*South African Family Practice* 2015; 57(6):12-15



S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

REVIEW

# Hot flushes

**Jacky van Schoor**[a*]

[a]*Amayeza Info Centre*
[*]*Corresponding author, email: jacky@amayeza-info.co.za*

## Abstract

Vasomotor symptoms, such as hot flushes and night sweats, are considered to be the cardinal symptoms of menopause, and are experienced by most women. The physiology of hot flushes is not fully understood, and is likely to reflect the interplay between multiple central and peripheral physiological systems. Reproductive hormones play an integral role, as evidenced by the onset of vasomotor symptoms during the dramatic reproductive hormone changes of the menopausal transition, and by the efficacy of exogenous oestrogen in the treatment of hot flushes. Menopausal hormone therapy with oestrogen, and with or without a progestogen, is the most widely studied and most effective treatment option for the relief of menopause-related vasomotor symptoms. It is also considered to be the standard of care for women with moderate to severe vasomotor symptoms.

**Keywords:** hot flushes, menopause, night sweats, oestrogen, vasomotor symptoms

## Introduction

Menopause, the cessation of menses, which results from loss of ovarian hormone secretion, affects all women. Menopause can occur naturally, or is induced through surgery, chemotherapy or pelvic irradiation. Natural menopause is diagnosed in women who have had menses for one year, i.e. one year after the final menstrual period.[1] After menopause, up to 85% of women experience vasomotor symptoms, such as hot flushes and night sweats, as well as other menopausal symptoms, including vaginal dryness and discomfort.[1] Most women rate menopausal vasomotor symptoms to be moderate to severe, and to significantly affect their quality of life.[2] The goal of menopausal hormone therapy (MHT) is to relieve the symptoms and improve quality of life, but the possible risks of MHT need to be weighed against the benefits in individual women[3,4] (Table 1).

**Table 1:** Potential risks and benefits of MHT in perimenopausal women[3,4]

| Potential risks | Potential benefits |
|---|---|
| Breast cancer | The suppression of vasomotor symptoms |
| Strokes | Relief from symptoms relating to urogenital atrophy |
| Venous thromboembolism | A reduced risk of osteoporosis and osteoporosis-related fractures, coronary heart disease, dementia and diabetes mellitus |
| Endometrial cancer* | |

* In women with an intact uterus treated with oestrogen alone

### The physiology of vasomotor symptoms

Vasomotor menopausal symptoms are episodes of profuse heat, lasting approximately 5–10 minutes, accompanied by sweating and flushing, experienced predominantly around the head, neck, chest and upper back.[5,9] The physiology of hot flushes is not fully understood, and is likely to reflect the interplay between multiple central and peripheral physiological systems.[4] Reproductive hormones play an integral role, as evidenced by the onset of vasomotor symptoms during the dramatic reproductive hormone changes of the menopausal transition, and by the efficacy of exogenous oestrogen in the treatment of hot flushes.[4] Higher follicle-stimulating hormone levels and lower oestradiol (E2) levels have been associated with a greater likelihood of menopausal vasomotor symptoms being reported.[4] However, while all perimenopausal women experience these hormonal changes, not all perimenopausal women experience vasomotor symptoms.[4]

Therefore, other physiological systems beyond the reproductive axis could be at play.[4]

Other systems include:[4]

- *Thermoregulatory systems:* Vasomotor symptoms may be characterised, at least in part, as thermoregulatory heat-dissipation events. There is some evidence of a narrowing of the thermoneutral zone in symptomatic postmenopausal women, or the zone in which core body temperature is maintained, without thermoregulatory homeostatic mechanisms, such as sweating, being triggered. Small fluctuations in core body

temperature in symptomatic women may exceed this zone, and trigger heat-dissipation mechanisms, such as sweating and peripheral vasodilation, i.e. hot flushes.

