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After reading the article "Risk Factors, Pathophysiology, and Treatment of Hot Flashes in Cancer," the learner should be able to:

1. Summarize current knowledge regarding the risk factors for hot flashes in individuals with and without cancer.
2. Summarize current understanding of the pathophysiology of hot flashes.
3. Review available evidence regarding pharmacological, nutraceutical, surgical, and complementary/behavioral interventions for hot flashes in women with breast cancer and men with prostate cancer.

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Risk Factors, Pathophysiology, and Treatment of Hot Flashes in Cancer

William I. Fisher, MA¹; Aimee K. Johnson, MA²; Gary R. Elkins, PhD, ABPP, ABPH³; Julie L. Otte, PhD, RN, OCN⁴; Debra S. Burns, PhD, MT-BC⁵; Menggang Yu, PhD⁶; Janet S. Carpenter, PhD, RN⁷

Hot flashes are prevalent and severe symptoms that can interfere with mood, sleep, and quality of life for women and men with cancer. The purpose of this article is to review existing literature on the risk factors, pathophysiology, and treatment of hot flashes in individuals with cancer. Electronic searches were conducted to identify relevant English-language literature published through June 15, 2012. Results indicated that risk factors for hot flashes in cancer include patient-related factors (eg, age, race/ethnicity, educational level, smoking history, cardiovascular risk including body mass index, and genetics) and disease-related factors (eg, cancer diagnosis and dose/type of treatment). In addition, although the pathophysiology of hot flashes has remained elusive, these symptoms are likely attributable to disruptions in thermoregulation and neurochemicals. Therapies that have been offered or tested fall into 4 broad categories: pharmacological, nutraceutical, surgical, and complementary/behavioral strategies. The evidence base for this broad range of therapies varies, with some treatments not yet having been fully tested or showing equivocal results. The evidence base surrounding all therapies is evaluated to enhance hot flash treatment decision-making by clinicians and patients. *CA Cancer J Clin* 2013;63:167-192. © 2013 American Cancer Society.

Keywords: hot flashes, sweating, menopause, neoplasms, palliative care.



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Introduction

Hot flashes are prevalent symptoms among individuals with cancer that require the attention of clinicians. Hot flashes are complex physiological events. Research in women without cancer suggests they begin with feeling chilled and an inspiratory sigh.¹ Data from women with and without cancer show they are concurrent with subsequent increased heart rate, metabolic rate, and sweating.²⁻⁶ Hot flashes are experienced as sudden and transient episodes of heat and sweating, with possible cooccurring palpitations and anxiety.^{7,8} Prevalence estimates range from 3% to 86% in women without cancer,⁹ 51% to 81% in women with breast cancer,¹⁰⁻¹² 69% to 76% in men with prostate cancer,^{13,14} and 85% to 90% in patients with carcinoid syndrome.¹⁵ Other cancer patients who may report hot flashes due to tumor secretion include those with medullary thyroid cancer, pancreatic cancer, or renal cell carcinoma; however, detailed descriptive studies in these populations could not be found in the literature.¹⁶ Hot flashes are known to cooccur with mood and sleep disturbances and negatively impact quality of life.^{10,17-19} In addition, hot flashes can interfere with adherence to lifesaving therapies such as estrogen- or testosterone-reducing or ablative therapies that are used to prevent or treat cancer.^{12,20}

This review is divided into 3 main sections including a discussion of risk factors; the pathophysiology of the symptom; and the presentation of evidence surrounding pharmacological, nutraceutical, surgical, and complementary/behavioral treatment options. Although the review focuses on hot flashes occurring in all cancer patients, most of the evidence base pertains to women without cancer; women with breast cancer; and, to a lesser extent, men with prostate cancer. Although information on women without cancer can be extrapolated to women with breast cancer, it is likely to be less relevant to

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men with prostate cancer or patients experiencing hot flashes as a result of tumor secretion (eg, carcinoid syndrome). Literature sources were identified using a multiple database search of MEDLINE, HealthSource: Nursing/Academic Edition, PsycINFO, PsycARTICLES, PsycCRITIQUES, and the Psychological and Behavioral Sciences Collection using a global field search. Search terms included “hot flash,” “hot flush,” “vasomotor symptoms,” “etiology,” “pathophysiology,” and “therapies or treatments.” Abstracts and articles published on or before September 30, 2012 were included in the review. All hot flash outcomes (frequency, severity, bother, and interference) are considered to be self-reported via diaries or questionnaires unless specified otherwise.

Risk Factors

Patient-Related Risk Factors

Factors associated with hot flashes for patients with and without cancer include age, race and ethnicity, educational level, smoking, cardiovascular risk including body mass index, and genetics. Both women and men can experience hot flashes due to hormonal changes that occur during the natural aging process,^[7] although hot flashes tend to be more common in midlife women^[21,22] than aging men.^[23] Greater hot flash prevalence and/or severity have been reported in African Americans compared with whites.^[24,25] Results from the Study of Women's Health Across the Nation (n = 16,065) indicated greatly varying combined hot flash and night sweat prevalence rates by race and ethnicity: 18% among Japanese women, 21% among Chinese American women, 31% among white women, 21% among Latina women, and 46% among African American women.^[25] However, there is contention over whether racial and ethnic differences are due to underlying physiological processes or differences in the interpretation or reporting of the symptom.^[26]

The association between educational level and hot flashes is equivocal. In one study of 81 women with breast cancer, education was not significantly associated with hot flash frequency (odds ratio [OR], 0.74; 95% confidence interval [95% CI], 0.25–1.54), average hot flash severity (OR, 0.75; 95% CI, 0.35–1.61), or menopausal quality-of-life scale scores (OR, 1.01; 95% CI, 0.90–1.16).^[27] However, in a large (n=8373) multinational study of vasomotor symptom prevalence, educational level was slightly but significantly lower in women reporting vasomotor symptoms compared with asymptomatic women (11.2 years vs 12.2 years; $P < .001$).^[28] Unfortunately, this study did not specify how many subjects were cancer survivors. It is possible that the association between education and hot flashes may be due at least in part to the interaction between hysterectomy and education. In a survey of 10,418 postmenopausal British women,

educational level was found to be slightly protective (OR, 0.98; 95% CI, 0.97–0.99); however, there was a stronger interaction between hysterectomy and level of education (OR, 0.57; 95% CI, 0.38–0.86).^[29]

Cigarette smoking may also be a risk factor for hot flashes.^[25] Although there have been a few studies that failed to find an association between smoking and hot flashes, most studies show that smoking increases a woman's risk of any hot flashes,^[30,31] or of frequent and bothersome hot flashes.^[32] The mechanism by which smoking affects hot flashes is, as yet, unknown, although some studies have related smoking and other demographics to an earlier age at menopause.^[33] In addition, there are at least 4 suggested pathways by which cigarette smoking might alter estrogen metabolism.^[34–37]

Growing evidence associates hot flashes with a woman's cardiovascular risk.^[38,39] Women who report hot flashes for 6 days or more over 2 weeks and particularly those who are overweight or obese were found to have high intima media thickness, the most widely used and well-validated measure of subclinical cardiovascular disease.^[39] However, the role of weight or body mass index on hot flashes is unclear.^[25,40] It has been suggested that obese women are more likely to experience ovarian insufficiency and, as a result, more hot flashes. Adipose tissue produces hormones (leptin, tumor necrosis factor- α) that suppress ovarian steroid production and may influence thermoregulation.^[41] It has been hypothesized that the influence of adipose tissue on estrogen levels increases the risk of hot flashes; however, there is inconsistent and conflicting evidence in the literature.^[41] The influence of body mass index on hot flashes is an area that needs additional investigation.

Polymorphisms in genes that control estrogen functioning, angiogenesis, and the cytochrome P450 enzymes may predispose women to hot flashes; however, it is unknown if such genotype-phenotype associations hold for women with breast cancer, men with prostate cancer, or other patients with other cancers. In data derived from participants in the Study of Women's Health Across the Nation, genetic polymorphisms in estrogen metabolism and receptor genes were associated with a decreased odds of reporting hot flashes but these associations varied by race (the CYP1B1 rs1056836 GC genotype in African American women; the 17HSD rs615942 TG, 17HSD rs592389 TG, and 17HSD rs2830 AG genotypes in white women; and the CYP1A1 rs2606345 AC genotype in Chinese women).^[42] Schneider et al^[43] suggested that hot flashes may be regulated by genes that control angiogenesis. In premenopausal white women, the eNOS-786 CT and TT genotypes were significantly associated with a greater likelihood of current hot flashes relative to women with the CC genotype, although this association failed to remain significant after controlling for clinical variables.^[43]

In postmenopausal women, the HIF1A 1744 CT and TT genotypes were significantly associated with a greater likelihood of current hot flashes even after controlling for clinical variables.^[43] In addition, there are several reports evaluating hot flashes and cytochrome P450 enzyme genes. In the Seattle Midlife Women's Health Study, women with the CYP19 7r allele reported less severe hot flashes than women with the CYP19 7r(-3) allele, who reported more severe hot flashes compared with women with other CYP19 alleles.^[44] In 2 other studies, the CYP17 MspAI polymorphism did not predict hot flash reporting^[45] or response to estrogen therapy,^[46] but these studies were small and likely underpowered to find genotype-phenotype associations. In another study, women with a CYP1B1 (Val432Leu) polymorphism were at an approximately one-third greater risk of reporting more severe and persistent hot flashes.^[47] Although the research into the genetic link to hot flashes is encouraging and has provided a foundation for possible personalized treatments, more work with larger and more heterogeneous samples is critically needed.

