

Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions

Deirdre R Pachman¹
Jason M Jones¹
Charles L Loprinzi²

¹Internal Medicine, Mayo Clinic, Rochester, MN, USA; ²Medical Oncology, Mayo Clinic, Rochester, MN, USA

Abstract: Hot flashes are one of the most common and distressing symptoms associated with menopause, occurring in more than 75% of postmenopausal women. They are especially problematic in breast cancer patients since some breast cancer therapies can induce hot flashes. For mild hot flashes, it is proposed that behavioral modifications are the first step in management. Hormonal therapies, including estrogens and progestogens, are the most well known effective agents in relieving hot flashes; however, the safety of these agents is controversial. There is an increasing amount of literature on nonhormonal agents for the treatment of hot flashes. The most promising data regard newer antidepressant agents such as venlafaxine, which reduces hot flashes by about 60%. Gabapentin is another nonhormonal agent that is effective in reducing hot flashes. While many complementary therapies, including phytoestrogens, black cohosh, and dehydroepiandrosterone, have been explored for the treatment of hot flashes; none can be recommended at this time. Furthermore, there is a lack of strong evidence to support exercise, yoga, or relaxation for the treatment of hot flashes. Paced respirations and hypnosis appear to be promising enough to warrant further investigation. Another promising nonpharmacological therapy, currently under investigation, involves a stellate ganglion block.

Keywords: vasomotor symptoms, hot flashes, menopause, therapy

Introduction

Menopause, an expected event in a woman's life, is commonly defined as 12 months of amenorrhea. This transition often begins in the late 40s, with a median age of 51 years.¹ Menopause is associated with multiple symptoms including vasomotor symptoms, vaginal symptoms, urinary incontinence, sexual dysfunction, and trouble sleeping.

One of the most common and distressing symptoms of menopause are hot flashes. Hot flashes occur in over 75% of menopausal women.^{2,3} Women often describe these episodes as recurrent periods of flushing, sweating, and an intense heat that begins on the face and upper chest. Hot flashes can also be associated with a feeling of anxiety, palpitations, and red blotching of the skin.^{3,4} These episodes usually last for 2–4 minutes and can vary in frequency, with some women experiencing episodes multiple times per day, while others experience them as infrequently as once a month. Although not life-threatening, hot flashes can have a detrimental effect on a woman's functional ability and quality of life.⁵

Hot flashes are especially problematic in breast cancer patients. Multiple preventative and treatment strategies for breast cancer can induce hot flashes, including anti-estrogenic medications, oophorectomy, and certain forms of chemotherapy.^{6,7} In addition, it has been reported that breast cancer survivors have more frequent and severe hot flashes than women who undergo normal menopause.⁸

Correspondence: Charles L Loprinzi
Mayo Clinic, 200 First Street SW,
Rochester, MN 55905, USA
Tel +1 507 284 4849
Fax +1 507 284 1803
Email cloprinzi@mayo.edu

The purpose of this article is to review the evidence for and against the current available treatments for hot flashes.

Etiology

The mechanism behind hot flashes is not completely understood. It has long been believed that hot flashes result from the decrease in estrogen levels associated with menopause. During menopause, the number of ovarian follicles and the production of estrogen decreases. Hot flashes seem to occur synchronously with these changes.⁹ However, the exact role of estrogens in the mechanism of hot flashes is unclear. There is research to support the hypothesis that it is the estrogen withdrawal, not low levels of estrogen that leads to hot flashes. For example, women with gonadal dysgenesis, who have consistently low levels of estrogen, do not experience hot flashes unless they are given estrogen replacement therapy, which is later discontinued. Also, women who experience abrupt estrogen withdrawal, such as from oophorectomy, have a rapid onset of hot flashes.^{10,11} In addition, hot flashes are often more prevalent at the beginning of menopause and do not usually continue throughout the postmenopausal time when circulating estrogens are low.¹¹

The perspiration and vasodilatation associated with hot flashes appears to be controlled by the thermoregulatory nucleus, which is located in the preoptic area of the hypothalamus. The thermoregulatory nucleus regulates core body temperature and works to keep it within a homeostatic range called the thermoregulatory zone.¹⁰ Hot flashes are triggered if body temperatures are elevated or sweating thresholds are lowered.¹² Women who suffer from hot flashes appear to have a thermoregulatory zone that is narrower and thus small increases in core body temperature can trigger hot flashes.¹³

Norepinephrine and serotonin may be involved in the complex neuroendocrine pathway controlling the thermoregulatory zone.⁹ It is proposed that elevated brain norepinephrine narrows the thermoregulatory zone.¹² In addition, there has been increased interest in the role of serotonin in the hot flash mechanism. Activation of specific serotonin receptors can cause hypothermia or hyperthermia.¹⁴ Estrogen withdrawal is associated with decreasing levels of serotonin and an increase in serotonin receptors in the hypothalamus.^{9,11} In one proposed model for the pathogenesis of hot flashes estrogen withdrawal leads to a decrease in endorphin and catecholesterol levels. This in turn leads to increased norepinephrine and serotonin release, which lowers the set point in the thermoregulatory nucleus, thus increasing the likelihood of hot flashes.⁹