- *Central serotonergic, noradrenergic, opioid, adrenal and autonomical systems:* Central serotonergic, noradrenergic, opioid, adrenal and autonomical systems, as well as vascular processes, may be involved.
- *Genetics:* Variants in genes that code for oestrogen receptor alpha, and in enzymes involved in the synthesis of and conversion between more and less potent oestrogen, have been found to predict the likelihood of vasomotor symptoms in different racial or ethnic groups. However, cultural variations in how women experience, interpret, label and report vasomotor symptoms also plays a role in observed racial or ethnic differences in menopausal vasomotor symptoms.

## The role of lifestyle in vasomotor symptoms

Obesity was considered to be protective against menopausal vasomotor symptoms for many years, because androgens are aromatised into oestrogen in body fat.[4] Therefore, women with more adipose tissue would be expe cted to have a lower risk of menopausal vasomotor symptoms because of a higher level of oestrogen.[4] However, obesity has been shown in more recent studies to be a key risk factor for menopausal vasomotor symptoms, rather than a protective factor.[4]

Smoking is a consistently reported health behaviour associated with menopausal vasomotor symptoms.[4] There was an over 60% increased likelihood of current smokers reporting vasomotor symptoms, relative to non-smokers, in the Study of Women's Health Across the Nation (SWAN), over the course of six years of follow-up. This was after adjusted for confounding factors, such as education, body mass index, menopausal status and race or ethnicity.[4] It has been hypothesised that the association between smoking and vasomotor symptoms is owing to the anti-oestrogenic effects of cigarette smoking.[4] However, it was indicated in the SWAN that differences in endogenous E2 levels did not account for the association between smoking and vasomotor symptoms.[4] A much weaker association with vasomotor symptoms was demonstrated with other notable health behaviour, such as dietary factors and physical activity.[4]

## Duration of vasomotor symptoms

Although most menopausal symptoms resolve spontaneously after approximately five years, vasomotor symptoms may continue for longer in a substantial number of women.[1] The median total duration of menopausal vasomotor symptoms was 7.4 years for more than half of the women in the SWAN.[2] The median persistence of vasomotor symptoms was 4.5 years in women who experienced an observable final menstrual period.[2] The longest total vasomotor symptom duration, i.e. a median of ≥ 11.8 years, was reported in women who were premenopausal or perimenopausal when they first reported experiencing frequent vasomotor symptoms.[2] The shortest total duration of symptoms, i.e. a median of 3.4 years, was noted in women who were postmenopausal at the onset of menopausal vasomotor symptoms.[2] Additional factors relating to a longer duration of menopausal vasomotor symptoms were younger age, lower educational level, greater perceived stress and symptom sensitivity, as well as higher depressive symptoms and anxiety when the menopausal vasomotor symptoms were first reported.[2]

The expected duration of menopausal symptoms is an important factor for women when making decisions about possible treatment.[2]

## An emerging link between vasomotor symptoms and disease outcomes

Vasomotor symptoms have traditionally primarily been considered to be a quality-of-life issue during the menopausal transition, and have generally not been assumed to have specific implications with respect to physical health. However, this assumption has been called into question as a result of emerging evidence from SWAN and other studies.

### *Cardiovascular risk*

Both the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS) suggested links between vasomotor symptoms and cardiovascular disease (CVD) risk.[4] The elevated coronary heart disease event risk associated with hormone therapy use was highest in women reporting moderate to severe vasomotor symptoms at study entry in both studies, and in older women with vasomotor symptoms in the WHI study.[4] Findings from the SWAN indicated that women who reported more frequent hot flushes had poorer endothelial function, greater aortic calcification and greater carotid intima-media thickness (IMT) than women without hot flushes.[4] An association between hot flushes and IMT were most pronounced in women who were overweight or obese, as well as in women who reported more frequent hot flushes. This is suggestive that hot flushes may be most informative with respect to CVD risk when they are persistent and occur in women with other CVD risk factors, such as obesity.[4]

### *Bone health*

Emerging evidence from the SWAN and other studies has linked vasomotor symptoms to bone mineral density and bone turnover.[4] Lower bone mineral density was established in women reporting vasomotor symptoms in the SWAN, and the association between vasomotor symptoms and bone mineral density varied by specific bone site.[4] For example, lower bone mineral density was most apparent at the lumbar spine and hip in postmenopausal women.[4] Nonetheless, further investigation is required to establish the potential reason for an association between vasomotor symptoms and bone health.[4]

