

State of the Science: Hot Flashes and Cancer, Part 2: Management and Future Directions

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Purpose/Objectives: To critically evaluate and synthesize intervention research related to hot flashes in the context of cancer and to identify implications and future directions for policy, research, and practice.

Data Sources: Published, peer-reviewed articles and textbooks; editorials; and computerized databases.

Data Synthesis: Although a variety of pharmacologic and nonpharmacologic treatments are available, they may not be appropriate or effective for all individuals.

Conclusions: The large and diverse evidence base and current national attention on hot flash treatment highlight the importance of the symptom to healthcare professionals, including oncology nurses.

Implications for Nursing: Using existing research to understand, assess, and manage hot flashes in the context of cancer can prevent patient discomfort and improve the delivery of evidence-based care.

Key Points . . .

- ▶ A variety of pharmacologic and nonpharmacologic interventions for hot flashes have been studied, primarily in terms of their effectiveness in reducing reported hot flash frequency and severity.
- ▶ Evidence-based treatment of hot flashes depends on careful application of existing research and continued monitoring of emerging evidence.

Part two of this state-of-the-science review focuses on two topics. First, research on pharmacologic and nonpharmacologic interventions is reviewed. Second, implications and future directions for research, policy, and practice are described. Similar to Part 1 (see page 959), much of the information presented is specific to cancer. However, data from healthy populations of men and women also are discussed.

Interventions

Pharmacologic and nonpharmacologic treatments for hot flashes are reviewed here and summarized in Tables 1 and 2. Although an exhaustive review was attempted, additional reviews by nationally known scientists will be forthcoming in peer-reviewed journals as a result of the 2005 National Institute on Aging conference on the management of menopause-related symptoms. In addition, several existing reviews are acknowledged (Barton & Loprinzi, 2004; Barton, Loprinzi, & Gostout, 2002; Carpenter, 2000; Clemons, Clamp, & Anderson, 2002; Holzbeierlein, Castle, & Thrasher, 2004; North American Menopause Society, 2004).

Most of the studies reviewed in this article are limited in two ways. First, most studies focused on healthy women or women with breast cancer. Findings from healthy women may not generalize to women with breast cancer or other populations because of differences in the underlying etiology of hot flashes (Moyad, 2002). In addition, although hot flashes in the groups appear to be physiologically similar (Carpenter, Gilchrist, Chen, Gautam, & Freedman, 2004), the higher frequency and severity of hot flashes experienced in breast cancer survivors (Carpenter, Johnson, Wagner, &

Andrykowski, 2002; Harris, Remington, Trentham-Dietz, Allen, & Newcomb, 2002) may require more intensive therapies. Thus, in general, additional testing in more diverse groups, with attention to gender effects, is warranted.

A second limitation of existing studies is that they have not differentiated the perceived impact of interventions from the physiologic effects. In most studies, hot flash frequency was measured only subjectively using self-reports without objective measurement. Although self-reports provide valuable information about whether subjects perceive an intervention to be effective, self-reports do not provide any evidence of physiologic effects. Changes in self-reports are not necessarily synonymous with physiologic effect. For example, women may report fewer hot flashes over time, making it appear as though hot flashes are decreasing when, in fact, such reporting changes may be caused by intervention expectancy effects, memory recall biases, or personal characteristics such as mood and not by a true decrease in the physiologic occurrence of the symptom (Carpenter, Azzouz, Monahan, Storniolo, & Ridner, in press; Pedhazur & Schmelkin, 1991). Furthermore, the inaccuracies of self-reported hot flash frequency have been

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Table 1. Pharmacologic Hot Flash Treatments

Drug	Number of Studies	Sample	Results
Antidepressants			
Venlafaxine	3 ^a	BC, PC	↓
Paroxetine	4 ^a	BC, PC	↓
Fluoxetine	2 ^a	BC	↓, —
Citalopram	2 ^a	HW, BC	↓, —
Anticonvulsants			
Gabapentin	4	BC, PC	↓
Antiandrogens			
Clonidine	2	HW, BC	↓
Anticholinergics			
Ergotamine, belladonna alkaloids, and phenobarbital combination	1 ^a	HW	—
Progestins			
Megestrol acetate	3	BC, PC	↓

^a includes controlled studies

BC—breast cancer, HW—healthy women, PC—prostate cancer, ↓—reduced (improved) hot flashes, —no change in hot flashes

