Published in final edited form as:
CA Cancer J Clin. 2013 May ; 63(3): 167–192. doi:10.3322/caac.21171.

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

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Abstract

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 persons 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 BMI, 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.

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 co-occurring 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 co-occur with mood and sleep disturbances and negatively impact quality of life.[10,17–19] In addition, hot flashes can interfere with adherence to life-saving 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 presentation of evidence surrounding pharmacological, nutraceutical, surgical, and complementary/behavioral treatment options. Although the review focuses on hot flashes on 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 less relevant to men with prostate cancer or patients experiencing hot flashes as a result of tumor secretion (e.g., carcinoid syndrome). Literature sources were identified using a multiple database search of MEDLINE, HealthSource: Nursing/Academic, 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 papers published on or before September 30, 2012, were included in the review. All hot flash outcomes (frequency, severity, bother, 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[212,12] although hot flashes tend to be more common in midlife women[22,23] than aging men.[24] Greater hot flash prevalence and/or severity have been reported in African-Americans compared to Whites.[25,26] Results from the Study of Women's Health Across the Nation (SWAN, n=16065) indicated greatly varying combined hot flash and night sweat prevalence rates by race and ethnicity: 18% Japanese women, 21% Chinese Americans, 31% Whites, 21% Latinas, 46% African-American women.[26] 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.[27]

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 (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.[28] 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 to asymptomatic women (11.2 years versus 12.2 years, $p < .001$).[29] 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 British postmenopausal 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).[30]

Cigarette smoking may also be a risk factor for hot flashes.[26] Though 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 for any hot flashes,[31,32] or for frequent and bothersome hot flashes.[33] The mechanism by which smoking affects hot flashes is, as yet, unknown, though some studies have related smoking and other demographics to earlier age at menopause.[34] In addition, there are at least 4 suggested pathways by which cigarette smoking might alter estrogen metabolism.[35–38]

Growing evidence associates hot flashes with a woman's cardiovascular risk.[39,40] Women who report hot flashes for ≥ 6 days 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.[40] However, the role of weight or body mass index on hot flashes is unclear.[26,41] 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 necrosing factor alpha) that suppress ovarian steroid production and may influence thermoregulation.[42] It has been hypothesized that the influence of adipose tissue on estrogen levels increases risk of hot flashes, however, there is inconsistent and conflicting evidence in the literature.[42] 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 cancer groups In data derived from participants in the Study of Women's Health Across the Nation (SWAN), genetic polymorphisms in estrogen metabolism and receptor genes were associated with decreased odds of reporting hot flashes but these associations varied by race: CYP1B1 rs1056836 GC genotype in African American women, 17HSD rs615942 TG, 17HSD rs 592389 TG, and 17HSD rs2830 AG genotypes in Caucasian women, and the CYP1A1 rs 2606345 AC genotype in Chinese women.[43] Schneider et al[44] suggested that hot flashes may be regulated by genes that control angiogenesis. In premenopausal Caucasian women, the eNOS-786 CT and TT genotypes were significantly associated with greater likelihood of current hot flashes relative to women with the CC genotype, though this association failed to remain significant after controlling for clinical variables.[44] In post-menopausal women, the HIF1a 1744 CT and TT genotypes were significantly associated with greater likelihood of current hot flashes even after controlling for clinical variables.[44] 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 to women with other CYP19 alleles.[45] In 2 other studies, the CYP17 MspAI polymorphism did not predict hot flash reporting[46] or response to estrogen therapy[47] 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 for reporting more severe and persistent hot flashes.[48] Though 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,[21] with a similar relationship assumed to hold for testosterone in men. In women, these cancer-related risk factors include discontinuation of hormone therapy when hormone-dependent cancers are diagnosed (eg, breast cancer),[12] 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 anti-androgen therapies for 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, though detailed studies in the literature are lacking.[16] Longitudinal study of hot flashes in breast and prostate cancer patients reveals that undergoing chemotherapy and hormone therapy are significantly associated with hot flashes.[28]

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 post-menopausal women report greater frequency of hot flashes during endocrine therapy.[12] Patients who are older or whose ovaries are in the radiation field during treatment suffer the most ovarian damage and have greater risk for 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, breast cancer) to others (eg, 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 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 inter-threshold 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, and glucose.[58]

Neurochemical Disruption

Estrogen, a steroid hormone, is the most commonly implicated neurochemical involved in hot flashes. Estrogen replacement therapy, though 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 non-hormonal 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 thermoregulatory dysfunction associated with estrogen depletion.[73] The mechanism by which estrogen affects serotonin metabolism may be via direct effect on serotonin neurons, which regulate the genes involved in serotonin production, transport and signaling.[74,75] Women after spontaneous or surgical menopause 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 to a control condition.[77]

Calcitonin gene-related peptide (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 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] Additionally, a study of castrated men showed CGRP increases of 46% during hot flashes.[87] However, a study of aging men without cancer reporting 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 to 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 (HOMA) 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, anticonvulsants, 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, 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, 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.

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) 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 and 4 provide a summary of the level of evidence for each therapy in breast cancer patients, prostate cancer patients, and other cancer patients 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.[93] Again, therapies appear within these tables in the order in which they appear in text.