Cancer-Related Risk Factors

Cancer-related risk factors are primarily those that increase the rapidity of hormone withdrawal. In women, the most commonly cited risk factor and hypothesized causal link for hot flashes is related to the rapidity of endogenous estrogen withdrawal,^[48] with a similar relationship assumed to hold for testosterone in men. In women, these cancer-related risk factors include the discontinuation of hormone therapy when hormone-dependent cancers are diagnosed (eg, breast cancer),^[12] the initiation and continued use of endocrine therapies,^[12,49-51] chemotherapy-induced ovarian disruption,^[50-52] and ovarian removal or damage due to surgical- or radiation-related interventions.^[52] In men, hot flashes are most commonly associated with antiandrogen therapies for the treatment of prostate cancer and orchiectomy for the treatment of metastatic prostate cancer.^[53,54] Women and men who are diagnosed with carcinoid tumors, medullary thyroid cancer, pancreatic cancer, or renal cell carcinoma may report hot flashes that are believed to be primarily due to tumor secretion, although detailed studies in the literature are lacking.^[16] A longitudinal study of hot flashes in patients with breast and prostate cancers reveals that undergoing chemotherapy and hormone therapy are significantly associated with hot flashes.^[27]

The specific effects of these cancer-related risk factors vary. Breast cancer therapy-induced hot flashes vary by age and by dose and type of treatment.^[52] Younger women are less likely than midlife women to experience induced menopause at higher dosages of chemotherapy,^[52] although younger postmenopausal women report a greater frequency of hot flashes during endocrine therapy.^[12] Patients who are

older or whose ovaries are in the radiation field during treatment experience the most ovarian damage and have a greater risk of hot flashes than those whose ovaries are not radiated.^[52]

Pathophysiology

The physiological mechanisms of hot flashes are still unknown but appear to involve thermoregulatory and neurochemical disruptions. One question that is still being debated is whether hot flashes are centrally mediated^[55,56] or both centrally and peripherally mediated.^[57] An answer to this fundamental question would likely lead to more appropriately targeted, and perhaps more effective, therapeutic interventions to prevent and/or treat hot flashes. Understanding whether hot flashes experienced by different cancer populations are physiologically similar would help the field in generalizing findings from clinical trials done in one population (eg, patients with breast cancer) to others (eg, patients with prostate cancer).

Thermoregulatory Disruption

Hot flashes have been characterized as an exaggerated response to changes in the thermoregulatory control system.^[55,56,58] Thermoregulation, a critical neuroendocrine and autonomic system for maintaining homeostatic temperature in the body, is believed to include a thermoregulatory null zone. This null zone is a threshold point between sweating and shivering sensitive to a 0.4-°C fluctuation in temperature, with excess sweating occurring at higher-than-threshold temperatures or shivering at lower temperatures. In women with hot flashes, the thermoregulatory system is disrupted, with small changes in body temperature eliciting an exaggerated sweating or shivering response, suggesting an absent interthreshold zone.^[59-63]

A similar mechanism is presumed to hold for men, although this has not been specifically studied. Why this thermoregulatory disruption occurs is not entirely clear, although it has been linked to changes in some neurochemicals, such as estrogen, norepinephrine, serotonin, calcitonin gene-related peptide (CGRP), and glucose.^[58]

Neurochemical Disruption

Estrogen, a steroid hormone, is the most commonly implicated neurochemical involved in hot flashes. Estrogen replacement therapy, although the most effective pharmacologic treatment known for hot flashes, is contraindicated for patients with a history of hormone-dependent cancer.^[64] Estrogen appears to stabilize thermoregulatory disruption, and this may be one mechanism by which this treatment alleviates hot flashes. In animals, estrogen reduces spontaneous fluctuations in core body temperature after ovariectomy.^[65,66] In women, estrogen therapy restores the

thermoregulatory null zone by raising the sweating threshold.^[67] Estrogen has also been found to restore vascular tone in animals,^[57] suggesting this therapy may also be acting peripherally to reduce hot flashes by increasing peripheral vasomotor stability.

It has been argued that estrogen therapy is not indicative of estrogen's sole role in the pathophysiology of hot flashes, since other nonhormonal agents reduce hot flashes without changing or directly affecting estrogen levels.^[68] Fluctuations in estrogen alter central nervous system (ie, central) levels of norepinephrine and serotonin and the action of these neurotransmitters and their involvement in the neurotransmission of thermoregulatory signals have been implicated in hot flashes.^[68–70] For example, norepinephrine is released in response to sympathetic nervous system activation. In animal studies, norepinephrine was found to decrease the thermoregulatory null zone.^[60] In humans, norepinephrine agonists, such as clonidine, do alleviate hot flashes, whereas norepinephrine antagonists, such as yohimbine, elicit hot flashes.^[60] Similarly, estrogen replacement therapy restores serotonin levels^[71] and estradiol has been shown to bolster serotonergic activity in postmenopausal women.^[72] In ovariectomized rats, activation of the serotonin 2A receptors can alleviate the thermoregulatory dysfunction associated with estrogen depletion.^[73] The mechanism by which estrogen affects serotonin metabolism may be via a direct effect on serotonin neurons, which regulate the genes involved in serotonin production, transport, and signaling.^[74,75] After spontaneous or surgical menopause, women have been shown to have low levels of peripheral (and presumably central) serotonin.^[71] Carcinoid tumors are associated with hot flashes and are presumed to lower central serotonin levels.^[15,16] One study showed peripheral (and presumably central) serotonin concentrations in perimenopausal women to be positively correlated with hot flashes.^[76] However, when central serotonin was acutely lowered using tryptophan depletion, breast cancer survivors did not exhibit more hot flashes compared with a control condition.^[77]

CGRP, a neuropeptide found centrally and peripherally, is known to cause facial flushing and has been investigated in women and men reporting hot flashes. As noted in a review by Hay and Poyner,^[78] 6 studies have evaluated plasma^[79–83] or urine^[84] CGRP concentrations in women with menopausal hot flashes. All studies found an association between higher CGRP and hot flash frequency, with one-half also showing temporal increases in plasma CGRP at the time hot flashes occurred.^[79,82,83] In a study of castrated male rats, CGRP caused skin temperature elevations^[85,86] that were resolved with testosterone or estradiol replacement therapy.^[86] In addition, a study of castrated men showed CGRP increases of 46% during hot flashes.^[87] However, a study of aging men without cancer who reported hot flashes

unrelated to surgery, cancer, or cancer treatment failed to find an association between plasma CGRP and hot flashes.^[88] Work in this area needs to be replicated since findings might lead to new treatment options.

Hypoglycemia may trigger menopausal hot flashes. One study of women without cancer found the frequency of hot flashes to be higher during hypoglycemia compared with euglycemia.^[89] Data analysis from this study^[89] and another study of self-reported hot flashes and nutrient intake^[90] indicated that eating provided an average of 90 minutes free from hot flashes. This finding may have implications for preventing weight gain in individuals who snack frequently in an attempt to keep hot flashes at bay. A more recent study of 12 women without cancer investigated the possible association between hot flashes and insulin resistance as interrelated to sympathetic activity; however, there was no significant association between hot flashes and glucose, insulin, or insulin resistance quantified with homeostatic model assessment, nor between hot flash severity and insulin resistance.^[91]

Therapeutic Options

Despite the lack of a full understanding of hot flash etiology, clinical trials testing different hot flash treatment options continue. A wide variety of options have been recommended by experts in the field and/or researched for treating hot flashes in populations with and without cancer. Pharmaceutical therapies include antidepressants, anti-convulsants, antiadrenergics, anticholinergics, progestins, and tibolone. (The antipsychotic veralipride is not included because it has not been approved in the United States and was withdrawn in European markets in 2007. A 2006 review indicated that 3 existing trials of veralipride were of poor quality, with small samples and limited data reporting.) Nutraceutical therapies include herbals, vitamins, and phytoestrogens. Surgical therapy includes the stellate ganglion block. Complementary/behavioral therapies include acupuncture, reflexology, exercise, yoga, relaxation training, paced respiration, clinical hypnosis, mindfulness-based stress reduction (MBSR), and psychoeducational/cognitive behavioral interventions. Treatments within each category are reviewed below.

Information on pharmaceutical therapies is summarized in Table 1, including generic and trade names, medication class, dose, side effects (common and rare but serious), and contraindications. Table 2 contains similar information for nutraceuticals, including the common and botanical names, dose, side effects, and contraindications. It should be noted here that few of these treatments have an empirically established mechanism of action. Therapies appear within these tables in the order in which they appear in text.

TABLE 1. Pharmaceutical Therapies for Hot Flashes: Name, Class, Daily Dose, Side Effects, and Contraindications

GENERIC (TRADE) NAME	CLASS	DAILY DOSE ^a	SIDE EFFECTS		CONTRAINDICATIONS ^b
			COMMON	RARE BUT SERIOUS SIDE EFFECTS	
Venlafaxine (Effexor)	AD	37.5-75 mg	Nausea, headache, somnolence, dry mouth, dizziness, insomnia, constipation.	Increased suicidality, infection, tachycardia.	
Desvenlafaxine (Pristiq)	AD	150 mg	Nausea, headache, dry mouth, hyperhidrosis, dizziness, insomnia, somnolence.	Increased suicidality, serotonin syndrome, neuroleptic malignant syndrome, elevated blood pressure, abnormal bleeding, mania/hypomania.	MAOIs.
Citalopram (Celexa)	AD	10-20 mg	Nausea, dry mouth, somnolence, insomnia.	Increased suicidality, tachycardia, migraine, pulmonary embolism.	MAOIs.
Paroxetine (Paxil)	AD	10-35 mg	Nausea, somnolence, dry mouth, headache, asthenia, constipation, dizziness, insomnia, ejaculatory disturbance.	Increased suicidality, neuroleptic malignant syndrome, serotonin syndrome, hallucination, slow heartbeat, anemia.	MAOIs, thioridazine, pimozide.
Fluoxetine (Prozac)	AD	20 mg	Nausea, headache, insomnia, nervousness, anxiety, somnolence, asthenia.	Neuroleptic malignant syndrome, serotonin syndrome, bronchospasm, stomach ulcer, hepatitis.	MAOIs, thioridazine, pimozide.
Sertraline (Zoloft)	AD	20-100 mg	Nausea, headache, insomnia, diarrhea, dry mouth, ejaculation failure, somnolence, dizziness.	Neuroleptic malignant syndrome, serotonin syndrome, hemorrhage, hepatitis, bleeding ulcer, fever.	MAOIs.
Mirtazapine (Remeron)	AD	30 mg	Somnolence, dry mouth, increased appetite, weight gain.	Increased suicidality, serotonin syndrome, erectile dysfunction, toxic epidural necrosis, hallucinations, seizure, partial transitory deafness.	MAOIs.
Moclobemide (Manerix)	AD	150-300 mg	Headache, anxiety, blurred vision, dizziness, high blood pressure, irritability.	Aggressive behavior, chest pain, memory problems, difficulty with speech, depression.	Acute confusional state, tricyclic antidepressants.
Gabapentin, pregabalin (Neurontin)	AC	200-900 mg	Dizziness, somnolence, ataxia.	Severe allergic rash, behavior changes, confusion, difficult or painful urination, fever, memory problems, new or worsening mental or mood changes.	
Clonidine (Catapres)	AH	0.1 mg	Dry mouth, drowsiness, dizziness, constipation, sedation.	Bradycardia, congestive heart failure, agitation, anxiety.	
Methyldopa (Aldomet)	AH	375-1125 mg	Clinical edema or weight gain, nausea, dizziness, fatigue.	Involuntary choreoathetotic movements.	Hepatic disease, liver disorders, MAOIs.
Belladonna, ergotamine, phenobarbital (Bellergal)	BA	0.2 mg, 0.6 mg, 40 mg	Blurred vision, dry mouth, tingling, somnolence.	Difficulty breathing, nausea, vomiting, impaired vision, confusion.	Coronary or peripheral vascular disease, hypertension, impaired hepatic or renal function.
Progestins (Megace)	SH	40 mg	Diarrhea, weight gain, nausea, rash, hypertension.	Cardiomyopathy, leukopenia.	Pregnancy.
Tibolone (Livial)	SH	1.5-2.5 mg	Lower abdominal pain, abnormal hair growth, vaginal discharge/bleeding.	Increased risk of breast cancer, endometrial cancer, stroke.	Pregnancy, history of breast or endometrial cancer, liver disease.
Cyproterone (Androcur)	SH	100 mg	Somnolence, drowsiness, skin sensitivity to sunlight.	Bleeding, blistering, burning, coldness, or discoloration of skin.	Ethinyl estradiol, pregnancy, history of blood clots.
Adjunct therapy: zolpidem (Ambien)	SE	10 mg	Drowsiness, dizziness, and diarrhea.	Syncope, cerebrovascular disorder, hypertension, ataxia, euphoria.	