Treatment of hot flashes

Hormonal therapies

Estrogen replacement

Estrogen replacement is the most effective treatment for reducing hot flashes, with reductions of more than 75% in frequency.^{15–17} Unfortunately, there are many situations in which estrogen therapy is contraindicated. The Women's Health Initiative (WHI) trial reported that the overall health risks of long-term estrogen therapy; including increased risk of venothrombotic disease, breast cancer, stroke, and coronary artery disease, exceed the benefits.¹⁸ However, hormone therapy is still approved for the treatment of moderate to severe vasomotor symptoms.¹⁷ When hormonal treatment is utilized for treating hot flashes, it is generally accepted that it should be used at the lowest dose and for the shortest effective length of time.^{17,19}

More recent literature has investigated short-term and low dose estrogens for the treatment of vasomotor symptoms. A double-blind, placebo-controlled trial was undertaken to investigate the efficacy of micro-dose transdermal estrogen for relief of hot flashes. Women used transdermal patches with low dose estrogen (0.023 mg/d 17 β -estradiol and 0.0075 mg/day levonorgestrel), micro-dose estrogen (0.014 mg/day 17 β -estradiol) or placebo. Women using the micro-dose estrogen had a significant reduction in hot flashes when compared to placebo with 41% of patients having a reduction in hot flashes of 75% or more.²⁰ Another study evaluated the efficacy of low dose estradiol gel for the treatment of hot flashes. Women received estradiol gel 0.1% at doses of 1.0, 0.5, and 0.25 mg/day. All three doses demonstrated a statistically significant reduction in the frequency of hot flashes, but these reductions were dose dependent.²¹ Currently, 0.0125 mg/day dose of Elestrin is the lowest effective dose of estradiol gel approved for the treatment of hot flashes.²² Studies have shown that low dose estrogen may be less likely to cause many of the serious complications associated with higher dose estrogen.^{19,20} However, the risks associated with long-term use of low dose estrogens are still unknown since this has not been evaluated in clinical trials.^{19,22}

The use of estrogen therapy in breast cancer survivors is also a controversial topic. While some literature suggests that estrogen therapy might be safe in breast cancer survivors,⁶ the current sentiment of most clinicians is to avoid the use of estrogen in this population.^{17,23}

Progestational agents

The North American Menopause Society determined that the primary menopausal-related indication for progesterone use is

to negate the increased risk of endometrial cancer from systemic estrogen therapy. Therefore, the recommendation is that all women with an intact uterus requiring hormonal therapy for menopausal symptoms should be prescribed progesterone.^{17,24} However, in recent years, there have been several trials that have shown progestational agents to be a reasonable alternative to estrogen, for the treatment of vasomotor symptoms.

Megestrol acetate was found to be effective in reducing hot flashes in a double-blind, placebo-controlled, randomized clinical trial that included 97 women with a history of breast cancer and 66 men receiving androgen deprivation therapy for prostate cancer. Patients receiving megestrol acetate, at a dose of 40 mg per day, showed an 85% reduction in hot flashes, as compared to a 21% reduction in the placebo group.²⁵ A substantial proportion of patients in this trial continued to use megestrol acetate for periods of up to 3 years or longer, with continued control of hot flashes.²⁶ In addition, a daily megestrol acetate dose of 20 mg appears to be equally efficacious to a 40 mg daily dose.²⁷

Medroxyprogesterone acetate (MPA), a similar medication, comes in both oral and intramuscular forms, both of which have been shown to decrease menopause related hot flashes. Multiple, double-blind, placebo-controlled trials, performed in the 1970s and 1980s, found intramuscular depomedroxyprogesterone acetate (DMPA) to be efficacious in reducing hot flashes.²⁸⁻³⁰ A more recent randomized, placebo-controlled clinical trial was undertaken to compare DMPA with megestrol acetate in postmenopausal women with a history of breast cancer; they found both agents to have similar efficacy with a reduction of 86%, on average, in both groups.³¹ In addition, an observational study of 15 women with a history of breast cancer reported that hot flashes were reduced by 90% in women receiving DMPA.³² Another randomized controlled trial demonstrated that DMPA and conjugated equine estrogen were equivalent in their efficacy at reducing hot flashes in patients who underwent hysterectomy/ovariectomy.³³

The role of progesterone cream for the treatment of hot flashes is controversial. One randomized placebo-controlled trial of a progesterone cream in healthy postmenopausal women found a significant reduction in hot flashes, 83% compared to 19% in the placebo group.³⁴ However, a recent double-blind, placebo-controlled trial of progestational progesterone cream in 223 healthy postmenopausal women found no statistically significant difference between the treatment group and placebo.³⁵

Despite the efficacy of progestational agents in the treatment of hot flashes, it can be associated with similar side effects as estrogen, and therefore it is contraindicated

in women with thromboembolic disorders, impaired liver function, and undiagnosed uterine bleeding.²⁴ The role of progestational agents in women with a history of breast cancer is still unclear. This is partially because it has been proposed that progestational agents may stimulate tumor growth.³⁶ An epidemiological study failed to find any increase in breast cancer risk in women who used progesterone alone.³⁷ Overall, the data on the association between progesterone and increased breast cancer risk is still controversial and to date no reliable conclusion can be made.²⁴

