Hot Flashes in Breast Cancer Survivors

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■ **Abstract:** Hot flashes can be a major problem for patients with a history of breast cancer. The precipitation of menopause in premenopausal women who undergo chemotherapy for breast cancer can lead to the rapid onset of hot flash symptoms that are more frequent and more severe than those associated with natural menopause. In addition, tamoxifen, historically the most commonly prescribed pharmacologic agent for the treatment of breast cancer, is associated with hot flashes in more than 50% of its users. Although estrogen relieves hot flashes in 80–90% of women who initiate treatment, its use in women with a history of breast cancer is controversial, and most physicians in the community will not use this treatment modality. In addition, the results of the long-awaited Women's Health Initiative study and other recent studies suggest that long-term estrogen therapy should not be recommended for most women for a variety of reasons. However, hot flashes in breast cancer survivors should no longer be considered untreatable, as there are many pharmacologic and nonpharmacologic treatments that can help alleviate this problem. This article reviews the current strategies for the management of hot flashes in breast cancer survivors and the evidence supporting their use. ■

Key Words: hot flashes, breast cancer antidepressants

Nearly three-quarters of menopausal women experience hot flashes (1), which are typically described as a sudden and disturbing sensation of intense warmth centered on the face and upper chest that rapidly becomes generalized. Red blotches can appear on the skin, and the increase in skin temperature can lead to profuse sweating. Palpitations and anxiety are not uncommon in this setting. Hot flashes usually last for 2–4 minutes and may occur several times per day, although their frequency among patients is very variable. In some women, hot flashes occur every 20 minutes, while in others they only occur once a month (2). Hot flashes typically start 1–2 years before menopause and continue to occur for 6 months to 5 years, but in some women they can occur for much longer periods of time. Hot flash symptoms can have serious detrimental effects on a woman's work, recreation, sleep, and general quality of life (3–7).

Hot flashes can be a major problem for patients with a history of breast cancer. The precipitation of menopause in premenopausal women who undergo chemotherapy for breast cancer can lead to the rapid onset of hot flash symptoms that are more frequent and more severe than those associated with natural menopause (8,9). In addition, tamoxifen, historically the most commonly prescribed pharmacologic agent for the treatment of breast cancer, is associated with hot flashes in more than 50% of its users (10). In women taking tamoxifen, hot flashes increase over the first 2–3 months and then tend to resolve gradually. Postmenopausal women with a history of hot flashes are more likely to have hot flashes when using tamoxifen (11).

Although estrogen relieves hot flashes in 80–90% of women who initiate treatment (12,13), its use in women with a history of breast cancer is controversial and most

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physicians in the community will not use this treatment modality. In addition, the results of the long-awaited Women's Health Initiative study (14) and other recent studies (15–18) suggest that long-term estrogen therapy should not be recommended for most women for a variety of reasons. However, hot flashes in breast cancer survivors should no longer be considered untreatable, as there are many pharmacologic and nonpharmacologic strategies that can help alleviate this problem.

PATHOPHYSIOLOGY OF HOT FLASHES

At menarche, cyclical release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland leads to monthly maturation of ovarian follicles that secrete estrogen and progesterone and exert a negative feedback on the hypothalamus and the pituitary gland. In the absence of fertilization, estrogen and progesterone secretion falls, negative pituitary feedback is lost, FSH and LH release increases, and the cycle begins again. At menopause, as the supply of ovarian follicles comes to an end, estrogen levels decrease dramatically, negative pituitary feedback is lost, and LH and FSH release increases. Hot flashes, which occur synchronously with these hormonal changes, are generally thought to be secondary to a thermoregulatory dysfunction initiated at the level of the hypothalamus by estrogen withdrawal (19–30).

In humans, perspiration and vasodilation, the classic mechanisms of heat loss that are activated during hot flashes, are regulated by the thermoregulatory nucleus in the medial preoptic area of the hypothalamus (19). The thermoregulatory nucleus activates perspiration and vasodilation to keep core body temperature within a tightly regulated range known as the thermoregulatory zone. In menopausal women with hot flashes, the thermoregulatory zone is shifted downward and is narrower than in menopausal women who do not have hot flashes (31). Thus, in women with hot flashes, small changes in body temperature (as low as 0.01°F) may trigger the mechanisms of heat loss that lead to hot flash symptoms (24).

Complex neuroendocrine pathways govern the thermoregulatory nucleus and are possible sites of dysfunction and therapeutic intervention (19,32,33). In individuals with hot flashes, estrogen withdrawal leads to a decrease of endorphin and catecholestrogen (an estrogen metabolite) levels, which, in turn, increase norepinephrine and serotonin release in the hypothalamus (19,32–36). This increase in hypothalamic norepinephrine and serotonin is thought to be responsible for lowering and narrowing the thermoregulatory set point and triggering the aforementioned heat loss mechanisms (19,31,33).

