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Symptoms and Treatment in Cancer Therapy-Induced Early Menopause

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Key Words. Hot flashes • Pathophysiology • Epidemiology • Complementary therapies • Clonidine Gabapentin • Selective serotonin reuptake inhibitors • Breast neoplasm

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the therapeutic options when hot flashes disrupt the quality of life or quality of sleep in breast cancer patients.
2. Select appropriate nonpharmacological or pharmacological options in the management of hot flashes in breast cancer patients.
3. Discuss the relative efficacy and safety of interventions in the treatment of hot flashes in breast cancer patients.

Abstract

Young women with breast cancer often experience early menopause as a result of the therapy for their malignant disease. The sudden occurrence of menopause resulting from chemotherapy, oophorectomy, radiation, or gonadal dysgenesis frequently results in hot flashes that begin at a younger age and may occur at a greater frequency and intensity than hot flashes associated with natural menopause.

Hormone therapy relieves symptoms effectively in 80%–90% of women who initiate treatment. This therapy, however, is generally contraindicated in estrogen-dependent cancers, such as breast cancer, because of the potentially increased risk for recurrence. Many agents have been investigated as potential means for alleviating hot flashes in survivors of breast cancer, such as progestagens, clonidine, gabapentin, and antidepressants. Several complementary and alternative medicines frequently used by patients have also been studied. These include black cohosh, phytoestrogens, homeopathy, vitamin E, acupuncture, and behavior strategies.

To support the use of one of more of these nonpharmacological or pharmacological options in the treatment of hot flashes in breast cancer patients, more evidence from well-controlled clinical trials is needed. In particular, soundly based scientific research with complementary and alternative medicine therapies is lacking. Pharmacological treatments appear to be more beneficial than nonpharmacological treatments.

This article reviews the current literature to assess the epidemiology and diagnosis of hot flashes and the nonpharmacological and pharmacological options for the treatment of hot flashes, in breast cancer patients in particular. When specific treatment options have not been evaluated in breast cancer patients specifically, published data on the management of hot flashes with this modality in healthy postmenopausal women are described. The Oncologist 2006;11:641–654
INTRODUCTION
Breast cancer is the most common life-threatening cancer diagnosis in women. Although primary local control surgery is still the mainstay of treatment for early breast cancer, it often may not cure patients, as it does not eradicate micrometastases that are present in a subset of patients. In order to decrease the risk for local and distant relapse, the addition of adjuvant local radiation therapy and/or systemic hormonal and/or chemotherapy is necessary to increase the cure rate.

However, the treatment of early or advanced breast cancer, with the aim to improve survival or palliation, may induce potentially severe short- and long-term toxicities. One disabling side effect of cancer treatment is premature menopause. The risk for the development of early menopause with polyagent adjuvant chemotherapy has been reported to be in the range of 53%–89% [1]. The frequency of chemotherapy-related amenorrhea varies with age, the cytotoxic agents used, and the cumulative dose [2, 3].

In premenopausal women with endocrine-responsive tumors, the additional benefit of endocrine therapies after locoregional treatment and chemotherapy has been shown in the adjuvant setting of breast cancer. Endocrine therapy results in a significant improvement in both recurrence-free survival and overall survival in patients younger than 50 years of age [4, 5]. Endocrine therapies include suppression of ovarian function by irradiation, surgery, or luteinizing hormone-releasing hormone (LHRH) or gonadotropin hormone-releasing hormone (GnRH) agonists. It is an option to combine ovarian ablation with other types of endocrine therapies, including aromatase inhibitors and selective estrogen receptor downregulators [6].

However, these therapies for breast cancer in premenopausal women increase the risk for early menopause, with the resulting loss of childbearing capacity and symptoms such as hot flashes, genitourinary atrophy, and psychological distress [2, 7, 8]. Hot flashes are one of the symptoms that occur with considerable frequency in premenopausal breast cancer patients. Hot flashes can interfere with quality of life and the quality or duration of sleep [9, 10].

There is a wide range of possible disruptions in day-to-day living because of the impact of hot flashes. When hot flashes disrupt quality of life or the quality of sleep in breast cancer patients, these patients should be informed about therapeutic options, and interventions should be considered in the prevention and management of hot flashes.

PATHOPHYSIOLOGY AND EPIDEMIOLOGY OF HOT FLUSHES

Definitions
A hot flash is a subjective sensation of heat that is associated with objective signs of cutaneous vasodilation and a subsequent drop in core temperature. Sweating, flushing, palpitations, anxiety, irritability, and even panic may accompany the hot flash, and women may also report night sweats. The frequency, duration, and intensity of hot flashes vary. The duration of hot flashes can last a few seconds to several minutes and vary from mild to intolerable. Some women will have hot flashes several times a month, whereas other women complain that symptoms occur every hour [11, 12].

“Hot flashes,” “vasomotor symptoms,” “hot flushes,” “night sweats,” and “climacteric symptoms” are all terms used to describe the same phenomenon. The term “hot flash” is used in this article.

Pathophysiology
The exact pathophysiological mechanisms of the occurrence of hot flashes are unknown. The theory of the cause of hot flashes is that there is a dysfunction in the central thermoregulatory set point in the hypothalamus as a result of decreased estrogen or decreased gonadal steroid levels. Studies suggest that estrogen withdrawal leads to an imbalance in plasma levels of several neurotransmitters. Norepinephrine is the primary neurotransmitter responsible for lowering the thermoregulatory set point. Plasma levels of norepinephrine metabolites are increased. The effect of higher norepinephrine and serotonin levels is to lower the thermoregulatory set point, which allows vasodilation and hot flash sensation.

The neurotransmitter serotonin might also have an important role in thermoregulation. Decreased blood serotonin levels and upregulation of serotonin receptors in the hypothalamus are associated with estrogen withdrawal. The thermoregulatory set point might be dependent on the balance of these plasma levels, and a change in the balance may trigger the hot flash sensation [11, 13, 14].

