Evidence-based Pharmacy Practice (EBPP):

HOT FLUSHES

Angelene van der Westhuizen, BPharm Department of Pharmacology, University of Pretoria

Abstract

Hot flushes are the most common complaint of perimenopausal and postmenopausal women.

Menopausal hormone therapy (HT) is the most effective treatment for vasomotor symptoms and improves the quality of life of women in which these symptoms can be distressing and incapacitating.

Non-hormonal medical treatments for the management of vasomotor symptoms are less effective than oestrogen and evidence of efficacy is conflicting. Non-hormonal therapies include clonidine, SSRI's (Selective Serotonin Reuptake Inhibitors) and SNRI's (Serotonin Noradrenaline Reuptake Inhibitors) and gabapentin.

Concerns about the safety of oestrogen-based HT after publication of the Women's Health Initiative Study and the Million Women Study has led many women to take alternative therapies, erroneously believing they are safer and 'more natural'.

Pharmacists need to be able to give women appropriate advice so they can make an informed decision on whether or not to take or continue taking HT. Advice on non-pharmacological treatments, CAM's (complementary and alternative medicines) and non-hormonal treatments will also benefit women unable to (such as patients diagnosed with breast cancer) or unwilling to take HT.

Pharmacists can help improve negative attitudes to the menopause and its symptoms by being knowledgeable and approachable on the subject. Women should be reassured that taking short term HT for the management of menopausal symptoms is a safe and therapeutic treatment for the majority of women.

Definitions

Hot flushes are otherwise known as hot flashes (in the United States of America [USA]), menopausal or climacteric symptoms. Vasomotor symptoms typically refer to hot flushes, night sweats, palpitations and associated sleep disturbances and mood changes. 17

Hot flushes are the most common complaint of perimenopausal and postmenopausal women.¹ Perimenopause is the period of transition from regular menstruation to its cessation.¹ The median onset of perimenopause is between 45.5 years and 47.5 years and it lasts for an average of four years.²

The menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity.² The diagnosis of menopause is made retrospectively, after 12 months of amenorrhoea. The median age of menopause is 51 years.³ Cigarette smokers undergo menopause about two years earlier than non-smokers.³ The menopause transition refers to the time of the perimenopause prior to the last menstrual period (where the oestrogen levels are generally normal or even slightly elevated and the level of follicle stimulating hormone begins to increase but is generally in the normal range) to the postmenopause (where there are low oestrogen and progester-

one levels and high gonadotrophin [follicle-stimulating hormone and luteinising hormone levels]).

A hot flush is a sudden feeling of warmth that is generally most intense over the face, neck and chest.³ Hot flushes can be accompanied by sweating, flushing, palpitations, anxiety, irritability and even panic,¹ and are often followed by chills and shivering.⁴

The average hot flush lasts about four minutes but it can last a few seconds or as long as ten minutes.¹ Hot flushes usually occur several times per day, but some women report hot flushes that occur only several times per week; others report one to two per day to as many as one per hour during the day and night. They cause arousal from sleep, which leads to sleep disturbances⁴ and thus may lead to insomnia, irritability and difficulties with memory and concentration.²

Epidemiology

A systemic review of the vasomotor symptoms of menopause estimated that symptoms occur in 14 to 51 percent of women before the perimenopause, 35 to 50 percent in perimenopause, and 30 to 80 percent after menopause.⁵ Hot flushes tend to occur most often in the first year after the final menstrual period and can occur at any time of day or night.² More than 80 percent of women who have hot flushes will continue to have

them for more than one year.⁴ In most women hot flushes stop spontaneously without treatment within a few years of onset.^{6,7} Almost a third of postmenopausal women will report symptoms that last up to five years after natural menopause, and hot flushes can persist for up to 15 years in 20 percent of women.¹

