Article

Hot Flash Management: Update of the Evidence for Patients With Cancer

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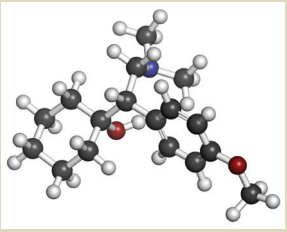

Hot flashes are a distressing symptom frequently experienced by survivors of breast cancer or prostate cancer who are receiving estrogen or androgen-deprivation therapies. The frequency and intensity of hot flashes can lead to diminished quality of life and decreased adherence with prescribed antineoplastic therapies. This evidence-based review synthesizes and updates the findings of the highest quality evidence-based studies of interventions to manage hot flashes resulting from cancer therapies in patients with breast or prostate cancer since the initial Putting Evidence Into Practice review of hot flashes in 2011. Recent studies involving a variety of pharmacologic and nonpharmacologic interventions were evaluated and, as reported in 2011, the drugs gabapentin and venlafaxine were the only therapies rated as likely to be effective. In addition, a strong placebo effect was noted in several studies that included a placebo intervention and should be considered when reviewing interventions for hot flashes.

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Hot flashes are often a lasting and distressing side effect of antineoplastic treatment, particularly for women with breast cancer and men with prostate cancer. Hot flashes have been reported in 65%–80% of breast cancer survivors (Kontos, Agbaje, Rymer, & Fentiman, 2010; Mann et al., 2012) and as many as 80% of men with prostate cancer treated with androgen-deprivation therapy (ADT) (Frisk, 2010). A hot flash has been defined as "a subjective sensation of heat that is associated with objective signs of cutaneous vasodilation and a subsequent drop in core temperature" (Boekhout, Beijnen, & Schellens, 2006, p. 642). Hot flashes generally involve the face and chest and are characterized by their transient and unpredictable nature (Jones, Kohli, & Loprinzi, 2012). The vasomotor symptoms that characterize hot flashes (e.g., feelings of intense heat, profuse sweating, flushing) have a negative effect on sleep, energy, sexuality, and overall quality of life (Kadakia, Loprinzi, & Barton, 2012).

Hot flashes are reported to be significantly more frequent and severe in women treated for breast cancer than in women undergoing natural menopause (Carpenter, 2005; Kadakia et al., 2012). Hot flashes are believed to be precipitated by the abrupt suppression of ovarian function caused by chemotherapy-induced premature menopause and/or the use of estrogen withdrawal therapies, including tamoxifen and aromatase inhibitors (Baber, Hickey, & Kwik, 2005; Howell et al., 2005; Morrow, Mattair, & Hortobagyi, 2011). Tamoxifen has been shown to produce more frequent and severe hot flashes than the aromatase inhibitors anastrozole and letrozole (Howell et al., 2005; Morrow et al., 2011). Men with advanced prostate cancer who receive ADT via surgical or chemical castration also experience distressing hot flashes that may persist for at least eight years following treatment (Frisk, 2010).

The exact physiologic mechanisms of hot flashes are unknown, and what is known comes mainly from studies with menopausal women (Shanafelt, Barton, Adjei, & Loprinzi, 2002). Core body temperature is regulated centrally in the hypothalamus and is maintained within a narrow physiologic set range called the thermoneutral zone. Elevations of core temperature above the set range stimulate the hypothalamus to activate such heat-dissipating mechanisms as profuse sweating and cutaneous vasodilation, manifested as hot flashes (Dalal & Zhukovsky, 2006; Morrow et al., 2011). Plasma sex hormones (estrogen in women, gonadal hormones in men) are involved in

regulating the hypothalamic thermoregulatory center through negative feedback mechanisms involving the neurotransmitters serotonin and norepinephrine (Shanafelt et al., 2002). The abrupt withdrawal of sex hormones, which occurs with estrogen therapy or ADT, leads to dysfunction of the thermoregulatory center in the hypothalamus whereby even small, transitory elevations in the core temperature trigger the heat-loss mechanisms characteristic of hot flashes (Boekhout et al., 2006; Kouriefs, Georgiou, & Ravi, 2002; Shanafelt et al., 2002).