Prevalence of Hot Flashes
Hot flashes affect two thirds of postmenopausal women, and 10%–20% of all postmenopausal women find them nearly intolerable [15]. Hot flashes are the most usual complaint of perimenopausal and postmenopausal women. Various entities—such as spicy foods, alcohol and drugs, systemic disease, neurological disorders, androgen deprivation, and carcinoid tumors—could lead to flashing reactions [16, 17]. Hot flashes are very common in breast cancer.
survivors after treatment as well as because of some adjuvant treatment, such as tamoxifen. They are significantly more frequent and more severe in breast cancer patients than in women without a diagnosis of breast cancer [7, 18].

The use of tamoxifen, aromatase inhibitors, or suppression of ovarian function in the adjuvant treatment of breast cancer increases the frequency and severity of hot flashes [19–21]. Hot flashes were the most common adverse event in the anastrozole (18%) and in the tamoxifen (26%) group in the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial and in the Arimidex®, Tamoxifen, Alone or in Combination (ATAC) trial [22, 23].

**TREATMENT OF HOT FLUSHES**

There is a diversity of treatments developed throughout the years, differing in safety, efficacy, and acceptability for alleviating hot flashes among women with a history of breast cancer. These include hormonal and nonhormonal and pharmacological and nonpharmacological treatments. Furthermore, women have also used simple strategies, such as wearing light clothes, dressing in layers, lowering the room temperature, using air conditioners, drinking cold beverages, and avoiding alcohol, spicy foods, hot drinks, and hot foods, to ameliorate their symptoms before starting complementary or pharmacological interventions [24, 25].

**Placebo Effect**

When reviewing published data on the effect of new therapies in the management of hot flashes, the placebo effect must be seriously considered. Several placebo-controlled trials showed a substantial placebo effect in intervention studies for hot flashes [26–31]. Four weeks of placebo treatment can reduce hot flash frequency and hot flash scores by about 25%. The placebo effect on hot flash scores is, in this regard, a consistent effect [32]. Therefore, when interpreting clinical data, the placebo effect must always be taken into consideration.

**Complementary Interventions**

Many alternative products have been used for alleviating menopausal symptoms in women with a history of breast cancer. The effect of black cohosh, phytoestrogens, homeopathy, vitamin E, acupuncture, and behavior strategies in the treatment of hot flashes are described in the next section. Clinical trials of complementary therapies are detailed in Table 1.

**Table 1. Summary of clinical trials of complementary therapies in the treatment of hot flashes**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Design</th>
<th>Sample and duration</th>
<th>Results</th>
<th>Side effects</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black cohosh Preparation of a standardized extract of Cimicifuga racemosa</td>
<td>Pilot</td>
<td>21 women with and without a history of breast cancer; 4 wks</td>
<td>Reduction in mean daily hot flash frequency was 50%, weekly hot flash scores reduced by 56%</td>
<td>Joint pain</td>
<td>Pockaj et al. [44]</td>
</tr>
<tr>
<td>Tamoxifen with or without Menofem®/Klimadynon® 20 mg daily (CR BNO 1055)</td>
<td>R, O</td>
<td>136 premenopausal breast cancer patients with tamoxifen-induced hot flashes; 12 mos</td>
<td>Reduction in the severity and frequency of hot flashes (hot flashes were reported by 24.4% of patients in the intervention group and 73.9% in the usual care group)</td>
<td>Adverse events not related to treatment</td>
<td>Hernandez Munoz and Pluchino [43]</td>
</tr>
<tr>
<td>Black cohosh tablets</td>
<td>R, DB, PC</td>
<td>69 breast cancer patients; 60 days</td>
<td>No treatment effect on hot flashes</td>
<td>Adverse events not related to treatment</td>
<td>Jacobsen et al. [45]</td>
</tr>
<tr>
<td>Phytoestrogens Soy capsules; 70 mg isoflavones daily</td>
<td>R, DB, PC</td>
<td>72 breast cancer patients; 12 wks</td>
<td>No statistical difference in menopausal symptom scores</td>
<td>No significant difference in toxicity between treatment arms</td>
<td>MacGregor et al. [55]</td>
</tr>
<tr>
<td>Promensil® (82 mg isoflavones) and Rimostil® (57 mg isoflavones) daily</td>
<td>R, DB, PC</td>
<td>252 postmenopausal women; 12 wks</td>
<td>Neither supplement had a clinically important effect on hot flashes</td>
<td>Headache</td>
<td>Tice et al. [53]</td>
</tr>
<tr>
<td>Soy tablets; 36 mg isoflavones daily</td>
<td>R, DB, PC</td>
<td>62 postmenopausal women; 24 wks</td>
<td>Soy tablets not more effective than placebo</td>
<td>No effect on endometrial thickness</td>
<td>Penotti et al. [54]</td>
</tr>
<tr>
<td>Soy beverage; 90 mg isoflavones daily</td>
<td>R, DB, PC</td>
<td>123 breast cancer patients; 12 wks</td>
<td>No treatment effect on hot flashes</td>
<td>Gastrointestinal</td>
<td>Van Patten et al. [52]</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Design</th>
<th>Sample and duration</th>
<th>Results</th>
<th>Side effects</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy tablets; 150 mg isoflavones daily</td>
<td>R, DB, PC, C</td>
<td>177 breast cancer patients; 9 wks</td>
<td>No treatment effect on hot flashes</td>
<td>No toxicity was observed</td>
<td>Quella et al. [51]</td>
</tr>
<tr>
<td>Soy tablets; 50 mg isoflavones daily</td>
<td>R, DB, PC</td>
<td>177 postmenopausal women; 12 wks</td>
<td>Hot flashes reduced by 27% vs. 19% with placebo</td>
<td>Gastrointestinal</td>
<td>Upmalis et al. [50]</td>
</tr>
<tr>
<td>60 g soy protein, 76 mg isoflavones</td>
<td>R, DB, PC</td>
<td>104 postmenopausal women; 12 wks</td>
<td>Hot flashes reduced by 45% (p &lt; .001)</td>
<td>Constipation, nausea, vomiting</td>
<td>Albertazzi et al. [49]</td>
</tr>
<tr>
<td>Homeopathy Individualized homeopathic single remedy, a homeopathic combination medicine or placebo</td>
<td>R, DB, PC</td>
<td>83 breast cancer patients; 1 yr</td>
<td>No treatment effect of hot flashes</td>
<td>Adverse events not reported</td>
<td>Jacobs et al. [58]</td>
</tr>
<tr>
<td>Homeopathic approach (consultation and prescription of an individualized homeopathic remedy)</td>
<td>P</td>
<td>45 breast cancer patients</td>
<td>Significant improvement in symptom scores of estrogen withdrawal</td>
<td>Adverse events not reported</td>
<td>Thompson and Reilly [59]</td>
</tr>
<tr>
<td>Vitamin E, 800 IU daily</td>
<td>R, DB, PC, C</td>
<td>120 breast cancer patients; 4 wks</td>
<td>Hot flashes reduced by 32% vs. 29% with placebo</td>
<td>No statistically significant difference in toxicity between the treatment arms</td>
<td>Barton et al. [60]</td>
</tr>
<tr>
<td>Acupuncture Electroacupuncture, superficial needle insertion and oral estradiol</td>
<td>R</td>
<td>45 postmenopausal women; 12 weeks (6-mo follow-up)</td>
<td>Electroacupuncture reduced hot flashes by 50%</td>
<td>No serious side effects</td>
<td>Wyon et al. [62]</td>
</tr>
<tr>
<td>Electroacupuncture, applied relaxation</td>
<td>R</td>
<td>38 postmenopausal breast cancer patients; 12 wks</td>
<td>Electroacupuncture reduced hot flashes</td>
<td>No serious side effects</td>
<td>Nedstrand et al. [63]</td>
</tr>
<tr>
<td>Behavioral therapies Structured education and exercise program or refrain from exercising during study period</td>
<td>R</td>
<td>35 women, 40–60 yrs old; 12 wks</td>
<td>Structured education and exercise program reduced hot flashes</td>
<td>Adverse events not reported</td>
<td>Ueda [67]</td>
</tr>
<tr>
<td>Exercise three times weekly or oral estradiol</td>
<td>R</td>
<td>75 postmenopausal women (10 women fulfilled 12 wks of exercise); 12 wks treatment, 24 wks follow-up</td>
<td>Hot flashes reduced by 28% after 12 wks and by 39% after 36 wks</td>
<td>Adverse events not reported</td>
<td>Lindh-Astrand et al. [68]</td>
</tr>
<tr>
<td>Comprehensive menopausal assessment intervention program</td>
<td>R</td>
<td>76 postmenopausal breast cancer patients; 4 mos</td>
<td>Reduction in menopausal symptoms and improvement in sexual functioning</td>
<td>Adverse events not reported</td>
<td>Ganz et al. [65]</td>
</tr>
<tr>
<td>Relaxation response training, reading, or control group</td>
<td>R</td>
<td>33 postmenopausal women; 10 wks</td>
<td>Hot flashes reduced in the relaxation response group</td>
<td>Adverse events not reported</td>
<td>Irvin et al. [69]</td>
</tr>
<tr>
<td>Eight sessions of paced respiration, muscle relaxation or alpha-wave electroencephalographic biofeedback (placebo control)</td>
<td>R</td>
<td>33 women</td>
<td>Subjects undergoing paced respiration had significant reductions in hot flash frequency</td>
<td>Adverse events not reported</td>
<td>Freedman and Woodward [66]</td>
</tr>
</tbody>
</table>

