Comparing Interventions for Management of Hot Flashes in Patients With Breast and Prostate Cancer: A Systematic Review With Meta-Analyses

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PROBLEM IDENTIFICATION: Hot flashes are common and bothersome in patients with breast and prostate cancer and can adversely affect patients' quality of life.

LITERATURE SEARCH: Databases were searched for randomized controlled trials (RCTs) evaluating the effects of one or more interventions for hot flashes in patients with a history of breast or prostate cancer.

DATA EVALUATION: Outcomes of interest included changes in hot flash severity, hot flash frequency, quality of life, and harms. Pairwise meta-analyses and network meta-analyses were performed where feasible, with narrative synthesis used where required.

SYNTHESIS: 40 RCTs were included. Findings from network meta-analysis for hot flash frequency suggested that several therapies may offer benefits compared to no treatment, but little data suggested differences between active therapies. Findings from network meta-analysis for hot flash score were similar.

IMPLICATIONS FOR RESEARCH: Although many interventions may offer improvements for hot flashes versus no treatment, minimal data suggest important differences between therapies.

Improvements in diagnosis and treatment of breast and prostate cancer are leading to a growing number of cancer survivors (American Cancer Society, 2019). A consequence of this is that many more patients are faced with managing the long-term side effects of their treatment. Treatments for breast or prostate cancer that target production of estrogen and testosterone can be associated with hormone-deprivation symptoms, the most common of which is hot flashes. The frequency, severity, and duration of hot flashes can vary widely from patient to patient but are reported in more than 65% of breast cancer survivors (Chang et al., 2016; Kontos et al., 2010; Mann et al., 2012) and in 80% of men undergoing androgen deprivation therapy (ADT) for prostate cancer (Frisk, 2010). Hot flashes not only can significantly affect a patient's quality of life (Goldman, 2017), but also can be significant enough to lead to discontinuation of cancer treatment (Buijs et al., 2009). Despite their frequency and significance, there is currently a lack of consensus on evidence-based interventions to treat hot flashes (Goldman, 2017).

A hot flash has been defined as "a subjective sensation of heat that is associated with objective signs of cutaneous vasodilation and a subsequent drop in core temperature" (Boekhout et al., 2006, p. 642). The concept of hot flashes in men has not been well explored in the literature. A concept analysis identified the key attributes of hot flashes in men to consist of physiologic (e.g., warmth, sweating, chills) and psychological factors (e.g., anxiety, impaired memory) (Engstrom, 2005). Hot flashes are also often referred to as hot flushes, night sweats, and vasomotor symptoms. The

exact pathophysiology of hot flashes in women or men has not been determined, leading to difficulty in understanding why some interventions or treatments may or may not work.

A wide variety of options for treatment of hot flashes has been researched in patients with and without cancer. Pharmacologic treatments (e.g., anticonvulsants, antidepressants, antiandrenergics, anticholinergics, progestins), natural health products (e.g., herbals, vitamins, phytoestrogens), and complementary medicine and physical and behavioral therapies (e.g., acupuncture, reflexology, exercise, yoga, relaxation training, mindfulness-based stress reduction, hypnosis, cognitive behavioral therapy) have all been evaluated in research studies (Fisher et al., 2013; Goldman, 2017; Marino et al., 2018; Santen et al., 2017; Zoberi & Tucker, 2019).

Although antidepressants have been shown to relieve hot flashes (Barton et al., 2002; Loprinzi et al., 2000) with positive efficacy and good tolerability, many patients look to alternative treatment options. Acupuncture has been studied as a treatment for hot flashes from menopause, as well as following treatment for cancer. Results have been mixed, with some studies finding no evidence of an effect and others finding some benefit (Dodin et al., 2013). Nutraceutical and complementary or behavioral therapies have also had mixed results, with insufficient data to firmly establish effectiveness (Kaplan et al., 2011). Collectively, many treatments are tried by patients to address hot flashes, but the evidence to support the presence of benefits for treatments of all forms is limited (Goldman, 2017).

Given the increased success of cancer therapies, physicians and nurses have an increasingly important need to address survivorship challenges. To improve treatment adherence and, ultimately, quality of life, it is important to identify evidence-based strategies that reduce the frequency and severity of hot flashes following cancer treatment (Kaplan et al., 2011; Pinkerton & Santen, 2019). A systematic review of the currently available evidence incorporating meta-analysis and network meta-analysis methodology was planned because of the potential to identify effective treatments while noting gaps in existing knowledge (Caldwell et al., 2005; Catalá-Lopez et al., 2014; Dias et al., 2011).

Methods

Research Question and Protocol Registration

This review was conducted to address the following research question: In breast cancer and prostate cancer survivors, what are the relative benefits of nonhormonal therapies on frequency and severity of hot flashes, quality of life, and quality of life related to depression and sleep quality? A protocol for the study was prepared a priori and followed throughout the review process (Hutton, Yazdi, et al., 2015). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Extension Statement for Network Meta-Analysis (Hutton, Salanti, et al., 2015) was used to guide authorship of this article, and a completed checklist is provided in the appendices. Adjustments to the protocol made because of characteristics of the data collected are described within the article.

Literature Search

The search strategy was developed and tested by an experienced medical information specialist in consultation with the review team. Using the OVID platform, Ovid MEDLINE®, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Embase®, AMED, and PsycINFO® were searched. The CENTRAL database using the Cochrane Library on Wiley was also searched. Strategies used a combination of controlled vocabulary (e.g., "breast neoplasms," "prostatic neoplasms," "hot flashes") and keywords (e.g., breast cancer, prostate cancer, vasomotor symptoms). Vocabulary and syntax were adjusted across databases, and no date restrictions were in place. Specific details regarding the strategies have been published previously in the related protocol (Hutton, Yazdi, et al., 2015). The final search strategy is provided in Appendix 1 and was last updated on November 13, 2018.

Eligibility Criteria

The study selection criteria employed for this study have been described previously (Hutton, Yazdi, et al., 2015). Briefly, the authors sought randomized controlled trials (RCTs) performed in patients with breast or prostate cancer with a history of hot flashes that compared different interventions in terms of their effects to improve quality of life endpoints and reduce hot flash frequency and severity. Studies evaluating the effects of nonhormonal pharmacologic, natural health product, and behavioral and physical interventions were of interest. Eligible pharmacologic interventions included antidepressants from the selective serotonin reuptake inhibitor (SSRI) and selective norepinephrine reuptake inhibitor (SNRI) classes, certain neuroleptic agents, and antihypertensive medications. Structured physical and behavioral interventions of interest included exercise programs,

acupuncture, hypnosis, yoga, relaxation techniques, and cognitive behavioral therapy. Natural health products of interest included ginseng, black cohosh, isoflavones, menerba, vitamin E, flax, and soy. A detailed account of the selection criteria is provided in Appendix 2.

Process of Study Selection

Pairs of reviewers among a set of six team members (M.H., M.P., P.B., F.Y., N.A., and S.M.) screened all citations independently, with a pilot phase being used at both phases of screening to ensure consistency between reviewers. Stage 1 review consisted of screening titles and abstracts, and stage 2 consisted of screening the full texts of citations that were considered potentially relevant. After each stage, reviewers resolved discrepancies through discussion or by consultation of a third party (B.H. or M.C.) if needed. The process of study selection is presented in a flow diagram provided in the appendices.

Data Collection and Risk of Bias Assessment

Data collection from the included studies was performed by pairs of reviewers among a set of six research team members (M.H., P.B., M.P., N.A., S.M., and F.Y.) using a standardized data extraction template implemented in the Systematic Review Data Repository (srdr.ahrq.gov) and Microsoft® Excel. A pilot test of the data collection form was performed on the first five studies and refined accordingly. Data items collected included the following: study design, patient eligibility criteria, patient demographics (e.g., type of malignancy; age distribution; menopausal status; baseline measures of hot flash frequency, severity, and composite scores), intervention details (e.g., type of drug, natural health product, therapy or activity and related frequency, dosage, duration), and outcome data (e.g., final values and/or changes in hot flash endpoints, quality-of-life endpoints, harms data). After data collection, the reviewers resolved any discrepancies and consulted a third party when needed.

Full-text articles were independently assessed for risk of bias by two reviewers (M.H., M.P.) using the Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011). The tool assessed potential areas of bias, including selection bias, performance/detection bias, attrition bias, and reporting bias. Discrepancies in the initial independent assessments were resolved by discussion or consultation of a third party (B.H.), if necessary. A narrative summary of findings from these assessments is provided in the current article, and a tabular summary of all assessments is provided in the appendices.

Methods for Evidence Synthesis

Prior to network meta-analyses, pairwise meta-analyses were performed using inverse variance random effects models where multiple studies informing the same treatment comparison were available; measures of I^2 were used to evaluate for the presence of statistical heterogeneity between studies. Where comparisons involving single studies existed and no connected network of evidence could be completed, narrative syntheses were prepared.

Network meta-analysis is an extension of traditional pairwise meta-analysis, which enables the comparison of multiple interventions in a single analysis and allows incorporation of direct and indirect evidence of relevance (Caldwell et al., 2005; Lu & Ades, 2004). In the current review, network meta-analyses of the change in hot flash daily frequency and the change in hot flash composite score (frequency × severity) were conducted (network structures for other endpoints were disconnected). The nature of reporting these endpoints varied across included studies, with some reporting changes from baseline and others reporting mean values of each endpoint at baseline and follow-up, with standard deviations for each. In some cases, the percentage change from baseline in each group was reported. To accommodate for these varied reporting structures, a network meta-analysis model based on the ratio of means (RoM) was developed and implemented using WinBugs and R Model code and is provided in Appendix 3, along with a detailed description of the underlying statistical methods. Random effects consistency models were considered using a Bayesian approach with burn-in of 100,000 iterations and sampling of 100,000 iterations, and model convergence was assessed using Gelman–Rubin plots and inspection of Monte Carlo standard errors. The adequacy of fit of each model was assessed through comparison of the mean posterior total residual deviance with the number of unconstrained data points (approximately equal values suggests strong fit), and the comparison of fit between models was based on deviance information criteria. The consistency assumption was evaluated by fitting corresponding inconsistency models for each analysis and comparing the deviance information criterion value with that from the corresponding consistency analysis. Although several secondary analyses using meta-regression analysis were planned to assess the impact of heterogeneity

between studies (with regard to factors including duration of hot flashes, baseline hot flash severity, smoking status, and concomitant treatments), limited reporting of patient characteristics precluded their performance. The median effect sizes of interventions versus standard care are reported along with corresponding 95% credible intervals (CrIs). League tables (a tabular approach to summarizing comparisons between treatments derived from network meta-analysis, listing the point estimate and related measure of uncertainty) are presented in this article to summarize findings from comparisons between interventions. Surface under the cumulative ranking (SUCRA) curve values and treatment rankings are provided in the appendices (Salanti et al., 2011). All network meta-analyses were performed using OpenBUGS software, version 3.2.3. Model convergence was assessed using established methods including Gelman–Rubin diagnostics and the Potential Scale Reduction Factor. Network diagrams (a commonly used visual for network meta-analyses used to present the totality of evidence available for quantitative analysis [Salanti et al., 2008]) were prepared to summarize the available evidence for each network meta-analysis, and patterns of comparisons between active interventions and control were assessed.