Several risk factors have been associated with the increased probability of hot flushes.1 Low oestradiol and oestrone concentrations, being underweight, doing little or no exercise and smoking have been associated with an increased risk of hot flushes.1 The frequency of vasomotor symptoms and the reporting thereof have been shown to be different between populations and cultures. In the USA, hot flushes are more common in African American and Latino women and less common in Chinese and Japanese women than in Caucasian women.3 The more highly educated a woman is, the more likely she is to be symptom free.2 It was originally thought that increased adiposity (obesity) in a woman would be associated with decreased hot flushes during the menopause because of the conversion of androgens to oestrogens in body fat.2 However it has also been postulated that increased adipose tissue would actually be associated with a greater likelihood of hot flushes.2 Women who become menopausal at a younger age are more likely to be bothered by symptoms than other women.1 Abrupt menopause induced by surgery has a 90% probability of hot flushes during the first year post surgery.1 Symptoms associated with surgical menopause are often more severe and can last longer than those associated with non-surgical menopause.1

About two-thirds of postmenopausal women who have had breast cancer report hot flushes, and just over half report these flushes to be severe.¹

Hot flushes can also be caused by systemic disease, neurological disorders, alcohol, drugs, eating habits and food additives.¹ Men on androgen deprivation therapy also suffer from hot flushes.¹

Aetiology/pathophysiology

Despite multiple theories, the exact pathophysiology of the hot flush is not yet known.² The physiological changes associated with hot flushes are different from any other flushing condition.⁸

It is thought that the physiological mechanism whereby a hot flush occurs is the result of elevated body temperature leading to cutaneous vasodilatation, which results in flushing and sweating in association with a subsequent decrease in temperature, chills and potentially relief. It is believed that within the hypothalamic thermoregulatory zone there is an interthreshold zone, which is defined as the threshold between sweating and shivering. There is evidence to indicate that after menopause this interthreshold zone becomes narrowed. Triggers for this change in interthreshold zone could include serotonin (5-hydroxytryptamine), noradrenaline (norepinephrine), and oestrogen deprivation.

The oestrogen effect on hot flushes is thought to be due to withdrawal of oestrogen rather than decreased oestrogen levels. Endogenous oestrogen levels do not differ substantially between postmenopausal women who have hot flushes and those who do not have them. Flushes do not occur in women with ovarian dysgenesis unless oestrogen therapy is used and then discontinued, which suggests that oestrogen withdrawal is important. In women with Turners syndrome (a chromosomal disorder in females who have only one X chromosome; marked by dwarfism and heart abnormalities and underdeveloped sex organs), hot flushes do not occur in those who were never treated with oestrogen but once treated with oestrogen they have hot flushes when therapy is discontinued.

Clinical approaches to hot flushes for the pharmacist

The pharmacist needs to exclude other causes for hot flushes before giving advice for the management of hot flushes due to the menopause. Flushing could be due to a number of systemic diseases e.g. hyperthyroidism, phaeochromocytoma, carcinoid syndrome, panic disorder, or diabetes. It could also be due to the side effects of drugs such as antioestrogens or selective oestrogen receptor modulators (SERMs), bromocriptine, calcium-channel blockers, cephalosporins, cholinergic drugs, ketoconazole or nicotinic acid. Interactions between certain drugs and alcohol could also cause flushing such as metronidazole and chlorpropamide.

Pharmacists can help improve the negative attitudes to menopause. Stressing the importance of healthy lifestyles including exercise, nutrition and spirituality will help women of any culture going through the menopause. ¹⁰ General advice to try and achieve a normal body-mass index, to stop smoking and to maintain a regular exercise regimen is reasonable since these behavioural changes will benefit long-term health. ¹¹ If trigger factors to hot flushes can be identified e.g. alcohol, hot drinks or spicy food, then these should be avoided. ¹¹ Most women unfortunately cannot identify triggers.