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documented (Carpenter, Andrykowski, Freedman, & Munn, 1999; Carpenter et al., in press; Carpenter, Monahan, & Azzouz, 2004; Freedman, 1989). In prior research, prospective daily diaries and recalled average summaries of hot flash frequency have been shown to significantly underestimate objective hot flash frequency as measured using ambulatory sternal skin conductance monitoring (Carpenter et al., 1999; Carpenter, Monahan, et al.). Measuring the perceived and physiologic impacts of pharmacologic treatments in particular is crucial to uncovering the physiologic mechanisms of hot flashes. Medications that demonstrate clear advantages in decreasing the physiologic occurrence of hot flashes can provide clues to understanding the underlying physiology of the symptom. Because subjective and objective outcomes may be important to researchers and in clinical practice, future research should include measurements of both outcomes to clearly differentiate the perceived versus physiologic impacts of treatments.

Table 2. Nonpharmacologic Hot Flash Treatments

Treatment	Number of Studies	Sample	Results
Vitamin E	1 ^a	BC	—
Soy	> 10 ^a	HW, BC	↓, —
Black cohosh	3 ^a	BC	↓, —
Homeopathy	2	HW, BC	↓
Relaxation	5 ^a	HW	↓
Exercise	2 ^a	HW	↑, —
Acupuncture	7 ^a	HW, BC, PC	↑, —
Reflexology	1 ^a	HW	—
Magnets	1 ^a	BC	—

^a includes controlled studies

BC—breast cancer, HW—healthy women, PC—prostate cancer, ↓—reduced (improved) hot flashes, —no change in hot flashes, ↑—increased (worsened hot flashes)

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Pharmacologic Management of Hot Flashes

Although selective serotonin reuptake inhibitors (SSRIs) are perhaps the most frequently used nonhormonal prescription agents for treating hot flashes (Hoda, Perez, & Loprinzi, 2003; Kockler & McCarthy, 2004), their mechanism of action on hot flashes may be different from their antidepressant effect. The effect of SSRIs on hot flashes occurs faster than the antidepressant response (e.g., one to two weeks versus four to six weeks) (Sloan et al., 2001). Furthermore, although adding yohimbine (an alpha-2 antagonist) to the SSRI fluoxetine significantly increased antidepressant response over fluoxetine alone among 50 patients with major depressive disorder (Sanacora et al., 2004), yohimbine provoked hot flashes in women (Freedman & Krell, 1999).

In addition, many SSRIs can inhibit cytochrome P450 enzymes involved in drug metabolism. For example, paroxetine and fluoxetine are known to inhibit CYP2D6 enzymes that also are involved in the metabolism of tamoxifen (Hiemke & Hartter, 2000). In one study of 12 women with breast cancer, metabolites of tamoxifen were studied before and after four weeks of paroxetine therapy (Stearns, Johnson, et al., 2003). Paroxetine significantly reduced concentrations of endoxifen, one of the most potent tamoxifen metabolites ($p < 0.01$). The findings were replicated in a larger study of 71 patients with breast cancer (Jin et al., 2005), suggesting that the effects of paroxetine on hot flashes may be caused by a decrease in tamoxifen metabolism. In contrast, in the larger study of 71 patients, plasma concentrations of endoxifen were reduced only slightly in women taking venlafaxine, a weak inhibitor of CYP2D6 enzymes (Jin et al.). The clinical significance of the interactions between hot flash treatments that are known CYP2D6 inhibitors and other medications used in the prevention or treatment of cancer (or other conditions) currently is unknown and merits further study.

Venlafaxine Hydrochloride

The antidepressant venlafaxine hydrochloride appears to be safe, effective, and minimally toxic in alleviating hot flashes in women with breast cancer (Barton, La, et al., 2002; Loprinzi et al., 1998, 2000; Schober & Ansani, 2003). Venlafaxine is a phenylethylamine derivative that potentially inhibits the reuptake of neuronal serotonin and norepinephrine (selective serotonin and norepinephrine inhibitor) (Beique, de Montigny, Blier, & Debonnel, 1999; Horst & Preskorn, 1998). The mechanism of action of venlafaxine in alleviating hot flashes is unknown. Paradoxically, one case study report described the return of hot flashes attributed to venlafaxine (75 mg by mouth daily) in a woman who had experienced complete relief of hot flashes for eight years with estrogen-replacement therapy (Grady-Weliky & Hartmann, 2001).

