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Hot Flashes: A Review of Pathophysiology and Treatment Modalities

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ABSTRACT

Many therapies are being studied for the treatment of hot flashes for individuals with cancer, yet few studies have demonstrated safe and effective clinical benefit for those who suffer from this distressing symptom. The purpose of this paper is to assess the current options for the management of hot flashes, examining key endpoints from recent clinical trials and reviewing future directions. Hot flashes are a common stressful symptom for individuals with cancer, particularly women with a history of breast cancer and men with prostate cancer. Lifestyle modifications are proposed as the first step in the management of less severe hot flashes. Several publications have addressed nonhormonal agents as a treatment option for hot flashes. Newer antidepressant and anticonvulsant agents have been studied and show potential in treating vasomotor symptoms. Although many complementary and alternative therapies, including herbal medications and phytoestrogens, have been studied for the treatment of hot flashes, none are clinically recommended at this time. Additionally, further evidence is needed for supportive exercise such as yoga and relaxation techniques. Acupuncture may warrant further investigation in the reduction and severity of hot flashes in both men and women. Hormonal therapies, including estrogens and progestogens, are the most well-known and efficient agents in alleviating hot flashes; however, the safety of these agents is disputable. ***The Oncologist*** 2011;16:1658–1664

INTRODUCTION

Menopause, an expected transitional life occurrence in women, is generally defined as the 12-month period of amenorrhea that occurs after the final menstrual period. This phase, which typically begins at a median age of 51 years, reflects ovarian follicular depletion and marked reduction in ovarian estrogen secretion. Clinical manifestations associated with menopause include, but are not limited to, vasomotor symptoms, genitourinary symptoms, sleep disturbance, and mood changes [1, 2]. One of the well-known symptoms of menopause is the occurrence of hot flashes, which occur in >75% of menopausal women [1]. Hot flashes are often described as episodic sensations of heat, intense sweating, and flushing affecting the face and chest, which are often accompanied by palpitations and anxiety [3]. Each particular episode lasts 3–10 minutes and episodes can recur with varying frequency [4]. Some women experience hot flashes hourly or daily, whereas for others they may occur occasionally. Similar to the variability in frequency of this symptom, the age at onset of hot flashes also varies from woman to woman. Although most women develop hot flashes during the perimenopausal and early postmenopausal periods, a minority of patients develop hot flashes while menstrual cycles remain regular. Furthermore, the majority of women have hot flashes for 1–2 years, but ~15% may have persistent hot flashes for up to 30 years.

Hot flashes are common among breast cancer patients resulting from multiple treatment options that can induce an estrogen deprivation state, including antiestrogenic medications, chemical or medical oophorectomy, and certain cytotoxic agents [1]. The average incidence of hot flashes in women

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treated with an antiestrogenic agent such as tamoxifen is 60%–70% [5, 6]. A placebo-controlled trial, specifically designed to evaluate the symptoms associated with tamoxifen treatment in postmenopausal women, demonstrated that tamoxifen was associated with hot flashes in up to 67% of patients [7, 8]. More recently, however, aromatase inhibitors have become widely used for the treatment of breast cancer in postmenopausal women. Studies comparing exemestane with tamoxifen for first-line hormonal therapy of metastatic breast cancer in postmenopausal women have shown that the incidence of hot flashes of any grade was slightly lower with exemestane (35.1%) than with tamoxifen (38.1%) [9, 10]. This difference between aromatase inhibitors and tamoxifen was echoed in the Breast International Group (BIG) 1–98 and the Arimidex, Tamoxifen, Alone, or in Combination trials [11, 12]. For example, in the BIG 1–98 clinical trial, hot flashes were more common among women who were randomized to a tamoxifen-containing regimen than among women who received letrozole monotherapy (41.7%–44% versus 37.7%; $p = .003$) [11, 13].