Subjective measures of hot flashes include assessing the frequency, severity, intensity, distress, and interference with daily activities (Carpenter, Wu, Burns, & Yu, 2012). Data collected from retrospective self-reported hot flash diaries that have been validated in women with breast cancer and men with prostate cancer (the Loprinzi and Sloan Self-Report Diary) (Sloan et al., 2001), as well as in women with breast cancer (the Hot Flash-Related Daily Interference Scale) (Carpenter, 2001), are deemed sufficient for clinical practice (Hanisch et al., 2009; Loprinzi & Barton, 2009).

For an overview of the methods used in creating the Putting Evidence Into Practice (PEP®) resources, see Johnson (2014). The current article updates and synthesizes the evidence for interventions to manage hot flashes in women with breast cancer and men with prostate cancer since those presented by Kaplan et al. (2011). Search methods are available at www.ons.org/content/hot-flashes-search-strategy. Sources of evidence are divided into pharmacologic and nonpharmacologic interventions.

Pharmacologic Interventions

Likely to Be Effective

Gabapentin: Several randomized, controlled clinical trials demonstrated the efficacy of gabapentin in reducing hot flashes in women with breast cancer, as described in Kaplan et al. (2011) and in a systematic review by Rada et al. (2010). In addition, a randomized crossover study of gabapentin and venlafaxine in women with breast cancer (N = 38) revealed that both agents decreased hot flashes. Gabapentin was associated with more dizziness ($p = 0.005$) and increased appetite ($p < 0.001$) (Bordeleau et al., 2010). A self-report study of 117 men with prostate cancer who received gabapentin 600 mg per day showed moderately decreased hot flash scores without substantial toxicities (Moraska et al., 2010).

Venlafaxine: Several randomized, controlled trials have demonstrated the efficacy of venlafaxine, a selective serotonin reuptake inhibitor (SSRI) antidepressant, in reducing hot flashes. A randomized crossover study of 38 women with breast cancer compared gabapentin and venlafaxine, and both agents were found to decrease hot flashes. Venlafaxine was associated with loss of appetite ($p = 0.003$), nausea ($p = 0.02$), and constipation ($p = 0.05$), but fewer negative mood changes ($p = 0.01$) than gabapentin (Bordeleau et al., 2010). A 12-week, double-blind trial comparing clonidine, venlafaxine, and placebo in 80 women with a history of breast cancer found venlafaxine and clonidine were slightly more effective than placebo in reducing hot flash symptoms. Of note, all study groups showed significant reduction in symptoms at 12 weeks, including the placebo group, which reported a 29% decrease in hot flashes (Boekhout et al., 2011). Venlafaxine was not found to be superior to cyproterone acetate and medroxyprogesterone acetate in a double-blind randomized study of men experiencing significant hot flushes during androgen-suppression therapy (N = 109). However, no placebo control group was included (Irani, Salomon, Oba, Bouchard, & Mottet, 2010).

Effectiveness Not Established

Clonidine: In prior randomized trials, clonidine demonstrated a moderate reduction in tamoxifen-induced hot flashes in women with breast cancer (Buijs et al., 2009), in association with a significant placebo effect (Pandya et al., 2000), and was shown to be less effective than venlafaxine (Loibl et al., 2007). A similar placebo-controlled trial in men treated with orchiectomy for prostate cancer found no significant benefit for clonidine (Loprinzi, Goldberg, et al., 1994). In a systematic review, Rada et al. (2010) reported that clonidine provided benefit in reducing hot flashes in women with breast cancer. A randomized, double-blind, placebo-controlled, 12-week study of 80 women with a history of breast cancer compared clonidine, venlafaxine, and placebo. Hot flash scores were found to be significantly lower in the clonidine group versus placebo ($p = 0.03$), were not significant for venlafaxine versus placebo ($p = 0.07$), and were equal in the clonidine and venlafaxine groups (Boekhout et al., 2011). However, Loprinzi, Barton, and Qin (2011) cited methodologic issues related to the study, including an inadequate sample size per study arm, an unbalanced randomization scheme (2:2:1), and an uneven dropout rate among treatment arms.

