Menopausal hot flushes and night sweats: where are we now?


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This review paper has been published in the peer-reviewed journal Climacteric: Archer DF, Sturdee DW, Baber R, et al. Menopausal hot flushes and night sweats: where are we now? Climacteric 2011;14:515–28.
ABSTRACT

Objective An overview of the current knowledge on the etiology and treatment of vasomotor symptoms in postmenopausal women.

Materials and methods Acknowledged experts in the field contributed a brief assessment of their areas of interest which were combined and edited into the final manuscript.

Results Women around the world experience vasomotor symptoms as they enter and complete the menopause transition. Vasomotor symptoms, specifically hot flushes, are caused by a narrowing of the thermoneutral zone in the brain. This effect, although related to estrogen withdrawal, is most likely related to changes in central nervous system neurotransmitters. Peripheral vascular reactivity is also altered in symptomatic women. Estrogen replacement therapy is the most effective treatment for hot flushes. Of the other interventions investigated, selective serotonin and selective norepinephrine reuptake inhibitors and gabapentin show efficacy greater than placebo. Objective monitoring of hot flushes indicates a robust improvement with hormone replacement therapy but little to no change with placebo. These data suggest that the subjective assessment of responses to therapy for vasomotor symptom results in inaccurate data. Hot flushes have recently been associated with increased cardiovascular risks and a lower incidence of breast cancer, but these data require confirmation.

Conclusions Vasomotor symptoms are experienced by women of all ethnic groups. They are caused by changes in the central nervous system associated with estrogen withdrawal and are best treated with estrogen replacement therapy. Objective monitoring of hot flushes indicates that placebo has little to no effect on their improvement. Subjective assessments of hot flushes in clinical trials may be inaccurate based on objective measurement of the frequency of hot flushes. Based on preliminary reports, women experiencing hot flushes have an increased risk of cardiovascular disease and a reduced incidence of breast cancer.
INTRODUCTION
The hot flush (HF) is widely recognized by women and the medical profession in many parts of the world as the most characteristic and troublesome symptom of the climacteric\(^1\,2\). Hot flushes and night sweats (NS) are referred to as vasomotor symptoms (VMS) because of the vascular reactivity with initial prominent vasodilatation and subsequent vasoconstriction. The precise mechanisms involved in causing the HF have not yet been established, but they are thought to result from disturbance of the temperature-regulating mechanism in the hypothalamus, triggered by a decline in estrogen levels after prior estrogen priming. Hormone replacement therapy (HRT), with either estrogen alone or in combination with a progestin, is accepted as the most effective treatment. Selective estrogen receptor modulators (SERMs) with anti-estrogen actions, such as tamoxifen and raloxifene, may also cause flushing that can be especially distressing in women being treated for breast cancer\(^3\). Whilst there have been concerns raised about the safety of HRT following the publication of the Women’s Health Initiative (WHI) studies\(^4\,5\), causing women and their medical advisers to lose confidence in the merits of HRT, it remains the most effective treatment for VMS and, for many women, a safe and simple method of improving their quality of life\(^6\,7\).

Hot flushes may occur at any time of day or night and be spontaneous or triggered by a variety of common situations such as embarrassment, sudden ambient temperature change, stress, alcohol, caffeine or any warm drink. The subjective features are individual and variable, but usually start with a sudden sensation of heat or warmth, often accompanied by sweating, some reddening of the skin and sometimes palpitations. Most often this will start in the upper body and spread upwards or downwards, and infrequently all over the body. The perceived duration of a flush ranges from 30 seconds to 60 minutes, with a mean between 3 and 4 minutes (because hot flushes are not transient events, the term ‘hot flush’ is preferred to ‘hot flash’\(^1\)). Hot flushes will continue for more than 1 year for most women and with a median symptom duration of about 4 years. Some women will still experience flushing for 20 years or more from the last menstrual bleeding episode\(^2\).

The impact of HF on quality of life may be considerable and is often underestimated. Flushing may interfere with work and daily activities as well as with sleep, causing subsequent fatigue, loss of concentration and symptoms of depression, all of which can interfere with family life as well as sexual function and partner relationships.
The aims of this document are to summarize current knowledge and to promote greater awareness of vasomotor symptoms as the hallmark of menopause and a major cause of decreased quality of life for women in many parts of the world.

**GLOBAL INCIDENCE**

Vasomotor symptoms occur in all regions of the world, although the prevalence of symptoms and demand for treatment differ widely among women of different ethnic origins and with different cultural backgrounds\(^8,9\). Enormous differences in the experience of VMS were identified among women within the same culture and across cultures in a recent systematic interview (Table 1)\(^9\). Thus, the frequency of VMS varies from up to 74% of women in Europe\(^10\), 38% in the US\(^11\), 36% in Canada\(^11\), 50–68.9% in Latin America\(^12\) and 22.1–63.1% in Asia\(^13\).

<table>
<thead>
<tr>
<th>Geographic area</th>
<th>Number of women</th>
<th>Age (years)</th>
<th>% experiencing hot flushes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe(^10)</td>
<td>4200</td>
<td>45–60</td>
<td>74</td>
</tr>
<tr>
<td>North America(^11)</td>
<td>3302</td>
<td>42–52</td>
<td>Symptoms in the last 2 weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hispanic: 49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>African-American: 46–45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caucasian: 37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Japanese-American: 34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chinese-American: 29</td>
</tr>
<tr>
<td>Latin America(^12)</td>
<td>409</td>
<td>40–59</td>
<td>68.9</td>
</tr>
<tr>
<td>Asia(^13)</td>
<td>1028</td>
<td>40–65</td>
<td>63.1</td>
</tr>
</tbody>
</table>

Considering the diversity of variables that influence VMS, it is not surprising that their prevalence differs in each study. This may be due to differences in study design, populations selected, sample size, and the use of dissimilar diagnostic or screening tools. VMS are a multidimensional phenomenon and reflect a combination of genetic bases, diet, physical changes, use of medications, cultural influences and individual experiences and expectations\(^9\).
Figure 1 (a) Small core body temperature ($T_c$) elevations acting within a reduced thermoneutral zone trigger hot flushes (HF) in symptomatic postmenopausal women; (b) the factors that influence the thermoneutral zone. SSRI, selective serotonin reuptake inhibitor; $5$-HT, serotonin; NS, night sweat

CENTRAL NERVOUS SYSTEM MECHANISMS

Core body temperature in homeotherms is regulated between an upper threshold for sweating and a lower threshold for shivering. Between these thresholds is a neutral zone within which major thermoregulatory adjustments (sweating, shivering) do not occur. The heat dissipation responses of the HF are triggered if the core body temperature crosses the upper threshold of the thermoneutral zone.