Evaluating the Strength of the Evidence

Two team members (R.M., B.S.A.) rated the certainty of evidence for each pairwise and network estimate using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Brignardello-Petersen et al., 2018; Guyatt et al., 2008; Puhan et al., 2014). For each direct comparison, the body of evidence from RCTs started at high certainty of evidence and could be rated down because of study limitations (risk of bias), inconsistency (heterogeneity), indirectness, imprecision, or publication bias (Guyatt et al., 2008).

For the assessment of the network, the certainty of evidence of the indirect evidence was rated with a focus on the dominant lowest order loop (Puhan et al., 2014). The certainty of evidence of the indirect evidence served as the lowest certainty of the contributing direct comparisons. The network estimate certainty of evidence started as the higher of the direct and indirect evidence; however, their relative contributions were considered for the final estimate. The network estimate could be rated downward because of incoherence between the direct and indirect estimates or an imprecise treatment effect (Brignardello-Petersen et al., 2018; Puhan et al., 2014).

The current authors present the network effect estimates and associated certainty of evidence using an approach that categorized interventions from most effective to least effective. For each outcome, groups of interventions are presented as follows: (a) the reference intervention (placebo) and interventions no different from placebo (i.e., 95% CrI includes null value), which the authors refer to as "among the least effective"; (b) interventions superior to placebo but not superior to any other of the intervention(s) superior to placebo, which the authors call category 2 and describe as "inferior to the most effective, but superior to the least effective"; and (c) interventions that proved superior to at least one category 2 intervention, which the authors call "among the most effective." The authors then divided all three categories into two groups: those with moderate or high certainty of evidence relative to placebo, and those with low or very low certainty of evidence relative to placebo (Florez et al., 2018). Details of the assessments are provided in the appendices.

Results

Extent of Literature Identified

The initial search identified a total of 3,901 citations. Duplicates were removed, leaving 2,992 unique citations for review. Stage 1 screening of titles and abstracts identified 570 potentially relevant citations, which were subsequently reviewed in full text. Of these citations, 41 met the a priori inclusion criteria, representing 40 unique individual studies that were included for analysis; 36 were in patients with breast cancer and 4 were in patients with prostate cancer. Reasons for study exclusion are listed in the flow diagram presented in Appendix 4 and reflected in the full listing of articles excluded during full-text screening provided in Appendix 5.

Study Characteristics

A total of 4,186 patients (4,075 with breast cancer and 111 with prostate cancer) participated in the included studies (see Table 1). Year of publication ranged from 1998 to 2016, and study size ranged from 24 to 422 patients (median = 88). Parallel group and crossover designs were used in 80% and 20% of studies, respectively, and patient follow-up ranged from 4 to 108 weeks (median = 8 weeks). The largest proportion of studies was conducted in the United States (50%), with smaller proportions conducted in the United Kingdom (10%), Italy (7.5%), Sweden (7.5%), Canada (5%), Germany (5%), the Netherlands (5%), and other countries (7.5%). Regarding study funding, 58% were

TABLE 1. Study Characteristics

Study	Treatment Comparison	Sample, Setting, and Design
Breast cancer studies		
Biglia et al., 2016	Duloxetine; escitalopram	58 participants from Italy with a mean age of 45 years in a 13-week single-center study (industry funding not reported)
Lesi et al., 2016	Acupuncture plus enhanced self-care; enhanced self-care	190 participants from Italy with a mean age of 49 years in a 39-week study (no industry funding)
Cramer et al., 2015	Yoga/meditation; waitlist	40 participants from Germany with a mean age of 49 years in a 24-week single-center study (industry funding not reported)
Mao et al., 2015	Gabapentin; electroacupuncture; sham acupuncture; placebo	120 participants from the United States with a mean age of 52 years in a 25-week single-center study (no industry funding)
Bao et al., 2014	Acupuncture; sham acupuncture	51 participants from the United States with a mean age of 61 years in a 13-week multicenter study (no industry funding)
Chen et al., 2014	Melatonin; placebo	95 participants from the United States with a mean age of 59 years in an 18-week single-center study (no industry funding)
Bokmand & Flyger, 2013	Acupuncture; sham acupuncture; no treatment	94 participants from Denmark with a mean age of 61 years in a 19-week study (no industry funding)
Duijts et al., 2012	Cognitive behavioral therapy plus exercise; exercise; waitlist	422 participants from the Netherlands with a mean age of 48 years in a 26-week multicenter study (mixed industry funding)
Liljegren et al., 2012	Acupuncture; sham acupuncture	84 participants from Sweden with a mean age of 58 years in an 18-week single-center study (no industry funding)
Mann et al., 2012	Cognitive behavioral therapy; usual care	96 participants from the United Kingdom with a mean age of 53 years in a 28-week multicenter study (no industry funding)
Boekhout et al., 2011	Venlafaxine; clonidine; placebo	102 participants from the Netherlands with a mean age of 49 years in a 14-week multicenter study (industry funding not reported)
Bordeleau et al., 2010	Gabapentin; venlafaxine	66 participants from Canada with a mean age of 56 years in a 6-week multicenter study (mixed industry funding)
Walker et al., 2010	Venlafaxine; acupuncture	50 participants from the United States with a mean age of 55 years in a 64-week multicenter study (no industry funding)
Biglia et al., 2009	Gabapentin; vitamin E	115 participants from Italy with a mean age of 50 years in a 25-week single-center study (no industry funding)
Carson et al., 2009	Yoga; waitlist	37 participants from the United States with a mean age of 54 years in a 23-week single-center study (no industry funding)
Hervik & Mjåland, 2009	Acupuncture; sham acupuncture	88 participants from Norway with a mean age of 52 years in a 108-week single-center study (no industry funding)
Wu et al., 2009	Sertraline; placebo	57 participants from the United States with a mean age of 55 years in a 6-week single-center study (industry funding not reported)

TABLE 1. Study Characteristics *(Continued)*

Study	Treatment Comparison	Sample, Setting, and Design
Breast cancer studies *(continued)*		
Elkins et al., 2008	Hypnosis; waitlist	60 participants from the United States with a mean age of 57 years in a 6-week study (no industry funding)
Fenlon et al., 2008	Relaxation; no treatment	150 participants from the United Kingdom with a mean age of 55 years in a 13-week single-center study (no industry funding)
Deng et al., 2007	Acupuncture; sham acupuncture	72 participants from the United States with a mean age of 55 years in a 7- or 27-week single-center study (depending on study arm) (no industry funding)
Loibl et al., 2007	Venlafaxine; clonidine	80 participants from Germany with a mean age of 53 years in a 5-week single-center study (industry funding not reported)
Loprinzi et al., 2007	Gabapentin plus antidepressant; gabapentin	118 participants from the United States with a mean age of 53 years in a 5-week study (no industry funding)
Kimmick et al., 2006	Sertraline; placebo	62 participants from the United States with a mean age of 53 years in a 7-week single-center study (industry funding reported)
MacGregor et al., 2005	Soy; placebo	72 participants from Scotland with a mean age of 51 years in a 12-week study (industry funding reported)
Nedstrand et al., 2005	Relaxation; electroacupuncture	38 participants from Sweden with a mean age of 53 years in a 40-week single-center study (no industry funding)
Pandya et al., 2005	Gabapentin (2 dose levels); placebo	420 participants from the United States with a mean age of 55 years in a 9-week multicenter study (mixed industry funding)
Stearns et al., 2005	Paroxetine (2 dose levels); placebo	151 participants from the United States with a mean age of 52 years in a 5-week multicenter study (industry funding reported)
Hernández Muñoz & Pluchino, 2003	Black cohosh; usual care	Participants from Venezuela with a mean age of 46 years in a 52-week single-center study (industry funding not reported)
Loprinzi et al., 2002	Fluoxetine; placebo	87 participants from the United States in a 5-week study (industry funding not reported)
Van Patten et al., 2002	Soy; placebo	157 participants from Canada with a mean age of 55 years in a 16-week study (no industry funding)
Jacobson et al., 2001	Black cohosh; placebo	85 participants from the United States in a 9-week single-center study (mixed industry funding)
Loprinzi et al., 2000	Venlafaxine (3 dose levels); placebo	229 participants from the United States in a 5-week study (no industry funding)
Pandya et al., 2000	Clonidine; placebo	198 participants from the United States with a mean age of 54 years in a 13-week study (no industry funding)
Quella et al., 2000	Soy; placebo	182 participants from the United States in a 5-week study (no industry funding)
Fenlon, 1999	Relaxation; no treatment	24 participants from the United Kingdom with a mean age of 48 years in a 4-week (unclear) single-center study (industry funding not reported)

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TABLE 1. Study Characteristics *(Continued)*		
Study	**Treatment Comparison**	**Sample, Setting, and Design**
Breast cancer studies *(continued)*		
Barton et al., 1998	Vitamin E; placebo	125 participants from the United States in a 5-week study (no industry funding)
Prostate cancer studies		
Stefanopoulou et al., 2015	Cognitive behavioral therapy; usual care	32 participants from the United Kingdom with a mean age of 69 years in a 4-week study (no industry funding)
Vitolins et al., 2013	Venlafaxine; venlafaxine plus milk powder; venlafaxine plus soy powder	13 participants from the United States with a mean age of 69 years in a 12-week multicenter study (mixed industry funding)
Frisk et al., 2009	Electroacupuncture; acupuncture	53 participants from Sweden with a mean age of 69 years in a 12-week multicenter study (no industry funding)
Loprinzi et al., 2009	Gabapentin (3 dose levels); placebo	13 participants from the United States with a mean age of 69 years in a 4-week multicenter study (no industry funding)

government or academically funded, 12.5% had mixed funding, 5% were industry funded, 2.5% had no funding, and 20% did not report on funding source (Biglia et al., 2009). A total of 42.5% of studies were at single sites, 27.5% were multicenter, and 30% did not report the number of participating centers.

Patient Population Characteristics

Regarding demographics, several patient descriptors were largely unreported in the included studies. This included details of patients' types of breast and prostate cancer diagnoses, average duration of hot flashes prior to the time of the study, concomitant interventions (for hot flashes or other indications), duration of time since cancer treatment, body mass index, smoking history, and socioeconomic status. Average or median patient age was available from 35 studies, with a median measure of 54 years (range = 45–70); patients in the four prostate cancer studies (Frisk et al., 2009; Loprinzi et al., 2009; Stefanopoulou et al., 2015; Vitolins et al., 2013) were all associated with higher values between 69 and 71 years. The median proportion of Caucasian patients was 85.5% (range = 40%–100%) among 19 studies with available data. A total of 31 studies (77.5%) reported patients' average daily number of hot flashes prior to randomization (weekly values were divided accordingly); the median value was 7.7, with some variation as expected (range = 2.8–12.5) based on studies' variable entry criteria regarding this trait. Only seven studies reported on the use of prior interventions for hot flashes, with

a median percentage of patients of 13.5% (range = 0%–61%) (Boekhout et al., 2011; Bordeleau et al., 2010; Hervik & Mjåland, 2009; Loibl et al., 2007; MacGregor et al., 2005; Mann et al., 2012; Mao et al., 2015). Time from diagnosis was reported in nine studies (Bordeleau et al., 2010; Carson et al., 2009; Chen et al., 2014; Cramer et al., 2015; Frisk et al., 2009; Mann et al., 2012; Nedstrand et al., 2005; Stefanopoulou et al., 2015; Van Patten et al., 2002), with a median of 3.28 years (range = 2–7.6). The ability to assess the extent of homogeneity amongst study populations was limited based on the lack of information available for inspection.