Progestin therapies: Mixed results were reported in studies examining the efficacy of megestrol and medroxyprogesterone in reducing hot flashes in men with prostate cancer and women with breast cancer (Bertelli et al., 2002; Frisk, 2010; Goodwin et al., 2008; Loprinzi, Michalak, et al., 1994). A systematic literature review of hot flash interventions for men treated for prostate cancer found that some hormone agents were able to decrease hot flashes by at least 75% but produced severe side effects. Cyproterone acetate was associated with fatigue, weight gain, depressed mood, gynecomastia, and hot flushes. Megestrol produced weight gain, edema, and nausea and increased the prostatic-specific antigen in one patient, raising concerns about promoting prostate cancer (Frisk, 2010). All studies were too limited to evaluate safety and long-term risks of treatment. Irani et al. (2010) conducted a 12-week double-blind study of three drugs to manage hot flashes in men receiving ADT for prostate cancer: venlafaxine 75 mg per day (n = 102), medroxyprogesterone acetate 20 mg per day (n = 108), or cyproterone acetate 100 mg per day (n = 101). No comparator placebo control arm was included. All three drugs were found to reduce hot flashes in men, but cyproterone acetate and medroxyprogesterone were most effective (Irani et al., 2010). However, cyproterone acetate is used to treat prostate cancer and could interfere with ADT (Jones et al., 2012). In general, hormone therapies are not recommended for patients with prostate or breast cancer because of concerns about promoting tumor growth (Rada et al., 2010).

Stellate ganglion block: A stellate ganglion block is an injection of local anesthetic into the sympathetic nerve tissue in the anterior neck. A small study (N = 13) that investigated the effectiveness of stellate ganglion block in women with breast cancer and hot flashes found a significant decrease in weekly

hot flash episodes during a 12-week period (Lipov et al., 2008). In a prospective single-arm trial, 34 women with breast cancer who were resistant to other therapies were treated with a stellate ganglion block. Although hot flashes were reduced initially, they gradually returned over time (Haest et al., 2012).

Zolpidem: In one study, 53 women with breast cancer were asked whether they were currently using an SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI) to treat hot flashes. Those taking an SSRI or SNRI were instructed to continue on the medication. Nonusers were started on venlafaxine (an SSRI) at 75 mg per day. All participants were then randomized to receive daily zolpidem 10 mg or placebo for five weeks. Although no change was seen in the number of hot flashes, zolpidem appeared to improve the perception of nighttime hot flashes, perhaps by allowing the patient to sleep through the hot flash (Joffe et al., 2010).

Other Interventions

Buproprion: In a randomized, double-blind, crossover, placebo-controlled pilot study of bupropion 150 mg in breast cancer survivors (N = 55), participants reported a larger reduction in hot flashes with placebo and a preference for placebo (Nuñez et al., 2013).

Citalopram: One randomized, placebo-controlled, double-blind trial evaluated three oral dosages of citalopram (10 mg, 20 mg, and 30 mg per day) versus placebo for six weeks in 254 postmenopausal women experiencing hot flashes. Ninety-one participants had a history of breast cancer, and 69 were receiving concurrent estrogen-deprivation therapy. Hot flash scores decreased from baseline with all dose levels of citalopram compared with placebo ($p \leq 0.002$). No significant response to doses of more than 10 mg per day was noted (Barton et al., 2010).

Magnesium: In a small observational study, 25 women with breast cancer experiencing hot flashes completed treatment with magnesium 400 mg per day for four weeks, escalating to 800 mg per day if needed. Reductions in weekly hot flash scores (frequency times severity) ranged from more than 50% to more than 25% (Park, Parker, Boardman, Morris, & Smith, 2011).

Miscellaneous agents: Other pharmacologic agents investigated in small studies that produced mixed results include transdermal estrogen patches in men (Gerber, Zagaja, Ray, & Rukstalis,

Patient Education: Hot Flashes Associated With Treatment for Breast or Prostate Cancer

Hot flashes may be an unpleasant side effect of cancer treatment, particularly for women with breast cancer and men with prostate cancer. Patients report periods of intense heat, sweating, and reddening of the skin on the face and chest. Hot flashes may occur often or only a few times each day or night. Patients may wake up several times during the night and feel tired during the day.

Studies show two drugs may help to decrease hot flashes.

Many studies have been done to see what types of treatment can help relieve hot flashes in patients with breast cancer or prostate cancer. Results of this research have shown that only two treatments are likely to be useful. They are both drugs.