Most HF are preceded by small elevations in core body temperature\textsuperscript{14} and the thermoneutral zone is greatly narrowed in symptomatic women\textsuperscript{15}. Elevated central noradrenergic activation narrows the thermoneutral zone, and symptomatic women have higher levels of central noradrenergic activation than asymptomatic women\textsuperscript{16}. The fact that peripheral estrogen levels do not differ between symptomatic and asymptomatic women suggests a central mechanism, which is further supported by reports that HF are reduced by clonidine, an $\alpha_2$-adrenergic agonist that reduces central sympathetic activation, and provoked by yohimbine, an $\alpha_2$-adrenergic antagonist that acts centrally to increase sympathetic activation\textsuperscript{17} (Figure 1).
Hot flushes frequently occur during sleep, but the causal relationship between HF/NS and sleep disturbance is not known. Freedman and colleagues found that HF in the second half of the night occurred after awakenings or arousals, whereas those in the first half of the night preceded such events and therefore could trigger NS\textsuperscript{18}. There is more rapid eye movement (REM) in the second half of the night, and REM sleep suppresses thermoregulatory effector responses, such as sweating and peripheral vasodilatation, which constitute the HF. The sympathetic activation of heart rate variability during sleep stages has also been investigated and correlated to HF occurrence\textsuperscript{19}.

It has been assumed that the triggering signal for HF originates in the preoptic area (POA) of the anterior hypothalamus. Recent data using blood oxygenation level-dependent-based functional MRI to measure neuronal activity in a group of postmenopausal women do not support this hypothesis. A rise in activity in the medulla, insular and prefrontal cortex around the onset of a HF was observed before the detectable onset of a HF. Insular and prefrontal activity trailed activity in the medulla by several seconds. The pre-hot flush medullary response may therefore reflect the earliest activity in the pathway associated with the origin of thermoregulatory events. Subsequent insular and prefrontal activity, in contrast, may be associated with the correlates of the HF demonstrated by skin conductance reflecting the thermoregulatory events.

**ROLE OF VASCULAR REACTIVITY**

The control of the peripheral vascular response to an increase in core body temperature is via the sympathetic, cholinergic neurons which stimulate the production of sweat that cools by evaporation and vasodilatation, where heat is lost to the environment. The sympathetic nervous system responds to sensors in the skin and also the hypothalamus. It is as yet unclear whether acetylcholine has a direct effect or whether it is mediated by paracrine vasodilator substances such as nitric oxide produced by the endothelial cell\textsuperscript{20}.

All blood vessels are lined by a layer of endothelium. The endothelium is single-cell thickness and endothelial cells produce vasodilators such as nitric oxide in response to stimulation by the neurotransmitter acetylcholine. The integrity of the endothelium is important, in that damaged cells cannot produce vasodilators in the same way and endothelial
cell dysfunction is a component of cardiovascular disease and is related to the formation of atheromatous plaque.

Physiological variations in body temperature occur during the menstrual cycle, in hypoestrogenic states and in fever, and there is a circadian rhythm to body temperature. The HF is due to vasodilatation and increased skin blood flow causing reddening of the skin and, often, sweating. Hot flushes are generally confined to the trunk, head and neck rather than to the periphery, as occurs with exercise, suggesting a complex and different control mechanism. Increased blood flow during a HF has been identified in the fingers and hands using venous occlusion plethysmography. Whether this is due to withdrawal of sympathetic vasoconstrictor activity, increases in sympathetic cholinergic vasodilator activity, or a combination of these together with non-neural mechanisms is uncertain. It has been demonstrated that symptomatic postmenopausal women have a greater vasodilator response than asymptomatic women. However, there was no statistically significant difference when comparing clonidine and placebo in the group of flushing women using a randomized, controlled design, even though the number of flushes per day and the HF score were decreased in both groups when compared to baseline. Skin blood flow is decreased when the selective serotonin reuptake inhibitor (SSRI) venlafaxine is administered, indicating that serotonin may be important in local vessel reactivity. Whether this response to venlafaxine is due to a peripheral or a central mechanism has not been determined.

Cardiovascular risk factors are often abnormal in women who experience significant HF as described in a group of 30 postmenopausal women. It is not clear how the two mechanisms fit together.

In conclusion, there is increased peripheral vascular responsiveness in women with HF, although it is likely that central control mechanisms play the major role.

**BRAIN SEROTONIN AND NOREPINEPHRINE**

Vasomotor symptoms result from thermoregulatory dysfunction, in which normal mechanisms of heat loss are activated inappropriately. This summary outlines the proposed role of serotonin (5-HT) and norepinephrine (NE) in the pathogenesis of VMS.

The area of the brain considered most important for thermoregulatory balance is the POA of the hypothalamus. Core body temperature is normally maintained within a thermoneutral
zone. Afferent pathways in the POA are activated when body temperature rises above a specific threshold, and efferent pathways lead to heat dissipation responses such as vasodilatation and sweating\textsuperscript{23-25}. A reduction of peripheral blood flow and shivering occur when body temperature drops below a specific threshold\textsuperscript{26}. The hypothesis presented above is that the thermoneutral zone is greatly narrowed in postmenopausal women with VMS, and the signals to the POA are most likely affected with small changes in core body temperature (Figure 1).