In addition to endocrine therapy, certain chemotherapeutic agents may increase the likelihood of hot flashes by inducing premature menopause. One prospective study demonstrated that, when compared with women who had undergone natural menopause, a greater proportion of patients who had undergone chemotherapy-induced menopause developed moderate to severe hot flashes [14]. The likelihood of chemotherapy-induced menopause is related to age at treatment, type of cytotoxic agent, and dose of chemotherapy. For example, ~40% of 40-year-old premenopausal women who receive chemotherapy undergo premature menopause, whereas >90% of 50-year-old women are likely to undergo early menopause after chemotherapy [15]. Additionally, a higher risk for menopause is associated with larger cumulative doses and with longer durations of cytotoxic therapy [16–17]. This chemically induced menopause thus leads to a higher incidence of vasomotor symptoms, including hot flashes.

For men, the phenomenon of hot flashes often occurs as a result of medical or surgical treatment for prostate cancer. Although up to 75% of men treated with androgen deprivation therapy may experience hot flashes, there are limited therapeutic options for the treatment of hot flashes [18–20].

This article focuses on the pathophysiology and management of hot flashes in cancer patients, with particular focus on the breast cancer and prostate cancer populations.

Methods

We used the following keywords in our search of the literature: vasomotor symptoms, hot flashes, hot flush, menopause, and quality of life. Recognizing that research in hot flashes is limited by the subjectivity of the patient and researcher, diverse methods of measuring hot flash improvement, and placebo effects, we focused primarily on placebo-controlled, randomized trials. We summarized significant clinical trials in Table 1.

Pathophysiology

Despite extensive research, the pathophysiology of hot flashes is not entirely understood. The onset of hot flashes is hypothesized to be related to dysfunction of the thermoregulatory nucleus, which is essential in regulating the homeostatic range and the core body temperature [1, 21]. The thermoregulatory nucleus maintains the core body temperature within a homeostatic range termed the thermoregulatory zone. Sweating occurs when the body's core temperature increases above the upper threshold of the thermoregulatory zone, whereas chills occur when the core temperature dips below the lower threshold of this zone. Freedman found that women who experience hot flashes demonstrated a smaller thermoregulatory zone, leading to a greater likelihood of crossing these thresholds and thus developing the sweats and chills that are associated with hot flashes [22].

In addition, as estrogen levels decline in menopause, norepinephrine levels rise, leading to an upregulation of hypothalamic serotonin receptors, which are involved in temperature regulation [3]. Central α-2 receptors may be affected by estrogen depletion, leading to higher central norepinephrine levels [23]. This activation of the noradrenergic and serotonin pathways may further narrow the upper threshold of the thermoregulatory zone, leading to a greater propensity for hot flashes [21]. However, *absolute* estrogen levels are not solely responsible for hot flashes, because researchers have found no significant correlation between plasma, urinary, or vaginal estrogen levels and the appearance of this symptom [23]. Instead, it is the *relative* decline in estrogen levels that appears to mediate these central changes in norepinephrine and serotonin. This theory was supported by the finding of a greater prevalence of hot flashes in women who develop acute estrogen withdrawal after bilateral oophorectomy than in those who experience gradual ovarian failure related to natural menopause [24]. Interestingly, involvement of the opioidergic system has been explored; however, there is no consistent evidence for opiate interaction [23].

Treatment Interventions

Hormonal Therapies

Estrogen Replacement Therapies

Hormone replacement therapy (HRT) is widely known as an effective therapeutic means for alleviating hot flashes. However, a number of endocrine factors have been linked to the incidence of breast cancer [25, 26]. Estrogen is effective in improving hot flashes caused by not only natural menopause but also by chemotherapy-induced ovarian failure, tamoxifen use, androgen ablation therapy, and the use of leuteinizing hormone-releasing hormone agonists such as goserelin [21]. To reduce the possible harmful effects of estrogen therapy, recent trials have focused on the use of lower estrogen doses in order to decrease hot flash symptomatology. For example, Bachmann and colleagues randomized healthy postmenopausal women who were experiencing hot flashes to either low-dose transdermal estrogen, microdose transdermal estradiol, or placebo. They found that even those patients who received the microdose estradiol had a 75% lower hot flash frequency than those receiving placebo ($p = .003$) [27]. However, although numerous randomized trials have demonstrated that estrogen therapy markedly reduces the frequency and intensity of hot