AD indicates antidepressant; MAOI, monoamine oxidase inhibitor; AC, anticonvulsant; AH, antihypertensive; BA, barbiturate, ergot alkaloid, and anticholinergic; SH, steroid hormone; SE, sedative/hypnotic.

^aDaily dose taken from published trials.

^bContraindications (if available) are from the most recent US Food and Drug Administration label or trial publications. All agents are contraindicated in persons previously shown to be intolerant.

TABLE 2. Nutraceutical Therapies for Hot Flashes: Name, Dose, Side Effects, and Contraindications

COMMON (BOTANICAL) NAME	DAILY DOSE ^a	SIDE EFFECTS	CONTRAINDICATIONS ^b
Black cohosh (<i>Cimicifuga racemosa</i>)	2.5-3150 mg	Gastrointestinal distress, cramping, headaches, rash, weight gain.	
St. John's wort (<i>Hypericum perforatum</i>)	Up to 5400 mg of dry herb (or hypericin exact 20%-30%)	Insomnia, vivid dreams, restlessness, anxiety, irritability.	Coadministration of Vfend, Velcade, Viramune, Norvir, and drugs metabolized through cytochrome P450 enzymes.
Vitamin E (tocopherol)	800 IU	May worsen clotting problems in individuals whose levels of vitamin K are too low, speed vision loss in patients with retinitis pigmentosa, aggravate bleeding disorders, and increase the risk of prostate and head and neck cancer recurrence.	Heart disease, diabetes, and hypertension.
Vitamin B9 (folic acid)	5 mg	Anorexia, nausea, insomnia, irritability.	
Soy isoflavones	54 mg	Nausea, vomiting, gastrointestinal distress.	
Red clover (<i>Trifolium pratense</i>)	40-120 mg	Rash, muscle aches, headache, nausea, vaginal spotting.	
Flax seed (<i>Linum usitatissimum</i>)	25-410 mg	Bloating, gas, diarrhea, stomach aches, nausea.	

^aDaily dose taken from published trials.

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Some therapies have shown strong, positive results in one population but remain relatively unstudied in other populations. Other therapies have remained relatively unproven, have equivocal evidence, or have not been widely studied. Differences in dosing, measures, and trial design may be factors contributing to equivocal evidence. Regarding trial duration, a pooled analysis of 5 studies (n = 641 patients) found no evidence that hot flash scores continued to decline after 4 weeks of therapy with gabapentin, paroxetine, or sertraline.⁹² Whether trial duration is a factor contributing to equivocal results for other agents is open to debate.

Tables 3,⁹³⁻¹²⁴ 4,¹²⁵⁻¹³⁵ and 5¹³⁶⁻¹⁵⁰ provide a summary of the level of evidence for each therapy in patients with breast cancer, prostate cancer, and other cancers for pharmaceutical therapies (Table 3), nutraceuticals (Table 4), and complementary/behavioral therapies (Table 5). The classification for these levels of evidence is based on definitions used in the Oncology Nursing Society Putting Evidence into Practice national initiative.¹⁵¹ Again, therapies appear within these tables in the order in which they appear in text.

Pharmaceuticals

Antidepressants

Venlafaxine and Desvenlafaxine. Venlafaxine and its metabolite desvenlafaxine are selective serotonin and norepinephrine reuptake inhibitors metabolized through the CYP2D6 pathway and appear to be reasonably safe to use in patients taking tamoxifen.¹⁵² Substantial research supports venlafaxine for the treatment of hot flashes in

women with breast cancer.^{93,94,153,154} The first investigation enrolled 23 patients with breast cancer and 5 patients with prostate cancer, 54% of whom reported a reduction of 50% or higher in hot flashes after 4 weeks of venlafaxine at a dose of 25 mg daily (12.5 mg twice a day).⁹⁴ In a follow-up dose-response study, 191 participants with breast cancer or who expressed concerns regarding the breast cancer risk associated with hormonal medications were randomized to treatment with venlafaxine at a dose of 37.5 mg, 75 mg, or 150 mg daily for 4 weeks.⁹³ Efficacy was greatest at the 75-mg dose, with a 61% reduction in the median daily hot flash score.⁹³ Continued follow-up of 102 participants showed a sustained reduction over time,¹⁵⁴ with side effects including nausea, nervousness, and constipation. In addition, among 77 patients with breast cancer, physiological monitor-recorded hot flashes were reduced 22% more than placebo with venlafaxine at a dose of 37.5 mg per day and 14% more than placebo with venlafaxine at a dose of 75 mg per day.⁹⁵ In 80 women without cancer, venlafaxine at a dose of 75 mg significantly improved hot flash scores and quality of life after 12 weeks.¹⁵⁵ In addition, desvenlafaxine at a dose of 150 mg per day significantly decreased hot flashes compared with placebo, whereas doses of 100 mg per day were not more effective than placebo when used for 12 weeks¹⁵⁶ or 26 weeks.¹⁵⁷

A recent study augmented venlafaxine and other antidepressants with a hypnotic agent in an attempt to optimize hot flash therapy by improving sleep and quality of life.¹²⁴ Women with breast cancer who were experiencing hot flashes and night sweats were randomized to receive either zolpidem at a dose of 10 mg or placebo for 5 weeks.

TABLE 3. Pharmaceutical Therapies for Hot Flashes: Levels of Evidence and Recommendations for Use in Practice

GENERIC (TRADE) NAME	LEVEL OF EVIDENCE	POPULATION	EVIDENCE BASE	USE?
Venlafaxine hydrochloride (Effexor)	Recommended for practice. Strong evidence from multiple rigorously designed studies.	Breast	Three studies found reductions in hot flash frequency and severity ⁹³⁻⁹⁵ . Tolerability poor when dose is not tapered ⁹⁶ .	Yes, caveats for side effects.
		Prostate	One pilot study including 5 patients with prostate cancer showed positive results ⁹⁴ . Results of RCT found venlafaxine is less effective than progestins ⁹⁷ .	No.
		Other	None.	No.
Desvenlafaxine (Pristiq)	Likely to be effective. Two RCTs in non-cancer populations show support.	Breast	None.	No.
		Prostate	None.	No.
		Other	None.	No.
Citalopram hydrobromide (Celexa)	Recommended for practice. Multiple RCTs showing positive results, one longer-term study reported null findings.	Breast	Phase 3 controlled trial found significant reductions in hot flash frequency and severity ⁹⁸ .	Yes.
		Prostate	None.	No.
		Other	None.	No.
Paroxetine hydrochloride (Paxil)	Likely to be effective. Two RCTs and 3 uncontrolled trials in breast and prostate cancer.	Breast	Uncontrolled trials and RCTs showed significant reduction in hot flash frequency and severity ⁹⁹⁻¹⁰² .	Yes, caveats for side effects.
		Prostate	Uncontrolled trial showed improvements in hot flash frequency, severity, mood, and anxiety ¹⁰³ .	Yes, caveats for side effects.
		Other	None.	No.
Fluoxetine (Prozac)	Effectiveness not established. One RCT shows support.	Breast	Phase 3, RCT showed fluoxetine is superior to placebo ¹⁰⁴ .	No.
		Prostate	None.	No.
		Other	None.	No.
Sertraline hydrochloride (Zoloft)	Effectiveness not established. Evidence mixed in 2 RCTs.	Breast	Results of initial RCT found 36% of patients had at least <50% reductions ¹⁰⁵ . Subsequent study was negative ¹⁰⁶ .	No.
		Prostate	None.	No.
		Other	None.	No.
Mirtazapine (Remeron)	Effectiveness not established. Current studies are few and underpowered.	Breast	Nonrandomized and open-label trial showed significant reductions in hot flashes ^{107,108} .	No.
		Prostate	None.	No.
		Other	None.	No.
Moclobemide (Manerix)	Effectiveness not established. Single small-sample study.	Breast	None.	No.
		Prostate	None.	No.
		Other	None.	No.
Gabapentin, pregabalin (Neurontin)	Recommended for practice. Strong evidence from multiple rigorous studies.	Breast	Randomized multiinstitutional trial of 900-mg dose showed <49% reduction in hot flash severity at wk 4, and 46% at wk 8 ¹⁰⁹ .	Yes, caveats for side effects.
		Prostate	Phase 3, double-blind, placebo-controlled trial showed <50% reduction in hot flashes, with results maintained 8 wk later ^{110,111} .	Yes, caveats for side effects.
		Other	None.	No.