Estrogen therapy is the most effective therapy for VMS. Estrogen is believed to reverse the thermoregulatory dysfunction that results from the fluctuation and decline of endogenous estrogen during the menopausal transition. Estrogen raises the sweating threshold and widens the thermoneutral zone in symptomatic postmenopausal women\textsuperscript{27}. Estrogen deficiency alone is not sufficient to explain the occurrence of VMS, because non-hormonal agents reduce VMS without directly affecting estrogen levels\textsuperscript{28}.

A hypothesis is that the fluctuating estrogen levels alter the central nervous system levels of NE and/or 5-HT involved in neurotransmission, leading to the inappropriate sweating and flushing that characterize VMS\textsuperscript{29-31}. Estrogen therapy is thought to reverse the changes to NE and 5-HT function. Estradiol administration results in an overall increase in NE and 5-HT synthesis and availability and modulates numbers, density, or sensitivity of receptor binding sites in animal models.

Preclinical studies have shown that changes in monoamine neurotransmission can alter sweating and shivering thresholds and narrow the thermoneutral zone. NE and 5-HT administered under controlled conditions have been shown to alter thermoregulatory function in animal models, healthy volunteers and menopausal women. NE administered directly to the POA in animal models generally results in activation of a heat-loss response (vasodilatation) and a drop in core body temperature\textsuperscript{30,32}. Results of 5-HT administration to the POA are mixed: a decrease in core body temperature has been reported in some animal models, whereas an increase has been reported in others. Generally, however, NE and 5-HT administered to the POA have opposing effects\textsuperscript{33,34}. Administration of the norepinephrine reuptake inhibitor reboxetine in healthy male volunteers produced a cold feeling, suggesting the lower threshold of the thermoneutral zone had been exceeded\textsuperscript{35}. 

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Studies in menopausal women with HF also support the role of NE and 5-HT in VMS. Plasma levels of the main metabolite of brain NE increase during HF, suggesting that acute increases in brain NE may be associated with the onset of HF\textsuperscript{36}. Clonidine, a presynaptic \( \alpha_2 \)-adrenergic receptor agonist which blocks release of NE and reduces brain NE, increased the sweating threshold in symptomatic women, widening their thermoneutral zone\textsuperscript{37}. Clonidine has reduced HF in some placebo-controlled trials\textsuperscript{38,39}. The \( \alpha_2 \)-adrenergic receptor antagonist yohimbine, which increases brain NE, triggered HF in symptomatic women\textsuperscript{37}. Although the evidence is indirect, the body of evidence suggests that both NE and 5-HT, potent neurotransmitters, are most likely involved in a dysregulation at and after the menopause which contributes to VMS.

**QUALITY OF LIFE**

Women’s experience of HF and NS (the occurrence of HF during sleep) throughout the menopause transition is highly varied\textsuperscript{8,40}. While HF/NS are highly prevalent in most western countries, their impact is not necessarily burdensome for women\textsuperscript{41}. Hot flushes and NS negatively affect quality of life for an estimated 20–25\% of women\textsuperscript{42,43}, due to physical discomfort and social embarrassment, with NS associated with sleep disruption. The sleep and mood disturbances that result from HF/NS can have a significant negative impact on overall quality of life\textsuperscript{44}. The most clinically relevant measure of HF/NS is the distress caused or problem-rating\textsuperscript{45} because this measure is closely associated with their impact on quality of life. Problem-rating can be measured using the Hot Flush Related Daily Interference Scale\textsuperscript{46} and the Hot Flush Rating Scale\textsuperscript{47}.

Risk factors that are associated with problem-rating symptoms include surgical menopause, childhood neglect/abuse, race/ethnicity, smoking, lower levels of education, socioeconomic status, and prior anxiety and depression\textsuperscript{8,40,43,48,49}. HF/NS that are chronic are more likely to impact on quality of life and recent research suggests that HF/NS continue for longer than was previously thought\textsuperscript{40}. Breast cancer patients have more severe and chronic HF/NS associated with sleep problems and reduced quality of life because of the acute loss of ovarian function associated with therapy\textsuperscript{3,50,51}. 

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The impact of HF upon quality of life is therefore dependent on a wide range of factors including their frequency, cause and duration, but also a woman’s lifestyle and her appraisal of the symptoms. Research examining the cognitive and emotional appraisals of HF/NS suggests that negative thoughts and beliefs about HF/NS and certain behavioral reactions, such as avoiding social situations, are associated with significant VMS, whereas calm thoughts and behaviors, such as using paced breathing, accepting the symptoms and not over-reacting, are associated with less problematic symptoms. A cognitive model of HF/NS describes how a range of psychological and social factors might influence the perception and appraisal of HF/NS (see Figure 2). Depressed mood and negative beliefs, for example, are associated with problem-rating, and in turn problematic HF/NS are likely to have negative impact upon sleep, emotional and social functioning. Once this vicious cycle becomes established, symptoms can affect daytime productivity as well as family and social relationships and, in turn, the woman’s ability to deal with symptoms.

**Figure 2** A cognitive model of hot flushes and night sweats. QOL, quality of life

Psychological therapies as well as medical approaches to symptom relief have been developed, based on cognitive behavior therapy, with promising reductions in HF problem ratings and benefits to quality of life. The aims are to help women to understand the factors
affecting HF/NS, to reduce triggers and stress, and to use paced breathing and cognitive and behavioral strategies to manage HF/NS and sleep.