- Gabapentin (Neurontin®), a drug used to treat epilepsy and some types of pain
- Venlafaxine (Effexor®), a type of antidepressant

Other treatment methods that do not have enough research to recommend use

Other treatment methods that have been studied for relieving hot flashes in patients with breast cancer or prostate cancer include the use of:

- Many different types of drugs
- Herbal or dietary supplements
- Acupuncture
- Hypnosis
- Relaxation therapy.

None of these treatments can be recommended for use at this time. More research is needed to see if any of these methods can help relieve hot flashes over a long period of time.

Some tips to help stay cool and decrease hot flashes

These tips are not based on the results of research studies.

- Learn what triggers your hot flashes, such as hot beverages and spicy foods. Avoid them.
- Limit coffee drinking.
- Do not drink alcohol.
- Dress in layers of clothing that can be removed.
- Keep the room cool for sleeping.
- Sleep on cotton sheets.
- Wear cotton or quick-drying sleepwear.

Note. Full Oncology Nursing Society Putting Evidence Into Practice information for this topic and description of the categories of evidence are located at www.ons.org/practice-resources /pep/hot-flashes. Users should refer to this resource for full dosages, references, and other essential information about the evidence.

Implications for Practice

- Ask women treated for breast cancer or who experience treatment-related premature menopause and men treated with androgen-deprivation therapy for prostate cancer, whether they have hot flashes. If they do, ask them to describe the frequency, severity, and effect on quality of life.
- Discuss some pharmacologic and nonpharmacologic interventions that have been studied in at-risk patient populations to manage hot flashes.
- Provide information about some behavioral techniques (emphasizing that they are not evidence based) that may help prevent or alleviate hot flashes.

2000), fluoxetine (Loprinzi et al., 2002), mirtazapine (Biglia et al., 2007), sertraline (Kimmick, Lovato, McQuellon, Robinson, & Muss, 2006; Wu et al., 2009), testosterone-replacement therapy in men (Agarwal & Oefelein, 2005), and vitamin E (Barton et al., 1998; Biglia et al., 2009), which was also found not effective in a systematic review by Rada et al. (2010).

Benefits Balanced With Harms

Paroxetine: A small randomized, placebo-controlled trial of two dose levels of paroxetine in women with breast cancer showed a significant reduction in hot flashes with both doses (Stearns et al., 2005). However, paroxetine is an SSRI antidepressant that is a strong inhibitor of the CYP2D6 enzyme system that acts to metabolize tamoxifen to its active form, endoxifen (Kaplan & Mahon, 2013). A retrospective study of women with breast cancer taking tamoxifen and paroxetine showed a significantly increased risk of death from breast cancer with overlapping use of both agents (Kelly et al., 2010). Caution is recommended in the use of paroxetine for women experiencing tamoxifen-induced hot flashes (National Comprehensive Cancer Network, 2013).

Not Recommended for Practice

Tibolone: A double-blind placebo-controlled trial comparing tibolone, a synthetic steroid with properties that mimic estrogen, progestins, and androgens, to placebo in women with tamoxifen-induced hot flashes showed no change in hot flash episodes in either arm after three months. Effects of tibolone on recurrence of breast cancer are unknown (Kroiss et al., 2005). A multinational, double-blind, placebo-controlled trial randomized 3,098 women with breast cancer to daily oral tibolone (2.5 mg) or placebo. Mean treatment duration was lengthy at 2.75 years. Tibolone was found to be effective in alleviating menopausal symptoms in breast cancer survivors overall but was less effective in women taking tamoxifen or aromatase inhibitors. A persistent placebo effect was noted (Sismondi et al., 2011). In a randomized, double-blind safety and efficacy trial of tibolone versus placebo in women with breast cancer and vasomotor symptoms, tibolone was found to be effective in relieving symptoms, but the trial was stopped prematurely because of increased recurrence of breast cancer in the tibolone group (Kenemans et al., 2009).