Abbreviations: C, crossover; DB, double blind; O, open-label; P, prospective observational; PC, placebo controlled; R, randomized.
**Black Cohosh**

Black cohosh (*Actaea racemosa*, synonym *Cimicifuga racemosa*) is a plant native to eastern parts of North America. In Europe, especially in Germany, black cohosh has been used in the treatment of menopausal symptoms. The mechanism of action is uncertain. There are conflicting data on the estrogenic effect of black cohosh [33–40]. The most recent data suggest that black cohosh has no estrogenic effects and is safe in the treatment of menopausal hot flashes [35, 40, 41].

There are differences in the results of published clinical data on the efficacy of black cohosh in the treatment of hot flashes. In an uncontrolled trial, 80% of women reported a reduction in hot flashes after 4 weeks of treatment [42]. In an open-label, randomized study of 12-months’ duration, a satisfactory reduction in the frequency and severity of hot flashes in the intervention group was observed [43]. A pilot study revealed that black cohosh reduced hot flashes significantly more than placebo [44]. In contrast, in a randomized, double-blind, placebo-controlled trial of 60 days’ duration in 69 women with a history of breast cancer, black cohosh was not significantly more effective than placebo [45]. A systematic review concluded that there is no evidence for the clinical efficacy of black cohosh in the treatment of hot flashes [46].

Drug-related toxicities such as nausea, vomiting, headache, and dizziness have been reported. One case suggests a relationship between black cohosh and hepatotoxicity, but assessment of a direct correlation between the two was not possible [47]. The published data on the effect of black cohosh in the treatment of hot flashes are conflicting. That black cohosh has beneficial effects on the relief of hot flashes is not supported by evidence from methodologically sound clinical trials.

**Phytoestrogens**

Phytoestrogens are plant-derived, naturally occurring estrogens and have the ability to bind and activate human estrogen receptor alpha (ER-α) and human estrogen receptor beta (ER-β). Phytoestrogens have both estrogenic and antiestrogenic effects [48]. Soy products and red clover are rich sources of phytoestrogens. Phytoestrogens include isoflavones, lignans, and coumestans.