The pharmacist can advise menopausal women on the treatment options for hot flushes which are:

- Non-pharmacological
- · Complementary and alternative medicines (CAMs)
- Pharmacological

Non-pharmacological treatment options

If a woman's symptoms are mild, then the pharmacist can give advice on non-pharmacological ways of managing symptoms. Examples of these include: tolerance, fans, air conditioners, or cold water to ameliorate their symptoms.¹ Reduction in the layers of clothing and wearing cool cotton clothing may reduce the severity of hot flushes. Other methods commonly used include exercise (although no conclusions can be made about efficacy due to lack of

trials), 12 diet, acupuncture, behavioural therapies and lifestyle modification. Behavioural therapies include meditation, applied relaxation, biofeedback and paced respiration. 1 Paced respiration which is slow, controlled diaphragmatic breathing performed either at regular intervals throughout the day or when a hot flush begins, has been shown to be beneficial in treating hot flushes. 10

Complementary and alternative medicines (CAMs)

Concerns about the safety of menopausal hormone therapy after publication of the Women's Health Initiative study¹³ and Million Women Study¹⁴ has led to many women turning to alternative therapies, erroneously believing that these are safer and 'more natural'.¹⁵ Pharmacists need to inform women of the many possible side-effects and interactions with other drugs and treatments with CAMs. 'Natural' does not necessarily mean it is safe! Some interactions may prove to be fatal.

Evidence from randomised trials that alternative and complementary therapies improve menopausal symptoms or have the same benefits as conventional medicine is poor.¹⁵

CAMs include: herbal (or botanicals), homeopathy, and physical interventions (these therapies do not involve ingestion or application of any agent). Physical interventions include acupuncture, reflexology, magnetism, acupressure, Alexander technique, Ayurveda, osteopathy and Reiki.

Women should be counselled that data regarding the

oestrogenic effects of soy are inconclusive. This means that women with a strong or personal history of hormone-dependent cancers (breast, uterine or ovarian), thromboembolic events or cardiovascular events should not use soy-based therapies. Phyto-oestrogens and possibly black cohosh bind oestrogen receptors and could cause adverse outcomes similar to those seen with oestrogens. Most evidence suggests that alternative therapies are no more effective than placebo for reduction in hot flushes.

Pharmacological treatments

These include hormonal and non-hormonal treatments.

· Hormonal treatments

Hormone therapy is recognised as the most effective form of treatment of menopausal symptoms. ¹⁰ Pharmacists can help advise patients about the factors they need to consider before deciding whether to take hormone therapy or not. Age, severity of symptoms, medical status and medical history are all key factors in this decision-making process. ¹⁶ Oestrogens should be avoided in women who have a history of or are at high risk of cardiovascular disease, breast cancer, uterine cancer, or venous thromboembolic events and in those with active liver disease. ³ Patients should be reassured that taking oestrogen (either alone or in combination with progestogen) for the management of menopausal symptoms is a safe therapeutic treatment for the majority of women.

Oestrogen virtually eliminates hot flushes but the mechanism of action is unknown.²

Table 1: CAMSs used to treat menopausal symptoms		
CAM	Effectiveness	Warnings
Soy (phyto-oestrogen)	Contradictory evidence difficult to evaluate	Few ADRs but endometrial hyperplasia in some studies
Red clover (phyto-oestrogen)	Majority of clinical data shows no superior efficacy	No serious ADRs but safety in Breast Ca unknown
Black cohosh (Actaea racemosa)	No definite conclusions	May have oestrogenic actions, reports of liver toxicity
Dong quai (Angelica sinesis)	Not superior to placebo	Interacts with warfarin, photosensitisation
Evening primrose (Oenothera biennis)	Ineffective for treatment of hot flushes	
Ginseng (Panax gingseng)	Not superior to placebo	Case reports of postmenopausal bleeding and mastalgia. Interacts with warfarin
Kava kava (Piper methysticum)	Data conflicting	Liver damage has led to withdrawal
Gingko (Gingko biloba)	Little evidence	
St Johns wort (Hypericum perforatum)	Little evidence to support efficacy for hot flushes	
Chasteberry (<i>Agnus castus</i>), liquorice root, hops, sage, valerian root	Little evidence to support efficacy for hot flushes	
Vitamin E	Small benefit over placebo (one less HF per day)	

Tabulated from data in reference 13

HT is acknowledged as the gold standard for the alleviation of vasomotor symptoms. Numerous studies have compared the efficacy of various types, routes and doses of HT on alleviating vasomotor symptoms but most have concluded that HT improves symptoms, irrespective of route or type of oestrogen or progestogen.² The placebo effect ranges from 20–50% reduction in hot flush frequency and severity in randomly controlled trials.⁹