## Treatment of vasomotor symptoms

Treatment guidelines, consensus statements or position statements with respect to the management of menopausal symptoms have been published by a number of professional societies, including the International Menopause Society,[6] the

South African Menopause Society[7] and the British Menopause Society.[8]

### *Pharmacological menopausal hormone therapy*

Menopausal hormone therapy consisting of oestrogen (in women without a uterus) or oestrogen plus progestogen (in women with a uterus), to protect against endometrial hyperplasia and cancer, is the most widely studied and most effective treatment option for the relief of menopause-related vasomotor symptoms. It is considered to be the standard of care for women with moderate to severe vasomotor symptoms.[3,6–8] A significant 75% reduction in the frequency of hot flushes experienced per week, and a significant 87% reduction in the severity of symptoms, was demonstrated in a Cochrane meta-analysis of 24 double-blind, randomised, placebo-controlled clinical trials.[9] These relative reductions are significant, considering that the placebo response rate in the meta-analysis was 56%.[9]

## Key points on menopausal hormone therapy

MHT should not be recommended without a clear indication for its use, i.e. the presence of significant symptoms or physical effects pertaining to oestrogen deficiency.[6]

MHT is most beneficial before the age of 60 years, or within 10 years of menopause.[6] MHT relieves vasomotor symptoms and also has a positive impact on cardiovascular and bone health during this "window of opportunity".[6]

The lowest dose of oestrogen which provides relief from menopausal symptoms should be used.[1] Lower doses of MHT than those previously tried may reduce the symptoms sufficiently, and maintain quality of life, for many women[3,6,10,11] (Table 2).

The choice of MHT should be based on patient preference and prior experience.[1] Currently, the data do not support the suggestion that one formulation is clinically superior over another.[3]

Oestrogen alone, and oestrogen plus progestogen, combination regimens, are available in various oral, transdermal, vaginal and injectable preparations.

Progestogen may be used continuously or cyclically (10–14 days per month) in women with an intact uterus. Cyclic progestogen administration produces monthly bleeding. Although continuous progestogen administration does not lead to monthly bleeding, most women experience breakthrough bleeding or "spotting", especially if the continuous combined MHT regimen is initiated within one year of menopause.[3]

The transdermal route may be preferred in certain clinical situations, such as in women with hypertension, hypertriglyceridaemia and with an increased risk of cholelithiasis, and possibly to reduce the risk of thromboembolic disease.[1]

Local vaginal oestrogen may be preferred in women with symptoms that are limited to the genitourinary tract.[1]

**Table 2:** Recommended dosing ranges for commonly used oral and transdermal hormonal and non-hormonal therapies used to treat menopause-associated vasomotor symptoms[3, 6,10,11]

| **Therapy** | | |
|---|---|---|
| **Oestrogen** | **Low initial dose** | **Usual daily dose range** |
| Conjugated equine oestrogen | 0.30 mg | 0.30–0.63 mg |
| Micronised 17β-oestradiol | 0.50 mg | 0.25–1.00 mg |
| Oestradiol valerate | 1.00 mg | 1.00–2.00 mg |
| Transdermal oestradiol | 14.00-37.50 µg | 14.00–100.00 µg |
| Vaginal oestradiol ring | - | 0.05–0.10 mg |
| | **Usual daily dose** | |
| **Progestogen** | | |
| Medroxyprogesterone acetate | 2.50 mg (or 5.00 mg for 10–14 days/ month) | |
| Micronised progesterone | 100.00 mg (or 200.00 mg for 10–14 days/month) | |
| Norethisterone (norethindrone) | 0.35 mg (or 5.00 mg for 10–14 days/month) | |
| Levonorgestrel | 0.08 mg | |
| Antidepressant drugs | | |
| Fluoxetine | 20.00 mg | |
| Paroxetine | 12.50–25.00 mg | |
| Venlafaxine | 75.00 mg | |
| **Anticonvulsant drugs** | | |
| Gabapentin | 900.00 mg (divided) | |
| **Antihypertensive agents** | | |
| Clonidine | 0.10 mg orally | |

Women who require vasomotor symptom suppression and contraception can be effectively treated with a low-dose oral contraceptive.