Table 1. Recent randomized trials for the treatment of hot flashes

Agent/technique	*n* of patients	Results	*p*-value	Reference
Megestrol acetate versus placebo	163	Effective treatment for men and women	$p < .001$	[33]
MPA versus oral megestrol acetate versus placebo	71	MPA is a long-lasting effective alternative to prolonged use of oral megestrol acetate	$p = .03$	[34]
Transdermal progesterone cream versus placebo	102	Effective treatment for vasomotor symptoms	$p < .001$	[35]
Progestelle progesterone cream versus placebo	223	Progesterone cream was no more effective than placebo	No significant differences	[36]
Clonidine	11	Effective treatment for hot flashes	$p < .001$	[38]
Clonidine versus placebo	86	Moderate reduction in hot flashes	(a) Clonidine before placebo, $p < .05$; (b) clonidine after placebo, $p < .0001$	[39]
Clonidine versus placebo	10	Modest improvement with toxicities	$p < .005$	[40]
Clonidine versus placebo	110	Moderate improvement with toxicities	$p < .0001$	[41]
Fluoxetine versus placebo	81	Moderate decrease in hot flashes	$p = .02$	[44]
Venlafaxine versus placebo	191	Moderate reduction in hot flashes	$p < .0001$	[45]
Citalopram versus placebo	254	Effective, well-tolerated treatment for hot flashes	$p \leq .002$	[46]
Gabapentin versus placebo	59	Effective treatment for hot flashes	$p = .01$	[49]
Gabapentin versus placebo	420	Effective treatment for hot flashes	$p = .007$	[50]
Gabapentin versus estrogen versus placebo	60	Gabapentin as effective as estrogen	(a) Estrogen versus placebo, $p = .016$; (b) gabapentin versus placebo, $p = .004$	[51]
Venlafaxine versus gabapentin	66	Venlafaxine preferred over gabapentin	$p = .01$	[52]
MPA versus venlafaxine	227	MPA more effective than venlafaxine	$p < .0001$	[53]
Gabapentin versus gabapentin and antidepressant	113	The combination of gabapentin and an antidepressant was not significantly better than gabapentin alone	$p = .37$	[54]
Vitamin E versus placebo	105	Minimal reduction in hot flashes	$p \leq .05$	[55]
Soy phytoestrogen versus placebo	149	Soy phytoestrogen is not effective in alleviating hot flashes	No significant differences	[56]
Acupuncture versus venlafaxine	50	Both groups had similar changes in hot flash frequency	$p < .036$	[59]
Hatha yoga	11	Effective for less severe hot flashes	$p = .02$	[61]
Yoga versus physical exercises (control)	120	Yoga effective in decreasing vasomotor symptoms	$p < .05$	[62]
Exercise versus oral estradiol	30	Exercise may decrease hot flashes	No significant differences	[64]
Structured education and exercise versus no exercise	35	Structured education and exercise had significant effects in terms of Kupperman index	$p < .05$	[65]
Moderate-intensity exercise versus stretching (control)	173	Exercise patients had a greater risk for moderate/severe hot flashes over time than controls	$p = .02$	[66]
Paced respiration versus muscle relaxation versus α-wave ECG biofeedback (control)	23	Hot flush frequency decreased significantly for the paced respiration group	$p < .02$	[67]
Applied relaxation and oral estradiol	30	Applied relaxation patients had a moderate reduction in hot flashes	$p < .001$	[68]

Abbreviations: ECG, electrocardiogram; MPA, medroxyprogesterone acetate.

flashes, results of the Women's Health Initiative (WHI) studies have raised concern about long-term adverse effects pertaining to receiving HRT. The results of the WHI trial identified net harm for combined hormonal therapy use [28]. In particular, estrogen plus progestin was associated with a higher incidence of breast cancers, many of which were higher stage. Breast cancer mortality also appears to be amplified with the combined use of estrogen and progestin [29]. Additionally, following the initial report of results from the WHI, a significant decrease in breast cancer incidence in the U.S. was noted, which was hypothesized to be related to a decline in HRT intake resulting from awareness of the WHI findings. On the other hand, long-term follow-up from that study demonstrated that estrogen replacement therapy alone did not increase the risk for breast cancer recurrence [30]. However, data from a meta-analysis of 16 studies evaluating the use of estrogen therapy alone demonstrated that long-term estrogen replacement therapy was associated with a 30% higher relative risk for breast cancer [31, 32]. Thus, the use of any HRT following a breast cancer diagnosis continues to be discouraged.

