CHAPTER 4

Vasomotor Symptoms

VMS affect 60% to 80% of women entering menopause.1 Hot flashes are common in the perimenopausal transition, when ovarian activity may be intermittent, and they have also been documented during the luteal and menstrual phases of the cycle in women with premenstrual dysphoric disorder.2 After menopause, it is important to be alert to atypical features or to a lack of response to effective therapy, which might indicate an alternative cause of the symptoms. The differential diagnosis includes hyperthyroidism, anxiety, panic attack, hypertension, emotional flushing, neurologic flushing, carcinoid, physical deconditioning, tumours, spinal cord injury, and reactions to food, drugs, and alcohol.3 In menopausal women hot flashes are thought to result from a disturbance of the temperature-regulating mechanism in the hypothalamus that is due to low estrogen levels after prior estrogen priming.

Although most postmenopausal women (60%) experience hot flashes for less than 7 years, up to 15% report that hot flashes persist for 15 years or more.4 The symptoms that can accompany hot flashes (including sweating, palpitations, apprehension, and anxiety) contribute to the woman’s discomfort, inconvenience, and distress, particularly when these episodes occur very frequently. They can be a significant contributor to sleep disturbance. VMS adversely affect quality of life for 20% to 25% of women, primarily owing to the physical discomfort and social embarrassment that they evoke, although night sweats and sleep disturbance are also reported to have a negative impact.5–7

A recent excellent review addresses the scientific basis for hot flashes, the strength of evidence suggesting associations between VMS and CVD, breast cancer, and osteoporosis, and treatment options.8

Normally the body maintains an optimal temperature for metabolic activity through vasodilatation and sweating when overheated and shivering when cold. Postmenopausal women are thought to have narrowing of this “thermoneutral zone” such that small changes in temperature can evoke the regulatory response of sweating or shivering.9 Risk factors for hot flashes include obesity, limited physical activity, and cigarette smoking and, along with a variety of known triggers (alcohol, warm ambient environment, hot drinks), form the basis for certain lifestyle recommendations to reduce VMS. The prevalence of these symptoms differs according to ethnicity. Compared with Caucasian women, VMS are reported less frequently by Japanese and Chinese women but more frequently by African-American women.10

TREATMENT OPTIONS

Multiple forms of treatment have been used to relieve hot flashes, including lifestyle modifications, non-prescription drugs, and prescription drugs. Prescription drugs may be grouped into hormonal and non-hormonal agents. Multiple placebo-controlled trials have shown a reduction of about 25% to 30% in the frequency of hot flashes within 4 weeks of placebo treatment. Moreover, a Cochrane review of ET has shown that placebo may cause a reduction of about 50%.11 These results highlight the importance of applying appropriate scientific scrutiny to anecdotal reports and uncontrolled trials that claim efficacy for treatment of hot flashes.

Since the report about risks associated with HT from the WHI in 2002, many physicians have abandoned the prescription of HT for VMS in favour of recommending lifestyle changes and cooling devices. Unfortunately, many women find that these approaches afford little relief and have turned to unproven and often untested complementary and alternative therapies. The scientific evidence, however, remains clear that the single most effective agent for treating VMS remains estrogen or, for women with an intact uterus, estrogen plus progestin. Both oral and transdermal routes of administration of estrogen are effective against VMS.

The most recent Cochrane review of RCTs of menopausal HT for the treatment of VMS concluded that HT is highly effective, with reductions in both frequency and severity in the order of 75%.11 The dropout rate was higher in the placebo arms for lack of effectiveness, but there was no difference between the treatment and placebo arms in the rate of dropout because of adverse effects.
Progestogens alone may be considered as an alternative for treating hot flashes if the benefit–risk profile is acceptable to the woman. The question of whether a progestin alone increases the risk of breast cancer is unanswered. MPA has been shown in several trials to relieve hot flashes in healthy women as well as in women with breast or endometrial cancer.12–14 Both intramuscular (150 mg) and oral forms (20 mg/d) have demonstrated efficacy. Micronized progesterone, 300 mg, is superior to placebo but possibly less effective than estrogen for in the treatment of VMS.15

Non-hormonal options that have shown some efficacy for relief of VMS include clonidine,16,17 SNRIs18 or their active metabolites, such as desvenlafaxine succinate,19 gabapentin,20 and pregabalin.21 None are as effective as estrogen, and the response rate among women is variable. These options can be offered to women with disruptive VMS for whom estrogen is contraindicated or unacceptable.

Two placebo-controlled trials of clonidine showed a reduction in the severity of hot flashes over placebo but were unable to demonstrate a statistically significant reduction in frequency.16,17 Sleep disturbance was reported as an unwanted side effect.