Menopausal hormone therapy (HT) includes oestrogen therapy (ET), combined oestrogen and progestogen therapy (EPT), combined sequential oestrogen and progestogen (CS-EPT), and combined continuous oestrogen and progestogen therapy (CC-EPT).¹⁷ CS-EPT produces endometrial shedding and monthly withdrawal bleeding while CC-EPT prevents endometrial proliferation and does not result in a monthly withdrawal bleed. The forms and most commonly used daily doses of oestrogens are as follows:

- Conjugated equine oestrogens (0.3 to 0.625mg)
- Micronised 17ß-oestradiol (0.5 to 1mg)
- Transdermal oestradiol (14 to 100 ¼g)

Pharmacists should counsel women suffering from oestrogen-related side effects such as mastalgia and breast tenderness that these symptoms are usually transient and that they should persist with treatment for at least three months before considering a change of regimen or dose.¹⁸

Oral, intramuscular and topical formulations of progestogens have also been used in the treatment of hot flushes in women who are unable to take oestrogen.⁹ Studies have shown effectiveness but the associated side-effects, including withdrawal bleeding and weight gain, often limit its use for this indication.⁹ Doses that achieve control of vasomotor symptoms may increase the risk of venous thromboembolism.¹⁵

The progestogens used in HT regimens include the testosterone analogues: norgestrel, levonorgestrel and norethisterone, and the progesterone analogues: dydrogesterone and medroxyprogesterone. Drospirenone is a progestogen that is chemically related to spironolactone.

Progestogen-related side effects often resemble premenstrual symptoms. The symptoms are usually related to the type and dose of progestogen, and duration of therapy. These can be managed by either changing the progestogen type, reducing the dose (so long as it is adequate for endometrial protection), changing the route of administration or duration of therapy.¹⁸

Tibolone (Livifem®) is an alternative to HT in women who have been postmenopausal for one year. It has weak oestrogenic, progestogenic, and androgenic effects. It does not induce withdrawal bleeding in postmenopausal women. It has been shown to increase bone-mass density and lower cholesterol¹ but it has also been shown that there is an increased risk of breast cancer recurrence.¹¹

Non-hormonal treatments

Non-hormonal treatments for the management of vasomotor symptoms are less effective than oestrogen and evidence of efficacy is conflicting. Non-hormonal treatments include clonidine, SSRIs, SNRIs and gabapentin.

Clonidine is a centrally acting alpha-2-adrenoreceptor agonist that was originally developed for the treatment of hypertension. The evidence for efficacy for treating hot flushes in randomised controlled trials is conflicting.¹⁵

Fluoxetine, paroxetine, citalopram and venlafaxine have been found to be effective in several studies. 15 The most convincing data is for venlafaxine at a dose of 37.5 mg twice daily. 15 However most beneficial effects are short-lived, lasting only a few weeks. 15

Gabapentin is a gamma-aminobutyric acid analogue used to treat epilepsy, neuropathic pain and migraine. It reduces hot flushes by about 50% when used at a dose of 900 mg per day.¹⁵

Evidence based guidelines approach to alleviating hot flushes during menopause

The FDA (Food and Drug Administration) and the American College of Obstetricians and Gynaecologists recommend that postmenopausal hormone therapy be used at the lowest dose that adequately controls symptoms and for the shortest possible time for the treatment of menopausal symptoms.3 The North American Menopause society recommends that women with mild vasomotor symptoms first consider lifestyle changes, either alone or combined with a non-prescription remedy (CAMs). Two antihypertensive agents, clonidine and methyldopa have shown modest efficacy but with a relatively high rate of adverse effects. 19 For moderate to severe hot flushes, hormone therapy is recommended as the gold standard. If the woman has not had a hysterectomy, oestrogen with an added progestogen is recommended to prevent the occurrence of endometrial hyperplasia. Short-term therapy is recommended which is considered to be two to three years and not more than five years.¹⁷ Therapy with progestogens, SSRIs or SNRIs, or gabapentin is suggested as an alternative for women who wish to avoid oestrogens.3,19 This could be for women where oestrogen is contraindicated, not well tolerated or for women who have stopped oestrogen and are experiencing recurrent symptoms.20 Women with predominantly night-time symptoms could benefit from gabapentin, taking advantage of the soporific effect of gabapentin while minimising daytime sedation. Women with predominantly daytime symptoms may find a SSRI or a SNRI more appropriate as they are less sedating than gabapentin.20