Venlafaxine first was evaluated in a phase II clinical trial involving 23 women with breast cancer and 5 men with prostate cancer (Loprinzi et al., 1998). The dosage of venlafaxine used was 25 mg by mouth daily (taken as 12.5 mg twice a day). Participants completed prospective daily hot flash diaries throughout a one-week baseline period and four-week treatment period. Mean hot flash frequency decreased from 6.6 hot flashes per day to 4.3 per day at the end of treatment (no standard deviations or p values were provided). In addition, 54% of the participants reported a decrease in hot flash

frequency of at least 50%. Using calculated hot flash scores, researchers found that the number of hot flashes rated as severe or very severe decreased from a mean of 1.4 per day at baseline to 0.1 per day at the end of treatment (no standard deviations were reported; $p < 0.001$).

Venlafaxine also was evaluated in a dose-response study (Loprinzi et al., 2000). Women with breast cancer or at high risk of developing breast cancer were stratified by age, hot flash frequency, tamoxifen use, and duration of hot flashes ($N = 191$). Groups received 37.5 mg, 75 mg, or 150 mg of oral venlafaxine daily for four weeks. Dose-response curves indicated that the 75 mg dosage was significantly more effective in decreasing self-reported hot flashes than the 37.5 mg dose or placebo. In a follow-up dose-continuation study, data for only 102 of the original 191 who completed the dose-response study were available (53%). Attrition was related to lack of information regarding dosing, lack of diary information, and disinterest in continuing the medication (Barton et al., 2002). Side effects of venlafaxine include nausea, nervousness, and constipation.

Other Antidepressants and St. John's Wort

Other antidepressants that are not in the same class as venlafaxine also may improve hot flashes. Paroxetine showed positive effects in three uncontrolled studies in women with breast cancer and men with prostate cancer (Loprinzi et al., 2004; Stearns et al., 2000; Weitzner, Moncello, Jacobsen, & Minton, 2002) and one controlled study (Stearns, Beebe, Iyengar, & Dube, 2003). In the uncontrolled studies, women with breast cancer ($N = 12$, $N = 13$) completed a baseline week and then received 10 mg paroxetine for three to seven days before moving to a 20 mg dose for four to five weeks (Stearns et al., 2000; Weitzner et al.). Men ($N = 24$) completed a baseline week and received paroxetine 12.5 mg before being moved to a 37.5 mg dose (Loprinzi et al., 2004). All three studies noted significant improvements in self-reported hot flash frequency and severity, mood, anxiety, and quality of life. In the controlled study, 165 postmenopausal women were randomized to one of three arms for six weeks: placebo, paroxetine 12.5 mg per day, or paroxetine 25 mg per day (Stearns, Beebe, et al.). Both paroxetine doses significantly decreased hot flash frequency and severity compared to placebo (Stearns, Beebe, et al.). Similarly, mirtazapine was effective in reducing hot flashes in one nonrandomized study of 22 women diagnosed with or at high risk for developing breast cancer (Perez et al., 2004). Fluoxetine 20 mg per day (after initial dosing of 10 mg per day for one week) was found to be moderately effective in treating hot flashes in women with a history of breast cancer (Loprinzi et al., 2002). Citalopram 20 mg per day (after 10 mg per day for one week) also has been shown to reduce self-reported hot flashes and improve mood in an open-label pilot study of patients with cancer (Barton et al., 2003). Conversely, fluoxetine and citalopram were no more effective than placebo in decreasing subjective hot flashes in a study of 150 healthy women (Suvanto-Luukkonen et al., 2005). The doses used were 10 mg for one month, 20 mg for five months, and 30 mg for three months for both drugs (Suvanto-Luukkonen et al.).

St. John's wort, an herbal preparation that is believed to have antidepressant properties, has been proposed as a potential hot flash treatment, at least for men with prostate cancer (Moyad, 2002). However, like paroxetine and fluoxetine, St.

John's wort mitigates the effects of several medications and generally is regarded as having high potential for interaction with prescription medications that are metabolized through cytochrome P450 (Mansky & Straus, 2002). Thus, treatment with St. John's wort should be considered carefully in patients taking prescription medications.