Pharmaceuticals

Antidepressants

Venlafaxine, 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.[94] Substantial research supports the treatment of hot flashes in women with breast cancer with venlafaxine.[95–98] The first investigation enrolled 23 breast cancer and 5 prostate cancer patients, 54% of whom reported a ≥ 50% reduction in hot flashes after 4 weeks of venlafaxine 25 mg daily

(12.5 mg bid).[96] In a follow-up dose response study, 191 participants with breast cancer or risk of cancer were randomized to venlafaxine 37.5 mg, 75 mg, or 150mg daily for 4 weeks.[95] Efficacy was greatest at the 75 mg dose, with a 61% reduction in the median daily hot flash score.[95] Continued follow-up of 102 participants showed a sustained reduction over time[98] with side effects including nausea, nervousness, and constipation. In addition, among 77 breast cancer patients, physiological monitor-recorded hot flashes were reduced 22% more than placebo with venlafaxine 37.5 mg per day and 14% more than placebo with venlafaxine 75 mg per day.[99] In 80 women without cancer, venlafaxine 75 mg significantly improved hot flash scores and quality of life after 12 weeks.[100] In addition, desvenlafaxine 150 mg per day significantly decreased hot flashes compared to placebo, whereas doses of 100 mg per day were not more effective than placebo when used for 12 weeks[101] or 26 weeks.[102]

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.[103] Women with breast cancer experiencing hot flashes and night sweats were randomized to receive either zolpidem 10 mg or placebo for 5 weeks. Those who were using antidepressants continued use and nonusers began venlafaxine 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 Index.[103] These findings suggest that combination therapy may be an option for those reporting both hot flashes and sleep problems.

Citalopram, escitalopram: Citalopram and its isomer escitalopram are selective-serotonin reuptake inhibitors generally employed 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 in breast cancer survivors for citalopram than escitalopram but these agents have not been studied with prostate or other cancers.

Short term research in women with and without cancer has been generally positive but 1 longer-term study reported null findings, suggesting these agents may not provide long term relief from hot flashes. Six weeks of citalopram at doses of 10, 20, 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.[104] A dose response was not seen for frequency or severity but effects on hot flash interference were greatest at the 20 mg dose.[104] Similarly, 8 week trials have shown escitalopram 10 mg per day (titrated up to 20 mg per day) to be superior to placebo for menopausal symptoms in depressed women[105] and non-depressed women.[106] 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 20mg) created > 50% decrease in menopausal symptom scores on the Greene Climacteric Scale in 56% of those taking escitalopram versus 31% taking hormone therapy.[105] In a recent, randomized, double-blind placebo-controlled multicenter trial of 205 post-menopausal 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.[106] Further, the escitalopram group showed significantly greater reductions in hot flash severity[106] and hot flash interference in daily life.[107] In a longer, 9 month studycitalopram 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.[108] However, this study did not have a true pre-treatment baseline, rather, baseline was concurrent with medication initiation.

Paroxetine, fluoxetine, sertaline: 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 two agents. In their comprehensive review, Nelson et al[109] 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.[109] 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 and colleagues[110] attempted to pool analyses for several agents. Although the review concluded that results were similar across users and non-users, there are several limitations including: pooling across agents that are and are not metabolized through CYP2D6 and use of data from trials not originally powered for this type of analysis with resulting small samples within subgroups and wide confidence intervals. 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 alleviation of hot flashes via reduction in tamoxifen metabolites.

Paroxetine in doses of 10 to 36.5 mg per day improved hot flash frequency, severity, mood, anxiety, and quality of life in 3 uncontrolled trials involving breast (including tamoxifen users) and prostate cancer patients.[111–113] 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 paroxetine 12.5 mg group and 65% in the 25 mg group compared to a 38 % reduction in the placebo group.[114] In a randomized crossover trial of 151 breast cancer patients (including tamoxifen users), patients who received 10mg of paroxetine showed a 46% reduction in hot flash scores while those who received 20mg had a 56% reduction.[115] Although the efficacy in both doses showed comparable reduction, 10 mg of paroxetine was reported by patients to result in fewer side effects and less treatment discontinuation.[115] Fluoxetine 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).[116] For sertraline, an initial randomized crossover study compared sertraline with placebo in 62 breast cancer patients (including tamoxifen users).[117] 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 to 27% reduction in placebo.[117] However, another study in women with or at high risk for breast cancer (including tamoxifen users) failed to find efficacy for sertraline on hot flashes.[118] 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.[119]

Mirtazapine: Mirtazapine, a nonadrenenergic and selective serotoninergic antidepressant (NaSSA), is a potent antagonist of noradrenergic receptors alpha 2,[69] which may contribute to the therapeutic effect reported in case studies.[120] A non-randomized study of mirtazapine 15 to 30 mg per day showed a 59% reduction in hot flashes in 22 women with a risk or history of breast cancer.[121] Recently, an open-label trial was conducted to assess the efficacy of mirtazapine for reliving vasomotor symptoms in 40 breast cancer patients.[122] Results showed a 56% reduction of hot flash frequency and 62% reduction in hot flash scores as compared to baseline; however only 20 participants (50%) completed the 12-week study. The limited sample size and compliance problem were likely due to side effects, 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, 150 mg or placebo.[123] Reductions from baseline in each group were 35% (300 mg), 70% (150 mg) and 24% (placebo). However, the limited data analysis, in which comparisons to placebo were not reported, and the small sample size indicate the evidence for this agent is currently insufficient.[109]

