reactions
Soy	Estrogenic effects	40-60 gm soy protein powder or 50-80 mg isoflavones daily	Soy foods are well tolerated, soy powder can cause GIT complaints
St. John`s Wort *(Hypericum Perforatum)*	Inhibit reuptake of serotonin, nor-epinephrin, dopamin	No widely accepted dose	GIT complaints, allergic reactions, neuropathy, anxiety, fatigue
Red Clover *(Trifolium Pratense)*	Estrogen like effects	40-80-160 mg isoflavones per day	Breast tenderness, menstrual changes, weight gain
Kava *(Piper Mythysticum)*	Anxiolytic	No widely accepted dose	Stomach complaints, restlessness, allergic reactions, mydriasis
Dong Quai *(Angelica Sinensis)*	Estrogenic effects	No widely accepted dose	Bleeding, photosensitivity
Burdock *(Arctium Lappa)*	Estrogenic effect	Not available	Data not available
Licorice *(Glycyrriza Glabra)*	Estrogenic effects	Not available	Data not available
Motherwort *(Leonorus Cardiaca)*	Stimulate uterine activity	Not available	Data not available
Wild Yam *(Dioscorea Barbasco)*	Mode of action is undetermined	No widely accepted dose	No adverse effects
Evening Primose Oil *(Oenothera Biennis)*	Part of pathway of prostaglandins E1 synthesis	2-4 gm daily	Headache, GIT complaints
Ginseng *(Panax Ginseng)*	Estrogenic effects	Not available	Insomnia, diarrhea, vaginal bleeding, can cause Steven Johnson syndromes
Chasteberry	Unknown	30-40 mg per day	Data is not available
Flaxseed *(Linum Ussitatissimum)*	Estrogenic, antiestrogenic and steroid-like actions	25-40 gm per day	No known side effects
Geranium *(Pelargonium graveolens)*	Unknown	Not available	Data not available
Sage *(Salvia officinalis)*	Anti-hydrotic properties	Not available	Data not available

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Geranium *(Pelargonium graveolens)*	Unknown	Not available	Data not available
Sage *(Salvia officinalis)*	Anti-hydrotic properties	Not available	Data not available

applying pressure at specific points or areas of the feet. Though therapeutic benefits of acupuncture are established in the literature, but further clinical trials are needed to establish its potential role in the management of menopausal symptoms.[41]

Although, several reports have demonstrated the valuable effects of CAM in menopause, but data indicating the superiority of bio-identical hormones upon conventional hormone therapies are currently lacking. Moreover, the risk profile of CAM has not investigated in the available literature.[41] Treatment summary of climacteric symptoms is shown in Figure 3.[22,30,33]

Clinical approach to manage hot flushes: Clinical approach and management of hot flushes should be subjected to patient`s clinical condition, as described in Figure 4.[42]

CONCLUSION

Climacteric symptoms significantly affect the quality of life during menopausal age. Numerous studies have addressed the need of management of menopausal symptoms among both pre- and post-menopausal women. The selection of treatment modalities should be based on patient`s history and severity of symptoms. Moreover, education programmes on menopausal symptoms should be carried out at community level in order to increase awareness among general population and healthcare professionals. The authors are conducting a nationwide survey to evaluate the knowledge and awareness of menopause among general public and healthcare professionals in Pakistan. Preliminary findings of this project indicated a low awareness of menopause and its treatment among women in Pakistan.[43]

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