Gabapentin

Several reports have suggested that gabapentin may be effective in treating hot flashes. Two separate case study reports described improvement in hot flashes after prescription of gabapentin in women taking tamoxifen and men with prostate cancer (Guttuso, 2000; Jeffery, Pepe, Popovich, & Vitagliano, 2002). Dosages ranged from 200–900 mg per day, and improvement was noted in one to three days. Similarly, one uncontrolled study of oral gabapentin (900 mg per day for four weeks) suggested that it reduced hot flash duration by 74%, frequency by 44%, and severity by 53% in 22 women with breast cancer taking tamoxifen (Pandya et al., 2004). Side effects leading to study dropouts included nausea, rash, and somnolence. In addition, one randomized, double-blind, placebo-controlled trial examining 59 postmenopausal women indicated that gabapentin 900 mg per day was effective in reducing hot flash frequency and severity, with approximately 15% of patients dropping out of the study because of side effects (Guttuso, Kurlan, McDermott, & Kiebertz, 2003). Although the mechanism of action of the agent is unclear, more studies are needed to carefully evaluate the benefits and side effects associated with the medication when used for treating hot flashes.

Clonidine Hydrochloride

Clonidine hydrochloride appears to be effective in reducing hot flashes but can be associated with significant side effects. Clonidine is a centrally (medullary) acting antiadrenergic agent effective for reducing hot flashes in healthy women (Nagamani, Kelder, & Smith, 1987) and women with breast cancer (Goldberg et al., 1994). A total of 110 women with breast cancer participated in a nine-week, randomized, double-blind crossover trial of transdermal clonidine (equivalent to 0.1 mg per day by mouth) versus placebo (Goldberg et al.). Women completed daily hot flash diaries throughout the study period. Significant decreases in subjective hot flash frequency, severity, and mean daily hot flash score (mean frequency \times mean severity) were seen at the end of the clonidine treatment period ($p < 0.05$). However, significantly more side effects were seen with clonidine as compared to placebo, including dry mouth, constipation, itching under the patch, and drowsiness ($p < 0.05$). Marginal differences in dizziness were seen between treatment periods ($p < 0.10$). When asked which treatment was more effective, only 48% chose clonidine. When asked to indicate preference while taking into account side effects, only 31% preferred clonidine. Thus, clonidine may not be acceptable to women with cancer.

Bellergal

Bellergal retard, belladonna alkaloids, and phenobarbital have been used to treat hot flashes. Bellergal retard was studied in an eight-week, double-blind study of 66 healthy women, 33 assigned to placebo and 33 assigned to receive bellergal one tablet per day (Bergmans, Merkus, Corbey, Schellekens, & Ubachs, 1987). Bellergal retard is composed

of ergotamine, belladonna alkaloids, and phenobarbital. Although self-reported hot flashes decreased during the study, differences were not significant after eight weeks of treatment. Thus, in addition to lack of demonstrated efficacy, the potential addictive risk and the availability of safer alternatives limit the usefulness of the agents.

Progestins

Similar to clonidine, megestrol acetate, a progestin used in the treatment of late-stage breast cancer, appears to be effective in decreasing hot flashes but also is associated with significant side effects (Loprinzi, Michalak, et al., 1994; Quella et al., 1998). In one clinical trial, 97 women with breast cancer and 66 men with prostate cancer were enrolled in a nine-week crossover trial (Loprinzi, Goldberg, et al., 1994). Participants completed a one-week baseline period and four weeks of treatment or placebo before crossing over to an additional four weeks on the opposite study arm. Hot flashes were measured using a daily, prospective diary methodology. Hot flashes decreased significantly with megestrol acetate (20 mg by mouth every day) (Loprinzi, Goldberg, et al.). Data from the first treatment arm for 80 women with breast cancer indicated that (a) hot flash frequency decreased by 74% over baseline in the megestrol acetate group and by 27% in women treated with placebo ($p < 0.001$) and (b) the median hot flash score decreased by 83% over baseline with megestrol acetate and only 27% with placebo (Loprinzi, Goldberg, et al.). However, when participants were followed long-term (three years after the original study), 69% of the women with breast cancer had discontinued the drug and 75% still were having hot flashes (Quella et al., 1998). In addition, 41% of those who continued taking the drug reported breakthrough hot flashes (Quella et al., 1998). Reported side effects included vaginal bleeding, chills, depression, and numbness and tingling in the hands (Loprinzi, Goldberg, et al.; Quella et al., 1998). Intramuscular depomedroxyprogesterone acetate was equally as effective as megestrol acetate in one randomized study of 71 postmenopausal patients with breast cancer (Bertelli et al., 2002). Long-term relief of symptoms six months after the study was higher in the depomedroxyprogesterone acetate group (Bertelli et al.). However, progestins may not be widely prescribed to patients because of concerns about stimulating breast and prostate cancer recurrence (Hoda et al., 2003; Sartor & Eastham, 1999).