TABLE 3 (Continued)

GENERIC (TRADE) NAME	LEVEL OF EVIDENCE	POPULATION	EVIDENCE BASE	USE?
Clonidine hydrochloride (Catapres)	Benefit balanced with harm. Ten studies reviewed in 2006, with 3 of fair quality, concerns over side effects.	Breast	Two fair-quality RCTs: one showed 37% reduction at 4 wk ^{112,113} . Comparative trials suggest that clonidine is well-tolerated in comparison with other agents.	Yes.
		Prostate	Positive case reports not confirmed with RCT ¹¹⁴⁻¹¹⁶	No.
		Other	None.	No.
Methyldopa (Aldomet)	Effectiveness not established. Three poor-quality studies.	Breast	None.	No.
		Prostate	None.	No.
		Other	None.	No.
Belladonna, ergotamine, phenobarbital (Bellergal)	Effectiveness unlikely. Negative results in single RCT.	Breast	None.	No.
		Prostate	None.	No.
		Other	None.	No.
Progestins (Megace)	Benefit balanced with harm. Three studies show positive results; however, side effect profiles and long-term acceptability are concerns.	Breast	9-wk crossover study showed significant reduction in hot flashes, long-term follow-up showed 75% of participants reporting hot flashes after 3 y ^{117,118} . RCT of 40-mg dose reported >75% reduction in hot flashes ¹¹⁹	Yes, caveats for side effects and risk.
		Prostate	9-wk crossover study showed significant reduction in hot flashes in 66 patients with prostate cancer ¹¹⁷ . Follow-up study showing patients still reporting hot flashes after 3 y ¹¹⁸	Yes, caveats for side effects and risk.
		Other	None.	No.
Tibolone (Livial)	Effectiveness not established. Initial trials positive, LIBERATE trial suggests increased risk of breast cancer recurrence.	Breast	Three pilots and a large RCT in patients with breast cancer found tibolone alleviated symptoms; the RCT showed an increased risk of breast cancer recurrence ¹²⁰⁻¹²³	No.
		Prostate	None.	No.
		Other	None.	No.
Cyproterone acetate (Androcur)	Effectiveness not established. Only one RCT.	Breast	None.	No.
		Prostate	Comparison study of venlafaxine, medroxyprogesterone acetate, and cyproterone showing a reduction of 83% in the cyproterone group with no significant difference from medroxyprogesterone ⁹⁷	No.
		Other	None.	No.
Adjunct therapy: zolpidem (Ambien)	Effectiveness not established. Single study using zolpidem to augment venlafaxine.	Breast	Augment to venlafaxine improved sleep outcomes ¹²⁴	No.
		Prostate	None.	No.
		Other	None.	No.

RCT indicates randomized controlled trial; LIBERATE trial, Livial Intervention Following Breast Cancer: Efficacy, Recurrence and Tolerability Endpoints trial.

Those who were using antidepressants continued their use and nonusers began venlafaxine at a dose of 75 mg per day. Of the 53 women randomized, more patients augmented with zolpidem than placebo reported an

improvement in subjective sleep quality as measured by the Pittsburgh Sleep Quality Index¹²⁴. These findings suggest that combination therapy may be an option for those reporting both hot flashes and sleep problems.

TABLE 4. Nutraceutical Therapies for Hot Flashes: Levels of Evidence and Recommendations for Use in Practice

COMMON (TAXA)	LEVEL OF EVIDENCE	POPULATION	EVIDENCE BASE	USE?
Black cohosh (<i>Cimicifuga racemosa</i>)	Not recommended for practice. Phase 3 trial failed to find significant effect.	Breast	Standard clinical trial failed to show superiority over placebo ¹²⁵	No.
		Prostate	None.	No.
		Other	None.	No.
St. John's wort (<i>Hypericum perforatum</i>)	Effectiveness unlikely. Negative results at endpoint of single RCT.	Breast	RCT utilizing 900 mg of dry herb daily for 3 mo results in no significant difference in hot flash scores ¹²⁶	No.
		Prostate	None.	No.
		Other	None.	No.
Homeopathic herbs (exact agents vary)	Not recommended for practice. Two RCTs failed to show benefits over placebo.	Breast	Although an uncontrolled study showed benefit, 2 RCTs of homeopathy failed to find benefits over placebo ¹²⁷⁻¹²⁹	No.
		Prostate	None.	No.
		Other	None.	No.
Vitamin E	Effectiveness unlikely. Negative results at endpoint of single RCT; concerns of carcinogenicity.	Breast	Single well-designed crossover RCT showed subjective decrease in hot flashes in 120 patients with breast cancer. However, reduction amounted to average of one hot flash per d ¹³⁰ Subsequent study showed only a 7% reduction in hot flashes from baseline compared with 40% with gabapentin ¹³¹	No.
		Prostate	None.	No.
		Other	None.	No.
Vitamin B9	Effectiveness not established. Single study in healthy women yielded initially positive results.	Breast	None.	No.
		Prostate	None.	No.
		Other	None.	No.
Soy isoflavones	Effectiveness not established. Meta-analyses suggest improvement over placebo, but 2 RCTs in patients with breast cancer were negative.	Breast	2 RCTs found no evidence that soy was more effective than placebo ^{132,133}	No.
		Prostate	One study failed to show benefit over placebo ¹³⁴	No.
		Other	None.	No.
Red clover (<i>Trifolium pretense</i>)	Not recommended for practice. Only one study of fair quality reported a significant reduction; a recent 4-arm RCT did not exceed placebo.	Breast	None.	No.
		Prostate	None.	No.
		Other	None.	No.
Flax seed (<i>Linum usitatissimum</i>)	Not recommended for practice. Initial pilot study results were mixed, 3 RCTs were negative.	Breast	Phase 3, placebo-controlled randomized double-blind trial failed to show significant difference from placebo ¹³⁵	No.
		Prostate	None.	No.
		Other	None.	No.

RCT indicates randomized controlled trial.

Citalopram and Escitalopram. Citalopram and its isomer escitalopram are selective serotonin reuptake inhibitors generally used to treat depression and generalized anxiety disorder. Citalopram and escitalopram are weak inhibitors of CYP2D6 and theoretically might interfere with tamoxifen metabolites. Overall, there is a larger body of evidence for citalopram

than escitalopram in breast cancer survivors, but these agents have not been studied in patients with prostate or other cancers.

Short-term research in women with and without cancer has been generally positive but one longer-term study reported null findings, suggesting these agents may not provide long-term relief from hot flashes. Six weeks of

TABLE 5. Complementary/Behavioral Therapies for Hot Flashes: Levels of Evidence and Recommendations for Use in Practice

THERAPY	LEVEL OF EVIDENCE	POPULATION	EVIDENCE BASE	USE?
Acupuncture	Effectiveness not established. Results from multiple reviews suggest methodological weaknesses across multiple studies, leading to unconvincing supporting evidence.	Breast	Six RCTs, one RCT of acupuncture vs sham acupuncture reported a 50% reduction in hot flashes by the end of treatment and a 66% reduction at 12 wk of follow-up. ¹³⁶⁻¹⁴¹	No.
		Prostate	Two uncontrolled trials were positive. ^{142,143}	No.
		Other	None.	No.
Reflexology	Not recommended for practice. Single RCT reported null findings.	Breast	None.	No.
		Prostate	None.	No.
		Other	None.	No.
Exercise	Effectiveness not established. Multiple RCTs failed to provide convincing results for efficacy; many trials were underpowered.	Breast	None.	No.
		Prostate	None.	No.
		Other	None.	No.
Yoga	Effectiveness not established. Efficacy for hot flashes is not yet supported. Clinical significance of positive outcomes not substantiated.	Breast	Randomized wait-list-controlled study showed significant improvements relative to control in hot flash frequency and severity, joint pain, fatigue, sleep disturbance, bother, and vigor, with improvements maintained at 3 mo of follow-up. Total hot flash score reduction (31%) was within the range found in placebo used in medication trials. ¹⁴⁴	Yes. ^a
		Prostate	None.	No.
		Other	None.	No.
Relaxation training	Effectiveness not established. Insufficiently powered RCTs to evaluate specific dose and type of relaxation training that alleviates hot flashes. Clinical significance of outcomes not substantiated.	Breast	RCT of single-session relaxation training and daily practice recordings vs a no-treatment control showed improvements in the treatment condition of 22% fewer hot flashes at end of one mo with improvement maintained at 3 mo of follow-up. ¹⁴⁵	Yes. ^a
		Prostate	None.	No.
		Other	None.	No.
Paced respiration	Effectiveness not established. Insufficiently powered RCTs to evaluate specific dose and type of relaxation training that alleviates hot flashes. Clinical significance of outcomes not substantiated.	Breast	A 16-wk, 3-group RCT of paced respiration found no significant differences in hot flash frequency, severity, or bother at 8 wk or 16 wk after randomization. Statistically significant differences in secondary did not achieve clinical significance. ¹⁴⁶	No.
		Prostate	None.	No.
		Other	None.	No.
Clinical hypnosis	Likely to be effective. Results from several studies were positive; recent large-sample RCT was positive.	Breast	Two studies in patients with breast cancer, ^{147,148} one study with 51 patients with breast cancer randomized to clinical hypnosis vs wait-list control showed 68% reductions in hot flashes in hypnosis condition.	Yes. ^a
		Prostate	None.	No.
		Other	None.	No.
Mindfulness-based stress reduction	Effectiveness not established.	Breast	Randomized wait-list-control trial showed no differences at endpoint and small improvements (27% vs 11% in control) at 3 mo of follow-up. ¹⁴⁹	No.
		Prostate	None.	No.
		Other	None.	No.
Psychoeducation/CBT	Effectiveness not established.: Insufficient trials to establish efficacy, clinical significance of outcomes not substantiated.	Breast	RCT in 3 arms (group CBT, self-help CBT, and no treatment control) showed significant reductions in night sweats in group and self-help CBT conditions. hot flash reductions were nonsignificant vs control. ¹⁵⁰	No.
		Prostate	None.	No.
		Other	None.	No.

RCT indicates randomized controlled trial; CBT, cognitive behavioral therapy.

^aYes: recommended on the basis of initial outcomes, no side effects and positive secondary outcomes, but not yet evidence-based.

citalopram at doses of 10 mg, 20 mg, or 30 mg per day was found to be more effective than placebo at decreasing hot flash frequency, severity, and interference in a sample of 254 women that included women with breast cancer.⁹⁸ A dose response was not seen for frequency or severity but effects on hot flash interference were greatest at the 20-mg dose.⁹⁸ Similarly, 8-week trials have shown escitalopram at a dose of 10 mg per day (titrated up to 20 mg per day) to be superior to placebo for menopausal symptoms in depressed women¹⁵⁸ and nondepressed women.¹⁵⁹ In an open-label, 8-week trial of escitalopram among 32 women with major depressive disorder, researchers found that 10 mg of escitalopram (titrated up to 20 mg) created a decrease of greater than 50% in menopausal symptom scores on the Greene Climacteric Scale in 56% of those taking escitalopram versus 31% of those receiving hormone therapy.¹⁵⁸ In a recent, randomized, double-blind placebo-controlled multicenter trial of 205 postmenopausal women, 10 mg daily of escitalopram (titrated up to 20 mg) over 8 weeks provided 55% of the women in the treatment group with a clinically significant decrease in hot flashes versus 36% in the control group.¹⁵⁹ Furthermore, the escitalopram group showed significantly greater reductions in hot flash severity¹⁵⁹ and hot flash interference in daily life.¹⁶⁰ In a longer, 9-month study, citalopram and fluoxetine (dosed at 10 mg for 1 month, 20 mg for 5 months, and 30 mg for 3 months) were no more effective than placebo in decreasing subjective hot flashes in a study of 150 women.¹⁶¹ However, this study did not have a true pretreatment baseline; rather, baseline was concurrent with medication initiation.