Anticonvulsants

Gabapentin/pregabalin: Multiple reports indicate that gabapentin, an anti-convulsant 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.[124,125] In women without cancer, 4 randomized controlled trials found that gabapentin in doses of 600 mg to 2400 mg per day reduced hot flash frequency and/or intensity.[126–129] Two of these trials reported comparable efficacy between gabapentin (600 mg at night)[126] or gabapentin titrated to 2,400 mg daily and estrogen therapy arms (transdermal estrogen 25 mcg daily or conjugated estrogens 0.625 mg daily).[126,129] 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 200 mg to 900 mg per day.[130,131] These initial positive findings have held in randomized controlled trials. In breast cancer survivors, a randomized, double-blind, placebo-controlled, multi-institutional trial of gabapentin 900 mg per day provided a 49% and 46% reduction in hot flash severity scores at weeks 4 and 8, respectively compared to a 21% and 15% in the placebo group and a 33% and 31% in the 300 mg dose group.[132] Similarly, a study of men with prostate cancer found moderate (~50%) reduction in hot flashes, without any evidence of side-effects surpassing that of placebo.[133] In a longitudinal continuation study from the same sample, the moderate reduction in hot flash frequency and severity was maintained for an additional 8 weeks with minimal toxicities.[134] Interestingly, when breast cancer patients were randomized to gabapentin (900 mg per day) plus continued or discontinued antidepressants for hot flashes (e.g., venlafaxine, paroxetine, other), both treatment arms showed similar reduction in hot flashes at four week follow-up.[135] In other words, there was not an additional benefit of 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.[136] A review done in 2006 summarized 10 equivocal studies comparing clonidine to placebo with 7 being poor quality and 3 being fair quality.[109] Two of the 3 fair quality trials included women with breast cancer.[137,138] Although clonidine appeared more effective than placebo, concerns about side effects were raised. In one study, 48% of women with breast cancer reported clonidine as more effective than placebo, and only 31% preferred clonidine when asked to consider side effects.[137] A subsequent trial in breast cancer showed that oral clonidine compared to placebo decreased hot flash frequency at 4 weeks (37% vs 20%) and 8 weeks (38% vs 24%).[138] Quality of life scores improved with treatment and the only significant side effect was difficulty sleeping.[138]

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,[139,140] a randomized, double-blind, crossover trial failed to confirm these results.[141] Seventy men with prostate cancer received transdermal clonidine 0.1 mg followed by placebo or placebo followed by clonidine.[141] No

statistically significant decreases in hot flash frequency were seen.[141] When asked to indicate their preference, 47% could not tell which was better, 34% preferred clonidine, and 19% preferred placebo.[141]

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.[109] All studies appeared to include women without cancer but sample sizes were small (n=10 to 40) 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.[142] In one double-blind study, 66 women without cancer received either Bellergal 1 tablet per day or placebo. No significant group differences were seen after 8 weeks of treatment.[142] In another study, women received either placebo or Bellargal 2 tablets 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).[143] 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 presentated in this article are minimal.[143] Given the lack of strong evidence and potential addictive risk, Bellergal 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 advanced endometrial and breast cancer. This agent demonstrates efficacy in reducing hot flashes in individuals with breast or prostate cancer. Megestrol acetate (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.[144] 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.[145] 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 on the placebo, 65% of participants on the 20 mg dose, and 48% of participants on the 40 mg dose reported > 75% reduction in hot flashes compared to baseline.[146]

Another progestin, intramuscular depot medroxyprogesterone acetate, was shown to be equally as effective as megestrol acetate. In 1 randomized study of 71 postmenopausal breast cancer patients, long-term relief of symptoms 6 months post-study was higher in the depot medroxyprogesterone acetate group.[147] Though these agents show promise in treating hot flashes, concerns over stimulating breast and prostate cancer recurrence may limit prescription.[145,148] Efficacy in reducing hot flashes should be balanced with concerns.

Tibolone, a synthetic steroid, possess tissue specific activity that may result from metabolism, enzyme regulation, and receptor activation varying between tissues.[149,150] The complex mechanism of tibolone involves the rapid metallization of the drug within the intestine and liver into active oestrogenic metabolites, and a third metabolite, delta −4 isomer, which binds to both progesterone and androgen receptors.[149,151] In Europe, tibolone has been utilized as a treatment for vasomotor symptoms; however, it is not available in the United States.[152] Placebo-controlled trials have shown positive results as tibolone as a potential treatment for hot flashes in healthy post-menopausal women. Results from a recent double blind study found the effects of tibolone to be comparable to estrogen trials in 437 postmenopausal women.[153] Furthermore, pilot studies of tribolone with breast cancer patients receiving adjunctive tamoxifen treatment showed a reduction in hot flashes.[154–156]