Progestational Agents

Recent studies have demonstrated that progestational agents have the ability to reduce the frequency and intensity of hot flashes. In a double-blinded, placebo-controlled, randomized clinical trial evaluating 97 women with a history of breast cancer and 66 men receiving androgen deprivation therapy for prostate cancer, the use of megestrol acetate resulted in a 85% reduction in hot flashes, versus a 21% reduction in the placebo group [33]. In addition, the use of an i.m. depot formulation of medroxyprogesterone acetate (MPA) was demonstrated to have comparable effects on hot flashes [34]. Indeed, when MPA was compared with oral megestrol in a randomized study, 89% of responders continued to show a decrease in hot flashes at week 24, compared with 45% in the megestrol group.

While the use of oral and i.m. progestational agents has demonstrated significant efficacy in randomized trials, the role of progesterone cream for alleviating hot flashes remains a controversial topic, because placebo-controlled, randomized trials involving these agents have provided conflicting evidence [35, 36].

Furthermore, although oral and i.m. progestational agents have been shown to have efficacy in the treatment of hot flashes, researchers have found that the use of these agents may stimulate epithelial proliferation in the breast and thus increase the risk for the development of breast cancer [37]. Thus, the use of these agents is controversial and is not recommended in patients with a history of breast cancer.

Neuroactive Agents

Clonidine

Given the proposed noradrenergic mechanism of hot flashes, the use of clonidine, a centrally acting α-adrenergic agonist, was explored for the treatment of this symptom [38–40]. However, this agent is associated with significant side effects, such as dry mouth, constipation, and drowsiness [41]. In addition, a meta-analysis of 10 trials involving clonidine found that $<50\%$ of the trials showed a benefit with the use of clonidine, when compared with placebo [42]. Thus, this agent is not recommended for treating hot flashes.

Serotonin Reuptake Inhibitors

Loprinzi and colleagues reported results from randomized, placebo-controlled clinical trials evaluating the treatment of hot flashes in women [43]. Two placebo-controlled trials involving fluoxetine and venlafaxine demonstrated a 50%–60% reduction in the incidence of hot flashes [44, 45]. In addition, a randomized, placebo-controlled trial demonstrated that citalopram led to significantly better hot flashes scores than with placebo [46]. However, the use of selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, in patients taking tamoxifen therapy must be evaluated with caution, given previous studies that have demonstrated that SSRI antidepressants, such as paroxetine, inhibit the cytochrome P450 2D (CYP2D6) pathway and may be associated with higher mortality from breast cancer in patients who are taking tamoxifen [47].

Gabapentin

In aggregate, three gabapentin trials have demonstrated a relatively lower incidence of hot flashes, by 35%–38%, in patients treated with this agent than in patients treated with placebo [48–51]. Furthermore, to evaluate patient preference for gabapentin versus venlafaxine, Bordeleau et al. [52] conducted a group-sequential, open-label, randomized, crossover trial of 4 weeks of venlafaxine (37.5 mg daily for 7 days followed by 75 mg daily for 21 days) versus gabapentin (300 mg once per day for 3 days, then 300 mg twice per day for 3 days, then 300 mg three times per day for 22 days) for breast cancer survivors, with a primary end result of patient preference. The study demonstrated that, of 66 patients who were randomly assigned to treatment with venlafaxine or gabapentin, 32% of the patients preferred gabapentin, versus 68% of the patients who preferred venlafaxine [52]. Interestingly, when comparing MPA with venlafaxine following the sixth week after random assignment, hot flash scores were 55% lower in the venlafaxine arm and 79% lower in the MPA arm [53]. In a phase III trial of gabapentin alone or in combination with an antidepressant in women who do benefit from an antidepressant alone, the combination of the two agents was not significantly better than gabapentin alone [54].