Paroxetine, Fluoxetine, and Sertraline. Paroxetine, fluoxetine, and sertraline are reviewed together here because they are all selective serotonin reuptake inhibitors that are CYP2D6 inhibitors that may interfere with tamoxifen metabolism. We note that the data for sertraline are weaker than for the other 2 agents. In their comprehensive review, Nelson et al¹⁶² differentiated the strength of evidence across trials for paroxetine and fluoxetine according to whether study participants were using tamoxifen. Greater benefits were seen in those using tamoxifen, with the reduction in hot flashes in those not using tamoxifen approaching 0 hot flashes per day.¹⁶² However, this review classified tamoxifen users at the study level and not the individual level so that if any patients were taking tamoxifen, the entire sample was considered as taking tamoxifen. To further assess this issue at the patient level, Bardia et al¹⁶³ attempted to pool analyses for several agents. Although the review concluded that results were similar across users and nonusers, there are several limitations, including pooling across agents that are and are not metabolized through CYP2D6 and the use of data from trials not originally powered for this type of analysis,

with resulting small samples within subgroups and wide CIs. Thus, we still do not have any evidence as to whether some of the favorable evidence discussed below may have been due to drug-drug interaction leading to the alleviation of hot flashes via a reduction in tamoxifen metabolites.

Paroxetine in doses of 10 mg to 36.5 mg per day improved hot flash frequency, severity, mood, anxiety, and quality of life in 3 uncontrolled trials involving patients with breast (including tamoxifen users) and prostate cancer.^{99,100,103} Similarly, in a randomized controlled trial of 165 menopausal women (including tamoxifen users), there were overall decreases in hot flash scores of 62% in the group receiving paroxetine at a dose of 12.5 mg and 65% in the 25-mg group compared with a 38% reduction in the placebo group.¹⁰¹ In a randomized crossover trial of 151 patients with breast cancer (including tamoxifen users), patients who received 10 mg of paroxetine showed a 46% reduction in hot flash scores while those who received 20 mg had a 56% reduction.¹⁰² Although the efficacy in both doses showed a comparable reduction, 10 mg of paroxetine was reported by patients to result in fewer side effects and less treatment discontinuation.¹⁰² Fluoxetine at a dose of 20 mg per day was superior to placebo in reducing hot flashes in a study of 80 women with a history of breast cancer (including tamoxifen users).¹⁰⁴ For sertraline, an initial randomized crossover study compared sertraline with placebo in 62 patients with breast cancer (including tamoxifen users).¹⁰⁵ Results showed that 36% of patients taking 50 mg of sertraline daily had at least a 50% or greater reduction in the frequency of their hot flashes compared with a 27% reduction in patients receiving placebo.¹⁰⁵ However, another study in women with or at high risk of breast cancer (including tamoxifen users) failed to find efficacy for sertraline for hot flashes.¹⁰⁶ In a double-blind, placebo-controlled crossover study of 102 midlife women without cancer, sertraline was superior to placebo for reducing hot flash scores but not hot flash severity.¹⁶⁴

Mirtazapine. Mirtazapine, a nonadrenergic and selective serotonergic antidepressant, is a potent antagonist of noradrenergic receptor alpha-2,⁶⁹ which may contribute to the therapeutic effect reported in case studies.¹⁶⁵ A nonrandomized study of mirtazapine at a dose of 15 mg to 30 mg per day showed a 59% reduction in hot flashes in 22 women with a risk or history of breast cancer.¹⁰⁷ Recently, an open-label trial was conducted to assess the efficacy of mirtazapine for relieving vasomotor symptoms in 40 patients with breast cancer.¹⁰⁸ Results showed a 56% reduction in hot flash frequency and a 62% reduction in hot flash scores as compared with baseline; however, only 20 participants (50%) completed the 12-week study. The limited sample size and compliance problem were likely due to side effects, with the most frequent being somnolence. Although this

pilot information does suggest some benefits, this agent has not been studied in a rigorous, randomized, placebo-controlled clinical trial.

Moclobemide. Moclobemide is a monoamine oxidase inhibitor not available in the United States. Use of this agent requires that patients follow a series of restrictions for foods, beverages, and other medications. In one study, 30 women without cancer were randomized to 3 groups: 300-mg dose, 150-mg dose, or placebo.¹⁶⁶ Reductions from baseline in each group were 35% (300-mg dose), 70% (150-mg dose), and 24% (placebo). However, the limited data analysis, in which comparisons with placebo were not reported, and the small sample size indicate the evidence for this agent is currently insufficient.¹⁶²

Anticonvulsants

Gabapentin/Pregabalin. Multiple reports indicate that gabapentin, an anticonvulsant used to treat seizures and some chronic pain syndromes, demonstrates efficacy in treating hot flashes. The clinical effects of gabapentin are thought to be mediated by its binding to the alpha 2-delta 1 and alpha 2-delta 2 subunits of the voltage-gated calcium channels, which present widely in the periphery and in the brain, respectively.^{167,168} In women without cancer, 4 randomized controlled trials found that gabapentin at doses of 600 mg to 2400 mg per day reduced hot flash frequency and/or intensity.^{169–172} Two of these trials reported comparable efficacy between gabapentin (600 mg at night)¹⁶⁹ or gabapentin titrated to 2400 mg daily and estrogen therapy arms (transdermal estrogen at a dose of 25 µg daily or conjugated estrogens at a dose of 0.625 mg daily).^{169,172} In women taking tamoxifen and men with prostate cancer, 2 case studies reported rapid improvement in hot flashes within 1 to 3 days with gabapentin at a dose of 200 mg to 900 mg per day.^{173,174} These initial positive findings have held in randomized controlled trials. In breast cancer survivors, a randomized, double-blind, placebo-controlled, multiinstitutional trial of gabapentin at a dose of 900 mg per day provided a 49% and 46% reduction in hot flash severity scores at weeks 4 and 8, respectively, compared with 21% and 15% reductions, respectively, in the placebo group and 33% and 31% reductions, respectively, in the 300-mg dose group.¹⁰⁹ Similarly, a study of men with prostate cancer found a moderate (approximately 50%) reduction in hot flashes, without any evidence of side effects surpassing that of placebo.¹¹⁰ In a longitudinal continuation study from the same sample, the moderate reductions in hot flash frequency and severity were maintained for an additional 8 weeks with minimal toxicities.¹¹¹ Interestingly, when patients with breast cancer were randomized to gabapentin (900 mg per day) plus continued or discontinued antidepressants for hot flashes (eg, venlafaxine,

paroxetine, other), both treatment arms showed a similar reduction in hot flashes at 4 weeks of follow-up.¹⁷⁵ In other words, there was no additional benefit to adding gabapentin to antidepressant therapy.

Antiadrenergics

Clonidine. Clonidine, a centrally acting antiadrenergic agent, was first reported to reduce menopausal hot flashes in women in 1974.¹⁷⁶ A review done in 2006 summarized 10 equivocal studies comparing clonidine with placebo, with 7 being of poor quality and 3 being of fair quality.¹⁶² Two of the 3 fair-quality trials included women with breast cancer.^{112,113} Although clonidine appeared to be more effective than placebo, concerns about side effects were raised. In one study, 48% of women with breast cancer reported clonidine to be more effective than placebo, and only 31% preferred clonidine when asked to consider side effects.¹¹² A subsequent trial in patients with breast cancer showed that oral clonidine compared with placebo decreased hot flash frequency at 4 weeks (37% vs 20%) and 8 weeks (38% vs 24%).¹¹³ Quality-of-life scores improved with treatment and the only significant side effect was difficulty sleeping.¹¹³

Results from men with prostate cancer are less encouraging. Although 3 case reports of men with prostate cancer (12 men total) have described reductions in hot flashes with transdermal or oral clonidine in doses at or exceeding 0.1 mg,^{114,115} a randomized, double-blind, crossover trial failed to confirm these results.¹¹⁶ Seventy men with prostate cancer received transdermal clonidine at a dose of 0.1 mg followed by placebo or placebo followed by clonidine.¹¹⁶ No statistically significant decreases in hot flash frequency were seen.¹¹⁶ When asked to indicate their preference, 47% of patients could not tell which was better, 34% preferred clonidine, and 19% preferred placebo.¹¹⁶

Methyldopa. Methyldopa is an alpha-2 adrenergic agonist commonly used to control hypertension. Three poor-quality studies of methyldopa were included in a 2006 review.¹⁶² All studies appeared to include women without cancer but sample sizes were small (10 patients–40 patients) and superiority over placebo was not established. This agent is not recommended based on the quality of the existing evidence.

Anticholinergics

Bellergal retard consists of belladonna alkaloids, ergotamine tartrate, levorotatory alkaloids, and phenobarbital. Two randomized trials have investigated the efficacy of bellergal to reduce hot flashes.¹⁷⁷ In one double-blind study, 66 women without cancer received either 1 tablet of Bellergal per day or placebo. No significant group differences were seen after 8 weeks of treatment.¹⁷⁷ In another study, women received either placebo or 2 tablets of Bellergal per

day for 6 weeks ($n = 64$), with a subset crossing over to the opposite agent and/or completing assessments at 12 weeks ($n = 50$).¹⁷⁸ Hot flashes were reported to be significantly less with the medication; however, outcomes of symptoms and response to therapy were based on nurses' assessments of patients and the data presented in this article are minimal.¹⁷⁸ Given the lack of strong evidence and potential addictive risk, Bellerger cannot be recommended as an effective, safe treatment for the alleviation of hot flashes.

Progestins and Tibolone

Megestrol acetate, an antineoplastic progestin, is used to treat endometrial cancer and palliate patients with advanced endometrial and breast cancer. This agent demonstrates efficacy in reducing hot flashes in individuals with breast or prostate cancer. Megestrol acetate (at a dose of 20 mg daily) was found to significantly decrease hot flashes in a 9-week crossover study of 97 women with breast cancer and 66 men with prostate cancer.¹¹⁷ Long-term follow-up showed that only 9% of the women with breast cancer had discontinued the drug; 75% were still having hot flashes after 3 years, with 41% of those continuing on the drug reporting breakthrough hot flashes.¹¹⁸ In a 6-month, randomized, placebo-controlled trial of megestrol acetate in 2 doses versus placebo for the treatment of hot flashes in breast cancer survivors, 14% of participants receiving the placebo, 65% of participants receiving the 20-mg dose, and 48% of participants receiving the 40-mg dose reported a greater than 75% reduction in hot flashes compared with baseline.¹¹⁹

Another progestin, intramuscular depot medroxyprogesterone acetate, was shown to be equally as effective as megestrol acetate. In one randomized study of 71 postmenopausal patients with breast cancer, long-term relief of symptoms 6 months after the study was higher in the depot medroxyprogesterone acetate group.¹⁷⁹ Although these agents show promise in treating hot flashes, concerns over stimulating breast and prostate cancer recurrence may limit their prescription.^{118,180} Efficacy in reducing hot flashes should be balanced with concerns.