TREATMENT OF HOT FLASHES

The Placebo Effect in Hot Flash Research

The importance of using a placebo controlled group in clinical studies is dramatically illustrated by the results of multiple placebo controlled, randomized clinical trials in women with hot flashes. In these trials, 20% of women in the placebo group showed a more than 50% reduction in hot flashes over a 3- to 4-week period that was consistent across the trials (37–41). These figures should be kept in mind when evaluating anecdotal or poorly designed studies. The placebo effect may play a substantial role in many unproven remedies for hot flashes.

Hormonal Therapy

Estrogen Replacement. Estrogen replacement is generally considered the most effective treatment for hot flashes. Estrogen relieves hot flashes in 80–90% of women who initiate treatment (12,13). However, there are many situations in which estrogen replacement is thought to be contraindicated. Patients with a history of coronary artery disease (42,43), ovarian cancer (16,44), venous thromboembolism (45,46), and uterine cancer (47,48) are just a few examples of women who should not use estrogen replacement. Though most physicians in the community will not use estrogen replacement to treat hot flashes in patients with a history of breast cancer, definitive evidence against their use in this patient population is lacking (15). In fact, several prospective and retrospective studies suggest that at least some breast cancer survivors (women with small tumors, negative lymph node status, long disease-free survival, or estrogen receptor [ER]-negative tumors) can be safely treated with estrogen replacement (49–58). However, in the absence of well-designed randomized clinical trials of the use of estrogen replacement in breast cancer survivors, physicians will be very reluctant to use estrogen in this patient population. This is more true in light of the results of the Women's Health Initiative study (14) and other recent reports (15–18), which showed that long-term estrogen use should not be recommended at this time, and that there are many other pharmacologic and nonpharmacologic strategies that can help alleviate this problem.

Progestational Agents

Several pilot studies in the 1970s and 1980s showed that progestational agents decreased hot flashes (59–62).

Based on these studies, a double blind, placebo controlled, crossover, randomized clinical trial of megestrol acetate at a dose of 40 mg/day was done in 97 women with a history of breast cancer and 66 men receiving androgen ablation therapy for prostate cancer (39). Women in the megestrol group had a 75–80% reduction in hot flashes compared to a 20–25% reduction in the placebo group after 4 weeks of therapy. Megestrol was equally efficacious in women and men. After stopping treatment, 31% of women had withdrawal bleeding within 4 weeks. A follow-up study of this cohort of patients (63) found that 3 years later, one-third of the women were still using megestrol acetate, and that those who were still taking megestrol had fewer hot flashes than those who had stopped taking it.

In addition to megestrol, depomedroxyprogesterone acetate (DMPA), an intramuscular, long-acting progestational agent, has also been found to be useful in the treatment of hot flashes (59,60,64). In a randomized clinical trial of DMPA versus oral megestrol acetate, both agents were found to be similarly efficacious (65).

Finally, a placebo-controlled, randomized clinical trial of a progesterone cream in 102 healthy postmenopausal women (66) showed an 83% reduction in hot flashes in the progesterone group compared with 19% in the placebo group after 4 weeks of treatment. This benefit was still present at 12 months with continued use of the progesterone cream.

Despite the evidence in favor of the use of progestational agents in the treatment of hot flashes, many physicians are still wary of using hormonally active agents in patients with a history of breast cancer. Some in vitro data suggest that progestational agents may increase epithelial cell proliferation (67), which may be undesirable in breast cancer survivors (68). However, there is also evidence that progestational agents have antitumor activity in breast cancer (69). Because of the ongoing debate over this issue, patients need to be appropriately counseled before starting a progestational agent if they are breast cancer survivors or are worried about increasing their risk of breast cancer.

Nonhormonal Treatments

Newer Antidepressants. In the 1990s, several authors reported a reduction in hot flashes in postmenopausal women being treated for depression with newer antidepressants. These reports involved fluoxetine, venlafaxine, paroxetine, and sertraline. Based on these reports, several pilot studies were undertaken. In a pilot study of venlafaxine at a very low dose of 12.5 mg twice a day (70), hot flashes decreased by about 50%. In another pilot study (71), paroxetine at a dose of 20 mg/day caused a 65% reduction in hot flashes. Because of these promising results, several placebo controlled, randomized clinical trials were undertaken.