Nonpharmacologic Management of Hot Flashes

The following nonpharmacologic treatments for hot flashes may be beneficial when used alone or in combination with pharmacologic agents. For specific guidelines for using the strategies, please refer to the position statement developed by the North American Menopause Society (2004).

Vitamin E

Vitamin E is relatively inexpensive and has been recommended for hot flashes since at least the mid-1940s (Christy, 1945; Finkler, 1949; Jubelirer, 1995; McLaren, 1949; Miller, 1992). However, only one published study was found examining vitamin E's efficacy in the past 20 years (Barton et al., 1998). Women with breast cancer ($N = 104$) completed nine

weeks of a randomized crossover trial of vitamin E versus placebo. Women completed a one-week baseline, four weeks of placebo or treatment involving 800 IU of vitamin E orally daily, and an additional four weeks of treatment or placebo. Hot flashes were assessed subjectively using a daily, prospective diary methodology at baseline and during the last week of treatment for each arm. Compared to baseline and placebo treatment periods, no significant differences were seen in mean daily hot flash frequency, severity, or mean daily hot flash score (mean frequency \times mean severity). Thus, vitamin E does not appear to be effective for alleviating hot flashes (Barton et al., 1998). In addition, women with heart disease, diabetes, or hypertension should consult a nurse practitioner or physician before taking vitamin E.

Soy

Increasing soy intake, either through dietary changes or supplement use, is another strategy commonly recommended for alleviating hot flashes. Recommendations to increase soy consumption stem from data regarding the low incidence of hot flashes in Asian women, a population known to consume large amounts of soy (Adlercreutz, 1990; Adlercreutz & Mazur, 1997; Albertazzi et al., 1998; Murkies et al., 1995; Soffa, 1996). Soy proteins and other plant estrogens have been described as phyto-SERMS (selective estrogen receptor modulators) rather than phytoestrogens (Messina & Barnes, 1991).

Studies on the use of soy for the management of hot flashes have produced conflicting results (Albertazzi et al., 1998; Knight, Howes, Eden, & Howes, 2001; Murkies et al., 1995; Nagata, Takatsuka, Kawakami, & Shimizu, 2001; Quella et al., 2000; Scambia et al., 2000; St. Germain, Peterson, Robinson, & Alekel, 2001; Upmalis et al., 2000; Van Patten et al., 2002). For example, in one randomized study, 40 women received 60 gm soy protein and 39 women received 60 gm casein protein (placebo) daily for 10 weeks (Albertazzi et al.). When compared to the two-week baseline, soy significantly decreased the number, but not severity, of subjectively recorded hot flashes ($p < 0.001$). In contrast, another randomized, double-blind study compared the effectiveness of soy flour versus wheat flour in decreasing hot flashes in healthy postmenopausal women (Murkies et al.). Although women who added 45 gm of soy flour per day to their diets reported a significant decrease in subjective hot flash frequency and severity during the 12 weeks of the study, no significant differences were seen between soy and wheat flour supplementation. Soy flour (highly phytoestrogenic) was no more effective than wheat flour (minimally phytoestrogenic) in reducing hot flashes. Thus, although soy commonly is recommended, the definitive benefits of soy in alleviating hot flashes are unclear (Swain, Santen, Burger, & Pritchard, 1999).

Black Cohosh

Black cohosh is one herb that increasingly has been evaluated as a hot flash treatment. Black cohosh and compounds containing it have been found to decrease self-reported hot flashes compared to baseline in noncontrolled trials (Liske et al., 2002; Sun, 2003). In the only controlled study, however, black cohosh was not more effective than placebo in decreasing self-reported hot flash frequency or intensity in patients with breast cancer (Jacobson et al., 2001). The mechanism of action of black cohosh in the uncontrolled studies does not

appear to be the result of phytoestrogenic effects. Black cohosh does not exhibit estrogenic activity (Burdette et al., 2003), has no proliferative effects on breast cancer cell lines *in vivo*, and actually may inhibit breast cancer cell growth (Einbond et al., 2004; Hostanska, Nisslein, Freudenstein, Reichling, & Saller, 2004). Black cohosh has been shown to act as a mixed competitive ligand and partial agonist of the 5-HT₇ receptor (Burdette et al.). The results may further implicate serotonin in the etiology of hot flashes. Serious side effects of black cohosh have been reported and include acute liver failure requiring liver transplantation (Lontos, Jones, Angus, & Gow, 2003) and autoimmune hepatitis (Cohen, O'Connor, Hart, Merel, & Te, 2004).