Several weeks of MHT may be required to determine efficacy with regard to relieving vasomotor symptoms.[3]

MHT should be used for the shortest possible duration (preferably ≤ 5 years).[3] The five-year cut-off for MHT is recommended because most women experience spontaneous cessation of the menopausal symptoms within five years of onset. However, the use of MHT for ≥ 5 years may be appropriate in some women.[3,6] If MHT is for required for ≥ 5 years, it is recommended that women who are on a cyclic or sequential combined MHT regimen should switch to a continuous combined regimen.[7]

Once the decision has been taken to discontinue MHT, the dose can be tapered over time before it is stopped.[7] Vasomotor symptoms may recur to a varying degree with the cessation of MHT.[7]

### *Non-hormonal therapy*

Non-hormonal therapies, such as antidepressant drugs, anticonvulsant drugs and antihypertensive agents, have been used to relieve vasomotor symptoms, but are less effective than MHT.[3] Antidepressants are generally considered to be the most effective non-hormonal therapy. Non-hormonal treatment alternatives may be used in women who cannot (e.g. those with a history or at risk of breast cancer), or will not, consider MHT to relieve their vasomotor symptoms.[3]The mechanisms by which these non-hormonal therapies reduce the frequency of vasomotor symptoms are unknown. Recommended agents and doses are listed in Table 2.

The use of unregulated, compounded bioidentical hormone therapy for vasomotor symptom control is not recommended owing to lack of efficacy and safety data.[7,8] High-quality studies have not consistently supported the efficacy of complementary or over-the-counter medicines in reducing the severity or frequency of hot flushes and night sweats.[6] Black cohosh and soy products are not superior to placebo in the treatment of hot flushes.[6]

## Conclusion

MHT, in conjunction with lifestyle changes, is likely to remain the treatment of choice for acute menopausal symptoms in the immediate future.[5] The optimum regimen, dose and duration of MHT should be decided based on an annual assessment of the potential risks versus benefits in the individual woman, and according to the severity of her symptoms and her response to therapy.[8] Age and years since menopause are now known to be important variables which the risk-benefit profile.[4] The benefits of MHT generally outweigh the risks in symptomatic menopausal women aged ≤ 60 years, or within 10 years of menopause.[4]

## References


1. Randel A. AACE releases guidelines for menopausal hormone therapy. Am Fam Physician. 2012;86(9):865–867.
2. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015;175(4):531–539.
3. Umland EM. Treatment strategies for reducing the burden of menopause-associated vasomotor symptoms. J Man Care Pharmacy. 2008;14(3):S14–S19.
4. Sood R, Faubion SS, Kuhle CL, et al. Prescribing menopausal hormone therapy: an evidence-based approach. Int J Women's Health. 2014;6:47–57.
5. Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the Study of Women's Health Across the Nation. Obstet Gynecol Clin North Am. 2011;38(3):489–501.
6. De Villiers TJ, Pines A, Panay N, et al. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric. 2013;16:316–337.
7. Guidozzi F, Alperstein A, Bagratee JS, et al. South African Menopause Society revised consensus position statement on menopausal hormone therapy, 2014. S Afr Med J. 2014;104(8):537–543.
8. Panay N, Hamoda H, Arya R, et al. The 2013 British Menopause Society and Women's Health Concern recommendations on hormone replacement therapy. Menopause Int. 2013;19(2):59–68.
9. MacLennan AH, Broadbent JL, Lester S, et al. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. [Cochrane review]. In: The Cochrane Library, Issue 4, 2004. Oxford: Update Software.
10. North American Menopause Society. The 2012 hormone therapy position statement of: the North American Menopause Society. Menopause. 2012;19(3):257–271.
11. Birkhäuser MH, Panay N, Archer DF, et al. Updated practical recommendations for hormone replacement therapy in the peri- and postmenopause. Climacteric. 2008;11(2):108–123.