Tibolone

Tibolone is a synthetic steroid that has both a weak estrogenic, progestagenic, and androgenic action.³⁸ It is proposed that tibolone has tissue specific activity which is the result of metabolism, enzyme regulation, and receptor activation that vary in different tissues.^{39,40} Tibolone has been used for almost 20 years in Europe for the treatment of vasomotor symptoms, but is not available in the United States.¹⁹ A double-blind, randomized controlled trial of 437 postmenopausal women found that treatment with tibolone significantly reduced the mean scores for hot flashes and was comparable to estrogen therapy.⁴¹ The most common adverse effects were weight gain and bloating.³⁸ However, the Million Women Study suggested that tibolone increased the risk of breast cancer.⁴² In addition, the Liberate trial showed that women with a history of breast cancer had increased recurrence of cancer if they were taking tibolone.⁴³ On the other hand, a trial investigating the use of tibolone in postmenopausal women with low bone density found that the women using tibolone had a decrease in breast cancer events.⁴⁴ One explanation for these various findings may be that tibolone affects healthy breast tissue differently than it does cancer cells.⁴³ Additional research is needed to investigate the effect of tibolone on the risk of breast cancer in healthy postmenopausal women.⁴⁵ At this time, tibolone should not be used in breast cancer patients, and should be used with caution in the general postmenopausal population.

Non-hormonal therapy

Many patients and physicians feel that the risks associated with hormonal therapy outweigh the therapeutic benefit. Consequently, nonhormonal therapies for hot flashes have received a significant amount of attention over the past 20 years.

Centrally acting compounds

Bellergal

Bellergal is a combination product of belladonna alkaloids and phenobarbital. It was used in the 1970s and 1980s as

a treatment for hot flashes. A placebo-controlled trial of 66 healthy women tested Bellergal Retard against placebo. The group of patients taking Bellergal had a decrease in the number of hot flashes by 75%, versus 68% in the placebo group. This small improvement was not significant.⁴⁶ Another study which included 50 patients demonstrated that patients taking Bellergal reported a moderate improvement in hot flashes over placebo.⁴⁷ Adverse effects associated with Bellergal included dry mouth, dizziness, rash, and sleepiness. Due to the moderate efficacy and the availability of safer therapies, Bellergal is not recommended for the treatment of hot flashes.

Clonidine

Clonidine is a centrally acting α -adrenergic agonist that was first proposed as a treatment for hot flashes in the 1970s.^{48–50} One proposed mechanism of action in the treatment of hot flashes is that clonidine raises the sweating threshold by reducing norepinephrine release.⁵¹ A randomized, double-blind, controlled trial was performed using a 0.1 mg transdermal clonidine patch versus placebo in 110 women with a history of breast cancer. Patients receiving clonidine had an additional 20% reduction in hot flashes, as compared to the placebo group. However, patients experienced significant adverse effects including mouth dryness, constipation, itchiness, and drowsiness.⁵² Another randomized controlled trial evaluated the efficacy of oral clonidine in 149 postmenopausal women with breast cancer receiving tamoxifen therapy. After 8 weeks of treatment, the mean decrease in hot flash frequency was 38%, as compared to 24% in the placebo group. Again, patients reported significant side effects, including difficulty sleeping.⁵³ A recent meta-analysis included 10 trials of clonidine for the treatment of hot flashes and found inconsistent results, with half of the trials showing that clonidine was effective in treating hot flashes.⁵⁴ Despite some positive results in these trials, the use of clonidine for hot flash treatment is not recommended because of significant side effects.

Methylodopa

Methylodopa is an antihypertensive agent that has been investigated as a treatment for hot flashes. A double-blind, placebo-controlled study was undertaken involving postmenopausal women, and demonstrated that 250 mg of methylodopa was more effective than placebo at decreasing hot flashes. There was a 30% to 37% reduction in frequency of hot flashes in the methylodopa group, as compared to a 10% to 20% reduction in the placebo group. Adverse reactions

including dizziness, nausea, and fatigue, occurred in 50% of the patients.⁵⁵ Therefore, due to its significant adverse effects, methylodopa is not recommended as a therapy for hot flashes.

Veralipride

Veralipride is a benzamide derivative with antidopaminergic effects, which has been studied as a treatment of hot flashes. A double-blind, randomized controlled study in 43 women compared treatment with veralipride to conjugated estrogens for the treatment of hot flashes. No significant difference in effectiveness or tolerance was found between the two treatments.⁵⁶ Another trial tested veralipride versus placebo in healthy postmenopausal women. In this study, veralipride was associated with a significant reduction in hot flashes.⁵⁷ Adverse effects of veralipride included breast tenderness, galactorrhea, gastrointestinal complaints, and dyspnea.^{58,59} Veralipride has also been associated with extrapyramidal disorders, including acute dyskinesia and Parkinsonism.⁶⁰ Due to its toxicities, veralipride is not approved for use in the United States and is currently not recommended for the treatment of hot flashes.

Newer antidepressants

In the 1990s it was recognized that women taking selective serotonin reuptake inhibitors (SSRI) had a decrease in hot flashes.⁹ As a result of these observations, it was hypothesized that such antidepressants may have a therapeutic effect on hot flashes. Since this time multiple randomized, placebo-controlled clinical trials have been undertaken to test this hypothesis, using several different agents. Overall, the results have been promising.