Despite the initially beneficial results, the Million Women Study (N=3,098) suggested tibolone increased risk of breast cancer recurrence, while alleviating vasomotor symptoms and preventing bone loss.[157] Results of another trial of tibolone in postmenopausal women with low bone density revealed a decrease in breast cancer events.[158] One potential explanation for these mixed results is tibolone may affect healthy breast tissue differently than it does cancerous tissue.[159] The LIBERATE trial was conducted to further determine the effects and the safety of tibolone as a potential treatment for vasomotor symptoms. LIBERATE trial results showed that tibolone was effective in reducing hot flashes and improving quality of life in symptomatic breast cancer patients.[160] However, tibolone did increase risk of reccurrence. Evidence to date suggest 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 to clonidine. In one randomized double-blind study of 80 breast cancer survivors, venlafaxine 37.5 mg per day was significantly more effective in reducing hot flash frequency and severity at four weeks follow-up compared to clonidine 0.075 mg per day.[161] However, this study was originally designed as a cross-over 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 venlafaxine 75 mg or clonidine 0.05 mg before switching to the opposite agent. There was a similar reduction of hot flashes (55% vs. 49%) during the first study arm but without tapering up of the venlafaxine dose, there was significantly more side effects with venlafaxine.[162] 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 75 mg per day dose.[163] In a third study, 102 breast cancer survivors were randomized to venlafaxine 75 mg, clonidine 0.1 mg, or placebo (2:2:1 ratio) with data from 80 women available at 12 week follow-up.[164] Again, there was a similar reduction in hot flashes for both agents but more side effects in the venlafaxine arm due to the lack of tapering up on the dose. It is important to note that non-inferiority or equivalence between venlafaxine and clonidine cannot be claimed because the studies were not powered for such conclusions.

Two studies have directly compared venlafaxine to other agents. Among 109 breast cancer survivors, venlafaxine 75mg per day was less effective than medroxyprogesterone acetate (46% vs. 74% reduction in hot flash scores) after 6 weeks.[165] This study allowed for tapering up of the venlafaxine dose but there were fewer side effects with the medroxyprogesterone acetate arm. In another randomized controlled trial of 309 evaluable men with prostate cancer, venlafaxine 75 mg per day was less effective than medroxyprogesterone acetate 20 mg per day and cyproterone 100 mg per day after 6 months of therapy.[166] 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 study[167] 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 21 days) or gabapentin (300 mg once per day for 3 days, then 300mg twice per day, then 300 mg 3 times a day for 22 days) followed by a 2 week washout and then the opposite agent. More preferred venlafaxine than gabapentin (68% vs. 18%). Though both pharmacological treatments reduced hot flashes (66% reduction), venlafaxine also improved mood (p=0.01). Venlafaxine side effects included nausea, loss of appetite, and constipation whereas gabapentin was associated with dizziness and increased appetite.[167]

Pooled analyses provide some additional information regarding the comparative efficacy of various pharmaceutical therapies. Loprinzi and colleagues[168] obtained individual patient data from 12 clinical trials published during 2000 to 2007. Forest plots provide evidence for the stacked efficacy of paroxetine > gabapentin or venlafaxine > sertraline.[168]

Nutraceuticals

Nutraceuticals include herbal therapies (black cohosh, St. John's Wort, homeopathic herbs), vitamins (E, multi, B9), and phytoestrogens (soy, red clover, flaxseed). For all of these therapies, differences in or lack of information about product purity, dosing, and side effects make cross-study comparisons difficult. Products lack standardization, partly due to lack of 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 women[169] 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.[170,171] A meta-analysis showed that 6 out of 9 randomized controlled trials demonstrated potential efficacy for black cohosh to reduce hot flashes.[172] 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 triterpine glycosides)[173] to 3150 mg (≥ 2.5% triterpine glycosides)[174] black cohosh helped alleviate tamoxifen-induced hot flashes when given in doses of 2.5 to 20 mg daily,[175,176] but was not effective in decreasing hot flashes in mixed samples of tamoxifen users and non-users at a higher dose of 40 mg per day[177] or at an unreported dose.[178] The most common side effects of black cohosh include mild gastric complaints, headaches, vomiting and dizziness in higher doses. It is important to note that recent critical reviews have disclaimed previous case reports of liver failure purportedly related to black cohosh.[179,180]

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 with 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 to placebo after 4- and 8-weeks of treatment.[181] In another study, a dose of 5400 mg dry herb (990 mcg hypericin, 9 mg hyperforin, 18 mg glycosides) in combination with *Vitex agnus-castus* (chaste tree/berry 500 mg dry fruit) was not more effective than placebo in reducing hot flashes recorded on daily diaries and standardized questionnaires.[182] A recent study randomized 47 women (including 26 breast cancer patients) to receive either St. John's Wort 900 mg dry herb daily (equivalent to 0.3% hypericin extract) or placebo for 3 months.[183] 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.[183] St. John's Wort is known to induce cytochrome P450 enzymes CYP3A4, CYP2C19, CYP2C9 and P-glycoprotein and should be avoided in certain individuals.[184,185]

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 homeopathy was associated with a 48% to 75% reduction in subjective hot flash frequency.[186] In an additional uncontrolled study, 45 breast cancer survivors showed improvements in vasomotor symptoms and quality of life.[187] A third observational study of 438 women without cancer showed a reduction in frequency of hot flashes and in daily discomfort.[188] In contrast, 2 randomized controlled trials of homeopathy for menopausal symptoms in breast cancer survivors failed to find any benefits over placebo.[189,190]

Vitamins—Vitamin E has received attention as possible treatment for the alleviation of hot flashes since the 1940's[191] and has been studied in three clinical trials. In one crossover trial, 120 breast cancer patients were randomized to 4 weeks of vitamin E (800 IU) followed by placebo or vice versa.[192] Although there was a subjective decrease in hot flashes in the vitamin E group, the reduction only amounted to about 1 hot flash per day.[192] However, another crossover trial of 50 postmenopausal women without breast cancer comparing 4 weeks of vitamin E (400 IU) followed by placebo or vice versa, found greater reduction in hot flash frequency (about 2 hot flashes per day, $p < .0001$) and hot flash severity ($p < .0001$) with vitamin E.[193] 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 to a 40% reduction from baseline with gabapentin 900 mg per day.[194] In this trial, 35% of 46 patients assigned to vitamin E dropped out within the first month due to lack of efficacy. Recent meta-analysis of 57 trials (total n = 246,371) showed no relationship between all-cause mortality and vitamin E (up to 5,500 IU per day). In addition, there is possible contraindication of Vitamin E for women with heart disease, diabetes, or hypertension, as well as concern for carcinogenicity.[195]