**VASOMOTOR SYMPTOMS AND CARDIOVASCULAR RISK**

Vasomotor symptoms appear to be associated with a higher degree of oxidative stress, higher body mass index, blood pressure and total cholesterol levels, lower levels of high density lipoprotein cholesterol, and higher levels of intercellular-adhesion-molecule-1, all indicating an adverse cardiovascular risk profile\(^{20,56}\). Vascular responses seem to be related to VMS as well: the brachial artery flow-mediated diameter response demonstrated a smaller post-occlusion magnitude of changes in women with moderate to severe HF, when compared to premenopausal women or women with none or only mild HF\(^{57}\). These results suggest an increase in cardiovascular risk in women with VMS, since a reduction in vascular reactivity reflects endothelial cell dysfunction. Better endothelial function in flushers compared to non-flushers has been reported in another study, leaving the implications of this endpoint uncertain\(^{20}\).

Carotid intima-media thickness, which correlates with coronary atherosclerosis, was greater in women suffering from VMS, especially in overweight or obese women\(^{58}\). A history of any VMS was significantly associated with reduced odds for coronary calcium, independent of traditional cardiovascular risk factors and other relevant covariates\(^{59}\). The severity of VMS did not affect the results, but a shorter duration of symptoms was associated with lower odds for having any calcifications. Pre-, peri- and young postmenopausal flushers demonstrated greater coronary artery and aortic calcifications in models adjusted for age, race, cardiovascular risk factors and estradiol. The most important endpoint would be the association between VMS and cardiovascular events. The relevant data from both the clinical and the observational WHI trials were summarized as follows: risk factors for coronary heart disease tended to be more adverse in the women with VMS, and early VMS were associated with decreased risk of stroke, total cardiovascular events, and all-cause mortality, but late VMS were associated with increased coronary events and all-cause mortality. The higher risks for coronary heart disease events in women more distant from menopause appeared to be concentrated in the small subset of women with moderate or severe VMS\(^{60}\).
VASOMOTOR SYMPTOMS AND BREAST CANCER RISK
The predictive value of VMS on breast cancer risk remains poorly documented. A recent paper has reported on a possible association of climacteric symptoms and a decrease in breast cancer risk\textsuperscript{61}. Compared with women who never had menopausal symptoms, those who reported ever experiencing symptoms had half the risk of both invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC). This publication presented a case–control study which had collected the information and included in this analysis some climacteric symptoms (HF and sweating, vaginal dryness, emotional distress, and insomnia) and their severity. There were 494 cases of IDC, 307 cases of ILC, and 187 cases of invasive ductal-lobular carcinoma, compared with 449 controls. Women who experienced the most severe climacteric symptoms had a lower risk of breast cancer: for IDC an odds ratio (OR) = 0.5 (95% confidence interval (CI) = 0.3–0.7) and for ILC an OR = 0.5 (95% CI = 0.3–0.8); in mixed carcinoma, the decrease was not significant. This decrease in the risk also involved women using HRT, across various ages at menopause, and also across quartiles of body mass index. It is important to note that the information was based on recall data about VMS in women where the diagnosis of breast cancer had just been made. This can constitute a recall bias. The specificity of the measures used should be noted, since the authors had not used a validated score and asked women to score the severity of the three classes of symptoms. The most surprising result of this publication was that the association of severe VMS and low risk in breast cancer was not altered by the use of HRT, which could suggest that there is no increase of breast cancer risk in women using HRT and having severe VMS.
Supporting these findings are studies that have shown a relationship between the intensity of HF and low endogenous total (bound and free) estradiol and estrone levels, polymorphisms in estrogen receptor-\(\alpha\) and in enzymes involved in its metabolism or production\textsuperscript{62-64}. Another positive finding is that, in the clinical trials and cohort of women treated by aromatase inhibitor, those who experienced the worse climacteric symptoms (VMS and joint pains) had more benefit from the treatment, but this concerned only women who had used hormone therapy\textsuperscript{65}. Similarly, hot flushes have been associated with low bone mineral density which could suggest lower sensitivity/responsivity to estrogens. There are arguments against the plausibility of this theory that lower levels of endogenous estrogens in postmenopausal women could be associated with a lower risk of breast cancer, as obese women who have an
increased risk of breast cancer experience more severe HF. There is also evidence of a positive association between mammographic breast density and bone mineral density. What we know about the pathogenesis of VMS is that they can be associated with fluctuating levels of estrogens (as in perimenopausal women) or very low levels of estrogens. Despite the interesting possibility of a relationship to breast cancer, confirmation must be awaited through other studies.

VASOMOTOR SYMPTOMS AFTER BREAST CANCER

Vasomotor symptoms following a diagnosis of breast cancer may result from chemotherapy-induced ovarian failure, endocrine treatment in younger women, cessation of HRT or endocrine treatment in older women. The nature, severity and duration of vasomotor symptoms following breast cancer are not well understood. Conservative measures may be helpful but may not improve VMS. When such measures fail, non-hormonal treatments such as clonidine, gabapentin and some antidepressants should be considered, although these therapies have side-effects that make long-term compliance poor.

Clonidine, an α-adrenergic agonist, in doses of 50 μg 2–3 times daily has been shown to reduce HF by a modest amount compared to placebo in short-term trials. Side-effects include constipation, dryness of the mouth and drowsiness.

Gabapentin, in doses of 900 mg per day, has been shown to be effective in reducing HF by 54% compared to 29% with placebo over a period of 12 weeks, the major side-effect being somnolence.

Venlafaxine 75 mg, desvenlafaxine 50–100 mg, paroxetine 20 mg, citalopram 10–20 mg and escitalopram 20 mg have proven effective in short-term, randomized trials in the treatment of HF (see below for a full discussion). Side-effect profiles are generally mild. The use of SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) which interfere with CYP450 enzymes (notably fluoxetine and paroxetine) may interfere with the metabolism of tamoxifen.

There is insufficient evidence regarding the efficacy or safety of phytoestrogens, dong quai, Chinese herbs or black cohosh in the treatment of menopausal symptoms after breast cancer and these compounds cannot be recommended. One randomized, controlled trial showed a reduction of one HF per day for users of 800 IU vitamin E per day. Data on acupuncture have
been inconclusive, with several small trials reporting benefit but two systematic reviews finding no benefit over placebo.