The effect of phytoestrogens on hot flashes has been studied in several clinical studies. Two studies showed the efficacy of soy protein in the treatment of hot flashes. In a double-blind, randomized trial of 12 weeks’ duration, 40 g of protein and 76 mg of phytoestrogens per day demonstrated a significant reduction in the incidence of hot flashes compared with placebo [49]. Another double-blind, controlled trial, comparing a soy isoflavone extract of 50 mg genistin and daidzin with placebo, also showed a statistically significant reduction in hot flashes [50]. In contrast, a double-blind, placebo-controlled trial that evaluated soy phytoestrogens for the treatment of hot flashes in 177 breast cancer survivors failed to show a beneficial effect in the incidence and severity of hot flashes. Four weeks of treatment did not show a difference between the group taking soy tablets containing 50 mg of soy isoflavones in each tablet and the placebo group [51]. In a second double-blind, placebo-controlled trial of 12 weeks of treatment in postmenopausal women who were previously treated for early-stage breast cancer, a soy beverage did not alleviate hot flashes more than placebo [52]. Results of other studies also suggest that soy is not better in the reduction of hot flashes than placebo [53–55].

Several clinical studies assessed the direct relationship between an individual’s dietary intake of soy products and the risk for the development of breast cancer. Few prospective data are available on the effects of phytoestrogens on breast cancer risk. Results do not show protective effects, with the exception of the consumption of phytoestrogens at young ages or the intake of high amounts [56]. The effect of increased phytoestrogens in breast tissue and on the endometrium is obscure. A recent trial of red clover-derived isoflavones did not show any increased mammographic breast density in 205 women, and no effects on estradiol, gonadotropins, lymphocyte tyrosine kinase activity, or menopausal symptoms were observed [57]. No randomized, controlled trials have addressed the long-term safety of phytoestrogens in patients after a diagnosis of breast cancer.

The results of the trials on the effect of phytoestrogens on hot flashes are contradictory. Comparison of all clinical studies is difficult because of the differences in products and dosages applied. It is not clear what the long-term safety of phytoestrogens is in women after a diagnosis of breast cancer. There is no evidence to support using high doses of soy products for alleviating hot flashes in breast cancer survivors.

**Homeopathy**

There are fewer published clinical trials to evaluate the effectiveness of homeopathy in the treatment of hot flashes. A randomized, placebo-controlled study with three arms—an individualized homeopathic single remedy (a homeopathic practitioner prescribed an individualized homeopathic medication), a homeopathic combination of three medicines (amyl nitrate 3x [1:1,000 dilution], *Sanguinaria canadensis* 3x [1:1,000 dilution], and *Lachesis* 12x [1:1,000,000,000,000 dilution]), and a placebo—revealed that there was no significant difference in the severity and frequency of hot flashes among the treatment arms [58]. Results from a prospective observational study suggested...
a significant improvement in symptom scores of estrogen withdrawal after a homeopathic approach in women with breast cancer [59].

Evidently, well-controlled and good quality clinical trials assessing the efficacy and safety of homeopathic treatments are needed in the treatment of hot flashes in women after a diagnosis of breast cancer before homeopathic treatments can be advised. For now, homeopathic therapies appear not to be effective for alleviating hot flashes.

**Vitamin E**

A double-blind, randomized, placebo-controlled, crossover clinical trial reported a marginal statistical effect of vitamin E (800 IU/day) in the treatment of hot flashes [60]. Four weeks of daily vitamin E was compared with placebo in 120 breast cancer patients. Vitamin E was associated with one less hot flash per person per day and did not induce toxicity. A crossover analysis showed that vitamin E was associated with a minimal decrease in hot flashes. At the end of the study, patients did not prefer vitamin E use over placebo.

The investigators of that study suggested that vitamin E at a dose of 800 IU daily can be used because it is inexpensive and nontoxic and it might result in a slightly better relief of hot flashes than placebo.

In other clinical trials, no statistically significant difference between treatment groups and placebo groups was found for adverse events [61]. Evidence is thus limited, and before supporting vitamin E in the management of hot flashes, more clinical data are warranted. Vitamin E is not registered for this indication and should be used with caution.

**Acupuncture**

A randomized study of 45 postmenopausal women with vasomotor symptoms suggested that electroacupuncture decreased the number of hot flashes by 50% in 11 of 15 women studied [62]. Other studies also reported a reduction in hot flashes with acupuncture [63].

A review article summarized the adverse reactions after acupuncture, such as hepatitis, subacute bacterial endocarditis, and dermatitis [64]. When acupuncture is used, sterile needles are obviously necessary for the safety of patients. Especially in women who have had axillary surgery for lymph node dissection, acupuncture must be used with care to the operated arm because of the risk for the development of lymphedema.

**Behavioral Therapies**

A comprehensive menopausal assessment (CMA) intervention program was tested in 76 breast cancer survivors with menopausal symptoms [65]. In this structured intervention program, the target symptoms were hot flashes, vaginal dryness, and stress urinary incontinence. The focus was on symptom assessment, education, counseling, and specific pharmacological and behavioral interventions. After randomization, a group of women received the usual care and another group received the interventions. Women in the usual care group were not precluded from these interventions but were not encouraged to do so. Women in the intervention group received an individualized plan of care including pharmacological and/or behavioral interventions. The symptom assessments resulted in a reduction in menopausal symptoms and an improvement in sexual functioning in the intervention group. The comprehensive menopausal assessment included so many interventions that it is not clear which intervention was essential to relieve women from menopausal symptoms. Thus, to date, it is unknown which specific component reduced the hot flashes.

A behavioral relaxation procedure significantly reduced the frequency of hot flashes [66]. The active component of this relaxation treatment was training in slow, deep breathing. Results of another study suggested that an education and exercise program alleviated climacteric symptoms [67]. In a prospective study of 75 postmenopausal women with vasomotor symptoms, women were randomized to a physical exercise program or oral estradiol therapy. Ten women fulfilled the 12-week exercise period. In five of these women, hot flashes decreased to 28% of baseline [68].

Results of a 10-week randomized trial including 33 postmenopausal women demonstrated that relaxation response training (including mental focusing, diaphragmatic breathing, and breath awareness) could significantly reduce hot flash intensity compared with that seen in a control group [69].

Behavioral interventions can be effective in the treatment of hot flashes. The drawback of behavioral trials is the impossibility of using a placebo. A substantial placebo effect must be accounted for when interpreting published behavioral therapy data in the treatment of hot flashes.

**Pharmacological Interventions**

Clinical trials of pharmacological therapies are outlined in Table 2.