Evidence for other vitamin supplements is mixed. A multi-vitamin 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 supplement group and placebo group.[196] In another study of 46 women without cancer, vitamin B9 (folic acid) 5 mg daily for 4 weeks was found to reduce plasma levels of a norepinephrine metabolite[197] that had been previously investigated for its role in hot flashes. Hot flashes also improved significantly more in the folic acid group than in the placebo group.[197] 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 al[198] recently conducted a systematic review and meta-analysis of 19 randomized controlled trials of soy isoflavones. Similar to findings from another review,[199] the conclusion was that soy isoflavones reduce hot flashes to a greater extent than placebo.[198] 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 1 report failed to find any benefit of soy isoflavones over placebo in men with prostate cancer experiencing hot flashes due to androgen deprivation therapy.[200] Reports regarding the safety of soy in men with prostate cancer have been conflicting.[201]

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.[169,202] Red clover has been employed 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: 1 good quality, 3 fair quality and 2 poor quality.[109] Of these 6 trials, only 1 fair-quality trial indicated improved hot flashed frequency, reporting a 44% reduction with a red clover supplement of Promensil 80 mg per day compared to 0% with placebo.[203] 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 398 mg per day (standardized to 120 mg isoflavones) did not exceed placebo.[173] 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.[193] Initial pilot research demonstrated mixed results.[194–196] Three randomized controlled trials have found no benefit of flax seed over placebo for hot flashes in women.[204–206] In one study, 99 women were randomized to a daily muffin containing soy flour, ground flax seed, or wheat flour (placebo).[204] In a 12-week study, 38 women without cancer were randomized to receive 2 slices of bread per day containing either flax seed 25 grams or wheat bran.[205] In another study, 188 women (including breast cancer patients) were randomized to either a bar containing flax seed 410 mg or placebo.[206] No significant improvement in hot flashes for flax seed over placebo was seen 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 and colleagues[207] 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 of 13 breast cancer survivors and showed significant reductions in hot flash frequency, severity, and nighttime awakenings during a 12-week follow-up period.[208] In another study, 10 breast cancer patients received stellate ganglion block, with 8 evaluable patients showing a decrease in hot flash frequency and hot flash scores of 44% and 45% respectively.[209] No significant adverse events were reported.[209] An additional uncontrolled trial showed similar benefits for reducing hot flash scores (64% after 1 week, 47% after 24 weeks) and improving sleep at 1 and 24 weeks.[210] In all studies, most women required more than 1 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 and colleagues. One evaluated 6 randomized controlled trials done in women without cancer.[211] The second evaluated 6 randomized controlled trials done in women with breast cancer.[212] The third evaluated 6 studies (1 randomized controlled, 5 uncontrolled) done in men with prostate cancer.[213] 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 hot flashes in these populations.[211–213]

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 study. This was a multi-site, randomized, controlled trial of 267 postmenopausal healthy women. Results indicated that participants in the individualized acupuncture group showed significant improvement in hot flashes compared to a no-treatment control at 12 weeks,[214] but without additional treatment sessions, these benefits were not sustained 6 or 12 months later.[215]

Subsequent studies in cancer patients have been positive. Two uncontrolled trials of acupuncture in men with hot flashes[216,217] and 2 uncontrolled trials in breast cancer[218,219]} 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 for hot flashes.[220] A final study demonstrated efficacy of acupuncture over sham acupuncture in 59 breast cancer patients for reducing daytime and nighttime hot flashes immediately post-treatment that were maintained 12 weeks later.[221]

Reflexology: Reflexology is a specific form of foot massage in which it is believed that areas of the feet and hands corresponds to certain glands, organs, and other parts of the body.[222] Practitioners of reflexology hypothesize that local finger pressure can influence the function of organs and promote homeostasis, relaxation, and a healing response. Reflexology for hot flashes has been examined in a single randomized study.[222] 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.[223] 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.[223] 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.[223] Three additional trials in healthy women not included in or published after the Cochrane review also found no benefits for hot flashes: 1 compared endurance exercise to a control in 175 healthy women over 12 weeks,[224] 1 compared exercise and phytoestrogens to exercise alone in 40 women over 6 months,[225] and 1 compared moderate-intensity exercise to control (ie, stretching).[226] The latter study actually found a significant increase in hot flash severity with exercise compared to the control at 12 months.[226]

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.[227] 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.[227] This study

indicates that 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.[228] The lack of efficacy in studies from healthy women suggests that this may not be an appropriate intervention for hot flashes, though other benefits for cancer patients in terms of fitness, mood, sleep, and health-related quality of life have been reported.[228]

Yoga: Yoga is an ancient Eastern tradition encompassing ethical principles, physical postures, and spiritual practices with the overall goal of uniting mind and body.[229] 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, altheticism, and restorative or relaxation components.