HRT after breast cancer may be justified when all other options have been exhausted and when the woman has been informed of relative risks. There is no certainty whether different types or regimens of HRT will affect the safety of HRT after breast cancer. Studies in non-breast cancer sufferers suggest that estrogen-alone therapy may be safer than combined HRT and that different progestins may have different effects. Micronized progesterone and dydrogesterone could be associated with a lower risk than synthetic progestin, but the safety of progestins after breast cancer remains uncertain and no large randomized trials have been performed.

**TREATMENT OF VASOMOTOR SYMPTOMS**

**Hormone therapy**

HRT is currently the only treatment that gives effective control of HF/NS and many other common menopausal symptoms. No other medical or alternative therapy gives significantly better relief of VMS than HRT compared to placebo in double-blind, randomized, controlled trials. In a Cochrane scientific review of quality trials of estrogen or combined estrogen and progestin therapies, the placebo effect was a 57.7% reduction in the frequency and severity of HF. Therefore the magnitude of the placebo effect must be considered when assessing claims for all other therapies.

The reduction in the frequency and severity of vasomotor symptoms with HRT is very impressive and sustained compared to the effect of placebo. Up to 90% of all vasomotor symptoms were abolished by 3 months, with a major effect being seen by 1 month in trials of oral HRT given as a fixed dose and route to all participants. Outside the fixed protocol of a research trial, it is normal clinical practice to adjust the dose and route of HRT to achieve a greater effect and to minimize side-effects, e.g. sore breasts when the estrogen dose is too high or uterine bleeding in the first few months of combined HRT.

Two common concerns about HRT should be addressed. First, a scientific review of HRT versus placebo shows that HRT is *not* associated with weight gain. About 70% of women gain weight at this time of life and only diet and exercise help to maintain optimal weight. Second, in the WHI long-term, randomized trial, women with a hysterectomy taking
Figure 3 Reduction in vasomotor symptoms with hormone replacement therapy (estradiol/norethisterone acetate, E2/NETA) or tibolone  

Estrogen-only HRT for 7 years had a non-significant reduction in breast cancer of eight cases per 10,000 women per year; women taking combined estrogen–progestin for the first time for less than 7 years had no statistically significant increase in breast cancer; and only if combined therapy was used for more than 7 years was there a statistically significant increase in breast cancer of eight cases per 10,000 women (< 0.1%) per year  

The response of regulatory authorities to the WHI data has universally stated that HRT may be used for women with significant menopausal symptoms at the lowest effective dose and for the shortest duration. Several studies of low and ultra-low doses have now demonstrated that regimens with daily doses of 0.5 mg estradiol, 0.3 mg conjugated equine estrogen (CEE) and 14 µg transdermal estradiol are effective in reducing HF/NS significantly  

Thromboembolism (clotting) is increased with oral HRT but it is not yet confirmed whether non-oral routes such as patches and gels have no increased risk. The type of progestin may also influence the risk  

Tibolone is a synthetic steroid that selectively mimics HRT in different tissues and is as effective in controlling vasomotor symptoms as effective in controlling vasomotor symptoms (Figure 3). It is less likely to increase breast density or tenderness and, in trials up to 4 years, has not been associated with an increase in breast cancer or thromboembolism but an increase in stroke in women over 65 years.
Progestins alone such as norethisterone, megestrol, medroxyprogesterone acetate (MPA) and micronized progesterone have also been shown to reduce flushes, though their potential for causing adverse events has to be considered. So-called ‘bioidentical’ or ‘natural’ steroid hormones are generally untested for long-term safety and efficacy and should be avoided. Locally compounded ‘bioidentical’ hormones are not subject to the scrutiny of pharmaceutical regulatory bodies in many countries and the manufacturers can avoid having to test their products for quality control, safety and efficacy. Effective control of menopausal symptoms is associated with an increased quality of life and, for symptomatic women commencing HRT within a few years of menopause the benefits outweigh the risks, especially when the HRT regimen can be tailored to the individual. More up-to-date information about HRT and the menopause for the public is available at www.menopause.org.au/images/stories/public/docs/Menopause2011.pdf.

**SSRIs, SNRIs and gabapentin**

Many women chose not to take HRT for menopausal symptoms, or have contraindications to HRT. Poor understanding of the mechanisms underlying menopausal VMS has limited the development of novel targeted therapies. Current non-hormonal therapies have largely arisen due to serendipitous observations of a reduction in HF as a ‘side-effect’ of medication prescribed for other indications. A number of preparations have been shown in prospective randomized, controlled trials to be superior to placebo for the management of VMS. In general, these preparations reduce the frequency and severity of HF by 50–60%. This level of reduction appears to be acceptable to many women who wish to avoid hormones. In comparison, standard-dose estrogen reduces HF by 80–90%.