The largest of these trials was a double blind, placebo controlled, randomized clinical trial of venlafaxine (41). In this study, venlafaxine was given at doses of 37.5, 75, and 150 mg/day. After 4 weeks of therapy, hot flashes had decreased by 27% in the placebo arm, 37% in those receiving 37.5 mg/day, and 61% in those receiving 75 mg/day and 150 mg/day. Side effects included dry mouth, decreased appetite, nausea, and constipation. However, venlafaxine was relatively well tolerated and significantly improved patients' quality of life.

A placebo controlled, crossover study of fluoxetine at a dose of 20 mg/day (72) showed a 50% reduction in hot flash scores (frequency × average daily severity) in the fluoxetine group compared with 36% in the placebo group. In addition, two pilot studies of paroxetine for the treatment of hot flashes in women with breast cancer (71,73) and a placebo controlled, double blind study in women without breast cancer (74) have shown that this antidepressant also decreases hot flashes. Lastly, several pilot trials of other newer antidepressants, including nefazodone, citalopram, and mirtazapine, are showing promising results (75,76). Results from other hot flash studies using this class of drugs should be forthcoming in the next couple years.

Gabapentin. Although the exact mechanism of action of the γ-aminobutyric acid analog gabapentin is not well understood, it is widely used in the treatment of a variety of ailments such as epilepsy, neuropathic pain, migraines, and other neurologic disorders. Its usefulness for the treatment of hot flashes was first noted anecdotally in a group of six patients at the University of Rochester (77). All six patients reported a 75–100% reduction in hot flashes within 72 hours of starting gabapentin for other reasons. In a pilot study (78), 16 of 20 women who completed the study (4 dropped out because of lightheadedness and dizziness) had a 66% reduction in hot flash frequency by 4 weeks. Similar results were observed in another pilot study (79). A recently published double blind, placebo controlled, randomized clinical trial of gabapentin at a dose of 900 mg/day in 59 postmenopausal women without breast cancer (80) showed a 54% reduction in hot flash scores compared with 31% in the placebo group after 12 weeks of therapy. Four patients (13%) in the gabapentin group and one (3%) in the placebo group withdrew from the study because of adverse events. Side effects from gabapentin include lightheadedness, dizziness, and edema (presumably related to resultant low

albumin concentrations in those patients who developed this side effect). Ongoing placebo controlled, randomized clinical trials are evaluating the use of gabapentin in breast cancer survivors and in men receiving androgen ablation therapy for prostate cancer.

Vitamin E. Vitamin E, thought to be an antioxidant, was initially hailed as a useful adjunct in the treatment of a variety of medical conditions including heart disease, Parkinson's disease, and hot flashes. Though the initial enthusiasm for the use of this vitamin in most medical conditions has waned, vitamin E can still play a small role in the treatment of hot flashes. A placebo controlled, crossover clinical trial (40) of vitamin E at a dose of 800 IU/day in 120 women showed that, on average, women taking vitamin E had one less hot flash per day than those taking placebo. Reported side effects were similar in the treatment and the placebo groups.

Clonidine. Clonidine is a centrally acting α_2-receptor agonist with antihypertensive properties. Because of the important role of norepinephrine in the pathophysiology of hot flashes, it was thought that clonidine might be useful for treating hot flashes. One study demonstrated the usefulness of transdermal clonidine in the treatment of hot flashes (37). However, the use of the patch was associated with significant side effects (fatigue, dry mouth, and constipation).

Another placebo controlled, randomized clinical trial of clonidine, at an oral dose of 0.1 mg every night in 194 women with history of breast cancer (38), showed a decrease in hot flashes of 37% in the clonidine group compared with 24% in the placebo group after 8 weeks of therapy. Patients using clonidine in this trial described a 3% improvement in their overall quality of life, whereas those using placebo described a 2% decrease. Patients in the clonidine group noticed more side effects, especially insomnia (41% with clonidine versus 21% with placebo). Thus, although clonidine has been shown to be effective in decreasing hot flashes, its side effects have tempered enthusiasm for its use.

Black Cohosh. Black cohosh (*Cimicifuga racemosa*) is one of many herbal remedies used to treat health ailments. Most of these remedies have been reported to be beneficial on an anecdotal basis. However, black cohosh has been approved for the treatment of hot flashes in Germany, where several studies have suggested that it might relieve hot flash symptoms (81,82). However, a recent placebo controlled, randomized clinical trial in the United States of black cohosh in 85 women over a 60-day period (83) failed to show any statistically significant difference in the frequency or severity of hot flashes between the black cohosh and the placebo groups. Nonetheless, this trial reported substantially fewer sweating problems in women taking black cohosh. A recent pilot study reported relatively impressive hot flash reductions with black cohosh, supporting an ongoing placebo controlled clinical trial (84). In the past there have been some concerns about the possible estrogenic effects of black cohosh, but many recent studies have not confirmed these concerns. In total, the jury is still out regarding the utility of black cohosh for treating hot flashes.