Well-designed studies in healthy women and breast cancer patients 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 employing an attention control condition.[230] Neither reported beneficial efficacy for hot flashes compared to control, although improvements in other outcomes were noted.[230] One randomized pilot study not included in the review was conducted to determine the efficacy of yoga for hot flashes in breast cancer patients.[231] Thirty-seven breast cancer patients were randomly assigned to either 8 weeks of yoga or a wait-list control.[231] Although the results showed the yoga group improved in frequency, severity and total score, the reduction in hot flash scores was only 31%,[231] similar to the placebo response seen in other trials.[232]

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 prostate cancer patients and for psychological adjustment and sleep quality in lymphoma patients.[233] Within the past few years, yoga has been studied as a treatment for a variety of issues in breast cancer patients such as arthralgias,[234] self-esteem,[235] fatigue,[236–238] lymphedema,[239] nausea and vomiting,[240] stress,[241] and other quality of life outcomes.[242–246] Thus, although yoga may have other benefits, 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 to improve hot flashes.[247] Interventions studied have included progressive muscle relaxation,[248], relaxation combined with temperature control biofeedback training,[249] paced respiration,[250] at-home relaxation audiotapes,[251] and applied relaxation.[252] These studies found significant reductions in hot flash frequency and severity via subjective diary or sternal skin conductance monitoring.[248,250,251] Though this line of research is very promising, there is some concern over 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-one-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. [248,250,253] 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.[254] The study involved 96 breast cancer survivors and 122 menopausal women without cancer who were stratified and randomized to paced respiration, an attention control condition of fast shallow breathing, or usual care control. Women were able to appropriately learn and return demonstrate paced respiration and practiced an average of once per day for 15 minutes. These recently published findings suggest 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.[255,256] 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 comparable to results of open label studies of venlafaxine.[255,256] A more recent randomized, single-blind, controlled clinical trial of 187 post-menopausal women reporting 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.[257] Participants in the clinical hypnosis arm reported significantly reduced hot flash frequency (74% vs 17%) and hot flash interference (80% vs 15%) compared to attention control. In addition, physiologically monitored hot flashes were significantly more reduced in the hypnosis versus attention control arm (57% vs 10%). Though these results are encouraging, the exact mechanism by which clinical hypnosis affects hot flashes is unknown.

Mindfulness-based stress reduction: Mindfulness-based stress reduction (MBSR) emphasizes acceptance, mindfulness meditation, and yoga as coping mechanisms to handle stress.[258] Two studies of MBSR for 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.[258] Results showed significant improvement in scores on quality of life measures and a 40% reduction in hot flash severity over baseline.[258] Subsequently, a randomized controlled trial was conducted with 110 women with moderate to severe hot flashes.[259] The MBSR intervention was a standardized widely used 8-week program involving 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 to a 7% reduction in the wait-list control which was not significant (P= 0.11). However, there was a significant difference between groups after 3 months of MBSR practice 25 minutes per day, with a 27% reduction in hot flash bother for the MBSR group and 11% for controls. These findings are comparable to the improvement in hot flash bother seen in a recent randomized trial of escitalopram.[106] 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.[236] Additionally, results of an unblinded trial of MBSR with breast cancer patients showed improved immune function in peripheral blood mononuclear cell natural killer cell

activity and cytokine levels.[260] Although, MBSR has yielded promising benefits in healthy postmenopausal women and other potential health benefits in breast cancer patients, it cannot be recommended as a treatment for 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 early-stage breast cancer patients were randomized to 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.[261] 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 hot flash severity and sexual functioning score compared to the standard care condition. However, the intervention patients 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 the combination. In the other study, 96 breast cancer patients were randomized to a group cognitive-behavioral intervention or usual care.[262] The intervention protocol has been published and included education, paced respiration, and cognitive and behavioral strategies to help the women manage their hot flashes.[263] Findings indicated that the intervention significantly improved hot flashes after 9 weeks with sustained improvements seen at 26 weeks.[262] These interventions were well-received and although time- and resource-intensive to deliver, may improve hot flashes in breast cancer survivors.

CONCLUSIONS

Though there is an increasing body of research into hot flash treatment options for 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 were conducted included small sample sizes. Complicating treatment investigation is an incomplete understanding of the underlying physiology, though some headway has been gained in the neurochemistry of hot flashes. Additionally, 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 cancer patients 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 number of studies specific to cancer populations, side effect profiles, and contraindications into account.

As more cancer survivors are employing non-pharmaceutical therapies, it is advisable for health care professionals to openly engage in discussing these options with patients since some of these commonly utilized 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 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 interventions. Though 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 RCTs in breast cancer and 1RCT in prostate cancer). Though several trials suggest clinical impact, several reviews suggest 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, though there is insufficient research to consider any as evidence-based treatments (for results from representative studies, and level of evidence, see Table 3). Though, to-date, only a single surgical intervention has been published for treating hot flashes, stellate ganglion block was studied in a pilot of breast cancer patients and showed significant results. Though intriguing and with promising results, the questions of procedure cost, patient discomfort and longevity of treatment effect prevent recommendation at this time.

In summary, investigation into hot flash treatments for cancer patients is insufficient. Though several treatment options have been researched, the lack of adequately powered, randomized controlled trials and replications across subgroups of cancer patients prevent determination of clinically significant impact, and thus prevent recommendation of many promising non-hormonal 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, 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.

Acknowledgments

Details of all funding sources: This manuscript was supported by award numbers U01 AT004634-05 from the National Center for Complementary and Alternative Medicine (Elkins) and 5 R01 CA132927 from the National Cancer Institute (Carpenter). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Complementary and Alternative Medicine, National Cancer Institute, or the National Institutes of Health.