**Progestagens**

Progestagens have been studied in the treatment of hot flashes. Megestrol acetate, a progestagen used in the treatment of breast cancer, decreased hot flashes by 80%, compared with a 20% decrease in hot flashes in the placebo group. The patients were women with a history of breast cancer and men with prostate cancer receiving androgen-
Table 2. Summary of clinical trials of pharmacological interventions in the treatment of hot flashes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Design</th>
<th>Sample and duration</th>
<th>Results</th>
<th>Side effects</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestagens</td>
<td>R</td>
<td>71 postmenopausal breast cancer patients; 6 wks</td>
<td>Hot flashes reduced by 86% in the whole group of patients</td>
<td>Skin rashes, fluid retention, dizziness, vaginal discharge, mouth dryness</td>
<td>Bertelli et al. [70]</td>
</tr>
<tr>
<td>Depot medroxyprogesterone acetate, 500 mg on days 1, 14, and 28, or oral megestrol acetate, 40 mg/d</td>
<td>R, DB, PC</td>
<td>102 postmenopausal women; 48 wks</td>
<td>Hot flashes reduced by 83%, and by 15% in the placebo group</td>
<td>Vaginal bleeding</td>
<td>Leonetti et al. [75]</td>
</tr>
<tr>
<td>Megestrol acetate, 20 mg twice daily</td>
<td>R, DB, PC</td>
<td>97 breast cancer patients and men with prostate cancer; 8 wks</td>
<td>Hot flashes reduced by 85% in the megestrol acetate group vs. 21% with placebo</td>
<td>Withdrawal menstrual bleeding</td>
<td>Loprinzi et al. [27]</td>
</tr>
<tr>
<td>Depot of medroxyprogesterone acetate, 50, 100, and 150 mg</td>
<td>DB, PC</td>
<td>48 peri- and postmenopausal women; 12 wks</td>
<td>Hot flashes reduced by 25%–45% in the medroxyprogesterone acetate group</td>
<td>Withdrawal menstrual bleeding</td>
<td>Morrison et al. [73]</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate, 20 mg/d</td>
<td>R, DB, PC, C</td>
<td>32 postmenopausal women; 12 wks</td>
<td>Frequency of hot flashes reduced by 73.9% in the medroxyprogesterone acetate group</td>
<td>Vaginal bleeding</td>
<td>Schiff et al. [72]</td>
</tr>
<tr>
<td>Gabapentin, 300 mg/d or 900 mg/d</td>
<td>R, DB, PC</td>
<td>420 breast cancer patients; 8 wks</td>
<td>Frequency of hot flashes decreased by 37% (vs. 20% for placebo) after 4 wks of treatment and by 38% (vs. 24% for placebo) after 8 wks of treatment</td>
<td>Difficulty sleeping</td>
<td>Pandya et al. [84]</td>
</tr>
<tr>
<td>Clonidine transdermal (equivalent to an oral dose of 0.1 mg/d)</td>
<td>R, DB, PC, C</td>
<td>116 breast cancer patients with tamoxifen-induced hot flashes; 8 wks</td>
<td>Frequency of hot flashes decreased by 20% from baseline ($p &lt; .0001$) and severity of hot flashes decreased by 10% from baseline ($p = .02$)</td>
<td>Mouth dryness, constipation, itchiness under the patch, drowsiness</td>
<td>Goldberg et al. [26]</td>
</tr>
<tr>
<td>Clonidine transdermal (equivalent to an oral dose of 0.1 mg/d)</td>
<td>R, DB, PC</td>
<td>30 postmenopausal women; 8 wks</td>
<td>80% reported fewer hot flashes (vs. 36% with placebo), 73% reported a decrease in severity (vs. 29% with placebo), 67% reported a decrease in duration (vs. 21% with placebo) of hot flashes</td>
<td>Transient local skin reactions (erythema and/or itching)</td>
<td>Nagamani et al. [79]</td>
</tr>
<tr>
<td>Clonidine oral, 0.1 mg/d, 0.2 mg/d, or 0.4 mg/d</td>
<td>PC</td>
<td>10 postmenopausal women; 2 wks</td>
<td>Clonidine significantly reduced the frequency of hot flashes ($p &lt; .005$)</td>
<td>Dizziness, mouth dryness</td>
<td>Laufer et al. [82]</td>
</tr>
<tr>
<td>Clonidine, 25 to 75 μg twice per day</td>
<td>DB, PC, C</td>
<td>100 postmenopausal women; 4 wks</td>
<td>Reduction in the frequency of hot flashes (clonidine before placebo, $p \leq .05$; clonidine after placebo, $p \leq .001$)</td>
<td>Mouth dryness</td>
<td>Cladyn et al. [81]</td>
</tr>
<tr>
<td>Gabapentin, 300 mg/d</td>
<td>R, DB, PC</td>
<td>420 breast cancer patients; 8 wks</td>
<td>Severity of hot flash score decreased by 31% in the 300 mg gabapentin group and 46% in the 900 mg gabapentin group (vs. 15% with placebo)</td>
<td>Not reported</td>
<td>Pandya et al. [31]</td>
</tr>
<tr>
<td>Gabapentin, 900 mg/d</td>
<td>Pilot study</td>
<td>22 postmenopausal breast cancer patients with tamoxifen-induced hot flashes; 4 wks</td>
<td>Mean decrease in hot flash duration of 73.6% ($p = .027$), frequency of 44.2% ($p &lt; .001$), severity of 52.6% ($p &lt; .001$)</td>
<td>Nausea, rash, excessive sleepiness</td>
<td>Pandya et al. [84]</td>
</tr>
<tr>
<td>Gabapentin, 900 mg/d</td>
<td>R, DB, PC</td>
<td>59 postmenopausal women; 12 wks</td>
<td>Reduction of 45% in hot flash frequency and 54% reduction in hot flash composite score (frequency and severity)</td>
<td>Somnolence, dizziness, rash (with or without peripheral edema)</td>
<td>Guttuso et al. [30]</td>
</tr>
<tr>
<td>Gabapentin, 300–900 mg/d</td>
<td>Pilot</td>
<td>20 breast cancer patients and men with prostate cancer; 4 wks</td>
<td>Hot flash score reduction of 70%</td>
<td>Light-headedness, dizziness</td>
<td>Loprinzi et al. [83]</td>
</tr>
</tbody>
</table>