Nonpharmacologic Interventions

Effectiveness Not Established

Acupuncture: Several randomized trials of acupuncture in women with breast cancer and men with prostate cancer that demonstrated a decrease in hot flashes were identified. However, methodologic issues included sample sizes of fewer than 75 participants in all studies combined and limited follow-up that did not exceed six months in any study (Deng et al., 2007; de Valois, Young, Robinson, McCourt, & Maher, 2010; Filshie, Bolton, Browne, & Ashley, 2005; Frisk et al., 2008; Frisk, Källström, Wall, Fredrikson, & Hammar, 2012; Hervik & Mjåland, 2009; Liljegren et al., 2012; Nedstrand, Wijma, Wyon, & Hammar, 2005; Otte, Carpenter, Zhong, & Johnstone, 2011; Walker et al., 2010). A prospective single-arm trial of 14 men with prostate cancer found a short-term decrease in hot flash intensity and frequency (Ashamalla, Jiang, Guirguis, Peluso, & Ashamalla, 2011). Similar findings were reported by Beer et al. (2010) in a study of 22 men with prostate cancer. A prospective, double-blind, randomized study in women with "troublesome" hot flashes related to breast cancer therapies tested the effect of real acupuncture (n = 31) against sham acupuncture (n = 29) and no treatment (n = 34). The researchers reported that significant relief was achieved after the second real acupuncture treatment compared to the sham acupuncture and no-treatment groups ($p < 0.05$) that lasted for at least 12 weeks. However, some women in all groups concurrently received a variety of other hot flash therapies, including clonidine and/or venlafaxine, mirtazapine with clonidine, and hormone replacement (Bokmand & Flyger, 2012).

In a systematic review of 41 randomized clinical trials, the efficacy of acupuncture for symptoms other than chemotherapy-induced nausea and vomiting could not be determined because of the high risk of bias among the studies (Garcia et al., 2013). A systematic review of 16 studies that compared acupuncture versus sham acupuncture did not provide sufficient evidence to determine whether acupuncture is an effective treatment for vasomotor symptoms. Debate exists about whether sham acupuncture is a placebo intervention or whether it possesses an active effect related to peripheral sensory stimulation (Dodin et al., 2013).

Cognitive-behavioral interventions: In a randomized, controlled trial, Ganz et al. (2000) studied the impact of comprehensive menopausal symptom assessment in 42 breast cancer survivors and found no change in the number of hot flashes. Using similar methodology, an exploratory trial of 17 women with breast cancer showed a decrease in the number of hot flashes (Hunter, Coventry, Hamed, Fentiman, & Grunfeld, 2009). In a study by Mann et al. (2012), 96 symptomatic women seen in a breast cancer clinic were enrolled in a randomized trial in which individualized "usual care" by breast care nurses was compared to usual care plus group cognitive-behavioral therapy (CBT) intervention. Group CBT incorporated group discussions, handouts, and weekly homework with audio instructions for daily relaxation and paced breathing exercises at home. Little difference in hot flash frequency and night sweats was found between the two groups at weeks 9 and 26 (Mann et al., 2012). Members of both groups received individualized attention and may have benefited from the placebo effect. A study of 422

women with breast cancer randomized to CBT, physical exercise, CBT and physical exercise, or a control group found that CBT resulted in a significant decrease in the perceived burden of hot flashes and night sweats using the problem-rating portion of the Hot Flush Rating Scale ($p < 0.001$, effect size = 0.39–0.56) (Duijts et al., 2012).

Other interventions: Several studies evaluating the effectiveness of black cohosh have provided conflicting evidence (Hernández Muñoz & Pluchino, 2003; Jacobson et al., 2001; Pockaj et al., 2006; Rostock et al., 2011). Other intervention strategies with limited research that demonstrated some decrease in hot flashes include peer counseling (Schover et al., 2006), relaxation therapy (Fenlon, Corner, & Haviland, 2008; Rada et al., 2010), yoga (Carson, Carson, Porter, Keefe, & Seewaldt, 2009), hypnosis (Elkins et al., 2008; Elkins, Marcus, Stearns, & Rajab, 2007; Younus, Simpson, Collins, & Wang, 2003), and *Salvia officinalis* (i.e., a medicinal herb more commonly known as sage) (Vandecasteele et al., 2012).

Effectiveness Unlikely

Homeopathy: The homeopathy approach to treating hot flashes usually involves a consultation with a homeopathic practitioner who prescribes an individualized homeopathic remedy. The ingredients and doses of the homeopathic remedies reported in several studies were unclear or lacking (Clover & Ratsey, 2002; Jacobs, Herman, Heron, Olsen, & Vaughters, 2005; Thompson & Reilly, 2003) making it impossible to replicate the intervention in clinical practice or truly evaluate the effectiveness of the intervention (Rada et al., 2010).