Venlafaxine

Venlafaxine selectively inhibits reuptake of serotonin, norepinephrine, and dopamine. Venlafaxine was first studied as a treatment for hot flashes in 1998 in a pilot trial which included 28 patients. This pilot trial involved both women with a history of breast cancer and men with prostate cancer who received androgen-deprivation therapy. The majority of patients reported a greater than 50% reduction in median hot flash scores after four weeks of treatment with venlafaxine, 12.5 mg twice daily. In addition, treatment with venlafaxine also seemed to alleviate other symptoms, including fatigue, sweating, and trouble sleeping. At the completion of the study, 64% of patients chose to continue treatment with venlafaxine.⁶¹

The same group conducted a placebo-controlled, randomized clinical trial in order to further evaluate the

efficacy of venlafaxine for hot flashes. This study included 191 women who were assigned to a placebo or to target venlafaxine doses of 37.5 mg daily, 75 mg daily, or 150 mg daily. All venlafaxine treatment started at 37.5 mg daily and gradually increased to the desired goal dose. After 4 weeks of treatment, hot flash scores reduced from baseline by 27%, 37%, 61%, and 61%, respectively, in the four groups. Although the 75 mg/d dose had a greater effect than the 37.5 mg/d dose, 150 mg/d was not superior to 75 mg/day. In fact the 150 mg daily group had more side effects, including mouth dryness, decreased appetite, nausea, and constipation.⁶²

Another randomized controlled trial of venlafaxine was performed in 80 postmenopausal women. Patients were randomized to receive extended-release venlafaxine at 37.5 mg daily for 1 week, followed by 75 mg daily for 11 weeks or placebo. In this trial, subjective assessments of hot flash symptoms on daily living were significantly improved in the treatment group.⁶³ However, this trial did not collect any baseline hot flash data, which makes it difficult to interpret.

A more recent randomized controlled trial was undertaken comparing venlafaxine to DMPA in the management of hot flashes. This trial involved 109 women who were randomly assigned to receive DMPA 400 mg intramuscularly as a single dose or venlafaxine 37.5 mg daily for a week, then 75 mg daily. After 6 weeks of treatment, there was a 55% reduction in hot flash score in the venlafaxine group, versus a 79% reduction in the DMPA group. In addition, less short-term toxicity was reported in the DMPA group.⁶⁴ However, the safety of progesterone for treatment of hot flashes, especially in breast cancer patients remains controversial and this should be discussed with a patient prior to starting therapy.

Desvenlafaxine

Desvenlafaxine is a new serotonin norepinephrine reuptake inhibitor (SNRI) and is the succinate salt form of the major active metabolite of venlafaxine.⁶⁵ Since venlafaxine was found to be successful in relieving hot flashes, it was hypothesized that desvenlafaxine may have a similar effect. A randomized, double-blind, placebo-controlled trial, including 707 healthy postmenopausal women, was undertaken to test this hypothesis. Women were randomized to receive desvenlafaxine 50 mg, 100 mg, 150 mg, 200 mg, or placebo daily. There was no significant difference in hot flashes between the 50 mg group (55%) and placebo (51%). However, there were significant reductions in the 100 mg, 150 mg, and 250 mg daily groups, with reductions of 64%, 60%, and 60%, respectively. The most common adverse drug reaction was

nausea, which was dose-dependent.⁶⁶ Another randomized, double-blind, placebo-controlled trial of desvenlafaxine for the treatment of hot flashes included 567 postmenopausal women who were assigned to receive desvenlafaxine 100 mg or 150 mg daily or placebo. After 12 weeks, reductions in the number of hot flashes in the 100 mg, 150 mg, and placebo group were 60%, 66%, and 47%, respectively.⁶⁷

Paroxetine

Paroxetine, an SSRI, was first explored as a treatment for hot flashes in a pilot trial conducted in 2000. The trial included 30 women with a history of breast cancer who received 10 mg of paroxetine daily for one week followed by four weeks of 20 mg daily. There was a significant reduction from baseline in hot flash frequency and score; 67% and 75%, respectively. In addition, there were improvements in depression, sleep, anxiety and quality of life scores.⁶⁸ Based on these promising findings, a randomized controlled trial of paroxetine for the treatment of hot flashes was undertaken. This trial included 156 menopausal women who were randomized to receive paroxetine at 12.5 mg daily, 25 mg daily, or placebo. After 6 weeks of treatment there was a 62% reduction in hot flash score in the 12.5 mg daily group, 65% reduction in the 25 mg daily group, and a 38% reduction in placebo group. The most frequently reported side effects with paroxetine were headache, nausea, and insomnia.⁶⁹ Another randomized, double-blind, cross-over, placebo-controlled trial involved 151 women who were assigned to receive 4 weeks of 10 mg or 20 mg of paroxetine followed by placebo, or placebo for 4 weeks followed by paroxetine 10 mg or 20 mg. Paroxetine 10 mg was found to reduce hot flash frequency by 40.6% compared to 13.7% with placebo. Paroxetine 20 mg daily reduced the frequency by 51.7% compared to 26.6% with placebo. Overall, both doses of paroxetine had similar efficacy but the 10 mg daily was better tolerated.⁷⁰