(continued)
Ablation therapy. The medication was equally efficacious in men and women. One of the main side effects was menstrual withdrawal bleeding 1–2 weeks after discontinuing the megestrol acetate [27]. In a randomized trial in postmenopausal breast cancer patients, one group of patients received an i.m. depot of medroxyprogesterone acetate (500 mg on days 1, 14, and 28) and another group of patients received oral megestrol acetate at a dose of 40 mg/d. Hot flashes were reduced by 86% in the entire group of patients without a significant difference between groups. The treatment was generally well tolerated. More patients in the megestrol group experienced adverse events, which, in six women, led to early discontinuation of the treatment [70]. Reasons for interruption of treatment were skin rashes, dyspnea, gastric pain, and increased arterial blood pressure. More clinical studies showed that depomedroxyprogesterone acetate and medroxyprogesterone acetate are effective in the treatment of hot flashes [71–74].

Transdermal progesterone cream has also been studied, and after 4 weeks of treatment, it was associated with an 83% reduction in hot flashes in progesterone-treated patients and a 19% reduction in placebo-treated patients [75].

High-dose megestrol acetate is an effective treatment in the management of breast cancer, but the theoretical concern is that low doses of progestagens may stimulate tumor growth [76, 77]. There are conflicting reports about the safety of progestagens in the treatment of hot flashes in breast cancer patients.

### Neuroendocrine Agents

**Clonidine hydrochloride.** Clonidine hydrochloride is a centrally active α-agonist that reduces vascular reactivity and is primarily indicated in the treatment of hypertension. Several studies suggest that oral or transdermal clonidine is effective in the treatment of hot flashes in postmenopausal women. Clonidine reduces brain norepinephrine release, raises the sweating threshold, and ameliorates hot flashes [78]. Transdermal clonidine was studied in a randomized, double-blind study in postmenopausal women with hot flashes. The reduction in hot flashes was significant in patients who received transdermal clonidine. Eighty percent of patients reported fewer hot flashes, 73% reported a decrease in severity, and 67% reported a decrease in duration [79].

### Table 2. continued

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Design</th>
<th>Sample and duration</th>
<th>Results</th>
<th>Side effects</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine, 75 mg/d</td>
<td>R, PC</td>
<td>80 postmenopausal women; 12 wks</td>
<td>Reduction in hot flashes by 51% (vs. 15% with placebo)</td>
<td>Mouth dryness, sleeplessness, appetite</td>
<td>Evans et al. [87]</td>
</tr>
<tr>
<td>Venlafaxine, 37.5 mg/d, 75 mg/d, or 150 mg/d</td>
<td>R, DB, PC</td>
<td>192 breast cancer patients; 4 wks</td>
<td>Reduction in hot flashes of 37% in the 37.5-mg venlafaxine group and of 61% in the 75-mg and 150-mg venlafaxine group (vs. 27% with placebo)</td>
<td>Mouth dryness, decreased appetite, nausea, constipation</td>
<td>Loprinzi et al. [29]</td>
</tr>
<tr>
<td>Venlafaxine, 37.5 mg/d, 75 mg/d, or 150 mg/d</td>
<td>O</td>
<td>Breast cancer patients; 8 wks</td>
<td>37.5-mg venlafaxine reduced hot flashes by 26% and 75-mg and 150-mg venlafaxine reduced hot flashes by 60%</td>
<td>Appetite loss, mouth dryness, dissipating nausea</td>
<td>Barton et al. [86] (follow-up of the Loprinzi et al. study [29])</td>
</tr>
<tr>
<td>Venlafaxine, 12.5 mg oral twice daily</td>
<td>Pilot study</td>
<td>28 breast cancer patients and men with prostate cancer; 4 wks</td>
<td>Reduction in hot flashes of more than 55% from baseline</td>
<td>Fatigue, sweating, trouble sleeping</td>
<td>Loprinzi et al. [28]</td>
</tr>
<tr>
<td>Fluoxetine, 20 mg/d</td>
<td>R, DB, PC</td>
<td>81 breast cancer patients; 4 wks</td>
<td>Reduction in hot flashes of 50% vs. 36% in the placebo group</td>
<td>Fluoxetine was well tolerated</td>
<td>Loprinzi et al. [89]</td>
</tr>
<tr>
<td>Paroxetine, 10 mg/d, 20 mg/d</td>
<td>R, DB, PC, C</td>
<td>151 women with and without a history of breast cancer; 8 wks</td>
<td>10-mg paroxetine reduced hot flash frequency and composite score by 40.6% and 45.6% (vs. 13.7% with placebo); 20-mg paroxetine reduced hot flash frequency and composite score by 51.7% and 56.1% (vs. 26.6% and 28.8% with placebo)</td>
<td>Drowsiness and nausea in the 20-mg paroxetine group</td>
<td>Stearns et al. [91]</td>
</tr>
<tr>
<td>Paroxetine, 12.5 mg/d or 25 mg/d</td>
<td>R, DB, PC</td>
<td>165 postmenopausal women; 6 wks</td>
<td>12.5-mg paroxetine reduced hot flashes by 62% and 25-mg paroxetine reduced hot flashes by 65% (vs. 38% with placebo)</td>
<td>Headache, nausea, insomnia</td>
<td>Stearns et al. [90]</td>
</tr>
</tbody>
</table>

Abbreviations: C, crossover; DB, double blind; O, open-label; P, prospective observational; PC, placebo controlled; R, randomized.
Another randomized, double-blind trial showed that clonidine reduced the hot flash frequency and severity, but this effect was clinically modest. Drug-related toxicities were mouth dryness, constipation, itchiness under the patch, and drowsiness [26].