Interventions Compared

Overall, the set of included studies evaluated a broad range of natural health product interventions (e.g., soy, melatonin, black cohosh, vitamin E), pharmacologic interventions (e.g., venlafaxine, paroxetine, fluoxetine, escitalopram, duloxetine, sertraline, gabapentin, clonidine), physical activity interventions (e.g., yoga, acupuncture, electroacupuncture), psychological interventions (e.g., relaxation, cognitive behavioral therapy, hypnosis), and combination interventions. Figure 1 presents network diagrams displaying the patterns of comparisons across the set of included studies prior to consideration of the availability of outcomes; data separated by population (breast cancer and prostate cancer) and considering data collectively from both populations are shown. The majority of comparisons in the included studies used placebo or standard care as the control group.
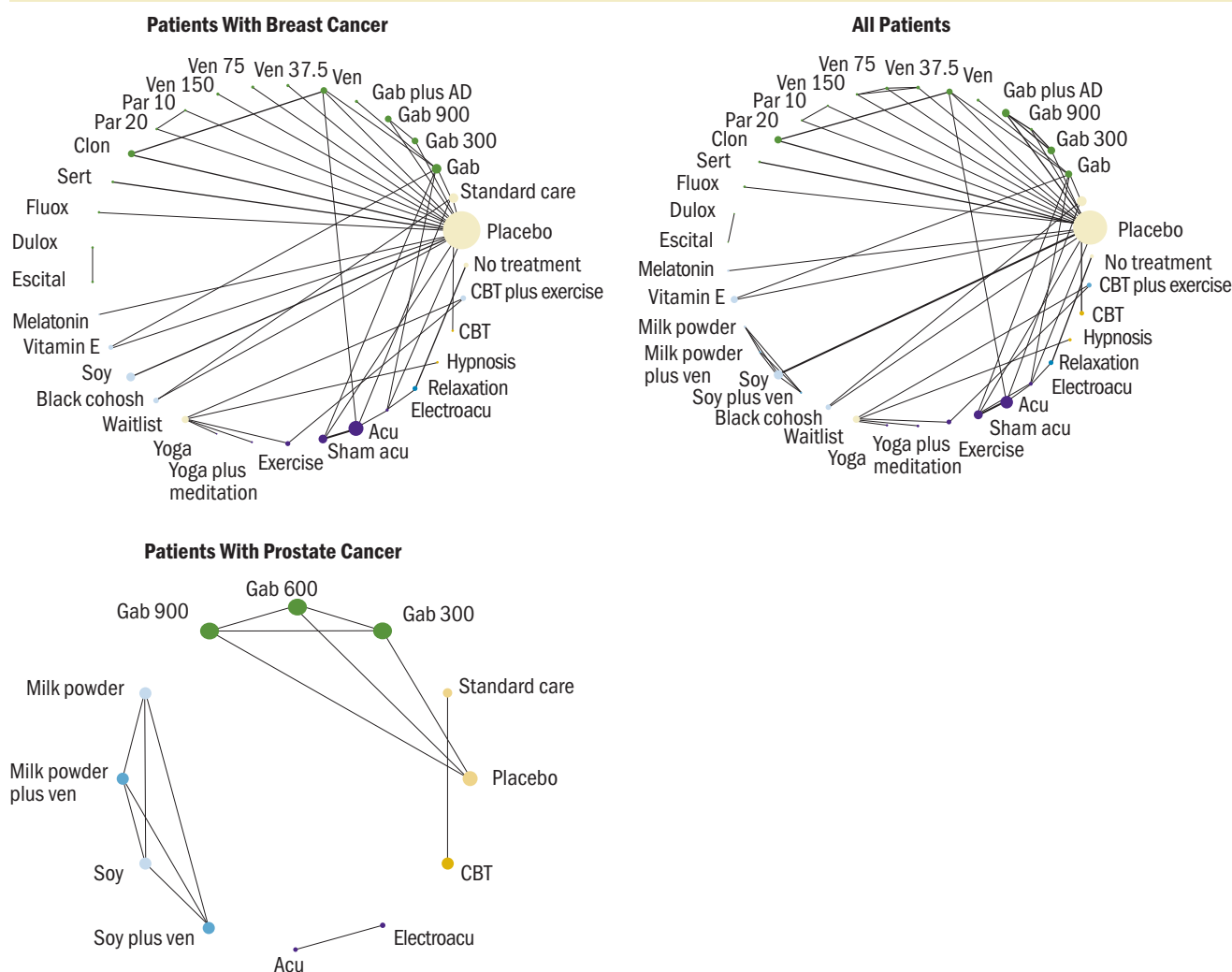
As the presence of outcomes per study was inspected, the scope and feasibility of network meta-analyses encompassing the broad range of therapies was limited; this is discussed further later in this article.

Outcomes Reported

A summary table provided in Appendix 6 provides a study-by-study account of the availability of the a priori outcomes of interest. Hot flash frequency was reported by 32 studies, hot flash severity was reported by 10 studies, and hot flash composite score was reported by 26 studies. Reporting format of outcome data varied across studies and included mean difference of change from baseline, mean percentage change from baseline, and values of endpoints at baseline and follow-up. Values were expressed as weekly measures in some cases and daily measures in other cases. In addition, treatment comparisons

FIGURE 1. Treatment Comparisons Among Included Studies

acu—acupuncture; AD—antidepressant; CBT—cognitive behavioral therapy; clon—clonidine; dulox—duloxetine; escital—escitalopram; fluox—fluoxetine; gab—gabapentin; par—paroxetine; sert—sertraline; ven—venlafaxine

Note. Treatment nodes are sized to reflect the proportionate numbers of patients studied in total for each intervention in the network, and the thickness of lines joining each pair of treatments reflects the available numbers of studies informing the treatment comparison. The comparisons made within randomized controlled trials are mapped overall and by tumor type. Although some head-to-head randomized controlled trials existed, most studies involved comparisons with placebo. Per study outcome, notably smaller numbers of trials reported findings, leading to a reduced number of studies per analysis and often excluding interventions from network meta-analysis (requiring separate description). In network meta-analyses, for each pharmacologic, doses were collapsed into a single node because of sparsity of data.

within studies could not be fully connected within evidence networks. Network meta-analyses consisting of a subset of all noted studies were feasible for each of the hot flash composite score and hot flash frequency outcome measures (supplemented by narrative description of unconnected studies), and only a narrative summary was feasible for hot flash severity.

Quality-of-life measures were heterogeneously reported across studies. General health-related quality of life was assessed by one of a broad range of scales in 21 studies including the SF-36®, European Organisation for Research and Treatment Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30), EuroQoL, Functional Assessment of Cancer Therapy (FACT)–Breast, FACT-General, FACT-Prostate, FACT-Endocrine Subscale, Global Rating of Well-Being, Menopause-Specific Quality of Life (MENQOL), Menopause Rating Scale, single-item global score, the Symptom Checklist, and a visual analog scale. Sleep-related quality of life was assessed by eight studies involving use of the Pittsburgh Sleep Quality Index, the Medical Outcomes Study (MOS) Sleep Scale, the Groningen Sleep Quality Scale, and the Women's Health Questionnaire sleep subscale. Depression-related quality of life was described in 15 studies based on the Hospital Anxiety and Depression Scale (HADS), Center for Epidemiologic Studies–Depression (CES-D), the Beck Depression Index (BDI), the Women's Health Questionnaire depression subscale, or the Profile of Mood States (POMS). Sexual function quality of life was described in five studies and assessed using the Sexual Activity Questionnaire, the MOS Sexual Problem Index, or a visual analog scale. Based on the disconnected patterns of treatment comparisons and diversity in assessment scales used, only narrative summaries were used to summarize the available evidence for these outcomes.

Risk of Bias Assessments

Appendix 7 provides a summary bar graph of the distribution of judgments across studies on all risk of bias domains, as well as a tabular summary of all risk of bias assessments performed for the set of included studies. Totals of 45% and 57.5% of included studies were assessed to be associated with an unclear risk of bias for randomization and allocation concealment. Blinding of patients, study personnel, and outcome assessors was inconsistent among studies and judged to be unclear in 22.5%, 57.5%, and 25% of studies, respectively. Risk of selective reporting was unclear in 62.5% of studies because of lack of availability of a study protocol. A total of 66.5% of studies

were judged to be at high risk of bias based on a lack of intention-to-treat analysis, and 52.5% of studies were judged at unclear risk of bias with regard to treatment compliance.
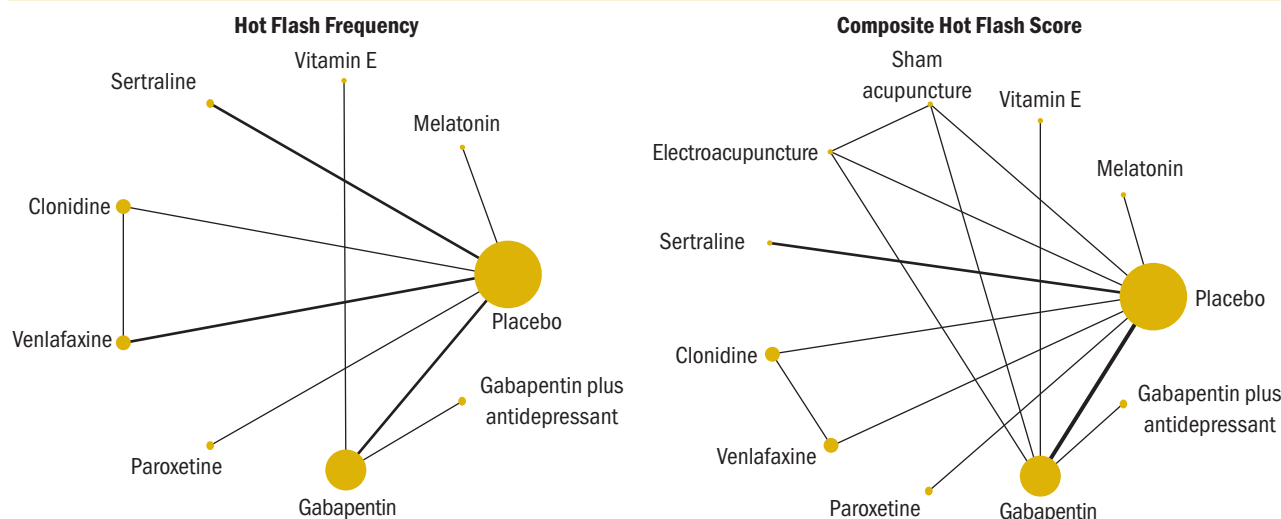
Findings
Syntheses of the Evidence

The following sections present findings from network meta-analyses (where they were feasible), as well as narrative summaries of individual study findings for studies that could not be included in network meta-analyses because of a lack of connectivity of the evidence base. Network meta-analyses were feasible using a subset of all available evidence for changes in hot flash frequency and hot flash composite score; for both analyses, model fit statistics suggested the fit of the random effects model to be adequate (see Appendix 8) and that there was minimal evidence to support a violation of the consistency of direct and indirect evidence (see Appendix 9). Secondary measures of treatment effect from network meta-analyses including SUCRA are described later in this article, with full details provided in Appendix 10. Where narrative summaries of study findings were required because of disconnected treatment networks (whether for all treatments or only a subset of treatments), the main text of the article mentions findings only briefly, and Appendix 11 presents additional numeric details from the individual studies with available data.