SSRIs and SNRIs have been used to reduce the frequency and severity of VMS. Desvenlafaxine, a SNRI, has been evaluated in prospective randomized, placebo-controlled trials and the results have been submitted for regulatory approval. Desvenlafaxine was superior to placebo in reducing HF in three of four clinical trials. A 65% reduction in the frequency of VMS by week 12 occurred with desvenlafaxine 100 mg per day. The 75% responder rate was 50% for desvenlafaxine, compared to 29% for placebo and was statistically significant. Nausea and vomiting were found to be significant within the first
week of treatment with desvenlafaxine 100 mg per day. The use of a titration up-and-down schedule upon initiation and discontinuation of desvenlafaxine was found to reduce the early nausea and vomiting, while reducing withdrawal symptoms at the conclusion of the study.\textsuperscript{85} Mirtazapine, a 5-hydroxytryptamine 2 receptor antagonist, was shown to be effective in a rodent model for HF,\textsuperscript{86} but in women with breast cancer provided only a 50% reduction in HF in a trial that was not placebo-controlled, and there was a high non-compliance rate due to side-effects of somnolence.\textsuperscript{89} Venlafaxine, a SNRI using 75 mg per day in an extended-release tablet, demonstrated efficacy in reducing the subjective assessment of HF frequency and severity on daily living in a small number of participants.\textsuperscript{90} Fluoxetine and citalopram did not improve HF compared to placebo in one prospective study,\textsuperscript{91} whereas paroxetine, venlafaxine, fluoxetine and sertraline were found to be more effective than placebo in another trial.\textsuperscript{92} Gabapentin, a centrally acting anti-epileptic agent, has been found to reduce HF frequency and severity in small clinical trials compared to placebo.\textsuperscript{93,94} These two trials used gabapentin in a titrated manner, with doses starting at 300 mg per day up to 2400 mg per day. A third small trial of gabapentin versus transdermal estradiol found both treatments improved HF frequency without any difference between the two arms of the study.\textsuperscript{95} Gabapentin (300 mg three times a day) was as effective as low-dose estrogen (0.5 mg Premarin\textsuperscript{96} or 25 μg estradiol patch\textsuperscript{95}) in reducing the frequency and severity of VMS. Venlafaxine (75 mg slow-release) has not been compared directly with estrogen, but was as effective as gabapentin for VMS and better tolerated in one cross-over trial,\textsuperscript{97} but long-term compliance is poor when compared to HRT.

Drugs that enhance brain 5-HT and NE have been shown to have a moderate effect on relief of VMS. Desvenlafaxine, which is approved for the management of VMS in a daily dose of 100 mg in Mexico and Thailand, is best used with a dose-increase titration to minimize the significant adverse effects, mainly nausea and vomiting as well as dizziness in the first week of starting therapy, and a down-titration to minimize withdrawal symptoms such as anxiety, depression and moodiness upon cessation of therapy.
Non-hormonal therapies

Around 50% of women in developed countries chose to use over-the-counter therapies for the management of menopausal symptoms\textsuperscript{98}. The majority of these are non-hormonal, but some, such as ‘bioidentical hormones’, are compounds containing ovarian and adrenal steroids and have commensurate actions on steroid receptors. Women visit alternative practitioners as often as they visit family doctors and spend as much on alternative therapies as that spent on (subsidized) pharmaceutical treatments. The principal concerns are the waste of health resources, the lack of efficacy of these compounds and their potential harmful effects.

Current non-hormonal therapies claim to reduce the frequency and/or severity of menopausal HF. Substantial funding from the National Institutes of Health and other non-pharmaceutical sources has failed to show any benefit of over-the-counter therapies compared to placebo for HF and the safety of these compounds is not confirmed. Large randomized, controlled trials have not shown that phytoestrogens, red clover isoflavone and black cohosh are superior to placebo in the reduction of HF\textsuperscript{99}. All main-stream scientific, clinical and regulatory bodies in women’s health advise against the prescription and use of these hormones.

There is little evidence that dietary modifications, acupuncture or exercise improve HF but they may improve mood and quality of life. Regular exercise, weight reduction, avoiding triggers to HF (such as caffeine or direct heat) may help to minimize HF or their impact\textsuperscript{100}. Meditation, relaxation, controlled breathing and cognitive behavior therapy show promise in reducing HF. Recent level-one data have shown that mindfulness therapy may be an effective and well-tolerated intervention for HF\textsuperscript{101}.

Alternative methods of treatment

Psychological interventions in the menopause are practices intended to relieve symptoms through their effects on behavior, understanding, cognitive processes (memory, beliefs), or emotions\textsuperscript{102}. Behavioral intervention techniques include paced respiration (slow, deep breathing), muscle relaxation and biofeedback. The first two are relaxation-based procedures intended to counteract the elevated sympathetic activation implicated in HF\textsuperscript{103}. Biofeedback is defined in a consensus agreement as ‘a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance’, by
using precise measurements: brainwaves, heart function, breathing, muscle activity, and/or skin temperature\textsuperscript{104}. In a comparative trial in symptomatic postmenopausal women using skin conductance responses, paced respiration showed a significant decrease in HF frequency, but not muscle relaxation or biofeedback\textsuperscript{105}. This effect of paced respiration was confirmed by the same investigators in a placebo-controlled study, although there were no changes in biochemical measures (cortisol, noradrenaline, etc.)\textsuperscript{106}.

\textbf{Acupuncture}

Acupuncture has been extensively studied for its effect on VMS, but the quality of the trials is variable. A detailed review of the effect of randomized, controlled trials of acupuncture for VMS found no evidence of efficacy\textsuperscript{107}. A Cochrane review\textsuperscript{108} reported no difference in VMS in one randomized, controlled trial evaluating real versus sham acupuncture\textsuperscript{109}. A multicenter, randomized, controlled trial in 267 women showed consistent significant improvement in vasomotor, sleep and somatic symptoms in women treated with acupuncture plus self-care advice compared to self-care alone\textsuperscript{110}. Thus, acupuncture may ameliorate climacteric symptoms but good-quality clinical trials are needed.

\textbf{Stellate ganglion block}

The stellate ganglion (SG) is a sympathetic ganglion located just below the subclavian artery and its intervention has diverse clinical applications. SG block with local anesthetic is used to treat chronic sympathetic mediated pain; surgical interruption of the SG decreases hyperhydrosis of the hands; and SG acupuncture needling is used in traditional Chinese medicine to decrease sympathetically mediated symptoms. The SG is directly connected to the insular cortex in the brain, which is highly active during a HF\textsuperscript{111}. Estrogen deficiency causes increased concentrations of nerve growth factor (NGF) which induces sympathetic nerve sprouting in the cortex and increased brain norepinephrine concentrations. These changes, resulting in an increase of norepinephrine, trigger HF in a rat model. The blockage of the SG reduces NGF, reversing the process that results in flushing\textsuperscript{112}. A 12-week pilot study in 13 breast cancer patients with severe HF demonstrated a significant and early reduction in HF frequency and very severe HF went to near zero. Night awakenings showed the same trend\textsuperscript{113}. A follow-up after 37–42 weeks found that ten patients required
another block around 11 weeks after the first procedure, and the decrease in symptoms remained highly significant\textsuperscript{114}. Complications related to SG block include oculosympathetic palsy (Horner’s syndrome), arterial or venous injection of the anesthetic agent, pneumothorax, and vocal cord paralysis. Pulsed radiofrequency may provide a more permanent lesion to the stellate ganglion and is not associated with Horner's syndrome\textsuperscript{115}.