A randomized, double-blind, placebo-controlled trial reported that oral clonidine (0.1 mg/d) given for at least 8 weeks is effective in the treatment of tamoxifen-induced hot flashes in women with a history of breast cancer. Hot flashes decreased by about 37% after 4 weeks of treatment compared with a 20% reduction with placebo, and after 8 weeks of treatment, a reduction in hot flashes of 38% in the clonidine group, versus 24% in the placebo group, was observed [80]. The patients in the clonidine group had significantly more difficulty sleeping than patients in the placebo group.

Clinical studies demonstrated that clonidine reduced the frequency of hot flashes, but the effect of clonidine on hot flash duration and severity was marginal [81, 82].

**Gabapentin.** Gabapentin is a gamma-aminobutyric acid analogue that is used in the treatment of epilepsy or neuropathic pain.

Two pilot studies suggested that gabapentin is effective in the treatment of hot flashes [83, 84]. A 12-week, randomized, placebo-controlled trial in postmenopausal women taking gabapentin at a dose of 900 mg/d showed a reduction of 45% in hot flash frequency and a 54% reduction in hot flash composite score (frequency and severity) [30]. Adverse events in the gabapentin group were somnolence, dizziness, and rash with or without peripheral edema. In some patients who took gabapentin, blood laboratory tests showed a decrease in serum albumin, total protein, total bilirubin, blood urea nitrogen, and platelets after 12 weeks of treatment, compared with baseline.

In a randomized, double-blind, placebo-controlled trial in 420 women with breast cancer, one group received a placebo, one group received gabapentin at a dose of 300 mg/d, and one group received gabapentin at a dose of 900 mg/d for 8 weeks. The percentage decreases in hot flash severity score between baseline and 8 weeks were: 31% in the 300-mg gabapentin group and 46% in the 900-mg gabapentin group. Gabapentin at a dose of 300 mg/d gave a significant reduction in hot flash frequency but not a significant reduction in the severity of hot flashes. There was a significant decrease in hot flash frequency and severity at a dose of 900 mg/d of gabapentin. A major limitation of this study is that the side effects of gabapentin have not been reported [31].

Based on these results, gabapentin can be considered effective in the management of hot flashes in postmenopausal women after a diagnosis of breast cancer. More clinical data are needed on the side effects and safety associated with the use of gabapentin in the treatment of hot flashes.

**Selective serotonin reuptake inhibitors.** Selective serotonin reuptake inhibitors (SSRIs) are antidepressants. Based on the modes of action of these antidepressants and the theory of the pathophysiology of hot flashes, SSRIs have been studied in the treatment of hot flashes. Specifically, the SSRIs venlafaxine, paroxetine, and fluoxetine were evaluated in the treatment of hot flashes.

**Venlafaxine.** Several clinical studies have been performed to evaluate the use of venlafaxine in the treatment of hot flashes. Venlafaxine affects both serotonin and norepinephrine reuptake in contrast to the SSRIs paroxetine and fluoxetine. Two pilot studies reported that hot flashes were reduced by approximately 55%–67% with venlafaxine [28, 85]. Results of a double-blind, placebo-controlled trial in 192 breast cancer patients showed a significant decrease in median hot flash scores in all venlafaxine groups compared with placebo. After 4 weeks of treatment, median hot flash scores were reduced by 27% in the placebo group, by 37% in the 37.5-mg venlafaxine extended release (XR) group, and by 61% in the 75-mg venlafaxine XR and 150-mg venlafaxine XR treated patients [29]. At the end of 4 weeks of treatment, the investigators of the study asked the participants to participate in an 8-week open-label study. Participants received 37.5–150 mg/day of venlafaxine XR. In the 37.5-mg group, hot flashes decreased by 26%. In the 75-mg and 150-mg group, hot flashes scores decreased by 60% [86].

In a 12-week placebo-controlled trial, postmenopausal women received 37.5 mg of venlafaxine XR for 1 week followed by 75 mg of venlafaxine XR for 11 weeks. After 4 weeks, the mean scores in the placebo and venlafaxine groups were the same. After 11 weeks of treatment, venlafaxine was associated with a 51% reduction in hot flashes, compared with a 15% reduction in the placebo group [87].

In all venlafaxine studies, venlafaxine was well tolerated. The most common adverse events included dry mouth, constipation, loss of appetite, nausea, and sleepiness. The 150-mg dose of venlafaxine XR was associated with more adverse events than the 37.5-mg and 75-mg doses of venlafaxine XR. The efficacies of 75 mg of venlafaxine XR and 150 mg of venlafaxine XR in the treatment of hot flashes were not different and were 60%. Based on these results, the advised dose of venlafaxine in the treatment of hot flashes is 75 mg/d [86].

Sexual dysfunction is a common adverse event of antidepressant treatment, especially when using SSRIs [88]. In
the study of Loprinzi et al. [29], the venlafaxine doses of 37.5–150 mg XR per day did not reduce libido after 4 weeks of treatment.

In conclusion, venlafaxine is effective and can be used in the treatment of hot flashes in women after a diagnosis of breast cancer. How long patients must take venlafaxine after starting this intervention and also the effectiveness of venlafaxine for durations of longer than 12 weeks are unknown. Further long-term, well-controlled clinical trials are needed to investigate the efficacy of venlafaxine in the management of hot flashes. These trials should include the side effects and, specifically, the possible interference of venlafaxine with sexual function after long-term treatment.

We are currently conducting a randomized, double-blind, placebo-controlled trial comparing venlafaxine with clonidine and placebo.

Fluoxetine. A randomized, double-blind, crossover, placebo-controlled trial in 81 breast cancer patients reported a decrease in the incidence of hot flashes by 50% using fluoxetine at a dose of 20 mg/d, versus a 36% decrease with placebo. There was no statistically significant difference in the toxicities in the two treatment arms [89]. More clinical data are needed on the efficacy of fluoxetine in the management of hot flashes.