Hot Flash Frequency Reduction

A total of 11 studies (Biglia et al., 2009; Chen et al., 2014; Kimmick et al., 2006; Loibl et al., 2007; Loprinzi et al., 2000, 2007, 2009; Pandya et al., 2000, 2005; Stearns et al., 2005; Wu et al., 2009) comparing 9 interventions (see Figure 2) that enrolled a total of 1,403 patients had outcome data for changes in hot flash frequency that could be synthesized using network meta-analysis. Overall, eight studies were placebo-controlled, all of which had two study arms.

Table 2 is a league table summarizing all pairwise RoMs comparing interventions included in the network. Paroxetine, venlafaxine, gabapentin plus antidepressant, gabapentin, clonidine, and sertraline were associated with more benefit than vitamin E. Only paroxetine and venlafaxine were better than placebo. The largest RoM versus placebo was associated with paroxetine (RoM = 3.15, 95% CrI [1.29, 7.58], SUCRA = 0.873). Based on descending magnitude of SUCRA value, the next best ranked interventions were venlafaxine (RoM versus placebo = 2.48, 95% CrI [1.36, 4.32], SUCRA = 0.8), gabapentin plus

FIGURE 2. Evidence Networks for Network Meta-Analyses of Hot Flash Frequency and Composite Hot Flash Score

Hot Flash Frequency — **Composite Hot Flash Score**

Note. Treatment nodes are sized to reflect the proportionate numbers of patients studied in total for each intervention in the network, and the thickness of lines joining each pair of treatments reflects the available numbers of studies informing the treatment comparison. For hot flash frequency, data from 11 randomized controlled trials comparing 9 interventions (n = 1,403 participants) were available, with most studies assessed versus control. The format of reporting was variable (5 studies reported mean change, and 6 reported percentage change). For composite hot flash score, data from a total of 12 randomized controlled trials comparing 11 interventions (n = 1,523 participants) were available for network meta-analysis. For both networks, most interventions were assessed versus placebo, and format of outcome reporting varied between mean change and percentage change from baseline.

antidepressant (RoM versus placebo = 1.8, 95% CrI [0.65, 4.65], SUCRA = 0.59), sertraline (RoM versus placebo = 1.67, 95% CrI [0.69, 3.94], SUCRA = 0.55), gabapentin (RoM versus placebo = 1.62, 95% CrI [0.92, 2.73], SUCRA = 0.53), clonidine (RoM versus placebo = 1.62, 95% CrI [0.86, 2.98], SUCRA = 0.52), melatonin (RoM versus placebo = 1.03, 95% CrI [0.11, 8.9], SUCRA = 0.39), and vitamin E (RoM versus placebo = 0.27, 95% CrI [0.06, 1.18], SUCRA = 0.033).

No physical or psychological interventions could be included in the analysis because they were disconnected from the evidence network, warranting separate description. In total, 20 additional studies (Barton et al., 1998; Biglia et al., 2016; Bordeleau et al., 2010; Carson et al., 2009; Deng et al., 2007; Duijts et al., 2012; Elkins et al., 2008; Fenlon, 1999; Fenlon et al., 2008; Frisk et al., 2009; Hervik & Mjåland, 2009; Liljegren et al., 2012; Loprinzi et al., 2002; Mann et al., 2012; Mao et al., 2015; Nedstrand et al., 2005; Quella et al., 2000; Stefanopoulou et al., 2015; Van Patten et al., 2002; Vitolins et al., 2013) reported data regarding changes in hot flash frequency that could not be included in the network meta-analysis. Briefly, findings related to pharmacologic interventions suggested that duloxetine and escitalopram may offer a reduction in hot flash frequency in women with breast cancer (Biglia

et al., 2016), as may fluoxetine (Loprinzi et al., 2002); gabapentin may offer fewer benefits than electroacupuncture (Mao et al., 2015); gabapentin and venlafaxine may offer benefits for patients with breast cancer, with patient preferences from a crossover study favoring venlafaxine (Bordeleau et al., 2010). Findings related to nonpharmacologic interventions suggested that cognitive behavioral therapy may reduce the number of hot flash episodes as compared to placebo among men with prostate cancer (Stefanopoulou et al., 2015); group cognitive behavioral therapy and usual care (including telephone support and information leaflets on symptom management) may offer reductions in hot flash frequency in women with breast cancer, with no significant difference identified between treatments (Mann et al., 2012); yoga may offer more improvement than no treatment for patients with breast cancer (Carson et al., 2009); and acupuncture and electroacupuncture may offer reductions for as long as one year in patients with prostate cancer (Frisk et al., 2009; Nedstrand et al., 2005); relaxation therapy may reduce frequency in women with breast cancer (Fenlon et al., 2008; Nedstrand et al., 2005); and hypnosis in women with breast cancer may offer benefits as compared to no treatment (Elkins et al., 2008). Two studies observed reductions in hot flash frequency in groups of patients

with breast cancer randomized to acupuncture versus sham acupuncture, with no statistically significant difference identified between groups (Deng et al., 2007; Liljegren et al., 2012); one other study making the same treatment comparison observed a significant difference favoring acupuncture (Hervik & Mjåland, 2009). There was little to no evidence of benefits with soy (Quella et al., 2000; Van Patten et al., 2002) or vitamin E (Barton et al., 1998) as compared to placebo or exercise (with or without cognitive behavioral therapy) and as compared to no treatment (Duijts et al., 2012).

Among the studies with high or moderate certainty of evidence relative to placebo, only venlafaxine reduced the mean hot flash frequency as compared to placebo (RoM = 2.48, 95% CrI [1.36, 4.3], moderate certainty of evidence) (see Appendix 12). Gabapentin was no more effective than placebo (RoM = 1.62, 95% CrI [0.92, 2.73], moderate certainty of evidence). Among the studies with low or very low certainty of evidence, paroxetine significantly reduced the mean hot flash

frequency (RoM = 3.15, 95% CrI [1.29, 7.58], low certainty of evidence). No other statistically significant differences were identified among the remainder of the interventions and placebo comparisons.

Hot Flash Composite Score Reduction

Data from 12 RCTs (Biglia et al., 2009; Chen et al., 2014; Kimmick et al., 2006; Loibl et al., 2007; Loprinzi et al., 2000, 2007, 2009; Mao et al., 2015; Pandya et al., 2000, 2005; Stearns et al., 2005; Wu et al., 2009) comparing 11 interventions that enrolled a total of 1,523 patients had outcome data for changes in hot flash score that could be synthesized using network meta-analysis. Overall, 9 studies (1,286 patients) were placebo-controlled, of which 5 studies had more than two arms.

Table 3 is a league table summarizing all pairwise RoMs comparing interventions included in the network. Paroxetine, clonidine, electroacupuncture, and venlafaxine were better than placebo, and vitamin E

TABLE 2. League Table of Comparisons Between All Interventions: Hot Flash Frequency Reduction

Paroxetine	0.684	0.821	0.848	0.908	0.9	0.829	**0.997**	**0.993**
1.27 [0.45, 3.68]	Venlafaxine	0.737	0.784	0.876	0.927	0.781	**0.996**	**0.995**
1.75 [0.49, 6.69]	1.38 [0.45, 4.39]	Gab Plus AD	0.546	0.61	0.581	0.676	**0.988**	0.891
1.89 [0.55, 6.55]	1.48 [0.53, 4.23]	1.07 [0.29, 3.9]	Sertraline	0.522	0.527	0.657	**0.908**	0.879
1.94 [0.7, 5.53]	1.53 [0.7, 3.37]	1 [0.48, 2.48]	1.03 [0.38, 2.86]	Gab	0.504	0.657	**0.993**	0.958
1.94 [0.7, 5.53]	1.53 [0.82, 2.8]	1.11 [0.34, 3.45]	1.03 [0.35, 2.97]	1 [0.44, 2.23]	Clonidine	0.653	**0.985**	0.943
3.07 [0.3, 32.3]	2.39 [0.26, 23.17]	1.73 [0.16, 19.14]	1.61 [0.16, 17.11]	1.57 [0.17, 15.18]	1.56 [0.17, 15.46]	Melatonin	0.842	0.511
11.69 [2.1, 65.56]	**9.14 [1.87, 44.28]**	**6.62 [1.31, 32.57]**	**6.16 [1.1, 33.84]**	**5.99 [1.5, 23.66]**	**5.97 [1.21, 29.83]**	3.77 [0.28, 51.41]	Vitamin E	0.04
3.15 [1.29, 7.58]	**2.48 [1.36, 4.32]**	1.8 [0.65, 4.65]	1.67 [0.69, 3.94]	1.62 [0.92, 2.73]	1.62 [0.86, 2.98]	1.03 [0.11, 8.9]	0.27 [0.06, 1.18]	Placebo

AD—antidepressant; CrI—credible interval; gab—gabapentin; RoM—ratio of means; SUCRA—surface under the cumulative ranking
Note. In the lower half of the table, the posterior median pairwise RoMs and CrIs (2.5% and 97.5% quantiles) from network meta-analysis are shown. A complete summary of estimates for efficacy from the random effects consistency model assuming vague priors is displayed. Treatments other than placebo are in the order of decreasing SUCRA value from upper left to lower right. For each comparison, the lower right–most treatment is the reference treatment; therefore, values greater than 1 favor the upper left–most intervention. Significant differences are shown in bold. For example, the RoM estimate of 2.48 (95% CrI [1.36, 4.32]) in the lower triangle suggests that venlafaxine is associated with 2.48 times the amount of hot flash frequency reduction as compared to placebo. In the upper half of the figure, the corresponding probability estimate in the upper triangle suggests a probability of 99.5% that venlafaxine is better than placebo in terms of hot flash frequency reduction.

was worse than placebo. The largest RoM versus placebo was associated with paroxetine (RoM = 2.83, 95% CrI [1.31, 6.09], SUCRA = 0.87). In order of descending magnitude of SUCRA value, the subsequently ranked interventions were clonidine (RoM versus placebo = 2.13, 95% CrI [1.27, 3.54], SUCRA = 0.76), electroacupuncture (RoM versus placebo = 2.07, 95% CrI [1.01, 4.24], SUCRA = 0.73), venlafaxine (RoM versus placebo = 1.71, 95% CrI [1.05, 2.76], SUCRA = 0.59), sham acupuncture (RoM versus placebo = 1.65, 95% CrI [0.83, 3.31], SUCRA = 0.57), sertraline (RoM versus placebo = 1.58, 95% CrI [0.7, 3.41], SUCRA = 0.54), gabapentin (RoM versus placebo = 1.43, 95% CrI [0.95, 2.12], SUCRA = 0.451), gabapentin plus antidepressant (RoM versus placebo = 1.34, 95% CrI [0.59, 3.01], SUCRA = 0.42), melatonin (RoM versus placebo = 0.7, 95% CrI [0.05, 11.19], SUCRA = 0.34), placebo (SUCRA = 0.21), and vitamin E (RoM versus placebo = 0.14, 95% CrI [0.03, 0.58], SUCRA = 0.02).