Soy supplements: Depending on the study, soy supplements were provided in the form of capsules, tablets, powder, or beverage (MacGregor, Canney, Patterson, McDonald, & Paul, 2005; Nikander, Metsa-Heikkilä, Ylikorkala, & Tiitinen, 2004; Quella et al., 2000; Sharma et al., 2009; Van Patten et al., 2002). A 12-week placebo-controlled study randomized 120 androgen-deprived men with prostate cancer and hot flashes to venlafaxine alone, venlafaxine plus soy, soy alone, or placebo. Results indicated that neither venlafaxine nor soy, alone or in combination, had a significant effect on hot flash symptom severity. At week 12, hot flashes decreased 28% in the venlafaxine plus soy arm, 35% in the venlafaxine arm, and 31% in the soy arm. The placebo arm had a 55% decrease in hot flashes (Vitolins et al., 2013).

The Placebo Effect on Hot Flash Interventions

Analysis of numerous hot flash intervention studies has revealed that even participants who received a placebo intervention reported significant reductions in hot flash activity. About 25% of participants who received a placebo reported a reduction of 50% or more in hot flashes and 15% indicated more than a 75% reduction (Boekhout et al., 2006). A review of data from 375 participants in seven randomized, placebo-controlled clinical trials found that those receiving the placebo intervention reported an average decrease of 25% in hot flash frequency and scores at four weeks (Sloan et al., 2001). A study comparing the efficacy of venlafaxine and clonidine versus placebo in reducing hot flash symptoms found that patients receiving placebo reported a 29% decrease in hot flashes (Boekhout et al., 2011). A small, double-blind, crossover study that compared bupropion to placebo reported a larger reduction in hot flashes in the placebo group and a preference for the placebo intervention (Nuñez et al., 2013). Patients randomized to venlafaxine, soy, or placebo reported a reduction in hot flash severity of 55% in the placebo arm compared to reductions ranging from 28%–35% in the treatment arms (Vitolins et al., 2013). Therefore, the beneficial results of placebo therapy should be considered when examining reports of new hot flash interventions that have not been studied in rigorous, randomized, controlled clinical trials.

- Identify and avoid hot flash triggers, such as hot beverages and spicy foods.
- Limit caffeine consumption.
- Avoid alcohol.
- Dress in layers of removable clothing.
- Carry a portable fan.
- Sleep in a cool room.
- Use cotton bed linens and sleepwear or fabrics that wick away moisture.

FIGURE 1. Non–Evidence-Based Behavioral Approaches to Managing Hot Flashes

Note. Based on information from Dalal & Zhukovsky, 2006; Richardson, 2013.

Conclusion and Implications for Practice

Women and men who experience hot flashes as a result of hormone-deprivation therapies may discontinue treatment prematurely and lose the potential survival benefit conferred by these therapies. Five years of tamoxifen use is associated with a 50% reduction in risk of breast cancer recurrence (Batur, Blixen, Moore, Thacker, & Xu, 2006), but early discontinuation rates for tamoxifen therapy range from 15%–35% (Buijs et al., 2009). Women at high risk for breast cancer who are recommended tamoxifen for chemoprevention often do not adhere because of concerns about side effects, including hormonal symptoms (Fagerlin et al., 2010). The persistence of hot flashes in men has been associated with their decision to discontinue ADT (Engstrom, 2008). Nurses should be aware that, although the U.S. Food and Drug Administration (2013) recently approved paroxetine as a nonhormonal treatment for postmenopausal hot flashes, caution is needed in women with tamoxifen-induced hot flashes because paroxetine is a strong inhibitor of the CYP2D6 enzyme system that metabolizes tamoxifen to its active form. Although the current evidence regarding effective interventions to manage hot flashes is limited, interventions including gabapentin and venlafaxine are emerging as potentially effective therapies. No high-quality evidence was found supporting the efficacy of dietary or lifestyle interventions (e.g., CBT, exercise, yoga) in reducing hot flashes in patients with cancer. Nurses can discuss with patients non–evidence-based behavioral approaches that may help to mitigate hot flashes (see Figure 1).

This article provides an overview and evaluation of the interventions that have been studied to manage hot flashes in cancer survivors, particularly individuals with breast or prostate cancer. Additional randomized clinical trials with long-term follow-up for safety and efficacy are needed for all interventions. Nurses should remember the contributions of the placebo effect when reviewing the results of published studies about hot flash management.

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