Complementary and Alternative Medicine Approaches

Given the paucity of U.S. Food and Drug Administration–approved regimens for the treatment of hot flashes, patients and providers have explored complementary and alternative regimens in an attempt to find a solution for these symptoms. However, many of these therapies have shown marginal, or no, benefit. For example, a placebo-controlled, randomized trial involving the use of vitamin E demonstrated that vitamin E administration resulted in a minimal decrease in hot flashes and was not preferred over placebo

[43, 55]. Additionally, placebo-controlled trials investigating soy phytoestrogen and black cohosh found no significant benefit from these agents [43, 56].

Furthermore, acupuncture has been studied as a nonpharmacologic method for the alleviation of hot flashes. Although several trials have evaluated the use of acupuncture for this symptom [57, 58], a recent meta-analysis of 11 studies (including five placebo-controlled trials) failed to confirm the benefit of acupuncture in the treatment of hot flashes [59, 60]. However, a subsequent trial comparing acupuncture with venlafaxine demonstrated that, although both groups had improvements in symptoms, the acupuncture group exhibited a sustained improvement at 2 weeks post-treatment, whereas the venlafaxine group developed more hot flashes post-treatment [57].

Behavioral Modifications

Although there have been multiple trials involving diverse medications for the treatment of hot flashes, the backbone of hot flash treatment involves behavioral modification. The North American Menopause Society recommends that, for mild hot flashes, patients should maintain a low core body temperature through dressing in layers, consuming cool or cold food or drinks, and using a fan as needed. In addition, further behavioral modifications are detailed below [61].

Yoga

Yoga has been examined as a technique for controlling hot flashes, and several trials have suggested yoga to be beneficial in alleviating hot flashes [62, 63]. However, a systematic review of seven clinical studies evaluating the use of yoga for menopausal symptoms found that there is currently insufficient evidence to suggest that yoga is an effective means for controlling hot flashes [60, 64].

Exercise

To explore the impact of exercise on hot flashes, several randomized trials compared the effect of exercise with other modalities (stretching, estrogen, or observation) and failed to demonstrate a significant benefit [65, 66]. In fact, exercise has been associated with an increase in the severity of these symptoms in postmenopausal, overweight women, a finding that is theorized to be a result of the fact that exercise increases the core body temperature, thus resulting in hot flashes in patients with a narrow thermoneutral zone [67].

Relaxation Techniques

Freedman et al. [68] studied the practice of slow-breathing techniques and found that these techniques may reduce small overall sympathetic tone, reducing the frequency of hot flashes 35% more than muscle relaxation alone. Another trial compared the use of applied relaxation with estradiol therapy; although estrogen therapy reduced hot flashes more quickly, climacteric symptoms improved in both groups over time [69]. A review of 14 studies, involving 475 patients who had received psychoeducational interventions, including relaxation, demonstrated an overall improvement in vasomotor symptoms. However, the experimental group in two studies, which had the greatest number of patients, also received pharmacologic therapies [70].

Conclusion

Research in the field of hot flashes has resulted in multiple options for the patient who is suffering from this significant symptom. A practical approach to these patients must first address behavior modification, including maintenance of a cool core body temperature (i.e., by drinking cool liquids, avoiding hot/spicy foods, and wearing looser clothing). Beyond these lifestyle interventions, there are diverse options for these patients. Given the potential long-term risks of hormonal therapies, patients should attempt nonhormonal options first. Although SSRIs have shown great promise in the treatment of hot flashes, the choice of agent should also include consideration of the patient's concomitant medications. If the patient is taking tamoxifen or other agents that are metabolized by the CYP2D6 pathway, the choice of SSRI should include venlafaxine, with careful avoidance of agents such as fluoxetine or paroxetine, which are potent inhibitors of the CYP2D6 pathway. For those who are not taking agents such as tamoxifen or other CYP2D6-dependent medications, the choice of SSRI is not limited by this consideration. Furthermore, although gabapentin was found to be less preferred than venlafaxine for the treatment of hot flashes, it remains an option for patients, especially for those who find nighttime hot flashes to be a greater concern, given the sedating effect of gabapentin. Finally, relaxation techniques should be considered as an alternative, or complementary, regimen for the treatment of this distressing symptom. Current trials involve the use of flaxseed, stellate ganglion injections, hypnosis, relaxation, and combined modalities for the treatment of hot flashes.

Author Contributions

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