Hot flushes gradually subside without therapy in most postmenopausal women so any drug can be gradually tapered after one to two years of administration.²⁰ Sometimes symptoms persist and yearly reviews of therapy should be undertaken. Abrupt discontinuation of hormone therapy can be attempted in women who only had mild-moderate symptoms but a more gradual taper (over six months to one year) is recommended in women who had severe vasomotor symptoms.²⁰ SSRIs, SNRIs and gabapentin would also require to be gradually tapered.

According to the South African Menopause Society the indications for using HT include²¹:

- Treatment of vasomotor symptoms and associated sleep disorders.
- 2. Symptomatic urogenital atrophy.
- 3. Prevention of bone loss in women with premature menopause, secondary amenorrhoea and women with osteopenia at risk of fracture.
- 4. Treatment of osteoporosis in 50–60 year old women at risk of fracture, with or without vasomotor symptoms. (If using solely for the prevention or treatment of osteoporosis, other proven bone-specific treatments should be considered.)

Contraindications: HT should not generally be prescribed when there is²¹:

- Current, past or suspected breast cancer.
- Known or suspected oestrogen-dependent malignant tumours.
- Undiagnosed genital bleeding.
- Untreated endometrial hyperplasia.
- Previous idiopathic or current VTE (venous thromboembolism).
- Known arterial CHD (Coronary Heart Disease).
- Active liver disease, or

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Porphyria cutanea tarda (absolute contraindication).

Other general guidelines include21:

- Systemic hormone therapy should not be initiated after the age of 60 years.
- If EPT is required for more than five years, it is recommended to convert from sequential HT to continuous combined HT.
- No published data exists on the use of traditional African medicine for menopausal symptoms.
- No therapy for menopausal symptoms should be initiated without proper clinical assessment, including breast and pelvic examination.

Treatment of menopausal symptoms after breast cancer

Both tamoxifen and raloxifene used in patients who have had breast cancer could worsen hot flushes. 11 Progestogens are the best-studied agents for the treatment of menopausal symptoms after a diagnosis of breast cancer and seem moderately effective. 11 Although high-dose megestrol acetate is an effective treatment of breast carcinoma, there is a theoretical risk that low-dose progestogen might induce tumour-cell growth and increase the risk of developing a new breast cancer or recurrence. 1 In women with a personal history of breast cancer, tibolone may increase the risk of recurrence so it is not recommended for symptom relief. 11

CAMs are probably used more by breast cancer patients with menopausal symptoms than those without breast cancer.20 An important concern is that phytoestrogens are SERMs so they have both oestrogen agonist and antagonist effects. This may mean they could stimulate breast cancer growth, and antagonise the antitumour effect of tamoxifen. 15 Black cohosh could also have a possible oestrogenic effect on the breast so should not be considered a safe therapy for breast cancer patients or women at high risk of breast cancer.15 SSRIs and SNRIs must be used with caution in women with breast cancer also receiving tamoxifen since SSRIs reduce the metabolism of tamoxifen to its most active metabolite, endoxifen. It does this by inhibiting CYP2D6. There is almost a 60% reduction in plasma endoxifen in women taking SSRIs and SNRIs with tamoxifen to those taking tamoxifen alone.23 The order of potency to inhibit CYP2D6 for the SSRIs and SNRIs from highest to lowest is: paroxetine, fluoxetine, sertraline, citalopram and venlafaxine.23 SSRIs and SNRIs should be reserved for treatment of hot flushes in women with breast cancer receiving aromatase inhibitors or no other treatment.