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Table 1

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

Generic (trade) name	Class[1]	Daily Dose[2]	Side Effects		Contraindications[3]
			Common	Rare but serious	
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 necrolysis, hallucinations, seizure, partial transitory deafness	MAOIs
Moblobemide (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 moments	Hepatic disease, liver disorders, MAOIs
Belladonna, ergotamine, phenobarbital (Bellargal)	BA	0.2mg, 0.6mg, & 40mg	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

CA Cancer J Clin. Author manuscript; available in PMC 2014 May 01.

Generic (trade) name	Class[1]	Daily Dose[2]	Side Effects		Contraindications[3]
			Common	Rare but serious	
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	

[1] Class: AC = anticonvulsant, AD= antidepressant, AH = antihypertensive; BA = Barbiturate + ergot alkaloid + anticholinergic; SE = sedative/hypnotic, SH = steroid hormone.

[2] Daily dose taken from published trials;

[3] Contraindications (if available) are from most recent FDA label or trial publications. All agents 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[1]	Side Effects	Contraindications[2]
Black cohosh (Cimicifuga racemosa)	2.5–3150 mg	Gastrointestinal distress, cramping, headaches, rash, weight gain	
St. John's Wort	Up to 5400 mg dry herb (or hypericin exact 20–30%)	Insomnia, vivid dreams, restlessness, anxiety, irrability	Coadministration of Vfend, Velcade, Viramune, Norvir and drugs metabolized through cytochrome P450 enzymes
Vitamin E (Tocopherol)	800 IU	May worsen clotting problems in people whose levels of Vitamin K are too low, speed vision loss in retinitis pigmentosa, aggravate bleeding disorders, increased chance of prostate, head and neck cancer recurrence.	Heart disease, diabetes, and hypertension
Vitamin B9 (Folic acid)	5 mg	Anorexia, nausea, insomnia, irritability	
Soy isoflavones	54mg	Nausea, vomitting, gastrointestinal distress	
Red Clover (Trifolium pratense)	40–120 mg	Rash, muscle aches, headache, nausea, vaginal spotting	
Flax seed (Linum usitatissimum)	25–410 mg	Bloating, gas, diarrhea, stomach aches, nausea	

[1] Daily dose taken from published trials;

[2] Contraindications (if available) are from most recent FDA label or trial publications. All agents contraindicated in persons previously shown to be intolerant.

Table 3

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

Trade (Generic) 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 HF frequency & severity,[95,96,99] Tolerability poor when dose not tapered[162]	Yes
		Prostate	One pilot study included 5 prostate cancer patients showed positive results,[96] Results of RCT found venlafaxine less effective than progestins[166]	No
		Other	None	No
Desvenlafaxine (Pristiq)	**Likely to be Effective**: 2 RCT in non-cancer populations show support.	Breast	None	No
		Prostate	None	No
		Other	None	No
Citalopram hydrobromide (Celexa)	**Recommended for Practice**: Multiple RCT showing positive results, 1 longer term study reported null findings.	Breast	Phase III controlled trial found significant reductions in HF frequency and severity[104]	Yes
		Prostate	None	No
		Other	None	No
Paroxetine hydrochloride (Paxil)	**Likely to be Effective**: 2 RCT, 3 uncontrolled trials in breast & prostate cancer	Breast	Uncontrolled trials and RCTs showed significant reduction in HF frequency & severity[112–115]	Yes, caveats for side effects.
		Prostate	Uncontrolled trial showed improvements in HF frequency, severity, mood & anxiety[111]	Yes, caveats for side effects.
		Other	None	No
Fluoxetine (Prozac)	**Effectiveness Not Established**: 1 RCT shows support.	Breast	Phase III, RCT showed fluoxetine superior to placebo[116]	No
		Prostate	None	No
		Other	None	No
Sertraline hydrochloride (Zoloft)	**Effectiveness Not Established**: Evidence mixed in 2 RCT	Breast	Results of initial RCT found 36% of patients had at least <50% reductions[117] Subsequent study was negative[118]	No
		Prostate	None	No
		Other	None	No

Trade (Generic) Name	Level of Evidence	Population	Evidence Base	Use?
Mirtazapine (Remeron) (Remeron)	**Effectiveness Not Established**: Current studies few and underpowered.	Breast	Non-randomized & open-label trial showed significant reductions in HF[121,122]	No
		Prostate	None	No
		Other	None	No
Moblobemide (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 multi-institutional trial of 900mg showed <49% HF severity at wk 4, and 46% at wk 8[132]	Yes, caveats for side effects.
		Prostate	Phase III, double-blind placebo-controlled trial <50% HF, with results maintained 8 wks later.[133,134]	Yes, caveats for side effects.
		Other	None	No
Clonidine hydrochloride (Catapres)	**Benefit Balanced with Harm**: 10 studies reviewed in 2006, with 3 of fair quality, concerns over side effects	Breast	Two fair quality RCT – one showed 37% reduction at 4 weeks[137,138] Comparative trials suggests that clonidine is well-tolerated in comparison to other agents.	Yes
		Prostate	Positive case reports not confirmed with RCT[139,140,141]	No
		Other	None	No
Methyldopa (Aldomet)	**Effectiveness Not Established**: 3 poor quality studies	Breast	None	No
		Prostate	None	No
		Other	None	No
Belladonna, ergotamine, phenobarbital (Bellargal)	**Effectiveness Unlikely**: Negative results in single RCT	Breast	None	No
		Prostate	None	No
		Other	None	No
Progestins (Megace)	**Benefit Balanced with Harm**: 3 studies show positive results, however side effect profiles and long term acceptability are concerns.	Breast	9-wk crossover study showed significant reduction in HF, long term follow up showed 75% of participants reporting HF after 3 years[144,145] RCT of 40mg dose reported >75% reduction in HF.[146]	Yes, caveats for side-effects and risk.
		Prostate	9 – wk crossover study showed significant reduction in HF in 66 prostate cancer patients[144] Follow-up study showing patients still report HF after 3 years[145]	Yes, caveats for side-effects and risk