Fluoxetine

Based on the positive results of previous trials of newer antidepressants and anecdotal information regarding the efficacy of fluoxetine in the treatment of hot flashes, a double-blind, randomized, cross-over study was performed. This trial included 81 women who were assigned to either fluoxetine 20 mg daily or placebo, after 4 weeks the groups switched. After the first treatment period, there was a 50% decrease in hot flash scores in the fluoxetine group versus a 36% reduction in placebo group. The cross-over analysis also found the fluoxetine group to have a greater reduction in hot

flash score. There were no statistically significant toxicities experienced in treatment groups.⁷¹

Another randomized, placebo-controlled, study compared the efficacy of citalopram to fluoxetine in the treatment of hot flashes. This trial included 150 women who were randomized into three groups: placebo, fluoxetine, or citalopram. Fluoxetine and citalopram were started at 10 mg and then increased to 20 mg at one month, and 30 mg at 6 months. The authors reported no statistically significant differences in the numbers of hot flashes between all groups.⁷² However, instead of collecting baseline hot flash data prior to initiation of the study treatments, the investigators used the first day of treatment as a baseline.⁷³ This is problematic, because antidepressants can have a significant immediate effect on decreasing hot flashes. In fact, a 31% reduction in hot flashes was seen in the first day of treatment with venlafaxine.⁷³ Thus, the reported results of this trial are suspect.

Citalopram

Citalopram was first tested as a treatment for hot flashes in a pilot trial in 2003, which involved 26 women with a history of breast cancer. After 4 weeks of treatment at 10 mg daily for the first week and 20 mg daily for the following weeks, patients had a decrease in hot flash frequency by 58%.⁷⁴ Another pilot trial evaluated the efficacy of citalopram for hot flash treatment in 22 patients who had inadequate relief while taking venlafaxine. After 4 weeks of treatment, hot flash scores were reduced by 53%. Citalopram was well tolerated and at the end of the trial 86% of the original participants chose to continue treatment.⁷⁵

These promising data led to further research, including randomized, placebo-controlled trials. One study involved 100 postmenopausal women who were randomized into four groups: citalopram, placebo, citalopram and hormone therapy, or placebo and hormone therapy. Mean hot flash scores improved in all groups with reductions of 37%, 13%, 50%, and 14%, respectively. Thus, this study supported the previous findings that citalopram was successful in relieving hot flashes and found that its beneficial effect was increased with adjuvant hormonal therapy. Of note, women with a history of breast cancer, venous thromboembolism, or women who did not want to take hormone therapy were excluded from the hormone therapy treatment groups.⁷⁶ A more recent randomized controlled trial was performed in 254 women who were allotted to receive either placebo or citalopram at 10 mg daily, 20 mg daily, or 30 mg daily. Hot flash frequency decreased by 20%, 46%, 43%, 50%, respectively.⁷⁷

CYP2D6

Although newer antidepressants have shown to be a promising therapy for hot flashes, some of them may be contraindicated in breast cancer patients. Tamoxifen is a selective estrogen receptor modulator that is widely used for both the treatment and prevention of breast cancer. Tamoxifen is metabolized into its active metabolite, endoxifen, by a cytochrome p450 enzyme CYP2D6.⁷⁸ Some newer antidepressants, especially paroxetine and fluoxetine, can inhibit this enzyme resulting in lower levels of endoxifen. Venlafaxine has less of an inhibitory effect on plasma levels of endoxifen.⁷⁹ The effect of citalopram on plasma levels of endoxifen is less clear. However, the isoenzymes involved in the metabolism of citalopram are mainly CYP3A4 and CYP2D6 and thus it is not expected that citalopram would have very much of an effect on tamoxifen metabolism.⁷⁵ Given currently available information, venlafaxine should, ideally, be selected if an antidepressant is chosen to treat a patient receiving tamoxifen.

Gabapentin

Gabapentin is structurally related to the neurotransmitter γ -aminobutyric acid and is currently used as an anticonvulsant and for neuropathic pain. Gabapentin was first recognized as a possible treatment for hot flashes in 2000 when Guttuso described 6 cases in which gabapentin treatment reduced the frequency of hot flashes.⁸⁰ Based on these data, a pilot trial was reported in 2002, which involved 20 women. Patients were treated with gabapentin for 4 weeks with increasing doses from 300 mg to 900 mg daily. Patients taking gabapentin experienced a decrease in hot flash frequency of 66%.⁸¹

Since this time, multiple randomized controlled trials have evaluated the efficacy of gabapentin for the treatment of hot flashes. The first randomized, double-blind, placebo-controlled trial, involved 59 postmenopausal women who were treated with either 900 mg daily of gabapentin or placebo. After 12 weeks of treatment, women receiving gabapentin experienced a 45% reduction in hot flash frequency, versus a 29% reduction seen in the placebo group. After the 12 week treatment period, there was an open-label treatment phase, during which patients increased the dose of gabapentin to 2700 mg per day. This higher dose was associated with a 54% reduction in hot flash frequency and was not associated with increased adverse events.⁸² Another large randomized, double-blind, placebo-controlled trial involved 420 women with breast cancer and assigned them to receive placebo, gabapentin 300 mg daily or 900 mg daily.