Homeopathy

Two uncontrolled, open-label studies suggested that individualized homeopathic treatments for hot flashes may be effective (Clover & Ratsey, 2002; Thompson & Reilly, 2003). Clover and Ratsey provided homeopathic treatment to 31 women, 20 of whom were breast cancer survivors. Hot flashes were measured (a) at baseline as the recalled average frequency during the past month and recalled average severity during the past month using a 3-point rating scale (slight, moderate, and severe) and (b) at the end of an unspecified treatment period as average recalled frequency and severity during the treatment period. Treatment was associated with a 48%–75% decrease in subjective hot flash frequency and a 53%–73% decrease in subjective hot flash severity. Similarly, Thompson and Reilly provided individualized consultation and treatment to 45 breast cancer survivors, with improvement seen in all symptoms over time. Limitations were that neither study proposed a mechanism of action, provided specific details regarding homeopathic treatment type or dose, or discussed side effects or negative reactions (Clover & Ratsey; Thompson & Reilly). However, the promising results from uncontrolled studies suggest that further, controlled research of homeopathy may be warranted.

Other Dietary Changes

Recommendations to decrease caffeine and alcohol consumption to control hot flashes are made commonly but appear to be untested. In previous studies, alcohol was endorsed by only a minority of women as a trigger of hot flashes (e.g., 14%–23%) (Carpenter, Johnson, et al., 2002; Kronenberg, 1990). However, women who identify caffeine and alcohol as hot flash triggers may benefit from reducing or eliminating the products from their diets for a trial period.

Relaxation Training

Relaxation training is recommended for alleviating hot flashes in women with cancer. Types of relaxation training shown to reduce hot flashes in healthy women include progressive muscle relaxation (Germaine & Freedman, 1984), relaxation combined with temperature control biofeedback training (Stevenson & Delprato, 1983), paced respiration (Freedman & Woodward, 1992), at-home relaxation audiotapes (Irvin, Domar, Clark, Zuttermeister, & Friedman, 1996), and applied relaxation (Wijma, Melin, Nedstrand, & Hammar, 1997). The strategies appear to decrease subjective hot flash severity (Irvin et al.) and frequency as measured using diaries or objective monitoring of sternal skin conductance (Freedman & Woodward; Germaine & Freedman).

Exercise

Research on exercise for hot flashes has produced conflicting results. In one study, hot flash severity, but not hot flash frequency, decreased significantly from baseline in 15 healthy women taking part in a 12-week exercise program (Lindh-Astrand, Nedstrand, Wyon, & Hammar, 2004). In another study, 35 women aged 40–60 were nonrandomly assigned to two groups: exercise and structured education ($n = 20$) and a no-exercise control group ($n = 15$) (Ueda, 2004). Although the 12-week exercise and education program reduced the severity of some symptoms such as nervousness, it did not significantly improve hot flashes (Ueda). Conversely, results from a randomized, controlled trial suggested that exercise actually increased hot flash severity. Overweight, postmenopausal women ($N = 173$) were randomized to take part in a moderate-intensity exercise program or control group (e.g., stretching). After 12 months, a significant increase in hot flash severity occurred in the exercise group compared to the control group (Aiello et al., 2004).

Acupuncture

Although useful for decreasing other symptoms (Cohen, Rousseau, & Carey, 2003; Sandberg, Wijma, Wyon, Nedstrand, & Hammar, 2002), acupuncture has shown mixed results in alleviating hot flashes. Uncontrolled studies showed significant improvement in subjective hot flash frequency (Hammar et al., 1999) and mean vasomotor symptoms (Dong et al., 2001; Porzio et al., 2002). However, acupuncture did not improve hot flashes consistently when compared to nonspecific acupuncture, estrogen therapy, or superficial needle insertion (Cohen et al., 2003; Ping, Ren-hai, & Zhong-xiang, 1998; Sandberg et al.; Wyon, Lindgren, Lundeborg, & Hammar, 1995). For example, when compared to placebo, acupuncture significantly improved hot flash severity in two studies (Cohen et al., 2003; Ping et al.), but electroacupuncture did not improve hot flash frequency or severity in two other studies (Sandberg et al.; Wyon et al.). The data provide some evidence to support the use of acupuncture for hot flashes, although further studies are needed.