Tibolone, a synthetic steroid, possesses tissue-specific activity that may result from metabolism, enzyme regulation, and receptor activation varying between tissues.^{181,182} The complex mechanism of tibolone involves the rapid metabolism of the drug within the intestine and liver into active estrogenic metabolites, and a third metabolite, delta-4 isomer, which binds to both progesterone and androgen receptors.^{181,183} In Europe, tibolone has been used as a treatment for vasomotor symptoms; however, it is not available in the United States.¹⁸⁴ Placebo-controlled trials have shown positive results with tibolone as a potential treatment for hot flashes in healthy postmenopausal women. Results from a recent double-blind study found

the effects of tibolone to be comparable to estrogen trials in 437 postmenopausal women.¹⁸⁵ Furthermore, pilot studies of tibolone in patients with breast cancer receiving adjunctive tamoxifen treatment showed a reduction in hot flashes.¹²¹⁻¹²³

Despite the initially beneficial results, the Million Women Study ($N = 3098$) suggested that tibolone increased the risk of breast cancer recurrence, while alleviating vasomotor symptoms and preventing bone loss.¹⁸⁶ Results of another trial of tibolone in postmenopausal women with low bone density revealed a decrease in breast cancer events.¹⁸⁷ One potential explanation for these mixed results is that tibolone may affect healthy breast tissue differently from cancerous tissue.¹⁸⁸ The LIBERATE (Livial Intervention Following Breast Cancer: Efficacy, Recurrence and Tolerability Endpoints) trial was conducted to further determine the effects and safety of tibolone as a potential treatment of vasomotor symptoms. Results from the LIBERATE trial showed that tibolone was effective in reducing hot flashes and improving quality of life in symptomatic patients with breast cancer.¹²⁰ However, tibolone did increase the risk of recurrence. Evidence to date suggests that tibolone is not recommended to alleviate hot flashes in breast cancer survivors with no available data in other cancer populations.

Comparative Effectiveness of Pharmaceutical Therapies

Three trials have directly compared venlafaxine with clonidine. In one randomized double-blind study of 80 breast cancer survivors, venlafaxine at a dose of 37.5 mg per day was significantly more effective in reducing hot flash frequency and severity at 4 weeks follow-up compared with clonidine at a dose of 0.075 mg per day.¹⁸⁹ However, this study was originally designed as a crossover trial but the crossover portion was not completed. In addition, the medication doses were lower for both drugs than previously studied. In a double-blind crossover study, 60 breast cancer survivors were randomized to receive venlafaxine at a dose of 75 mg or clonidine at a dose of 0.05 mg before switching to the opposite agent. There was a similar reduction in hot flashes (55% vs 49%) during the first study arm but without tapering up of the venlafaxine dose, there were significantly more side effects with venlafaxine.⁹⁶ Dosing for depression typically starts at 75 mg per day but in hot flash studies, dosing has more typically started at 37.5 mg per day for one week prior to tapering up to a dose of 75 mg per day.¹⁹⁰ In a third study, 102 breast cancer survivors were randomized to venlafaxine at a dose of 75 mg, clonidine at a dose of 0.1 mg, or placebo (2:2:1 ratio), with data from 80 women available at 12 weeks of follow-up.¹⁹¹ Again, there was a similar reduction in hot flashes for both agents, but more side effects were noted in the venlafaxine arm due to the lack of tapering up of the dose. It is important to note that

noninferiority or equivalence between venlafaxine and clonidine cannot be claimed because the studies were not powered for such conclusions.

Two studies have directly compared venlafaxine with other agents. Among 109 breast cancer survivors, venlafaxine at a dose of 75 mg per day was less effective than medroxyprogesterone acetate (46% vs 74% reduction in hot flash scores) after 6 weeks.¹⁹² This study allowed for tapering up of the venlafaxine dose but there were fewer side effects noted in the medroxyprogesterone acetate arm. In another randomized controlled trial of 309 evaluable men with prostate cancer, venlafaxine at a dose of 75 mg per day was less effective than medroxyprogesterone acetate at a dose of 20 mg per day and cyproterone at a dose of 100 mg per day after 6 months of therapy.⁹⁷ There was no tapering up of the venlafaxine dose. Cyproterone is a steroidal antiandrogen that does not appear to have been tested in any other randomized controlled trials.

One study¹⁹³ suggested that breast cancer survivors may prefer venlafaxine over gabapentin. In a crossover trial, 66 breast cancer survivors were randomized to venlafaxine (37.5 mg daily for 7 days followed by 75 mg daily for 21 days) or gabapentin (300 mg once per day for 3 days, followed by 300 mg twice per day, and then 300 mg 3 times a day for 22 days) followed by a 2-week washout and then the opposite agent. More survivors preferred venlafaxine to gabapentin (68% vs 18%). Although both pharmacological treatments reduced hot flashes (66% reduction), venlafaxine also improved mood ($P = .01$). Side effects of venlafaxine included nausea, loss of appetite, and constipation whereas gabapentin was associated with dizziness and increased appetite.¹⁹³

Pooled analyses provide some additional information regarding the comparative efficacy of various pharmaceutical therapies. Loprinzi et al¹⁹⁰ obtained individual patient data from 12 clinical trials published during 2000 to 2007. Forest plots provide evidence of the stacked efficacy of paroxetine greater than gabapentin greater than venlafaxine greater than sertraline.¹⁹⁰

Nutraceuticals

Nutraceuticals include herbal therapies (black cohosh, St. John's wort, and homeopathic herbs), vitamins (vitamin E, multivitamins, and vitamin B9), and phytoestrogens (soy, red clover, and flaxseed). For all of these therapies, differences in or a lack of information about product purity, dosing, and side effects make comparisons across studies difficult. Products lack standardization, partly due to the minimal US Food and Drug Administration oversight of these agents. The evidence for these therapies is detailed below.

Herbals

Black Cohosh (*Cimicifuga racemosa*). Black cohosh, an herb derived from a North American perennial plant, is a widely studied botanical for menopausal symptoms in women¹⁹⁴ but has not been studied in men with prostate cancer. Also known as *Cimicifuga racemosa*, it was historically used as a remedy for menstrual problems. It contains triterpine glycosides, flavonoid, aromatic acids, and numerous other constituents. Black cohosh does not have an estrogenic mechanism of action, but rather acts on serotonin receptors.^{195,196} A meta-analysis showed that 6 out of 9 randomized controlled trials demonstrated potential efficacy for black cohosh to reduce hot flashes.¹⁹⁷ However, it is important to note that most trials were conducted in the 1980s and more recent randomized trials have failed to demonstrate efficacy in women without cancer using doses of 128 mg (7.27 mg of triterpine glycosides)¹⁹⁸ to 3150 mg (2.5% or more of triterpine glycosides).¹⁹⁹ Black cohosh helped alleviate tamoxifen-induced hot flashes when given in doses of 2.5 to 20 mg daily,^{200,201} but was not effective in decreasing hot flashes in mixed samples of tamoxifen users and nonusers at a higher dose of 40 mg per day²⁰² or at an unreported dose.¹²⁵ The most common side effects of black cohosh include mild gastric complaints, headaches, vomiting, and dizziness at higher doses. It is important to note that recent critical reviews have disclaimed previous case reports of liver failure purportedly related to the use of black cohosh.^{203,204}

St. John's Wort (*Hypericum perforatum*). St. John's wort, *Hypericum perforatum*, a perennial herb indigenous to Europe, has been reported to have antidepressant properties. Most studies investigating its potential efficacy for the relief of vasomotor symptoms have been limited to women experiencing natural or surgical menopause with mild to severe symptoms. In one study, a dose of 60 drops per day standardized to 0.2% hypericin extract resulted in a greater reduction in hot flashes on the Blatt-Kupperman Index questionnaire compared with placebo after 4 weeks and 8 weeks of treatment.²⁰⁵ In another study, a dose of 5400 mg of dry herb (990 μ g of hypericin, 9 mg of hyperforin, and 18 mg of glycosides) in combination with *Vitex agnus-castus* (chaste tree/berry; 500 mg of dry fruit) was not more effective than placebo in reducing hot flashes as recorded in daily diaries and standardized questionnaires.²⁰⁶ A recent study randomized 47 women (including 26 patients with breast cancer) to receive either St. John's wort at a dose of 900 mg of dry herb daily (equivalent to 0.3% hypericin extract) or placebo for 3 months.¹²⁶ Group differences in hot flash scores were not significant; however, those taking the herb reported significantly better menopausal quality of life and sleep

quality after 3 months of treatment.¹²⁶ St. John's wort is known to induce cytochrome P450 enzymes CYP3A4, CYP2C19, CYP2C9, and P-glycoprotein and should be avoided in certain individuals.^{207,208}

Homeopathic Herbs. Homeopathy, based on the principals of "*Similia*" first coined by Hippocrates, today is guided by the Homeopathic Pharmacopeia of India. Although uncontrolled trials were initially positive, randomized controlled trials have failed to demonstrate efficacy. An initial pilot study of 31 patients showed that homeopathy was associated with a 48% to 75% reduction in the subjective frequency of hot flashes.²⁰⁹ In an additional uncontrolled study, 45 breast cancer survivors showed improvements in vasomotor symptoms and quality of life.¹²⁷ A third observational study of 438 women without cancer showed a reduction in the frequency of hot flashes and in daily discomfort.²¹⁰ In contrast, 2 randomized controlled trials of homeopathy for menopausal symptoms in breast cancer survivors failed to find any benefits over placebo.^{128,129}

Vitamins

Vitamin E has received attention as possible treatment for the alleviation of hot flashes since the 1940s²¹¹ and has been studied in 3 clinical trials. In one crossover trial, 120 patients with breast cancer were randomized to 4 weeks of vitamin E (800 IU per day) followed by placebo or vice versa.¹³⁰ Although there was a subjective decrease in hot flashes in the vitamin E group, the reduction only amounted to about one hot flash per day.¹³⁰ However, another crossover trial of 50 postmenopausal women without breast cancer comparing 4 weeks of vitamin E (400 IU per day) followed by placebo or vice versa found a greater reduction in hot flash frequency (about 2 hot flashes per day; $P < .0001$) and hot flash severity ($P < .0001$) with vitamin E.²¹² In the third trial, 115 breast cancer survivors received 3 months of vitamin E (800 IU per day) or placebo. With vitamin E, there was a 7% reduction in hot flash scores from baseline as compared with a 40% reduction from baseline with gabapentin at a dose of 900 mg per day.¹³¹ In this trial, 35% of 46 patients assigned to receive vitamin E dropped out within the first month due to a lack of efficacy. Recent meta-analysis of 57 trials (total $n = 246,371$ patients) showed no relationship between all-cause mortality and vitamin E (up to 5500 IU per day). In addition, there is possible contraindication of vitamin E for women with heart disease, diabetes, or hypertension, as well as a concern for carcinogenicity.²¹³

Evidence for other vitamin supplements is mixed. A multivitamin and mineral supplement was studied in a double-blind, randomized, placebo-controlled trial of women without cancer. Both groups improved over time, but at 3 months there was no significant difference in hot flashes

between the group receiving the supplement and the placebo group.²¹⁴ In another study of 46 women without cancer, vitamin B9 (folic acid) at a dose of 5 mg daily for 4 weeks was found to reduce plasma levels of a norepinephrine metabolite²¹⁵ that had been previously investigated for its role in hot flashes. Hot flashes also improved more significantly in the folic acid group than in the placebo group.²¹⁵ Further trials are needed to attempt to replicate these findings in larger, more diverse samples.