After 4 weeks, the reduction in hot flash severity scores was 21%, 33%, 49%, respectively. Overall, gabapentin at 900 mg daily was associated with a greater hot flash reduction than 300 mg daily.⁸³

The efficacy of gabapentin was then compared to estrogen and placebo in a third randomized controlled trial. This study involved 60 postmenopausal women who received either 625 µg/day of conjugated estrogens, placebo, or gabapentin titrated to 2400 mg/day. After 12 weeks, the hot flash composite score reduced by 72% in the estrogen group, 71% in the gabapentin group, and 54% in the placebo group.⁸⁴ While this study supports a higher dose of gabapentin, the treatment groups only involved 20 women and the overall improvement was only 20% more than placebo.⁷³ Therefore, the recommended dose for treatment of hot flashes is currently 900 mg/day.

Pregabalin

Pregabalin is a newer generation compound with a mechanism of action similar to gabapentin. Therefore, it was hypothesized that it would also be effective against hot flashes. This hypothesis was first tested in a pilot study involving 6 patients and demonstrated a median reduction in hot flashes of 65% in patients taking pregabalin.⁸⁵ To further investigate these positive findings, a randomized, double-blind, placebo-controlled trial was performed. 163 women either received pregabalin at a target dose of 75 mg twice a day, 150 mg twice a day, or placebo. After 6 weeks, hot flash scores decreased by 65%, 71%, and 50%, respectively. Toxicities included weight gain, sleepiness, dizziness, and cognitive troubles that were more significant with the higher dose. Nonetheless the dropout rates for toxicity were similar in all three groups, which implies that these symptoms were mild.⁸⁶

Complementary and alternative therapies

Phytoestrogens

It has been reported that only 10%–20% of women in Asia experience hot flashes. This is significantly less than the 80%–90% prevalence in the United States.^{87,88} One theory for this difference is the predominance of soybeans and soy-based dishes in the Asian diet. Soy is a potent source of phytoestrogens, which are naturally occurring compounds with both estrogenic and anti-estrogenic properties.⁸⁹ Phytoestrogens can be classified into two main classes: isoflavones and lignans. Recently, there has been interest in phytoestrogens as treatment for hot flashes.

Soy is a common source of isoflavones and has been studied as a treatment for hot flashes. In a randomized, double-blind, placebo-controlled trial, 91 perimenopausal women were given isoflavone-rich soy protein, isoflavone-poor soy protein, or whey protein. After 12 weeks there were no significant differences in hot flash frequency or severity between the 3 groups.⁹⁰ A recent meta-analysis reviewed 11 trials of soy isoflavone extracts for treatment of hot flashes and overall the data was not positive.⁵⁴ Soy phytoestrogens were also explored for the treatment of hot flashes in breast cancer patients. One double-blind clinical trial involved 177 breast cancer survivors who received either soy tablets or placebo. After 4 weeks there was no difference in hot flash frequency between groups. This trial had a double-blind cross-over component. The cross-over study results were also negative. Interestingly, at the end of the trial more women chose to continue placebo than the soy product.⁹¹ Further clinical trials of soy phytoestrogens in breast cancer patients also showed similar negative results.⁹²

Isoflavones can also be derived from red clover. A large clinical trial tested two dietary supplements derived from red clover, promensil and rimostil. 252 menopausal women were randomized to receive promensil, rimostil, or placebo. After 12 weeks there was no clinically important reduction in hot flash frequency in either treatment group.⁹³ A recent meta-analysis reviewed 6 trials of red clover for the treatment of hot flashes with similar negative results.⁵⁴

Lignan is another form of phytoestrogen, which is found in whole grains, legumes, vegetables, and in especially high concentrations in flaxseed.⁸⁹ Lignan is structurally similar to estradiol and tamoxifen and has possible tumor inhibitory effects on estrogen positive breast cancer.⁹⁴ An increasing amount of research is currently being undertaken on flaxseed as a treatment for hot flashes. A pilot trial involved 30 women who received 40 g of crushed flaxseed daily. After 6 weeks of therapy there was a 50% reduction in hot flash frequency.⁹⁵ A double-blind, randomized controlled trial included 87 women who ingested either muffins with 25 g of flaxseed, 25 g grams of soy, or wheat. After 16 weeks, neither flaxseed or soy flour affected hot flash frequency but there was a significant reduction in severity of hot flashes for those consuming the flaxseed muffins.⁹⁶ Another double-blind, placebo-controlled, randomized clinical trial of flaxseed has completed its accrual goals and, hopefully, should be reported by 2011. A recent Cochrane meta-analysis summarizes the findings of 30 clinical trials, which investigated the effect of various forms of phytoestrogens on hot flashes. According to this meta-analysis there is currently

no evidence that phytoestrogen supplementation reduces either the frequency or severity of hot flashes.⁹⁷ However, a meta-analysis of isoflavone therapy did report a slight to modest reduction in the number of hot flashes experienced by menopausal women.⁹⁸ Therefore, although at this time phytoestrogens are not recommended for the treatment of hot flashes, it is quite feasible that with further research some phytoestrogen products will be demonstrated to be effective in the alleviation of hot flashes.