In summary, procedures based on relaxation that include paced respiration are effective in managing HF and are safe and could be used in women with contraindication for hormone therapy. Acupuncture may ameliorate climacteric symptoms and could be tried in women with contraindication for hormone therapy. SG block may be a helpful therapy for HF in extreme cases when hormone therapy is contraindicated. Larger controlled trials are needed to quantify the effect on VMS and to evaluate long-term safety.

**Relaxation techniques**

Relaxation therapies, including mind–body and behavioral therapies such as exercise, relaxation breathing, progressive muscle relaxation, stress management and menopause education, have been tried for relief of VMS.

Many alternative therapies, such as massage, aromatherapy, yoga and ayurvedic therapy, have also been tried. There are few good-quality studies done to assess their efficacy and more randomized, controlled trials are needed to assess efficacy. Ethnic differences, causes and phases of menopause also prevent reliable comparisons between such therapies. Women who are experiencing mild VMS could use measures with limited effectiveness. These include relaxing therapies and mind–body therapies and have been suggested by the North American Menopause Society\textsuperscript{116}. A meta-analysis\textsuperscript{117} has studied mind–body and behavioral therapy for VMS. Only nine trials met the inclusion criteria for this meta-analysis out of the numerous trials conducted for such therapies. The analysis included exercise, relaxation breathing, progressive muscle relaxation, audiotape relaxation, stress management and menopause education, and counselling support. Four of the nine trials were of poor quality whilst the other studies did not improve symptoms significantly.

The age-old science of yoga has been studied for various medical disorders. A systematic review of yoga\textsuperscript{118} for menopausal symptoms concluded that the evidence is insufficient to suggest that yoga is an effective intervention for menopause and further research is required.
to investigate whether there are specific benefits of yoga for treating menopausal symptoms\textsuperscript{118}.

**Selective estrogen receptor modulators**

SERMs have mixed estrogen receptor (ER) agonist or antagonist activity, depending on the level of expression of the co-activator proteins present in target tissue. The ideal SERM will protect against fractures, prevent ER-positive breast cancer, suppress VMS, offer cardiovascular protection, maintain vaginal and bladder health and prevent endometrial stimulation. A class effect of all recent SERMs is the inability to suppress VMS and indeed they can increase VMS, when compared to placebo. In a recent report, more patients ($p < 0.001$) treated with bazedoxifene ($n = 245$ or 23\%) experienced HF compared to placebo ($n = 124$ or 6.6\%). Most HF were mild or moderate in severity and did not result in study discontinuation\textsuperscript{119}. These findings restrict the use of SERMs to patients outside the window of early menopause where there are significant VMS. Bazedoxifene offers superior endometrial protection compared to other SERMs. This enables bazedoxifene to be paired with CEE to avoid the negative effects of estrogen on the endometrium and the breast, while suppressing VMS and maintaining vaginal health and bone mineral density\textsuperscript{120}.

**Role of the placebo**

The use of skin conductance monitors to objectively measure HF holds great promise in clinical trials of VMS in women. Recent clinical trials indicate that subjective reports of menopausal HF are particularly vulnerable to the placebo effect. Some early studies report placebo effects of between 10 and 36\%, but effects as high as 63\% have been seen in year-long clinical trials\textsuperscript{99}. Studies using ambulatory skin conductance monitors to objectively measure physiological HF demonstrate that, in ambulatory settings, women underreported the number of true HF by as much as 50\%\textsuperscript{121,122}. This finding raises questions about the validity of self-reported HF as an index of the frequency of physiological HF. One study demonstrated that memory dysfunction in women was related to objective but not subjective HF\textsuperscript{123}. Clinical trials employing both subjective and objective HF measurements also demonstrate that objective measurements are impressively immune to the placebo effect\textsuperscript{123,124}. For example, in a placebo-controlled clinical trial of black cohosh, red clover
and CEE/MPA, subjective HF decreased significantly from baseline to 12 months for all groups. However, the magnitude of change in the number of objective HF from baseline to 12 months was 0% for the placebo group, and the correlation between the numbers of objective HF at baseline and at 12 months in the placebo group was 0.98\textsuperscript{123}. Although subjective HF can be viewed as more clinically relevant than objective HF, one clinical trial reported improvements in quality of life, fatigue and sleep quality only in women who showed decreases of at least 50% in objective HF\textsuperscript{124}. In summary, the large placebo effect in clinical trials of HF and the tendency of women to underreport true HF underscore the benefits of measuring objective HF with ambulatory skin conductance monitors or a miniature hygrometric flush recorder in clinical trials\textsuperscript{125}.

**FLUSHING IN WOMEN THAT IS NOT RELATED TO MENOPAUSE OR ESTROGEN DEFICIENCY**

Flushing in women is quite common and continues to be a major source of concern and embarrassment. There are very many causes of flushing other than menopause or an estrogen deficiency state. It is important to rule out these causes, particularly in women who tend to have more atypical symptoms, and/or are unresponsive to normal treatment regimens for menopausal flushing, as described in other sections.

Two general categories of flushing may be encountered. The more common involves activation of the autonomic system, so-called thermoregulatory flushing, and presents with both flushing (redness due to vasodilatation) and diaphoresis (a heat dissipatory mechanism). The second category occurs merely with vasodilatation and redness, and is due to endogenous or exogenous vasoactive substances. Table 2 lists the most common causes of autonomic and vasodilatory flushes\textsuperscript{126}.