Recent systematic reviews of SSRIs and SNRIs have found these classes of medication to be more effective than placebo in reducing VMS. Successful placebo-controlled trials have been reported with paroxetine, fluoxetine, sertraline, venlafaxine, desvenlafaxine, and citalopram. These agents may be used together with HT and can be offered to women in menopause with coexisting depression.22–24 In Canada since 2002 there has been an inverse relationship between the numbers of prescriptions for HT and SSRIs, those for HT declining and those for SSRIs rising, which led the investigators to conclude that “the simultaneous increase in prescriptions of serotonergic antidepressants suggests that antidepressants are being prescribed for symptoms (psychological, physical) previously controlled with the use of HRT”.25

Antidepressant agents, though moderately effective for the treatment of VMS, are not without significant side effects36–39 and afford none of the other health benefits seen with HT that directly impact quality of life (e.g., prevention of urogenital atrophy and osteoporosis).20 Recent reports suggest that rates of osteoporotic fractures have started to increase since 2002.29,30

A recent meta-analysis of gabapentin for the treatment of VMS analyzed the experience of 901 women in 7 trials conducted between 2002 and 2008, including 1 Canadian trial.31 Reductions in hot-flash severity and frequency were between 20% and 30%. Doses were between 900 and 2400 mg, and treatment was associated with dizziness, unsteadiness, somnolence, and fatigue.32 Useful strategies to reduce the risk of such side effects include slowly titrating the dose over 12 days or more, using a lower dose, or prescribing the drug for bedtime.33

Pregabalin, 75 mg twice a day, reduced the hot-flash score (frequency times mean severity) by 65% compared with 50% for a placebo.21 Combined treatment with gabapentin and an antidepressant was not superior to treatment with either treatment alone.34

Herbal remedies have become a popular alternative in North America,35 yet few of those promoted for VMS treatment have met the rigorous testing criteria required of pharmaceutical products by the US Food and Drug Administration. The current regulatory requirement for pharmaceutical products with purported benefit for hot flashes is that participants in clinical trials must experience on average 7 hot flashes per day, or 50 per week. Most reported studies of herbal products have been open-label and conducted in women with as few as 1 or 2 hot flashes per day. Recent reports caution about potential adverse safety profiles of marketed herbal products, and cautions have appeared about interactions of NHPs with pharmaceutical and anesthetic agents.36–39 Canadian legislation in January 2004 removed NHPs from the food category and placed them in a special drug category to allow regulation of manufacturing, labelling, and indications for use.40 To date, little appears to have been accomplished in the regulation of NHPs in Canada. Several recent systematic reviews have examined options for treatment of moderate to severe VMS.41–45 None of these found any single complementary therapy to have proven efficacy for moderate to severe hot flashes, and the most recent review concluded by stating that “although individual trials suggest benefits from certain therapies, data are insufficient to support the effectiveness of any complementary and alternative therapy in this review for the management of menopausal symptoms.” A direct head-to-head comparison of HT with black cohosh, soy, or multibotanicals showed only HT to have an effect greater than that of placebo.46

In light of the evidence supporting the effectiveness of HT for treatment of VMS and the apparent underuse owing to fear and uncertainty about the safety of menopausal HT, a dozen leading North American medical organizations collaborated to produce the following clear statement about HT:47

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Leading medical societies devoted to the care of menopausal women agree . . . there is no question that hormone therapy has an important role in managing symptoms for women during the menopause transition and in early menopause.

A tissue-selective estrogen compound consisting of the SERM bazedoxifene combined with an oral conjugated estrogen has recently been shown to suppress VMS, and prevent postmenopausal bone loss while having a favourable safety profile with respect to breast and endometrium.48 This combination will obviate the need for progestin cotherapy in women using systemic estrogen, both simplifying therapy and avoiding progestin-associated adverse effects.

**Recommendations**

1. Lifestyle modifications, including reducing core body temperature, regular exercise, weight management, smoking cessation, and avoidance of known triggers such as hot drinks and alcohol, may be recommended to reduce mild vasomotor symptoms. (I-C)

2. Health care providers should offer hormone therapy, estrogen alone or combined with a progestin, as the most effective agents for the medical management of menopausal symptoms. (I-A)

3. Progestins alone or low-dose oral contraceptive can be offered as alternatives for the relief of menopausal symptoms during the menopausal transition. (I-A)

4. Non-hormonal prescription drugs, including certain antidepressant agents, gabapentin, and clonidine, may afford some relief from hot flashes but have their own side effects. These alternatives can be considered when hormone therapy is contraindicated or not desired. (I-B)

5. There is limited evidence of benefit for most complementary and alternative approaches to the management of hot flashes. Without good evidence for effectiveness, and in the face of minimal data on safety, these approaches should not be recommended. Women should be advised that, until January 2004, most natural health products were considered when hormone therapy is contraindicated or not desired. (I-B)

6. Estrogen therapy can be offered to women who have undergone surgical menopause for the treatment of endometriosis. (I-A)

**REFERENCES**