As was observed for the hot flash frequency analysis, no physical or psychological interventions could be included in the analysis because they were disconnected from the evidence network. An additional 14 studies (Bao et al., 2014; Barton et al., 1998; Biglia et al., 2016; Boekhout et al., 2011; Bordeleau et al., 2010; Carson et al., 2009; Elkins et al., 2008; Frisk et al., 2009; Jacobson et al., 2001; Lesi et al., 2016; Loprinzi et al., 2002; Quella et al., 2000; Van Patten et al., 2002; Vitolins et al., 2013) reported data regarding composite hot flash score that could not be included in the network meta-analysis. Briefly, findings regarding pharmacologic interventions suggested that escitalopram and duloxetine may reduce hot flash scores in women with breast cancer (Biglia et al., 2016); venlafaxine and clonidine offered improvements as compared to placebo for patients with breast cancer (Boekhout et al., 2011), as did fluoxetine (Loprinzi et al., 2002). Venlafaxine and gabapentin offered reductions from baseline in patients with breast cancer that were of comparable magnitude (Bordeleau et al., 2010). Among nonpharmacologic interventions, findings suggested that acupuncture with enhanced self-care (i.e., provision of an information booklet about climacteric symptom management addressing considerations for diet, physical exercise, and psychological support) improved hot flash score as compared to enhanced self-care alone (Lesi et al., 2016); yoga provided significant benefits as compared to waitlist control post-treatment in patients with breast cancer after three months of follow-up (Carson et al., 2009); hypnosis as compared to waitlist control may provide improved change in hot flash score in patients

with breast cancer (Elkins et al., 2008); vitamin E may offer some improvement as compared to placebo for patients with breast cancer (Barton et al., 1998); acupuncture and electroacupuncture may reduce distress from hot flashes in patients with prostate cancer (Frisk et al., 2009). No statistically significant differences were reported in trials that involved comparisons of acupuncture versus sham acupuncture (Bao et al., 2014); however, a significant change from baseline in the acupuncture group was noted. No statistically significant differences were reported in trials that involved comparisons of soy versus placebo (Quella et al., 2000; Van Patten et al., 2002), black cohosh versus placebo (Jacobson et al., 2001), or exercise (with or without cognitive behavioral therapy) versus no treatment (Duijts et al., 2012).

No interventions demonstrated high or moderate certainty of evidence when compared to placebo. Among the studies with low or very low certainty of evidence, venlafaxine (RoM = 1.71, 95% CrI [1.05, 2.76], low certainty of evidence), paroxetine (RoM = 2.83, 95% CrI [1.31, 6.09], low certainty of evidence), clonidine (RoM = 2.13, 95% CrI [1.27, 3.54], low certainty of evidence), and electroacupuncture (RoM = 2.07, 95% CrI [1.01, 4.24], low certainty of evidence) significantly reduced the mean hot flash composite score as compared to placebo. Vitamin E significantly increased the mean hot flash composite score when compared to placebo (RoM = 0.14, 95% CrI [0.03, 0.58], very low certainty of evidence). No other statistically significant differences were identified among the remainder of the interventions and placebo comparisons.

Hot Flash Severity
The authors identified 10 studies that reported on the outcome of hot flash severity (Barton et al., 1998; Bordeleau et al., 2010; Carson et al., 2009; Chen et al., 2014; Fenlon et al., 2008; Hernández Muñoz & Pluchino, 2003; Jacobson et al., 2001; Pandya et al., 2000; Vitolins et al., 2013; Walker et al., 2010). Because of the variety of reporting formats and low number of studies evaluating the outcome measure, a narrative approach to synthesis was used.

There was uncertainty of effects based on the small amounts of evidence available for venlafaxine, gabapentin, and clonidine. Each may offer some benefits related to hot flash severity, but the clinical relevance is unclear (Bordeleau et al., 2010; Loibl et al., 2007; Pandya et al., 2000; Walker et al., 2010). In patients with breast cancer, acupuncture may provide beneficial effects comparable to those of

venlafaxine, yoga, and black cohosh (but studies for the latter conflicted) as compared to no treatment (Carson et al., 2009; Hernández Muñoz & Pluchino, 2003; Jacobson et al., 2001). There was insufficient evidence of any important effects associated with vitamin E, melatonin, or soy (Barton et al., 1998; Chen et al., 2014; Vitolins et al., 2013). Relaxation therapy may reduce hot flash severity as compared to control in patients with breast cancer (low certainty of evidence) (Fenlon et al., 2008).

TABLE 3. League Table of Comparisons Between All Interventions: Hot Flash Composite Score Reduction

Par	Clon	Electro	Ven	Sham Acu	Sert	Gab	Gab Plus AD	Mela	Vit E	Placebo
Par	0.738	0.722	0.869	0.856	0.858	0.944	0.915	0.82	1	0.995
1.34 [0.52, 3.37]	**Clon**	0.527	0.829	0.728	0.741	0.895	0.846	0.776	1	0.995
1.36 [0.47, 3.98]	1.03 [0.42, 2.45]	**Electro**	0.677	0.751	0.697	0.88	0.831	0.768	1	0.976
1.66 [0.66, 4.08]	1.24 [0.76, 2.01]	1.21 [0.52, 2.87]	**Ven**	0.536	0.573	0.726	0.717	0.733	0.999	0.984
1.7 [0.61, 4.84)	1.28 [0.54, 3.04]	1.25 [0.63, 2.54]	1.04 [0.44, 2.40]	**Sham Acu**	0.535	0.688	0.683	0.721	0.999	0.93
1.78 [0.62, 5.49]	1.35 [0.54, 3.47]	1.32 [0.46, 3.82]	1.09 [0.44, 2.77]	1.05 [0.37, 3.01]	**Sert**	0.59	0.623	0.703	0.998	0.876
1.98 [0.83, 4.77]	1.49 [0.78, 2.86]	1.45 [0.75, 2.84]	1.2 [0.64, 2.25]	1.16 [0.61, 2.21]	1.11 [0.45, 2.65]	**Gab**	0.584	0.693	0.999	0.958
2.12 [0.69, 6.58]	1.6 [0.61, 4.15]	1.55 [0.59, 4.14]	1.29 [0.5, 3.32]	1.24 [0.48, 3.25]	1.19 [0.38, 3.63]	1.07 [0.52, 2.16]	**Gab Plus AD**	0.672	0.997	0.77
4.09 [0.23, 68.7]	3.06 [0.18, 48.22]	2.97 [0.17, 48.09]	2.48 [0.15, 38.65]	2.37 [0.13, 38.33]	2.28 [0.12, 37.93]	2.05 [0.12, 31.54]	1.92 [0.11, 33.93]	**Mela**	0.848	0.397
20.89 [4.04, 105.1]	**15.75 [3.29, 71.45]**	**15.4 [3.33, 69.75]**	**12.65 [2.78, 56.85]**	**12.23 [2.71, 54.47]**	**11.56 [2.19, 59.69]**	**10.6 [2.64, 40.69]**	**9.9 [2.09, 45.02]**	5.15 [0.23, 123.96]	**Vit E**	0.003
2.83 [1.31, 6.09]	**2.13 [1.27, 3.54]**	**2.07 [1.01, 4.24]**	**1.71 [1.05, 2.76]**	1.65 [0.83, 3.31]	1.58 [0.7, 3.41]	1.43 [0.95, 2.12]	1.34 [0.59, 3.01]	0.7 [0.05, 11.19]	**0.14 [0.03, 0.58]**	**Placebo**

acu—acupuncture; AD—antidepressant; clon—clonidine; Crl—credible interval; electro—electroacupuncture; gab—gabapentin; mela—melatonin; par—paroxetine; RoM—ratio of means; sert—sertraline; SUCRA—surface under the cumulative ranking; ven—venlafaxine; vit—vitamin
Note. In the lower half of the table, the posterior median pairwise RoMs and Crls (2.5% and 97.5% quantiles) from network meta-analysis are shown. A complete summary of estimates for efficacy from the random effects consistency model assuming vague priors is displayed. Treatments other than placebo are in the order of decreasing SUCRA value from upper left to lower right. For each comparison, the lower right–most treatment is the reference treatment; therefore, values greater than 1 favor the upper left–most intervention. Significant differences are shown in bold. For example, the RoM estimate of 1.71 (95% Crl [1.05, 2.76]) in the lower triangle suggests that venlafaxine is associated with 1.71 times the amount of hot flash composite score reduction as compared to placebo. In the upper half of the figure, the corresponding probability estimate in the upper triangle suggests a probability of 98.4% that venlafaxine is better than placebo in terms of hot flash composite score reduction.

General Quality of Life

The authors identified 19 studies that reported on measures of quality of life (Bao et al., 2014; Biglia et al., 2009; Bordeleau et al., 2010; Cramer et al., 2015; Fenlon et al., 2008; Jacobson et al., 2001; Kimmick et al., 2006; Loprinzi et al., 2000, 2002, 2007, 2009; MacGregor et al., 2005; Nedstrand et al., 2005; Pandya et al., 2000; Stearns et al., 2005; Stefanopoulou et al., 2015; Vitolins et al., 2013; Walker et al., 2010; Wu et al., 2009). A variety of general quality-of-life measures were assessed across trials, as described previously. Because of the diversity of measurements and treatment patterns, only pairwise comparisons were possible, primarily based on single studies. Only three studies that reported data related to general quality of life identified statistically significant differences between groups. One identified a difference between venlafaxine and placebo in patients with breast cancer based on single-item global quality-of-life items (Loprinzi et al., 2000). The second identified a difference between yoga and no treatment in patients with breast cancer on the FACT-Breast scale and the related physical, social, and emotional well-being subscales (Cramer et al., 2015). The third identified a difference between soy and no soy in patients with prostate cancer with regard to FACT-General, FACT-Prostate, and related emotional and functional domains (Vitolins et al., 2013). Limited data exist to suggest important general quality-of-life improvements for any intervention. Two studies reported that relaxation training may improve quality of life, but there is a low certainty of evidence (Fenlon et al., 2008). Yoga as compared to placebo may improve quality of life in patients with breast cancer, as measured by FACT-Breast (low certainty of evidence) (Cramer et al., 2015).

Depression-Related Quality of Life

The authors identified 15 studies that reported on measures of quality of life related to depression (Bao et al., 2014; Biglia et al., 2016; Boekhout et al., 2011; Chen et al., 2014; Cramer et al., 2015; Duijts et al., 2012; Elkins et al., 2008; Jacobson et al., 2001; Kimmick et al., 2006; Loprinzi et al., 2000, 2009; Mann et al., 2012; Stearns et al., 2005; Stefanopoulou et al., 2015; Walker et al., 2010). Depression outcomes were assessed in a variety of formats and tools, including the BDI (various approaches, including mean change and amount reaching certain thresholds), CES-D (mean values and amount reaching certain threshold), HADS, Montgomery–Åsberg Depression Rating Scale, POMS, and Women's Health Questionnaire depression subscale. Because of the diversity of measurements and treatment patterns, only pairwise comparisons were possible, most informed by single studies. There is very low certainty that hypnosis reduces depression as compared to a waitlist (Elkins et al., 2008). Among women with breast cancer and men with prostate cancer, cognitive behavioral therapy may reduce depression (measured with HADS) as compared to placebo, but it is unlikely (very low certainty of evidence) (Stefanopoulou et al., 2015). Among women with breast cancer, cognitive behavioral therapy may reduce depression (measured with Women's Health Questionnaire; low certainty of evidence) (Mann et al., 2012). Yoga is unlikely to change depression when compared to placebo (measured with HADS; low certainty of evidence) (Cramer et al., 2015). Acupuncture is unlikely to affect depression as compared to placebo (low certainty of evidence) (Bao et al., 2014).