Phytoestrogens

Soy Isoflavones. Soy supplements, extracts, and isoflavones have been widely studied for the treatment of hot flashes. Citing inconsistencies in existing reviews, Taku et al²¹⁶ recently conducted a systematic review and meta-analysis of 19 randomized controlled trials of soy isoflavones. Similar to findings from another review,²¹⁷ the conclusion was that soy isoflavones reduce hot flashes to a greater extent than placebo.²¹⁶ The median dose across studies was 54 mg per day. However, these reviews focused only on trials done in women and excluded studies in men. At least one report failed to find any benefit of soy isoflavones over placebo in men with prostate cancer who were experiencing hot flashes due to androgen deprivation therapy.¹³⁴ Reports regarding the safety of soy in men with prostate cancer have been conflicting.²¹⁸

Red Clover (*Trifolium pratense*). Similar in chemical profile to soy, red clover (*Trifolium pratense*) contains genistein, daidzein, formononetin, and biochanin A; however, red clover has higher levels of the O-methylated isoflavone, formononetin, and biochanin A than soy.^{194,219} Red clover has been used for the treatment of menopausal symptoms despite largely negative clinical trials. A meta-analysis of nonhormonal treatments of hot flashes included 6 trials of red clover: one of good quality, 3 of fair quality, and 2 of poor quality.¹⁶² Of these 6 trials, only one fair-quality trial indicated an improvement in the frequency of hot flashes, reporting a 44% reduction with a red clover supplement at a dose of 80 mg per day compared with 0% with placebo.²²⁰ In a more recent, randomized, 4-arm, double-blind clinical trial of black cohosh, red clover, placebo, and hormone therapy, hot flash reductions from red clover at a dose of 398 mg per day (standardized to 120 mg of isoflavones) did not exceed those of placebo.¹⁹⁸ To date, red clover does not appear to be effective for hot flashes in women and it has not been studied in men.

Flax Seed (*Linum usitatissimum*). Flax seed (*Linum usitatissimum*) is the richest source of lignans, another class of phytoestrogens. Flaxseed and its lignans are believed to have estrogen agonist, estrogen antagonist, and antioxidant effects.^{221,222} Three randomized controlled trials have found no benefit of flax seed over placebo for the treatment

of hot flashes in women.^{135,221,222} In one study, 99 women were randomized to receive a daily muffin containing soy flour, ground flax seed, or wheat flour (placebo).²²¹ In a 12-week study, 38 women without cancer were randomized to receive 2 slices of bread per day containing either 25 g of flax seed or wheat bran.²²² In another study, 188 women (including patients with breast cancer) were randomized to receive either a bar containing 410 mg of flax seed or placebo.¹³⁵ No significant improvement in hot flashes was seen for flax seed over placebo in any of the 3 studies. Thus, flax seed does not appear to be beneficial for women and has not been studied in men.

Surgical Therapies

Stellate Ganglion Block

Stellate ganglion block, a procedure in which an anesthetic is injected into the stellate ganglion, has been used to induce a sympathetic block for treating hot flashes. In 2005, Lipov et al²²³ were the first to report using stellate ganglion block to alleviate hot flashes in a case series of 6 breast cancer survivors. The same investigators conducted an uncontrolled pilot study of 13 breast cancer survivors and showed significant reductions in hot flash frequency, severity, and nighttime awakenings during a 12-week follow-up period.²²⁴ In another study, 10 patients with breast cancer received stellate ganglion block, with 8 evaluable patients showing a decrease in the frequency of hot flashes and hot flash scores of 44% and 45%, respectively.²²⁵ No significant adverse events were reported.²²⁵ An additional uncontrolled trial showed similar benefits for reducing hot flash scores (64% after 1 week and 47% after 24 weeks) and improving sleep at 1 week and 24 weeks.²²⁶ In all studies, most women required more than one injection to maintain relief. Further controlled trials are needed to fully test this treatment when used alone or in combination with other therapies.

Complementary/Behavioral Therapies

Acupuncture

There are several conflicting reports surrounding the efficacy of acupuncture for hot flashes, and several reviews exist. For example, in 2009 there were 3 reviews of acupuncture for hot flashes done by Lee et al. One evaluated 6 randomized controlled trials conducted in women without cancer.²²⁷ The second evaluated 6 randomized controlled trials done in women with breast cancer.²²⁸ The third evaluated 6 studies (one randomized controlled and 5 uncontrolled) done in men with prostate cancer.²²⁹ The conclusions in all 3 reviews were that 1) existing studies suffered from methodological weaknesses, including small sample sizes, failure to mask patients or data collectors, and other issues;

and 2) there was an overall lack of supporting evidence for the use of acupuncture for the treatment of hot flashes in these populations.^{227–229}

Subsequent to the above reviews, several additional randomized controlled trials of acupuncture for hot flashes have been published. One large controlled trial in women without cancer that was published was the ACUFLASH (Acupuncture on Hot Flashes Among Menopausal Women) study.²³⁰ This was a multisite, randomized, controlled trial of 267 postmenopausal healthy women. Results indicated that participants in the individualized acupuncture group showed significant improvement in hot flashes compared with a no-treatment control at 12 weeks,²³⁰ but without additional treatment sessions, these benefits were not sustained 6 or 12 months later.²³¹

Subsequent studies in cancer patients have been positive. Two uncontrolled trials of acupuncture in men with hot flashes^{142,143} and 2 uncontrolled trials in patients with breast cancer^{232,233} showed improvement in symptoms over baseline but did not include rigorous control groups. Another study comparing the efficacy of acupuncture versus venlafaxine in treating hot flashes in 50 breast cancer survivors found that acupuncture showed comparable favorable improvements to the medication, while remaining a safe, effective, and durable treatment of hot flashes.²³⁴ A final study demonstrated the efficacy of acupuncture over sham acupuncture in 59 patients with breast cancer for reducing daytime and nighttime hot flashes immediately after treatment that were maintained 12 weeks later.¹³⁶

Reflexology

Reflexology is a specific form of foot massage in which it is believed that areas of the feet and hands correspond to certain glands, organs, and other parts of the body.²³⁵ Practitioners of reflexology hypothesize that local finger pressure can influence the function of organs and promote homeostasis, relaxation, and a healing response. Reflexology for the treatment of hot flashes has been examined in a single randomized study.²³⁵ Seventy-six healthy women experiencing hot flashes were randomized to receive either foot reflexology or a routine foot massage control in 6 weekly sessions for 45 minutes, followed by 3 monthly sessions. The groups showed equal improvements in anxiety, depression, and hot flash frequency and severity. Foot reflexology was not shown to be more effective than a standardized foot massage, and without further evidence it cannot be recommended for hot flashes.

Exercise

Although exercise has been well-documented to alleviate many adverse symptoms, few randomized controlled trials of exercise for hot flashes exist. A 2010 Cochrane review of

exercise for hot flashes in healthy women found only 9 published reports representing 6 randomized controlled trials.²³⁶ Despite variations in interventions and reporting quality, meta-analyses of these studies in healthy women indicated 1) no differences between exercise and no treatment/control; 2) no differences between exercise and yoga interventions; and 3) exercise was less effective than hormone therapy.²³⁶ However, vasomotor symptoms were not always the primary outcome in these trials, and several trials with small samples may have been underpowered to find group differences.²³⁶ Three additional trials in healthy women not included in or that were published after the Cochrane review also found no benefits for hot flashes: one compared endurance exercise with a control in 175 healthy women over 12 weeks,²³⁷ one compared exercise and phytoestrogens with exercise alone in 40 women over 6 months,²³⁸ and one compared moderate-intensity exercise with control (ie, stretching).²³⁹ The latter study actually found a significant increase in hot flash severity with exercise compared with the control at 12 months.²³⁹

There are concerns that exercise may acutely increase core body temperature and trigger hot flashes. However, a recent study suggests that exercise may acutely alleviate hot flashes but longer-term relief may depend on a woman's fitness level. A recent study of 92 healthy women found that immediately after a 30-minute session of moderate-intensity aerobic exercise, women reported significantly fewer hot flashes ($P < .05$) and fewer hot flashes tended to be recorded objectively ($P = .05$) on physiological monitors.²⁴⁰ Conversely, this study also revealed that women who were not as physically fit reported more hot flashes on the days they participated in more moderate-intensity physical activity.²⁴⁰ This study indicates that the timing of outcome assessments and participant fitness levels should be important considerations in any future studies.

Although exercise has been well studied in individuals with cancer, there do not appear to be any studies of exercise specifically targeted to hot flashes in cancer.²⁴¹ The lack of efficacy in studies from healthy women suggests that this may not be an appropriate intervention for hot flashes, although other benefits for cancer patients in terms of fitness, mood, sleep, and health-related quality of life have been reported.²⁴¹

Yoga

Yoga is an ancient Eastern tradition encompassing ethical principles, physical postures, and spiritual practices with the overall goal of uniting mind and body.²⁴² Research suggests that yoga is beneficial for the alleviation of many conditions such as asthma, carpal tunnel syndrome, multiple sclerosis, anxiety, and depression. Many different

styles of yoga exist such as Hatha, restorative, and Iyengar. These vary with respect to intensity, athleticism, and restorative or relaxation components.