Black cohosh

Black cohosh, also known as *Cimicifuga racemosa*, is a plant native to the eastern United States and Canada. American Indians originally used it as a remedy for menstrual and menopausal conditions.⁹⁹ A meta-analysis reviewed 4 randomized controlled trials of black cohosh and this report stated that 3 of the 4 trials found black cohosh to be beneficial for the treatment of hot flashes.⁹² However, most of these trials were from the 1980s. More recent clinical trials have not found any beneficial effect from black cohosh. In 2006, a double-blind, randomized cross-over clinical trial was undertaken where patients received black cohosh for 4 weeks and then placebo or placebo and then black cohosh treatment. The trial failed to show any evidence that black cohosh was more effective at relieving hot flashes than placebo.¹⁰⁰ A recent randomized, double-blind clinical trial from 2009 compared black cohosh, red clover and placebo for the relief of hot flashes. 89 women were randomized to receive black cohosh 128 mg/day, red clover 120 mg/day, or hormone therapy (625 µg estrogen and 2.5 mg progestin). At the end of 12 months the reduction in vasomotor symptoms was 34% in the black cohosh group, 57% in the red clover group, 63% in the placebo group, and 94% in the hormone therapy group. Thus, neither red clover nor black cohosh significantly reduced hot flashes.¹⁰¹ In addition, there is some concern regarding possible adverse effects of black cohosh on the liver and its overall long-term safety.^{19,92} Therefore, black cohosh is not recommended as a treatment for hot flashes

Vitamin E

Vitamin E was first recognized as a possible treatment for hot flashes in the 1940s.^{102,103} The first randomized, cross-over, clinical trial took place in 1998 when 120 women received 4 weeks of vitamin E (800 IU daily) then 4 weeks of placebo or *vice versa*. On crossover analysis, vitamin E was associated with a reduction of hot flashes of about 1 hot flash per day. However, at the end of the study patients did not prefer vitamin E over the placebo.¹⁰⁴ In recent years there has been

concern about the carcinogenicity of vitamin E, however there is reported evidence that vitamin E does not increase cancer risk.¹⁰⁵ Therefore, at this time vitamin E cannot be strongly recommended as an effective treatment for hot flashes.

DHEA

Dehydroepiandrosterone (DHEA) is proandrogen produced by the adrenal glands and liver. It is proposed that DHEA levels decrease as women age and supplementing DHEA may have some effect in treating menopausal symptoms.^{106,107} A small trial in 2000 studied 6 months of DHEA supplementation in postmenopausal women and reported a significant decrease in vasomotor symptoms.¹⁰⁸ A more recent pilot study was performed in 22 women and found a decrease in mean hot flash scores of 50% and an improvement in quality of life related to hot flashes after 4 weeks of DHEA therapy.¹⁰⁶ These positive findings still need to be evaluated in a large randomized placebo-controlled trial.

Other herbal remedies

Evening primrose oil (*Oenothera biennis*) is rich in linoleic acid and is extracted from seeds of the evening primrose plant.¹⁰⁹ A randomized, double-blind, placebo-controlled study was undertaken to evaluate the efficacy of evening primrose oil in treating hot flushes and found that evening primrose oil to have no benefit for hot flash relief.¹¹⁰

Dong quai (*Angelica sinensis*) is a Chinese herb which is traditionally used to treat menopausal symptoms. A randomized controlled trial in 71 women demonstrated no difference in hot flashes between dong quai treatment and placebo groups.¹¹¹ In addition, dong quai has been found to have estrogen like activity.^{112,113} Therefore, not only does dong quai lack any established efficacy for treating hot flashes, its safety in breast cancer patients remains unclear.

Ginseng (*Panax ginseng*) is one of the most popular herbal supplements sold in the United States. It is often used as a restorative agent to treat fatigue or exhaustion.¹⁰⁹ A randomized double-blind trial investigated the effects of ginseng extract on the quality of life and physiological parameters in women experiencing hot flashes. There was no significant difference in vasomotor symptoms between the treatment group and a placebo group.¹¹⁴

Wild Yam (*Dioscorea villosa*) is a natural progesterone cream, which contains phytosteroids and has been promoted for the treatment of hot flashes.¹¹⁵ However, a double-blind, placebo-controlled, cross-over study found no significant difference in menopausal symptoms between the treatment and placebo group.¹¹⁶

Currently there is no sound evidence demonstrating that evening primrose oil, dong quai, ginseng, or wild yam are effective in treating hot flashes and therefore should not be used as a therapy for vasomotor symptoms.

Mind-body and behavior therapies

Behavioral modifications

Despite the large variety of pharmacological options for the treatment of hot flashes, the North American Menopause Society recommends lifestyle changes as the first line therapy for patients suffering from mild vasomotor symptoms.¹¹⁷ One key lifestyle modification involves keeping the core body temperature cool using techniques such as loose clothing, sipping cold drinks, avoiding spicy food, and keeping a lower room temperature.^{117,118}

Exercise

An increasing amount of research is being undertaken on the effect of exercise on hot flashes. However, there is currently no evidence from randomized controlled trials that show that exercise is an effective treatment for hot flashes.^{119,120}

Yoga

Yoga is a combination of exercise and meditation, which involves gentle stretching and breath control. Recently yoga has been studied as a treatment for menopausal symptoms. One large clinical trial involved 108 women who received either 8 weeks of yoga or regular physical exercises. The symptom assessment was made using the Greene Climacteric Scale and it was reported that there was a decrease in vasomotor symptoms in the group involved in the yoga program.¹²¹

A recent randomized pilot trial studied the use of yoga for hot flash treatment in breast cancer survivors. This study involved 37 breast cancer survivors who received either 8 weeks of yoga or were on a wait-list control. After the treatment, women who were involved in the yoga program showed improvements in hot flash frequency, severity, and total scores.¹²² However, the reduction in hot flash score was only 31%, which could be attributed to placebo response. A recent review of the literature on this topic concluded that current evidence does not support the use of yoga for menopausal symptoms.¹²³ Further research is needed to better investigate this area.