Sleep-Related Quality of Life

The authors identified eight RCTs that reported on the outcome of sleep quality (Bao et al., 2014; Biglia et al., 2009; Boekhout et al., 2011; Carson et al., 2009; Chen et al., 2014; Elkins et al., 2008; Mann et al., 2012; Stearns et al., 2005). Because of the diversity of measurements and treatment patterns, only pairwise comparisons were possible based mainly on single studies. Based on one study, paroxetine may offer benefits as compared to placebo for patients with breast cancer (Stearns et al., 2005); however, the benefits of venlafaxine and clonidine are unclear (Boekhout et al., 2011). Based on one small study, gabapentin may offer greater benefits than vitamin E in patients with breast cancer (Biglia et al., 2009). Based on small single studies, evidence suggested no clear benefits of acupuncture over sham acupuncture (Bao et al., 2014), statistically significant gains in sleep quality with melatonin as compared to placebo (Chen et al., 2014), reduced sleep problems in those receiving cognitive behavioral therapy as compared to usual care (Mann et al., 2012), improvements in sleep disturbance attained with yoga as compared to no therapy (Carson et al., 2009), and improvements in sleep achieved with hypnosis as compared to no treatment (Elkins et al., 2008). Hypnosis may improve sleep compared to placebo (low certainty of evidence) (Elkins et al., 2008).

Sexual Function Quality of Life

The authors identified five RCTs that reported on the following interventions: cognitive behavioral therapy, exercise, venlafaxine, clonidine, paroxetine, and fluoxetine (Boekhout et al., 2011; Duijts et al., 2012; Loprinzi

et al., 2000, 2002; Stearns et al., 2005). Because of the diversity of measurements and treatment patterns, only pairwise comparisons were possible.

Among studies of pharmacologic interventions, improvement in sexual function from venlafaxine, clonidine, or paroxetine as compared to placebo is unlikely (very low certainty of evidence). Fluoxetine may improve sexual function as compared to placebo (very low certainty of evidence); however, it is unlikely. Among the studies reporting on nonpharmacologic interventions (cognitive behavioral therapy and exercise), the combination of cognitive behavioral therapy with exercise may improve sexual function as compared to no intervention; however, it is unlikely (very low certainty of evidence).

Tolerability

Reporting of adverse events related to the interventions varied by type of outcome reported and measure of the outcome. In addition, the reporting of adverse events raised concerns with selective reporting because many studies failed to report disaggregated data, instead narratively stating whether or not there were differences between the two arms. Because of the diversity of measurements and treatment patterns, only pairwise comparisons were possible.

The most common adverse events reported were constipation, headache, nausea, and fatigue/sleepiness. When compared to placebo, no statistically significant difference was found for sertraline, electroacupuncture, gabapentin, melatonin, soy, or vitamin E (Barton et al., 1998; Chen et al., 2014; Kimmick et al., 2006; MacGregor et al., 2005; Mao et al., 2015; Wu et al., 2009). For the outcome of constipation, one small trial suggested lower risk with venlafaxine as compared to placebo (Boekhout et al., 2011). The remaining interventions did not suggest significance as compared to placebo for the outcome of constipation (i.e., soy, black cohosh, clonidine, electroacupuncture, gabapentin, and sertraline) (Jacobson et al., 2001; Kimmick et al., 2006; MacGregor et al., 2005; Mao et al., 2015; Van Patten et al., 2002). When compared to placebo, sertraline, soy, clonidine, venlafaxine, and vitamin E did not suggest a difference in risk for nausea (Barton et al., 1998; Boekhout et al., 2011; Kimmick et al., 2006; MacGregor et al., 2005; Van Patten et al., 2002; Wu et al., 2009). No study suggested a difference between the interventions of clonidine, electroacupuncture, gabapentin, melatonin, sertraline, soy, or venlafaxine as compared to placebo for the outcome of fatigue (Barton et al., 1998; Boekhout et al., 2011; Chen et al., 2014; Kimmick et al.,

2006; Mao et al., 2015). Acupuncture as compared to placebo may not increase risk of fatigue (low certainty of evidence) (Mao et al., 2015). Review of data related to headache occurrence showed no statistically significant differences between pairs of therapies with available data.

Discussion

To the authors' knowledge, this is the first systematic review to incorporate network meta-analyses for the comparison of nonhormonal therapies to manage hot flashes in patients who have a history of breast or prostate cancer. In patients with breast cancer, hormonal therapies for hot flashes are generally contraindicated, unlike in the general population, where these treatments are often offered in the first-line setting (Harris et al., 2020). Given these unique challenges, clinicians and nurses must use alternative treatment strategies, with limited evidence guiding selection of interventions. A total of 40 trials met eligibility criteria, 36 being conducted with patients with breast cancer. As demonstrated by the network diagrams, the patterns of treatment comparisons for the outcomes studied were sparse, with most involving inactive control groups and interventions assessed by few studies in the context of generally small trials. The a priori outcomes of interest were not consistently assessed or reported among all trials, and measurement scales and reporting formats were also varied. Based on these obstacles, the ability to compare therapies within inclusive network meta-analyses was limited, the certainty of evidence was judged to be low, and no interventions were considered to be supported by strong evidence for use in the management of hot flashes in the target population.

Network meta-analyses were feasible in the current review to assess relative changes in hot flash frequency and composite hot flash score. However, the evidence base for these analyses was limited, and additional relevant interventions and data disconnected from networks also warranted consideration; the ability to consider recommendations among all previously studied therapies is, therefore, compromised. Network meta-analyses for the endpoints of hot flash composite score and hot flash severity were primarily focused on pharmacologic and natural health product interventions. Psychological and physical therapies required assessment from other study data. Findings from network meta-analyses generally suggested that most therapies in the analyses (including antidepressants and natural health products primarily) offered benefits relative to no

treatment but little to suggest certain active therapies over others. In addition, tolerability data were limited, creating additional challenges for physicians and nurses when trying to counsel patients on expected side effects for these interventions. Additional trial data external to network meta-analyses for these endpoints, as well as changes in hot flash severity, provided additional data supporting other therapies (e.g., cognitive behavioral therapy, yoga, acupuncture/electroacupuncture), which again suggested benefits relative to no treatment. These findings generally align with findings from other reviews that have studied subsets of clinically relevant interventions (Chien et al., 2017; Guo et al., 2019; Li et al., 2019; Shan et al., 2019; Tao et al., 2017) and have noted benefits associated with a broad range of therapies, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), neuroleptic agents, acupuncture, hypnosis, cognitive behavioral therapy, soy, and omega-3 supplementation. They also align with the American Cancer Society/American Society of Clinical Oncology breast cancer care survivorship guideline (Runowicz et al., 2016) that recommended that physicians offer SSRIs/SNRIs, gabapentin, lifestyle modification (e.g., vitamins, exercise, rhythmic breathing, reductions of alcohol and caffeine intake), and/or environmental modifications (e.g., layered dressing, cool rooms) for management of vasomotor symptoms.

Although past evidence supports that many forms of therapy may help patients in reducing hot flash frequency and severity relative to no treatment, there is a clear need to enhance research in this area in multiple ways to improve decision-making ability and the development of recommendations in the future. These include enhanced reporting of study population characteristics in clinical trials to better understand to whom findings apply; the development of a core outcome set (Williamson et al., 2012) in this area to guide the design and reporting of future RCTs, which may standardize measurements related to hot flashes while encouraging more regular assessment of other outcomes, such as generic quality of life and measures related to key symptoms (e.g., sleep quality, depression, sexual function); and enrichment of the treatment comparisons made in future RCTs to improve the robustness of evidence available for meta-analyses in the future.

Strengths and Limitations

Strengths of the current review include the use of rigorous review methods, including a robust search

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SUPPLEMENTARY MATERIAL AVAILABLE ONLINE

All appendices mentioned within this article can be accessed online at https://bit.ly/2WGzi30.

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of the literature, detailed appraisal of the evidence, a thorough analysis plan, and an assessment of the certainty of the evidence. However, several limitations should also be noted. First, the set of included trials were all assessed to be at a high or unclear risk of bias, bringing into question the validity of findings generated from a synthesis of their outcome data. Second, from the perspective of evaluating between-study heterogeneity of patient populations, many characteristics, including prior/concomitant treatments, baseline duration of hot flashes, and duration of time since cancer treatment, were unreported by many studies, limiting the ability to compare populations based on aggregate baseline information and to assess appropriateness of the transitivity assumption for network meta-analysis (Donegan et al., 2013; Salanti, 2012). Third, reporting of study findings was mixed in terms of the scales used to assess different outcomes and the reporting format (e.g., mean change from baseline, percentage change from baseline). The ability to perform meta-analyses was limited, and simple narrative descriptions were often necessary; the development of core endpoint sets (Boers & Kirwan, 2017; Williamson et al., 2017) and efforts among researchers to establish consistent reporting are needed. Fourth, the degree of confidence in the treatment comparisons presented varies according to gaps in available direct information, and overall evidence for active therapies was sparse. Future studies in this area should be designed to reinforce gaps in the currently available set of studied treatment comparisons in areas of clinical relevance in the network and should ensure thorough outcome assessment, detailed summary of patient demographics, and transparent reporting of methods. Fifth, vitamin E and gabapentin plus antidepressant were the only two interventions in the evidence networks informing network meta-analyses that had not been compared directly with placebo; therefore, caution in the interpretation of related findings is warranted. Finally, the approach to network meta-analysis in the current review was adjusted from the original study protocol to employ an RoMs approach; this was done to maximize the ability to include outcome data reported in the encountered range of reporting formats.

An important additional limitation of this review specific to the prostate cancer population should be noted. Studies evaluating hormonal interventions were excluded from consideration in this review, with the aim of ensuring uniform study selection criteria across breast cancer and prostate cancer trials. It is acknowledged, however, that hormonal therapies (particularly progestastional agents such as medroxyprogesterone) are commonly used in the treatment of hot flashes in patients with prostate cancer receiving ADT and have been studied in a large randomized trial (Irani et al., 2010). The exclusion of hormonal interventions does partially limit the generalizability of the findings of this review to the prostate cancer population.

Implications for Nursing

Nurses and other healthcare providers working with patients treated for breast or prostate cancer should ensure that patients are educated on the potential side effects of treatment, including hot flashes. Patients should understand that hot flashes are common, can affect quality of life, and can be a challenge to manage. Patients should notify their nurse or healthcare provider if they experience hot flashes, and clinicians should assess patients at high risk. Working together, patients and clinicians can be proactive to manage this challenging side effect of treatment (Kaplan & Mahon, 2014; Qan'ir et al., 2019).

Conclusion

In the current review, treatment comparisons derived from network meta-analyses and narrative review of individual trials generally highlight the presence of small differences between interventions; therefore, there is limited evidence and considerable uncertainty to guide the selection of certain interventions over others for management of vasomotor symptoms. The ability for physicians and nurses to provide specific suggestions regarding management of hot flashes based on the available evidence when asked by patients is challenging. At this time, for patients who are motivated to try an intervention to relieve their symptoms, physicians and nurses may wish to focus on those in which tolerability risks are felt to be minimal. Additional trials of high methodologic quality and improved reporting and that add to the robustness of currently available networks are needed. The development of a structured set of outcomes for measurement in future research, ideally established by methodologists, clinical experts, patients, and stakeholders, would also enhance the design of future clinical trials.