Well-designed studies in healthy women and patients with breast cancer have not shown yoga to be very effective in alleviating hot flashes. A systematic review of studies of yoga for hot flashes in healthy women noted that only 2 of 7 existing reports were randomized controlled trials using an attention control condition.²⁴³ Neither reported beneficial efficacy for hot flashes compared with the control, although improvements in other outcomes were noted.²⁴³ One randomized pilot study not included in the review was conducted to determine the efficacy of yoga for the treatment of hot flashes in patients with breast cancer.¹⁴⁴ Thirty-seven patients with breast cancer were randomly assigned to either 8 weeks of yoga or a wait-list-control group.¹⁴⁴ Although the results showed the yoga group improved with regard to hot flash frequency, severity, and total score, the reduction in hot flash scores was only 31%,¹⁴⁴ which is similar to the placebo response seen in other trials.²⁴⁴

Although other reports of yoga in cancer patients have been published, no other studies have focused on hot flashes as the primary outcome. For example, yoga has been investigated for improving quality of life in patients with prostate cancer and for psychological adjustment and sleep quality in patients with lymphoma.²⁴⁵ Within the past few years, yoga has been studied as a treatment for a variety of issues in patients with breast cancer such as arthralgias,²⁴⁶ self-esteem,²⁴⁷ fatigue,²⁴⁸⁻²⁵⁰ lymphedema,²⁵¹ nausea and vomiting,²⁵² stress,²⁵³ and other quality-of-life outcomes.²⁵⁴⁻²⁵⁸ Thus, although yoga may have other benefits, its efficacy for hot flashes has not yet been supported and it therefore cannot be recommended for alleviating hot flashes at this time.

Relaxation Training

Relaxation training has been recommended for treating hot flashes. A 2008 systematic review of psychoeducational interventions to alleviate hot flashes identified 9 trials involving relaxation techniques.²⁵⁹ Interventions studied have included progressive muscle relaxation,²⁶⁰ relaxation combined with temperature-control biofeedback training,²⁶¹ paced respiration,²⁶² at-home relaxation audiotapes,²⁶³ and applied relaxation.²⁶⁴ These studies found significant reductions in hot flash frequency and severity via subjective diary or sternal skin conductance monitoring.^{260,262,263} Although this line of research is very promising, there is some concern over the placebo effect and methodology since several studies lacked a suitable attention control group. Further research is needed to evaluate specific doses and types of relaxation training that will provide the most benefit in alleviating hot flashes.

Paced Respiration

Paced respiration involves taking 6 to 8 slow deep breaths per minute while inhaling through the nose and exhaling through the mouth. In small studies of women without cancer, when paced respiration was delivered during one-to-one, biweekly, hour-long laboratory sessions and practiced twice daily (30 minutes total), it was significantly more efficacious in reducing physiologically recorded and/or self-reported hot flashes than an attention control condition.^{260,262,265} However, the first large-scale randomized controlled trial of paced respiration failed to demonstrate efficacy using electronic hot flash diaries, hot flash interference, and other menopausal symptom questionnaires.¹⁴⁶ The study involved 96 breast cancer survivors and 122 menopausal women without cancer who were stratified and randomized to practice paced respiration, an attention control condition of fast shallow breathing, or usual-care control. Women were able to appropriately learn and in return demonstrate paced respiration and practiced an average of once per day for 15 minutes. These recently published findings suggest that paced respiration is unlikely to provide any benefit for patients.

Clinical Hypnosis

Hypnosis, a mind-body therapy that involves a deeply relaxed state and individualized mental imagery and suggestion, has been used to manage chronic symptoms such as pain and anxiety. Hypnosis has been studied for the treatment of hot flashes in 2 studies of breast cancer survivors.^{147,148} In each study, breast cancer survivors received 5 sessions of hypnotherapy that were provided weekly and gained instruction in self-hypnosis. These studies showed a 69% or greater reduction in hot flashes from baseline that was comparable to the results of open-label studies of venlafaxine.^{147,148} A more recent randomized, single-blind, controlled clinical trial of 187 postmenopausal women who reported at least 50 hot flashes a week at baseline evaluated clinical hypnosis over 12 weeks against an active structured attention control for the treatment of hot flashes.²⁶⁶ Participants in the clinical hypnosis arm reported a significantly reduced hot flash frequency (74% vs 17%) and hot flash interference (80% vs 15%) compared with the attention control. In addition, physiologically monitored hot flashes were significantly more reduced in the hypnosis versus attention control arm (57% vs 10%). Although these results are encouraging, the exact mechanism by which clinical hypnosis affects hot flashes is unknown.

Mindfulness-Based Stress Reduction

MBSR emphasizes acceptance, mindfulness meditation, and yoga as coping mechanisms to handle stress.²⁶⁷ Two studies of MBSR for the alleviation of hot flashes have

been done in healthy women. First, an uncontrolled pilot study was conducted with 15 women who attended an 8-week MBSR program for the treatment of hot flashes.²⁶⁷ Results showed significant improvement in scores on quality-of-life measures and a 40% reduction in hot flash severity over baseline.²⁶⁷ Subsequently, a randomized controlled trial was conducted in 110 women with moderate to severe hot flashes.¹⁴⁹ The MBSR intervention was a standardized, widely used 8-week program that involved attending to relevant aspects of experience in a nonjudgmental manner, and the control condition was wait list. The intervention required 8 weekly classes that lasted 2.5 hours each, an all-day face-to-face class on a weekend day of the sixth week, and 45 minutes of at-home practice 6 times a week. After the intervention, the MBSR group showed a 15% reduction in hot flash bother compared with a 7% reduction in the wait-list control, which was not significant ($P = .11$). However, there was a significant difference between groups after 3 months of practicing MBSR for 25 minutes per day, with a 27% reduction in hot flash bother for the MBSR group and an 11% reduction for controls. These findings are comparable to the improvement in hot flash bother seen in a recent randomized trial of escitalopram.¹⁵⁹ Because MBSR works by reframing women's interpretations, its differential effects for hot flash bother over hot flash frequency were not unexpected.

To date, MBSR has not been examined as a potential treatment for hot flashes in persons with cancer. However, improvements in depression, anxiety, and fear were significantly greater with MBSR than with standard care in a 6-week randomized trial of 84 breast cancer survivors.²⁴⁸ In addition, the results of an unblinded trial of MBSR in patients with breast cancer showed improved immune function in peripheral blood mononuclear cell natural killer cell activity and cytokine levels.²⁶⁸ Although MBSR has yielded promising benefits in healthy postmenopausal women and other potential health benefits in patients with breast cancer, it cannot be recommended as a treatment of hot flashes until further randomized controlled studies are done.

Psychoeducational/Cognitive Behavioral Interventions

Psychoeducational and cognitive behavioral interventions are widely used to alleviate symptoms and improve quality of life, but have not yet been well studied for hot flashes. However, 2 studies done in breast cancer survivors are promising. In one study, 76 patients with early stage breast cancer were randomized to receive standard care or comprehensive care that included an individualized plan of education, counseling, specific pharmacologic and behavioral interventions, and psychosocial support for hot

flashes and other vasomotor symptoms.²⁶⁹ Patients were seen 3 times by a nurse practitioner over the course of 4 months. Results showed that patients receiving the intervention had significant improvements in their hot flash severity and sexual functioning score compared with the standard-care arm. However, the patients receiving the intervention used medication more frequently than those in the control group as a result of the intervention, and it is not clear if benefits were due to the medication, other intervention components, or a combination of both. In the other study, 96 patients with breast cancer were randomized to a group receiving a cognitive behavioral intervention or usual care.²⁷⁰ The intervention protocol has been published and included education, paced respiration, and cognitive and behavioral strategies to help the women manage their hot flashes.²⁷¹ Findings indicated that the intervention significantly improved hot flashes after 9 weeks, with sustained improvements seen at 26 weeks.²⁷⁰ These interventions were well received and, although time- and resource-intensive to deliver, may improve hot flashes in breast cancer survivors.

Conclusions

Although there is an increasing body of research into treatment options for hot flashes in cancer survivors, most studies are focused on pharmaceutical therapies. Treatment studies in men with prostate cancer or individuals with other cancers are specifically lacking and the few studies that have been conducted included small sample sizes. Complicating treatment investigation is an incomplete understanding of the underlying physiology, although some headway has been gained in the neurochemistry of hot flashes. In addition, it has yet to be determined if all hot flash symptoms share the same underpinnings across populations. To date, and to the best of our knowledge, no study has identified a differing physiological mechanism for hot flashes in cancer survivors versus healthy women. However, it is unclear to what degree hot flashes in men with prostate cancer or individuals with other cancers are physiologically similar. The genesis of hot flashes may differ across populations, but the expression, and presumably treatment, of these symptoms may be identical. If one assumes that research in healthy women can be extrapolated to women with breast cancer, the available evidence for treatment options for patients with cancer is substantially expanded. This review has identified several areas that have been investigated for treating hot flashes and made recommendations from the aggregate of published outcomes, taking quality and the number of studies specific to cancer populations, side effect profiles, and contraindications into account.

As more cancer survivors are using nonpharmaceutical therapies, it is advisable for health care professionals to openly engage in discussing these options with patients since some of these commonly used treatments are not recommended due to adverse risks, potentially deleterious interactions with existing medications, or published inefficacy in randomized controlled trials. Nutraceuticals in particular have been studied to alleviate hot flashes, but to date, absent or mixed results in randomized controlled trials in cancer survivors prevent their recommendation (for a listing of available evidence, see Table 2).

Other complementary and behavioral interventions for hot flashes have been examined in a range of trials. Although the investigations of many of these modalities are in their nascent stage, the literature is mixed. Acupuncture in particular has been well investigated in cancer populations (6 randomized controlled trials in breast cancer and 1 randomized controlled trial in prostate cancer). Although several trials have indicated a clinical impact, several reviews suggest that the methodological weaknesses spanning across multiple studies fail to provide convincing supporting evidence. Clinical hypnosis, relaxation training, and yoga are recommended on the basis of their published outcomes, positive secondary outcomes, and absence of side effects, although there is insufficient research to consider any as evidence-based treatments (for results from representative studies and level of evidence, see Table 3).⁹³⁻¹²⁴ Although to date only a single surgical intervention has been published for treating hot flashes, stellate ganglion block was studied in a pilot study of patients with breast cancer and showed significant results. Although intriguing and with promising results, the questions of procedure cost, patient discomfort, and longevity of the treatment effect prevent its recommendation at this time.

In summary, investigation into treatments in cancer patients experiencing hot flashes is insufficient. Although several treatment options have been researched, the lack of adequately powered randomized controlled trials and replications across subgroups of cancer patients prevent the determination of a clinically significant impact, and thus prevent the recommendation of many promising nonhormonal alternative treatment options. There is hope for cancer survivors, however, as an increasing number of studies are showing significant improvements in hot flash frequency, severity, and tolerability, with high levels of treatment satisfaction and adherence. In time and given additional study, it is likely that physicians and cancer survivors will have a number of effective treatment options available to them. ■

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