Soy. There have been a number of studies evaluating soy, a prominent source of phytoestrogens, for the treatment of hot flashes. The North Central Cancer Treatment Group (NCCTG) conducted a double blind, placebo controlled, randomized clinical trial of a soy isoflavone, at a dose of 150 mg/day, in 177 women with a history of breast cancer (85). The study failed to demonstrate any significant effect on hot flash severity or frequency. Though other studies have reported that the use of soy products was beneficial in women with hot flashes (86), the vast majority of the literature suggests that soy products do not reduce hot flashes significantly. A recent meta-analysis of hot flash trials of soy products concluded that, overall, soy decreased hot flashes 5% more than placebo (87). Given the well-known publication bias and the fact that this meta-analysis excluded the trials involving breast cancer survivors (including a large trial where the soy product did numerically worse than did the placebo), this minimal difference does not bode well for soy as a hot flash remedy. In addition, there is an ongoing debate over whether soy decreases or increases the risk of breast cancer. Nonetheless, in all, dietary soy in moderation probably does not help or hurt women significantly if they have a history of breast cancer (88). Pharmacologic use of soy for hot flashes, however, cannot be supported.

Bellergal. Belladonna, from the Italian *bella donna* (beautiful lady), is a plant extract that has antimuscarinic properties. During the Renaissance, dilated pupils were considered beautiful, and belladonna was used as eyedrops (89). In combination with phenobarbital and ergotamine (Bellergal), belladonna was used in the 1970s and 1980s for the treatment of hot flashes. However, available data suggest only a small benefit from Bellergal over placebo. In one placebo controlled, randomized clinical trial (90), women taking Bellergal had a 75% reduction in hot flashes compared with 68% in the placebo group after 2 weeks of therapy, but this small difference was lost after 8 weeks. Because of the availability of safer, more efficacious therapies, Bellergal has fallen out of favor.

Nonpharmacologic Measures. Although there is a reasonable abundance of research on pharmacologic therapies for hot flashes, research on nonpharmacologic strategies is lacking. Some studies, nonetheless, have shown a reduction in hot flashes with the use of paced respirations and progressive muscle relaxation (91,92). After 1- to 12-week training periods, hot flashes decreased 30–100% in patients with mild to moderate symptoms. Other possible interventions include exposure to cold (19), which, understandably, appears to cause cessation of hot flash episodes. Other measures that have not been tested include wearing loose-fitting clothing, avoiding alcohol and spicy foods, sipping cold drinks, and lowering the room temperature. All these nonpharmacologic strategies theoretically would work by lowering core body temperature. Exercise has also been advocated as a means of decreasing hot flashes (93). Much more work is needed in this area to properly inform patients about the use of nonpharmacologic strategies to reduce hot flashes.

CONCLUSION

Based on the best available evidence and the risks, benefits, and side effects associated with each treatment modality, the following recommendations can be made. After doing a thorough history and physical examination and assessing the severity of the hot flashes, including their impact on occupation, recreation, and sleep, a treatment regimen can be instituted. If a patient has mild symptoms that do not interfere with daily activities, a trial of 800 IU/day of vitamin E is reasonable. This readily available, inexpensive, nontoxic therapy may allow a patient to get the well-described placebo effect plus a little more. It should be kept in mind though that it may take several weeks for this effect to take place.

When a patient has more severe symptoms that interfere with daily activities, it is reasonable to start one of the newer antidepressants. Venlafaxine has the best studied doses and it can be started at a low dose of 37.5 mg/day and slowly titrated up to a dose of 75 mg/day while keeping side effects in mind. Alternatively, paroxetine can be utilized at a dose of 12.5 mg/day.

There is now appreciable data to support the use of gabapentin as an agent to treat hot flashes, either as an initial treatment or as something to try if antidepressants don't work. In using this agent, it is reasonable to start with 300 mg at bedtime for 3 days and then titrate up to 300 mg three times a day. There is some suggestion that even higher doses may more effectively decrease hot flashes.

If all the nonhormonal options noted above fail, the physician must weigh with the patient the risks and benefits of using a progestational agent. If the decision to use a progestin is made, it is reasonable to use intramuscular DMPA or oral megestrol acetate.

Agents such as clonidine, methyldopa, and Bellergal, which were once used in the treatment of hot flashes, have limited utility given their limited efficacy and unfavorable side effect profiles. There are many more studies being done, including the completion of trials of gabapentin as well as other newer antidepressants, which will add much more to the therapeutic arsenal. Thus many more choices should become available within the next few years.

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