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REFERENCES

American Cancer Society. (2019). *Cancer facts and figures, 2019.* https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf

Bao, T., Cai, L., Snyder, C., Betts, K., Tarpinian, K., Gould, J., . . . Stearns, V. (2014). Patient-reported outcomes in women with breast cancer enrolled in a dual-center, double-blind, randomized controlled trial assessing the effect of acupuncture in reducing aromatase inhibitor-induced musculoskeletal symptoms. *Cancer, 120*(3), 381–389. https://doi.org/10.1002/cncr.28352

Barton, D., La Vasseur, B., Loprinzi, C., Novotny, P., Wilwerding, M.B., & Sloan, J. (2002). Venlafaxine for the control of hot flashes: Results of a longitudinal continuation study. *Oncology Nursing Forum, 29*(1), 33–40. https://doi.org/10.1188/02.ONF.33-40

Barton, D.L., Loprinzi, C.L., Quella, S.K., Sloan, J.A., Veeder, M.H., Egner, J.R., . . . Novotny, P. (1998). Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *Journal of Clinical Oncology, 16*(2), 495–500. https://doi.org/10.1200/JCO.1998.16.2.495

Biglia, N., Bounous, V.E., Susini, T., Pecchio, S., Sgro, L.G., Tuninetti, V., & Torta, R. (2016). Duloxetine and escitalopram for hot flushes: Efficacy and compliance in breast cancer survivors. *European Journal of Cancer Care, 27*(1), e12484. https://doi.org/10.1111/ecc.12484

Biglia, N., Sgandurra, P., Peano, E., Marenco, D., Moggio, G., Bounous, V., . . . Sismondi, P. (2009). Non-hormonal treatment of hot flushes in breast cancer survivors: Gabapentin vs. vitamin E. *Climacteric, 12*(4), 310–318. https://doi.org/10.1080/13697130902736921

Boekhout, A.H., Beijnen, J.H., & Schellens, J.H.M. (2006). Symptoms and treatment in cancer therapy-induced early menopause. *Oncologist, 11*(6), 641–654. https://doi.org/10.1634/theoncologist.11-6-641

Boekhout, A.H., Vincent, A.D., Dalesio, O.B., van den Bosch, J., Foekema-Töns, J.H., Adriaansz, S., . . . Schellens, J.H.M. (2011). Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: A randomized, double-blind, placebo-controlled trial. *Journal of Clinical Oncology, 29*(29), 3862–3868. https://doi.org/10.1200/JCO.2010.33.1298

Boers, N., & Kirwan, J. (2017). *OMERACT Handbook.* https://omeracthandbook.org/handbook

Bokmand, S., & Flyger, H. (2013). Acupuncture relieves menopausal discomfort in breast cancer patients: A prospective, double blinded, randomized study. *Breast, 22*(3), 320–323. https://doi.org/10.1016/j.breast.2012.07.015

Bordeleau, L., Pritchard, K.I., Loprinzi, C.L., Ennis, M., Jugovic, O.,

Warr, D., . . . Goodwin, P.J. (2010). Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. *Journal of Clinical Oncology, 28*(35), 5147–5152. https://doi.org/10.1200/JCO.2010.29.9230

Brignardello-Petersen, R., Bonner, A., Alexander, P.E., Siemieniuk, R.A., Furukawa, T.A., Rochwerg, B., . . . Guyatt, G.H. (2018). Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *Journal of Clinical Epidemiology, 93*, 36–44. https://doi.org/10.1016/j.jclinepi.2017.10.005

Buijs, C., Mom, C.H., Willemse, P.H.B., Marike Boezen, H., Maurer, J.M., Wymenga, A.N.M., . . . Mourits, M.J.E. (2009). Venlafaxine versus clonidine for the treatment of hot flashes in breast cancer patients: A double-blind, randomized cross-over study. *Breast Cancer Research and Treatment, 115*(3), 573–580. https://doi.org/10.1007/s10549-008-0138-7

Caldwell, D.M., Ades, A.E., & Higgins, J.P.T. (2005). Simultaneous comparison of multiple treatments: Combining direct and indirect evidence. *BMJ, 331*(7521), 897–900. https://doi.org/10.1136/bmj.331.7521.897

Carson, J.W., Carson, K.M., Porter, L.S., Keefe, F.J., & Seewaldt, V.L. (2009). Yoga of Awareness program for menopausal symptoms in breast cancer survivors: Results from a randomized trial. *Supportive Care in Cancer, 17*(10), 1301–1309. https://doi.org/10.1007/s00520-009-0587-5

Catalá-López, F., Tobías, A., Cameron, C., Moher, D., & Hutton, B. (2014). Network meta-analysis for comparing treatment effects of multiple interventions: An introduction. *Rheumatology International, 34*(11), 1489–1496. https://doi.org/10.1007/s00296-014-2994-2

Chang, H.Y., Jotwani, A.C., Lai, Y.H., Jensen, M.P., Syrjala, K.L., Fann, J.R., & Gralow, J. (2016). Hot flashes in breast cancer survivors: Frequency, severity and impact. *Breast, 27*, 116–121. https://doi.org/10.1016/j.breast.2016.02.013

Chen, W.Y., Giobbie-Hurder, A., Gantman, K., Savoie, J., Scheib, R., Parker, L.M., & Schernhammer, E.S. (2014). A randomized, placebo-controlled trial of melatonin on breast cancer survivors: Impact on sleep, mood, and hot flashes. *Breast Cancer Research and Treatment, 145*(2), 381–388. https://doi.org/10.1007/s10549-014-2944-4

Chien, T.J., Hsu, C.H., Liu, C.Y., & Fang, C.J. (2017). Effect of acupuncture on hot flush and menopause symptoms in breast cancer: A systematic review and meta-analysis. *PLOS ONE, 12*(8), e0180918. https://doi.org/10.1371/journal.pone.0180918

Cramer, H., Rabsilber, S., Lauche, R., Kümmel, S., & Dobos, G. (2015). Yoga and meditation for menopausal symptoms in breast cancer survivors-a randomized controlled trial. *Cancer, 121*(13), 2175–2184. https://doi.org/10.1002/cncr.29330

Deng, G., Vickers, A.J., Yeung, K.S., D'Andrea, G.M., Xiao, H., Heerdt, A.S., . . . Cassileth, B.R. (2007). Randomized, controlled trial of acupuncture for the treatment of hot flashes in breast cancer

patients. *Journal of Clinical Oncology, 25*(35), 5584–5590. https://doi .org/10.1200/JCO.2007.12.0774

Dias, S., Welton, N.J., Sutton, A.J., & Ades, A.E. (2014). *NICE DSU technical support document 2: A generalised linear modelling frame- work for pairwise and network meta-analysis of randomised controlled trials*. National Institute for Health and Care Excellence. https:// www.ncbi.nlm.nih.gov/books/n/nicedsutsd2/pdf

Dodin, S., Blanchet, C., Marc, I., Ernst, E., Wu, T., Vaillancourt, C., . . . Maunsell, E. (2013). Acupuncture for menopausal hot flushes. *Cochrane Database of Systematic Reviews,* (7), CD007410. https:// doi.org/10.1002/14651858.CD007410.pub2

Donegan, S., Williamson, P., D'Alessandro, U., & Tudur Smith, C. (2013). Assessing key assumptions of network meta-analysis: A review of methods. *Research Synthesis Methods, 4*(4), 291–323. https://doi.org/10.1002/jrsm.1085

Duijts, S.F.A., van Beurden, M., Oldenburg, H.S.A., Hunter, M.S., Kieffer, J.M., Stuiver, M.M., . . . Aaronson, N.K. (2012). Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: Results of a randomized, controlled, multicenter trial. *Journal of Clinical Oncology, 30*(33), 4124–4133. https://doi.org/ 10.1200/JCO.2012.41.8525

Elkins, G., Marcus, J., Stearns, V., Perfect, M., Rajab, M.H., Ruud, C., . . . Keith, T. (2008). Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. *Jour- nal of Clinical Oncology, 26*(31), 5022–5026. https://doi.org/10.1200/ JCO.2008.16.6389

Engstrom, C. (2005). Hot flash experience in men with prostate cancer: A concept analysis. *Oncology Nursing Forum, 32*(5), 1043–1048. https://doi.org/10.1188/05.ONF.1043-1048

Fenlon, D. (1999). Relaxation therapy as an intervention for hot flashes in women with breast cancer. *European Journal of Oncology Nursing, 3*(4), 223–231. https://doi.org/10.1016/s1462-3889 (99)81335-0

Fenlon, D.R., Corner, J.L., & Haviland, J.S. (2008). A randomized controlled trial of relaxation training to reduce hot flashes in women with primary breast cancer. *Journal of Pain and Symptom Management, 35*(4), 397–405. https://doi.org/10.1016/j.jpainsym man.2007.05.014

Fisher, W.I., Johnson, A.K., Elkins, G.R., Otte, J.L., Burns, D.S., Yu, M., & Carpenter, J.S. (2013). Risk factors, pathophysiology, and treat- ment of hot flashes in cancer. *CA: A Cancer Journal for Clinicians, 63*(3), 167–192. https://doi.org/10.3322/caac.21171

Florez, I.D., Veroniki, A.A., Al Khalifah, R., Yepes-Nuñez, J.J., Sierra, J.M., Vernooij, R.W.M., . . . Thabane, L. (2018). Comparative effectiveness and safety of interventions for acute diarrhea and gastroenteritis in children: A systematic review and network meta-analysis. *PLOS ONE, 13*(12), e0207701. https://doi.org/ 10.1371/journal.pone.0207701

Frisk, J. (2010). Managing hot flushes in men after prostate cancer— A systematic review. *Maturitas, 65*(1), 15–22. https://doi.org/ 10.1016/j.maturitas.2009.10.017

Frisk, J., Spetz, A.C., Hjertberg, H., Petersson, B., & Hammar, M. (2009). Two modes of acupuncture as a treatment for hot flushes in men with prostate cancer—A prospective multicenter study with long-term follow-up. *European Urology, 55*(1), 156–163. https:// doi.org/10.1016/j.eururo.2008.02.002

Goldman, M.E. (2017). Life after treatment: Quality-of-life concerns in patients treated for cancer. *Journal of the National Compre- hensive Cancer Network, 15*(5S), 744–747. https://doi.org/10.6004/ jnccn.2017.0090

Guo, P.P., Li, P., Zhang, X.H., Liu, N., Wang, J., Chen, D.D., . . . Zhang, W. (2019). Complementary and alternative medicine for natural and treatment-induced vasomotor symptoms: An overview of systematic reviews and meta-analyses. *Complementary Therapies in Clinical Practice, 36*, 181–194. https://doi.org/10.1016/j.ctcp .2019.07.007

Guyatt, G.H., Oxman, A.D., Vist, G.E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schünemann, H.J. (2008). GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ, 336*(7650), 924–926. https://doi.org/ 10.1136/bmj.39489.470347.AD

Harris, B.S., Bishop, K.C., Kuller, J.A., Ford, A.C., Muasher, L.C., Cantrell, S.E., & Price, T.M. (2020). Hormonal management of menopausal symptoms in women with a history of gynecologic malignancy. *Menopause, 27*(2), 243–248. https://doi.org/10.1097/ GME.0000000000001447

Hernández Muñoz, G., & Pluchino, S. (2003). Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer. *Maturitas, 44*(Suppl.), S59–S65. https://doi.org/10.1016/S0378 -5122(02)00349-3

Hervik, J., & Mjåland, O. (2009). Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial. *Breast Cancer Research and Treatment, 116*(2), 311–316. https:// doi.org/10.1007/s10549-008-0210-3

Higgins, J.P.T., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., . . . Sterne, J.A.C. (2011). The Cochrane Collabora- tion's tool for assessing risk of bias in randomised trials. *BMJ, 343*, d5928. https://doi.org/10.1136/bmj.d5928