Paroxetine. Controlled-release paroxetine was evaluated in a randomized, double-blind, placebo-controlled trial in 165 postmenopausal women with hot flashes. After 6 weeks of treatment, 12.5 mg/d of paroxetine reduced hot flashes by 62% and 25 mg/d of paroxetine reduced hot flashes by 65%, whereas there was a 38% reduction in hot flashes by placebo. The most frequently reported adverse events in the controlled-release paroxetine group were headache, nausea, and insomnia. Paroxetine was well tolerated, with more adverse events in the 25-mg than in the 12.5-mg treatment group [90].

Recently published data reported that paroxetine in doses of 10–20 mg is effective in the treatment of hot flashes in women with and without a history of breast cancer. This randomized, double-blind, crossover, placebo-controlled trial demonstrated that 10 mg of paroxetine reduced hot flash frequency and the composite score by 40.6% and 45.6%, respectively, compared with 13.7% and 13.7% reductions, respectively, with placebo. Paroxetine at a dose of 20 mg reduced hot flash frequency and the composite score by 51.7% and 56.1%, respectively, versus 26.6% and 28.8% reductions, respectively, in the placebo group. The most common adverse events were drowsiness and nausea in the 20-mg paroxetine group [91]. These trials demonstrated that paroxetine is effective in the treatment of hot flashes, but further clinical trials assessing the efficacy and safety of paroxetine in breast cancer survivors are needed.

Safety of SSRIs. The SSRIs are also commonly prescribed in the treatment of hot flashes in women who take tamoxifen. SSRIs are known to inhibit cytochrome P450 (CYP)2D6, an enzyme that is important for the metabolism of many drugs, such as tamoxifen, to its active metabolite endoxifen. Some studies reported an interaction of CYP2D6 polymorphisms and CYP2D6 inhibitors. Plasma concentrations of endoxifen were lower in patients who were treated with SSRIs than in patients who did not receive treatment with SSRIs in combination with tamoxifen [92]. The weak inhibitor of CYP2D6, venlafaxine, had very little effect on plasma endoxifen concentrations, which is in contrast to the combination of paroxetine or sertraline with tamoxifen, which resulted in substantially lower plasma endoxifen concentrations. The variations in plasma endoxifen concentrations that are associated with CYP2D6 gene polymorphisms and CYP2D6 inhibitors can affect the antitumor efficacy or adverse events of tamoxifen [93].

Further clinical trials are needed to evaluate the safety of SSRIs in combination with tamoxifen. It is advisable to inform women after a diagnosis of breast cancer of the uncertainties about the interactions of some SSRIs and tamoxifen.

Conclusions and Recommendations

Many published results of clinical trials are available in the management of hot flashes, but there are limited well-controlled trials assessing the role of pharmacologically and nonpharmacologically based treatments of hot flashes in breast cancer patients. A limitation of most trials is the duration of the treatment and follow-up of patients. The U.S. Food and Drug Administration recommended a study period of 12 weeks for trials in the treatment of hot flashes [94]. Several trials in the management of hot flashes have a shorter duration than 12 weeks.

Another limitation of studies in patients with hot flashes is the absence of a placebo group. Several trials have shown a significant placebo effect in the relief of hot flashes. A placebo group as a control group is thus necessary in these studies. Therefore, when interpreting clinical data, the placebo effect should always be taken into consideration.

Only 13 trials that we found meet the criteria of a study period of 12 weeks or longer and were placebo controlled. Six studies were performed with phytoestrogens in the management of hot flashes, but the results of those studies were contradictory. One preliminary homeopathic trial
showed no treatment effect on hot flashes. Four trials were performed with progestagens and all showed a reduction in the incidence and severity of hot flashes. One trial was performed with gabapentin and one trial was performed with venlafaxine in the management of hot flashes. Both showed a reduction in the incidence and severity of hot flashes in postmenopausal women. However, only two trials performed with phytoestrogens were evaluated in breast cancer patients. The other trials evaluated treatment options in the management of hot flashes in postmenopausal women without a history of breast cancer. This emphasizes the need for larger-scale and long-term prospective trials to test the efficacy and safety of selected pharmacological and nonpharmacological strategies in the management of hot flashes after the diagnosis of breast cancer and induction of early menopause. Several questions are still unanswered, including the time period that patients need pharmacological interventions after starting with the intervention in the management of hot flashes. The optimal time period of use can be based on the natural history of hot flashes, which mostly resolve within 2–3 years of menopause. Hence, one may consider tapering and discontinuation of SSRIs after about this length of time.

The first step to control hot flashes in breast cancer patients is advice and information about simple strategies in the management of hot flashes, such as wearing light clothes, dressing in layers, lowering the room temperature, using air conditioners, drinking cold beverages, and avoiding alcohol, hot drinks, or hot food to ameliorate symptoms. For pharmacological intervention of hot flashes, venlafaxine can be used. Venlafaxine is preferable to the other SSRIs for several reasons. Most clinical data are available for venlafaxine. The safety of the other SSRIs is unclear in combination with tamoxifen, and a possibly clinically relevant reduction in endoxifen, the active metabolite of tamoxifen, may take place. Another possible treatment option is clonidine, an antihypertensive agent. Gabapentin was reported to be effective in the treatment of hot flashes; however, more information on the toxicity profile of this agent is needed before prescribing gabapentin outside clinical trials.

Behavioral relaxation is preferable as a nonpharmacological treatment, as it was found to reduce hot flashes. Vitamin E and acupuncture can also be effective, but only a few clinical data are available, and therefore, these modalities cannot be recommended outside clinical trials. Progestagens, black cohosh, and phytoestrogens should be used with caution in the treatment of hot flashes because of the unavailability of long-term safety and efficacy data and the lack of knowledge and conflicting data on possible estrogenic effects. An algorithm for the treatment of hot flashes in breast cancer patients is proposed and outlined in Figure 1.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicate no potential conflicts of interest.

**Figure 1.** Proposed algorithm for the treatment of hot flashes in cancer therapy-induced early menopause, based on a literature review of pharmacological and nonpharmacological interventions.
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Symptoms and Treatment in Cancer Therapy-Induced Early Menopause
Annelies H. Boekhout, Jos H. Beijnen and Jan H.M. Schellens
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