Reflexology

Foot reflexology has not been shown to be more effective than foot massage in reducing hot flashes. A single, small, randomized study compared the use of foot reflexology ($n = 35$) to a predefined routine of foot massage with no reflexology ($n = 31$) (Williamson, White, Hart, & Ernst, 2002). Women without cancer were randomized to receive reflexology or foot massage given in six weekly 45-minute sessions, followed by three monthly 45-minute sessions, for a total of nine sessions. No untoward reactions were noted, although no specific assessment strategies for assessing negative side effects were discussed. Outcomes in the two groups improved equally over time.

Magnets

A single pilot study investigated the use of magnets for hot flash relief (Carpenter, Wells, et al., 2002). In the randomized, placebo-controlled crossover study, 11 breast cancer survivors completed a 24-hour baseline hot flash monitoring session; wore the magnetic or placebo devices for three days; completed a post-treatment, 24-hour hot flash monitoring session; experienced a 10-day washout period; and then crossed over

to the opposite study arm. Magnetic devices (Magna Bloc[®], Robert Holcomb, MD, PhD, Nashville, TN) and placebos were placed over six acupressure sites used in the treatment of hot flashes. Results indicated that magnetic therapy was no more effective than placebo in decreasing hot flash severity, and, contrary to expectations, placebo was significantly more effective than magnets in decreasing objective hot flash frequency and subjective hot flash bother.

Multimodal Interventions

Very few studies have evaluated multimodal or multicomponent interventions for reducing hot flashes. One group studied the Comprehensive Menopausal Assessment intervention program for relief of menopausal symptoms, including hot flashes (Ganz et al., 2000). The intervention included an educational component, nonhormonal medications for hot flashes (e.g., clonidine, bellergal, megestrol acetate), and slow abdominal breathing. Compared to a usual-care group (n = 39), the intervention group (n = 33) evidenced improvement in menopausal symptom bother, including hot flash bother, measured using seven items (p < 0.001). Use of several interventions in combination may be most effective for reducing hot flashes.

In summary, most available research suggests that individuals perceive currently available treatments as effective; however, the physiologic impact of the therapies has been underexplored. When recommending various therapies for hot flashes, healthcare providers should pay careful attention to the potential for drug interactions and to tolerability and effectiveness. Clinicians can use existing research to educate patients regarding the safety, appropriateness, effectiveness, and tolerability of the various treatments and implement agreeable and evidence-based treatment plans.

Implications and Future Directions

Numerous implications and opportunities arise from this review in the areas of ethics, policy, research, and practice. They are summarized below and presented in Table 3.

Ethics and Policy

Oncology nurses and other healthcare professionals have an ethical obligation to assess and manage uncomfortable symptoms, such as hot flashes, to prevent unnecessary patient suffering and promote quality of life. The available evidence suggests that hot flashes should be a priority for assessment in high-risk groups and, if troublesome, should be treated with the most appropriate and available pharmacologic or nonpharmacologic therapies. When hot flashes are left untreated, symptom distress and poor quality of life can result.

National attention to hot flash measurement as a result of the National Institutes of Health workshop and request for development of new measurement tools is likely to have an impact on design of future clinical trials. Specifically, the U.S. Food and Drug Administration may have to revisit its draft recommendations for defining hot flash severity in clinical trials (U.S. Department of Health and Human Services, 2003) or propose different standards for hot flash measurement. Attention to gender differences in measurement may help to elucidate gender differences in hot flash physiology and treatment efficacy. In addition, development of new measurement standards may affect interpretation of existing empirical evidence.

The need for evidence-based hot flash treatment guidelines never has been greater. In addition to people with cancer, more and more healthy women are seeking nonhormonal therapies for hot flash relief following publication of findings from the Women's Health Initiative concerning the negative consequences of estrogen-progestin therapy (Cauley et al., 2003; Chlebowski et al., 2003, 2004; Cushman et al., 2004; Manson et al., 2003; Rossouw et al., 2002; Shumaker et al., 2003). To address the growing need for treatment guidelines, the North American Menopause Society (2004) issued a position statement on the treatment of hot flashes. In addition, in March 2005, the National Institute on Aging convened a state-of-the-science conference to review the evidence base surrounding treatment of hot flashes in people with cancer and healthy women. One important outgrowth of the conference will be the generation of evidence-based summaries and guidelines regarding the safety and efficacy of available hot flash treatments. The evidence-based summaries and guidelines may highlight gender differences in treatment efficacy.