Autonomic flushing, which includes typical menopausal flushes, can be due to various common occurrences such as exercise, fever, heat exposure, including foods and beverages, emotional flushing and neurological disorders. The latter is a large category which requires a thorough neurological investigation if the autonomic flushing cannot otherwise be explained. This includes tumors compressing the third ventricle, spinal cord injury, certain types of epilepsy and headaches, Parkinson’s disease and multiple sclerosis.
### Table 2 Differential diagnosis of autonomic and vasodilatory flushing

<table>
<thead>
<tr>
<th>Autonomic flushing (thermoregulatory flushing) (includes menopausal flushing)</th>
<th>Vasodilatory flushing</th>
</tr>
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<tbody>
<tr>
<td>Exercise</td>
<td>Rosacea</td>
</tr>
<tr>
<td>Fever/heat exposure</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Emotional flushing</td>
<td>Medications (e.g. calcium channel blockers, nicotinic acid)</td>
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<tr>
<td>Neurologic (CNS tumor, autonomic epilepsy, spinal cord injury, certain headaches, Parkinson’s, multiple sclerosis)</td>
<td>Certain foods</td>
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<td></td>
<td>Alcohol (with enzyme deficiency or concomitant drugs)</td>
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<tr>
<td></td>
<td>Carcinoid syndrome</td>
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<tr>
<td></td>
<td>Mastocytosis</td>
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<tr>
<td></td>
<td>Pheochromocytoma</td>
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<tr>
<td></td>
<td>Medullary thyroid carcinoma</td>
</tr>
<tr>
<td></td>
<td>Rarely (VIPoma, renal cell cancer, Dumping syndrome, sarcoidosis, bronchogenic carcinoma)</td>
</tr>
</tbody>
</table>

Vasodilator-mediated flushing includes skin disorders, such as rosacea, and medications (nitroglycerine, phosphodiesterase 5 inhibitors such as sildenafil, calcium channel blockers such as nifedipine, nicotinic acid, calcitonin, opiates, cholinergic drugs, contrast media, vancomycin, amphotericin B, certain chemotherapeutic agents and tamoxifen). Certain foods can also elicit vasodilator flushing if they contain capsaicin (in red peppers), sodium nitrate or sulfites. A well-known substance which can cause vasodilator flushing is monosodium glutamate, often found in Chinese food, although this cause may be overstated, as studied in placebo-controlled trials. Alcohol can cause flushing in individuals with aldehyde dehydrogenase deficiency, which is common among Asians. This can also occur when alcohol is combined with disulfiram, sulfonylureas, metronidazole, ketoconazole, griseofulvin and other drugs.

The major causes of vasodilatory flushing that cannot be ruled out by history alone and that warrant an investigation include carcinoid syndrome due to serotonin excess; this may be diagnosed by elevated levels of 24-h urinary 5-hydroxyindoleacetic acid (5-HIAA). Mastocytosis causes the release of histamine and prostaglandin, and narcotics and aspirin...
may precipitate symptoms. Pheochromocytoma can cause flushing and is associated with hypertension, often during ‘attacks’; it can be ruled out with urinary measurements of catecholamines and fractionated metanephrine. Medullary thyroid carcinoma, which causes the release of calcitonin, can cause vasodilatory flushing, as does simple hyperthyroidism on occasion. A rare pancreatic tumor releasing vasoactive intestinal polypeptide (VIP) can cause flushing in conjunction with watery diarrhea and hypokalemia. Other rare causes of vasodilatory flushing include renal carcinoma, Dumping (short gut) syndrome, sarcoidosis and bronchogenic carcinoma.

The work-up involves a careful history and physical examination to determine whether the flushing is autonomic or vasodilatory alone. With autonomic flushing that is not easily explained by history, neurological consultation should be considered. All patients should probably have blood obtained for a complete blood count, liver function and thyroid tests. Vasodilatory flushing that is often associated with gastrointestinal symptoms warrants measurement of 24-h urinary 5-HIAA, histamine, prostaglandin D2 and serum tryptase to rule out carcinoid syndrome and systemic mastocytosis, and urinary catecholamines and fractionated metanephrine to rule out pheochromocytoma, particularly if there is also hypertension and tachycardia. If no cause can be found, the more rare causes may be ruled out by obtaining a renal ultrasound (renal cell carcinoma), serum VIP (VIPoma), calcitonin (medullary thyroid carcinoma) and lung imaging (bronchogenic carcinoma).

**CONCLUSIONS**

Vasomotor symptoms are prevalent in all women despite their cultural and ethnic backgrounds. Moderate to severe VMS have a negative impact on women’s quality of life. Reduced levels of estradiol are associated with VMS although there is no correlation between estradiol levels and the suppression of HF. Central nervous system neurotransmitters may be involved in altering the thermoneutral zone in the thermoregulatory center in the brain such that small changes in core body temperature result in significant changes in the central nervous system, resulting in HF. Hormone replacement therapy has demonstrated significant reduction in HF frequency and severity compared to placebo and is the optimum and standard treatment for HF/NS. Selective serotonin and/or norepinephrine reuptake inhibitors and gabapentin have shown some efficacy compared to placebo but the overall reduction in
HF is not as robust as hormone therapy. Non-hormonal non-prescription agents do not have any significant efficacy compared to placebo. The response to an investigative treatment is significantly compromised by the individual’s subjective assessment of improvement in HF that may result in up to a 50% reduction by a placebo. But objective monitoring of HF in clinical trials shows significant improvement with hormones while there is minimal effect of placebo. Hot flushes may be associated with cardiovascular disease and breast cancer but definitive statements cannot be made because the studies are unconfirmed but provocative.

Conflict of interest The contributors report no associations or financial relationships with any pharmaceutical company, other than consultative agreements, honoraria for lecturing at scientific meetings, and research support. Details of all disclosures have been updated and are on file in the IMS Secretariat.

Source of funding The costs of writing this paper have been supported entirely from the funds of the International Menopause Society.

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