Hormone therapy could be justified to improve quality of life when other interventions have failed for severe menopausal symptoms; so long as the woman has been informed of the relative risk of recurrence and the risk of new primary breast cancer. It could also be considered for women with metastatic disease in whom the quality of life benefits overrides the risks.¹¹

Lower doses of HT

Lower than standard doses of oestrogen and oestrogen and progestogen therapy should be considered as many studies have demonstrated nearly equivalent vasomotor and vulvovaginal symptoms and preservation of bone mineral density.²⁴ Some women may require additional local therapy for persistent vaginal symptoms.²⁴ Lower doses are better tolerated and may have a better risk-benefit ratio than standard doses although lower doses have not been tested in long-term trials.²⁴

Non-oral routes of administration of HT

Non-oral routes of administration of oestrogen or oestrogen and progestogen therapies may offer advantages and disadvantages over the oral route but the long-term risk-benefit ratio has not been demonstrated.²⁴ With transdermal oestrogen there has been shown to be a decreased risk of DVT but similar increased risks for breast cancer with both oral and transdermal oestrogens. The non-oral route avoids the first-pass effect on the liver and may be preferable in conditions such as hypertriglyceridaemia, liver disease, migraine, glucose intolerance and increased risk of VTE (venous thromboembolism) and in smokers.²¹

Evidence for safety of HT

Endometrial carcinoma

Oestrogens given without progestogens to women with an

intact uterus cause endometrial proliferation. All women who have not had a hysterectomy should be given EPT to prevent endometrial hyperplasia and carcinoma.17

Breast carcinoma

The use of HT for longer than five years is associated with a small but statistically significant increase in the incidence of breast cancer. The increased incidence is mainly associated with EPT and the addition of progestogens.¹⁷ ET is associated with a much smaller statistically significant increased risk of breast cancer.17

All women, regardless of whether receiving HT or not, should have a breast examination annually and mammography at least every three years from the age of 50.17

Deep vein thrombosis (DVT) and pulmonary embolism (PE)

HT is associated with a small but significant increased incidence of DVT and PE.17 This is especially evident during the first 6-12 months of taking HT.17 HT is contraindicated in women with a previous proven DVT or PE. Non-proven cases of DVT or PE should be managed with caution and transdermal HT may be a better treatment option.

All women on HT should be given prophylactic anticoagulant therapy before undergoing surgery or immobilisation for any length of time.17

Cardiovascular and cerebrovascular disease

In postmenopausal women over 60 years of age HT may be associated with an increased risk of coronary heart disease and of cerebrovascular disease, including stroke.¹⁷ It is possible that the effect on stroke is dose related.21 Smaller doses may be protective and larger doses harmful.21

The risks of breast cancer, DVT or PE and cardiovascular disease increase with increasing age.17 If women have stopped using HT for more than 6-12 months they do not have any increase in risk over and above that normally associated with increasing age.17

Conclusion

Hot flushes can have a significant impact on the quality of life. There is limited information available regarding the aetiology of hot flushes and effective treatment other than hormone therapy with oestrogen alone or combined oestrogen and progestogen.

Pharmacists are well placed to advise women who wish to understand the latest evidence on hormone therapy so they can make an informed decision as to whether or not to start or continue with HT. Expert and public opinion has fluctuated over the last two decades. From the 1990's where there was a strong pro-HT stance to the early 2000's where there was a limited use position. New trials are underway to clarify the role of HT at menopause. A woman needs to consider the severity of her symptoms and her risk factors for using or not

using HT e.g. osteoporosis, heart disease and hormonedependent cancers before making an informed decision. For many women the immediate need for relief of menopausal symptoms outweighs consideration of both long-term risks and benefits.16 HT is the most effective treatment for vasomotor symptoms and markedly improves the quality of life of women going through the menopause. Non-hormonal therapy such as the SSRIs, SNRIs or gabapentin can also be considered in women where HT is contraindicated. Women should also not be led to believe that natural or alternative therapies are 'safe' and be informed about the many possible drug-herb interactions that could take place. It is the responsibility of pharmacists to keep up to date with the latest evidence and literature so they can advise women appropriately on the management of hot flushes due to menopause.

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