Research

The available empirical evidence raises many questions for researchers to address. Additional descriptive research is needed regarding the scope and impact of hot flashes in populations without breast cancer to fully understand the phenomenon. Better conceptualization of hot flashes can improve subsequent measurement and intervention research. In addition, continued exploration of the physiologic mechanisms of hot flashes, including genetic and behavioral factors and the interplay of gluconeuroendocrine and thermoregulatory systems, will be important in providing an empirical basis for the development of novel pharmacologic and nonpharmacologic treatments. Subsequent testing of the treatments in large-scale clinical trials will be necessary. Finally, continued development and testing of improved methods for measuring hot flashes will contribute to all areas of research.

Practice

Practice implications that emerge from this state-of-the-science review focus on monitoring emerging evidence and integrating emerging and existing evidence into practice. The diversity of populations affected by cancer and questions regarding whether hot flashes are experienced similarly in all populations speak to the importance of assessment. A need exists to identify high-risk groups to target for assessment and to use the data as benchmarks to determine the scope and impact of the problem. Standardized clinical assessment should acknowledge the problem of under-reporting by recognizing that subjective assessment may underestimate the scope of the problem. In addition, a growing need exists to generate and evaluate treatment guidelines and algorithms with careful attention to safety and pharmacogenetics. Although at least one algorithm for managing hot flashes is available (Stearns & Loprinzi, 2003), it is specific to pharmacologic management and does not include alternative therapies (Carpenter & Ridner, 2003). Further work is needed in that area. In addition, clinicians increasingly will be needed as collaborators on multidisciplinary teams of investigators seeking to elucidate the nature, impact, measurement, and management of the bothersome symptom of hot flashes.

Table 3. Implications and Future Directions for Ethics Policy, Research, and Practice

Category	Ethics and Policy	Research	Practice
Definition and scope	Prioritize hot flashes as a problem in the context of cancer.	Clarify similarities and differences in conceptual definitions of hot flashes across populations; determine whether hot flashes represent a singular phenomenon across populations; quantify impact of risk factors.	Consider all populations affected when addressing hot flashes; identify high-risk groups and begin the process of obtaining benchmarking data to determine prevalence and severity.
Physiology	Prioritize evaluation of gender differences in hot flash physiology.	Evaluate similarities and differences in physiologic mechanisms across populations; replicate existing research in diverse populations; explore new biobehavioral mechanisms in animal models and humans.	Monitor emerging evidence and adjust treatments accordingly.
Measurement	Reevaluate the appropriateness of the U.S. Food and Drug Administration's recommended definitions for mild, moderate, and severe hot flashes; recognize potential impact of objective monitoring for differentiating physiologic and perceived impacts of interventions; develop position statements and guidelines for measurement.	Recognize limitations of existing measures; evaluate accuracy and precision of sternal skin conductance in men; combine sternal skin conductance with subjective measures; disentangle whether lack of concordance between measurements is a reporting or perception issue; evaluate and refine existing and alternative measurement technologies.	Review the National Center for Complementary and Alternative Medicine measurement workshop statement; acknowledge the issue of underreporting; institute standardized assessments.
Treatment	Prioritize evaluation of gender differences in treatment efficacy; develop evidence-based summaries of existing research; develop position statements and guidelines for treatment decisions.	Replicate existing research in more diverse populations; examine gender differences in response to treatments; develop novel therapeutics based on physiologic mechanisms; differentiate physiologic and perceived impacts of interventions; include pharmacogenetics in future clinical trials.	Continually monitor emerging evidence; develop treatment algorithms based on available evidence; discontinue use of ineffective or unproven treatments; consider combining pharmacologic and nonpharmacologic therapies; institute quality-assurance programs to document and monitor tolerability and effectiveness of therapies; monitor emerging pharmacogenetic data to prevent drug interactions.

Conclusions

In summary, this state-of-the-science review supports the importance of understanding, assessing, and treating hot flashes in the context of cancer to prevent discomfort and improve the delivery of evidence-based care. Although the literature continually is expanding, more research is needed for practitioners to be able to provide appropriate, safe, and effective evidence-based treatments for patients. The importance of research in guiding clinical practice and policy should not be underestimated.

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