Trade (Generic) Name	Level of Evidence	Population	Evidence Base	Use?
		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 BC patients found tibolone alleviated symptoms, the RCT showed increased risk for breast cancer recurrence[160,154–156]	No
		Prostate	None	No
		Other	None	No
Cyproterone acetate (Androcur)	**Effectiveness Not Established**: Only 1 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[166]	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[103]	No
		Prostate	None	No
		Other	None	No

RCT = randomized controlled trial.

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 (Cimicifuga racemosa)	**Not Recommended for Practice**: Phase III trial failed to find significant effect.	Breast	Standard clinical trial failed to show superiority over placebo.[178]	No
		Prostate	None	No
		Other	None	No
St. John's Wort	**Effectiveness Unlikely**: Negative results at end-point of single RCT.	Breast	RCT utilizing 900mg dry herb daily for three months results in no significant difference in HF scores.[183]	No
		Prostate	None	No
		Other	None	No
Homeopathic herbs (exact agents vary)	**Not Recommended for Practice**: 2 RCTs failed to show benefits over placebo.	Breast	Though an uncontrolled study showed benefit, 2 RCTs of homeopathy failed to find benefits over placebo.[187,189,190]	No
		Prostate	None	No
		Other	None	No
Vitamin E	**Effectiveness Unlikely**: Negative results at end-point of single RCT; concerns of carcinogenicity.	Breast	Single well-designed crossover RCT showed subjective decrease in HF in 120 BC patients, however reduction amount to average of one HF/day.[192] Subsequent study showed only a 7% reduction in HF from baseline compared to 40% with gabapentin.[194]	No
		Prostate	None	No
		Other	None	No
Vitamin B9	**Effectiveness Not Established**: Single study in healthy women yielded initial 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 breast cancer negative.	Breast	2 RCTs found no evidence that soy was more effective than placebo.[264,265]	No
		Prostate	One study failed to show benefit over placebo.[200]	No
		Other	None	No
Red Clover (Trifolium pretense)	**Not Recommended for Practice**: Only 1 study of fair quality reported significant reduction, recent 4-arm RCT did not exceed placebo.	Breast	None	No

Common (Taxa)	Level of Evidence	Population	Evidence Base	Use?
		Prostate	None	No
		Other	None	No
Flax Seed (Linum usitatissimum)	**Not Recommended for Practice**: Initial pilots mixed, 3 RCTs negative.	Breast	Phase III, placebo-controlled randomized double blind trial failed to show significant difference from placebo.[206]	No
		Prostate	None	No
		Other	None	No

RCT = randomized controlled trial.

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	6 RCTs, one RCT of acupuncture vs. sham acupuncture reported 50% HF reduction by end of treatment and 66% reduction at 12 wk. follow-up.[221,266–270]	No
		Prostate	Two uncontrolled trials positive[216,217]	No
		Other	None	No
Reflexology	**Not Recommended for Practice**: Single RCT reporting null findings.	Breast	None	No
		Prostate	None	No
		Other	None	No
Exercise	**Effectiveness Not Established**: Multiple RCTs fail to provide convincing results for efficacy; many trials 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 HF frequency & severity, joint pain, fatigue, sleep disturbance, bother and vigor, with improvements maintained at 3 month follow-up. Total hot flash score reduction, (31%) are within the range found in placebo used in medication trials.[231]	Yes*
		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 versus a no-treatment control showed improvements in the treatment condition of 22% less HF at end of 1 month with improvement maintained at 3 month follow-up. (Fenlon, Corner, Haviland, 2008).	Yes*
		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	16-week 3-group RCT of paced respiration found no significant differences for HF frequency, severity or bother at 8 or 16	No

Therapy	Level of Evidence	Population	Evidence Base	Use?
			weeks post-randomization. Statistically sifniciant differences in secondary did not achieve clinical significance[254]	
		Prostate	None	No
		Other	None	No
Clinical Hypnosis	**Likely to be Effective**: Results from several studies positive; recent large sample RCT positive.	Breast	2 studies in BC patients,[255,256] 1 study with 51 BC patients randomized to clinical hypnosis vs. wait-list control showed 68% reductions in HF in hypnosis condition	Yes*
		Prostate	None	No
		Other	None	No
Mindfulness-based stress reduction	**Effectiveness Not Established**:	Breast	Randomised wait-list control trial showed no differences at end-point and small improvements (27% vs 11% in control) at 3 months follow-up[259]	No
		Prostate	None	No
		Other	None	No
Psychoeducation/Cognitive Behavioral Therapy	**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. HF reductions were nonsignificant versus control[271]	No
		Prostate	None	No
		Other	None	No

RCT = randomized controlled trial.

Yes* - recommended on the basis of no side effects and positive secondary outcomes, but not yet evidence based.