Relaxation training

Relaxation techniques are methods of reducing stress and anxiety. Many different forms of relaxation have been investigated for the treatment of menopausal symptoms. One form of relaxation training is paced breathing, which involves

slow, rhythmic, diaphragmatic breathing. Small randomized trials have investigated paced breathing for hot flashes and claimed positive results.^{124,125} These encouraging results led to a randomized phase II study to evaluate the efficacy of paced breathing for hot flashes; the results from this trial, which has completed its accrual goal, are pending.

The efficacy of relaxation as a treatment for hot flashes has also been studied in breast cancer patients. A recent randomized controlled trial investigating relaxation involved 150 women with a history of breast cancer who received either a single relaxation training session with instruction to use practice tapes daily for one month versus no intervention. After one month, the incidence and severity of hot flashes significantly declined in the treatment group. However, there was no difference between groups at 3 months.¹²⁶

Mindfulness-based stress reduction (MBSR) is another form of trained relaxation. It is a program that teaches mindfulness meditation and yoga as a way to cope with stress.¹²⁷ A pilot study investigated the effect of an MBSR program on hot flashes. This study included 15 women who attended the 8-week MBSR program. At the end of the 11-week assessment period, the hot flash severity decreased by 40%.¹²⁸ However, this may result from a placebo effect alone.

A recent review of the literature on the efficacy of relaxation techniques on hot flash control concluded that most trials had positive results. However, the trials were designed with small sample sizes and included a variety of interventions and outcome measures. Therefore, more large well-designed randomized controlled trials are needed to further evaluate the efficacy of these various forms of relaxation on hot flash control.¹²⁹

Hypnosis

Hypnosis is a mind-body therapy that uses mental imagery to induce a state of deep relaxation and heightened focus. Hypnosis has been found to be useful in the management of multiple medical conditions including pain, anxiety, and insomnia.¹³⁰⁻¹³³ It also has been reported to reduce anxiety and distress in breast cancer patients.¹³⁴⁻¹³⁶ Hot flashes are often associated with anxiety and stress. Therefore, it has been proposed that hypnosis may act to reduce hot flashes. This theory was evaluated by a pilot trial of hypnosis in breast cancer patients suffering from hot flashes. The trial reported positive results, with a 59% decrease in total daily hot flashes from baseline.¹³⁷ A larger trial of hypnosis for the treatment of hot flashes was performed in 51 breast cancer survivors and found similar results with hot flashes decreasing by 68% in the hypnosis group.¹³⁸ These preliminary data are encouraging and larger randomized clinical trials of hypnosis for hot flashes are currently underway.

Acupuncture

Acupuncture involves the use of thin needles inserted into specific points of the body. It has been used in Asia for thousands of years and has recently gained popularity in the west as a treatment for multiple conditions. Over the past decade many trials have explored the effect of acupuncture on hot flash symptoms. A recent review of the literature included trials of acupuncture for the treatment of hot flashes that were performed prior to July 2008. This review included six trials that compared acupuncture treatment to sham or placebo acupuncture, five of those trials found no significant difference between groups.¹³⁹ Another recent review explored the literature regarding the effect of acupuncture on hot flashes in breast cancer patients. This review found three randomized controlled trials, which compared the effects of acupuncture to sham procedure. Two of these trials failed to show any positive results from the acupuncture.¹⁴⁰ Therefore, to date, there is no evidence that acupuncture is an effective treatment for hot flashes.

Stellate ganglion block

Stellate ganglion block (SGB) is commonly used to treat a variety of pain syndromes and vascular insufficiency.¹⁴¹ The positive effect of SGB on hot flashes was first reported in a case report by Lipov and colleagues. The series involved 6 women, all of whom experienced a significant reduction in hot flashes after the SGB.¹⁴² In response to these encouraging results the same researchers performed a pilot study involving 13 women with a history of breast cancer. Again, it was reported that a SGB significantly reduced the frequency and severity of hot flashes. In addition, there were no significant adverse events related to the procedure.¹⁴³ A more recent pilot trial was undertaken to evaluate the efficacy of SGB for hot flashes and involved 9 women with a history of breast cancer. The results of this pilot trial supported those reported by Lipov and colleagues.¹⁴⁴

The mechanism by which SGB might reduce hot flashes is unclear. However, Lipov and colleagues proposed that the stellate ganglion has links with the areas of the central nervous system that control body temperature. A SGB may interrupt these connections and allow the body temperature regulating mechanisms to reset.¹⁴⁵ Large randomized controlled trials are needed to further clarify the use of SGB for hot flashes, and are currently underway.

Conclusion

Hot flashes are one of the most common and distressing symptoms associated with menopause. Hot flashes are especially problematic because the most well recognized effective treatment, estrogen, is often contraindicated. This dilemma has led to an extensive amount of research

exploring different therapeutic options for the treatment of hot flashes. Currently, multiple safe and efficacious non-hormonal modalities exist. As the mechanism of hot flashes is further elucidated and research in this area grows, newer therapies for hot flashes will most likely become established.

Disclosure

The authors report no conflicts of interest in this work.

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