Hutton, B., Salanti, G., Caldwell, D.M., Chaimani, A., Schmid, C.H., Cameron, C., . . . Moher, D. (2015). The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Annals of Internal Medicine, 162*(11), 777–784. https:// doi.org/10.7326/M14-2385

Hutton, B., Yazdi, F., Bordeleau, L., Morgan, S., Cameron, C., Kanji, S., . . . Clemons, M. (2015). Comparison of physical interventions, behavioral interventions, natural health products, and pharma- cologics to manage hot flashes in patients with breast or prostate cancer: Protocol for a systematic review incorporating network meta-analyses. *Systematic Reviews, 4*, 114. https://doi.org/10.1186/ s13643-015-0099-y

Irani, J., Salomon, L., Oba, R., Bouchard, P., & Mottet, N. (2010). Efficacy of venlafaxine, medroxyprogesterone acetate, and

cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: A double-blind, randomised trial. *Lancet Oncology, 11*(2), 147–154. https://doi.org/10.1016/S1470-2045(09)70338-9

Jacobson, J.S., Troxel, A.B., Evans, J., Klaus, L., Vahdat, L., Kinne, D., . . . Grann, V.R. (2001). Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *Journal of Clinical Oncology, 19*(10), 2739–2745. https://doi.org/10.1200/JCO.2001.19.10.2739

Kaplan, M., & Mahon, S. (2014). Hot flash management: Update of the evidence for patients with cancer. *Clinical Journal of Oncology Nursing, 18*(6 Suppl.), 59–67. https://doi.org/10.1188/14.CJON.S3.59-67

Kaplan, M., Mahon, S., Cope, D., Keating, E., Hill, S., & Jacobson, M. (2011). Putting evidence into practice: Evidence-based interventions for hot flashes resulting from cancer therapies. *Clinical Journal of Oncology Nursing, 15*(2), 149–157. https://doi.org/10.1188/11.CJON.149-157

Kimmick, G.G., Lovato, J., McQuellon, R., Robinson, E., & Muss, H.B. (2006). Randomized, double-blind, placebo-controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. *Breast Journal, 12*(2), 114–122. https://doi.org/10.1111/j.1075-122X.2006.00218.x

Kontos, M., Agbaje, O.F., Rymer, J., & Fentiman, I.S. (2010). What can be done about hot flushes after treatment for breast cancer? *Climacteric, 13*(1), 4–21. https://doi.org/10.3109/13697130903291058

Lesi, G., Razzini, G., Musti, M.A., Stivanello, E., Petrucci, C., Benedetti, B., . . . Pandolfi, P. (2016). Acupuncture as an integrative approach for the treatment of hot flashes in women with breast cancer: A prospective multicenter randomized controlled trial (AcCliMaT). *Journal of Clinical Oncology, 34*(15), 1795–1802. https://doi.org/10.1200/JCO.2015.63.2893

Li, T., Yang, J., Lv, Y., Yin, F., Xu, L., Liu, H., . . . Li, L. (2019). Quantitative comparison of drug efficacy in treating hot flashes in patients with breast cancer. *Breast Cancer Research and Treatment, 173*(3), 511–520. https://doi.org/10.1007/s10549-018-5029-y

Liljegren, A., Gunnarsson, P., Landgren, B.M., Robéus, N., Johansson, H., & Rotstein, S. (2012). Reducing vasomotor symptoms with acupuncture in breast cancer patients treated with adjuvant tamoxifen: A randomized controlled trial. *Breast Cancer Research and Treatment, 135*(3), 791–798. https://doi.org/10.1007/s10549-010-1283-3

Loibl, S., Schwedler, K., von Minckwitz, G., Strohmeier, R., Mehta, K.M., & Kaufmann, M. (2007). Venlafaxine is superior to clonidine as treatment of hot flashes in breast cancer patients—A double-blind, randomized study. *Annals of Oncology, 18*(4), 689–693. https://doi.org/10.1093/annonc/mdl478

Loprinzi, C.L., Dueck, A.C., Khoyratty, B.S., Barton, D.L., Jafar, S.,

Rowland, K.M., . . . Fitch, T.R. (2009). A phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB). *Annals of Oncology, 20*(3), 542–549. https://doi.org/10.1093/annonc/mdn644

Loprinzi, C.L., Kugler, J.W., Barton, D.L., Dueck, A.C., Tschetter, L.K., . . . Jaslowski, A.J. (2007). Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. *Journal of Clinical Oncology, 25*(3), 308–312. https://doi.org/10.1200/JCO.2006.07.5390

Loprinzi, C.L., Kugler, J.W., Sloan, J.A., Mailliard, J.A., LaVasseur, B.I., Barton, D.L., . . .Christensen, B.J. (2000). Venlafaxine in management of hot flashes in survivors of breast cancer: A randomised controlled trial. *Lancet, 356*(9247), 2059–2063. https://doi.org/10.1016/S0140-6736(00)03403-6

Loprinzi, C.L., Sloan, J.A., Perez, E.A., Quella, S.K., Stella, P.J., Mailliard, J.A., . . . Rummans, T.A. (2002). Phase III evaluation of fluoxetine for treatment of hot flashes. *Journal of Clinical Oncology, 20*(6), 1578–1583. https://doi.org/10.1200/JCO.2002.20.6.1578

Lu, G., & Ades, A.E. (2004). Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine, 23*(20), 3105–3124. https://doi.org/10.1002/sim.1875

MacGregor, C.A., Canney, P.A., Patterson, G., McDonald, R., & Paul, J. (2005). A randomised double-blind controlled trial of oral soy supplements versus placebo for treatment of menopausal symptoms in patients with early breast cancer. *European Journal of Cancer, 41*(5), 708–714. https://doi.org/10.1016/j.ejca.2005.01.005

Mann, E., Smith, M.J., Hellier, J., Balabanovic, J.A., Hamed, H., Grunfeld, E.A., & Hunter, M.S. (2012). Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): A randomised controlled trial. *Lancet Oncology, 13*(3), 309–318. https://doi.org/10.1016/S1470-2045(11)70364-3

Mao, J.J., Bowman, M.A., Xie, S.X., Bruner, D., DeMichele, A., & Farrar, J.T. (2015). Electroacupuncture versus gabapentin for hot flashes among breast cancer survivors: A randomized placebo-controlled trial. *Journal of Clinical Oncology, 33*(31), 3615–3620. https://doi.org/10.1200/JCO.2015.60.9412

Marino, J.L., McNamara, H.C., & Hickey, M. (2018). Managing menopausal symptoms after cancer: An evidence-based approach for primary care. *Medical Journal of Australia, 208*(3), 127–132. https://doi.org/10.5694/mja17.00693

Nedstrand, E., Wijma, K., Wyon, Y., & Hammar, M. (2005). Vasomotor symptoms decrease in women with breast cancer randomized to treatment with applied relaxation or electro-acupuncture: A preliminary study. *Climacteric, 8*(3), 243–250. https://doi.org/10.1080/13697130500118050

Pandya, K.J., Morrow, G.R., Roscoe, J.A., Zhao, H., Hickok, J.T., Pajon, E., . . . Flynn, P.J. (2005). Gabapentin for hot flashes in 420 women with breast cancer: A randomised double-blind placebo-controlled

trial. *Lancet, 366*(9488), 818–824. https://doi.org/10.1016/S0140 -6736(05)67215-7

Pandya, K.J., Raubertas, R.F., Flynn, P.J., Hynes, H.E., Rosenbluth, R.J., Kirshner, J.J., . . . Morrow, G.R. (2000). Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: A University of Rochester Cancer Center Community Clinical Oncology Program study. *Annals of Internal Medicine, 132*(10), 788–793. https://doi.org/10.7326/0003 -4819-132-10-200005160-00004

Pinkerton, J.V., & Santen, R.J. (2019). Managing vasomotor symptoms in women after cancer. *Climacteric, 22*(6), 544–552. https://doi.org/ 10.1080/13697137.2019.1600501

Puhan, M.A., Schünemann, H.J., Murad, M.H., Li, T., Brignardello-Petersen, R., Singh, J.A., . . . Guyatt, G.H. (2014). A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ, 349*, g5630. https:// doi.org/10.1136/bmj.g5630

Qan'ir, Y., DeDeaux, D., Godley, P.A., Mayer, D.K., & Song, L. (2019). Management of androgen deprivation therapy-associated hot flashes in men with prostate cancer. *Oncology Nursing Forum, 46*(4), E107–E118. https://doi.org/10.1188/19 .ONF.E107-E118

Quella, S.K., Loprinzi, C.L., Barton, D.L., Knost, J.A., Sloan, J.A., LaVasseur, B.I., . . . Novotny, P.J. (2000). Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial. *Journal of Clinical Oncology, 18*(5), 1068–1074. https://doi.org/10.1200/ JCO.2000.18.5.1068

Runowicz, C.D., Leach, C.R., Henry, N.L., Henry, K.S., Mackey, H.T., Cowens-Alvarado, R.L., . . . Ganz, P.A. (2016). American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. *CA: A Cancer Journal for Clinicians, 66*(1), 43–73. https://doi.org/10.3322/caac.21319

Salanti, G. (2012). Indirect and mixed-treatment comparison, network, or multiple treatments meta-analysis: Many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods, 3*(2), 80–97. https://doi .org/10.1002/jrsm.1037

Salanti, G., Ades, A.E., & Ioannidis, J.P.A. (2011). Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. *Journal of Clinical Epidemiology, 64*(2), 163–171. https://doi.org/10.1016/ j.jclinepi.2010.03.016

Salanti, G., Kavvoura, F.K., & Ioannidis, J.P.A. (2008). Exploring the geometry of treatment networks. *Annals of Internal Medicine, 148*(7), 544–553. https://doi.org/10.7326/0003-4819-148-7-2008 04010-00011

Santen, R.J., Stuenkel, C.A., Davis, S.R., Pinkerton, J.V., Gompel, A., & Lumsden, M.A. (2017). Managing menopausal symptoms and associated clinical issues in breast cancer survivors. *Journal of Clinical Endocrinology and Metabolism, 102*(10), 3647–3661. https:// doi.org/10.1210/jc.2017-01138

Shan, D., Zou, L., Liu, X., Shen, Y., Cai, Y., & Zhang, J. (2019). Efficacy and safety of gabapentin and pregabalin in patients with vasomotor symptoms: A systematic review and meta-analysis. *American Journal of Obstetrics and Gynecology.* https://doi.org/ 10.1016/j.ajog.2019.12.011

Stearns, V., Slack, R., Greep, N., Henry-Tilman, R., Osborne, M., Bunnell, C., . . . Isaacs, C. (2005). Paroxetine is an effective treatment for hot flashes: Results from a prospective randomized clinical trial. *Journal of Clinical Oncology, 23*(28), 6919–6930. https://doi.org/10.1200/JCO.2005.10.081

Stefanopoulou, E., Yousaf, O., Grunfeld, E.A., & Hunter, M.S. (2015). A randomised controlled trial of a brief cognitive behavioural intervention for men who have hot flushes following prostate cancer treatment (MANCAN). *Psycho-Oncology, 24*(9), 1159–1166. https://doi.org/10.1002/pon.3794

Tao, W.W., Tao, X.M., & Song, C.L. (2017). Effects of non-pharmacological supportive care for hot flushes in breast cancer: A meta-analysis. *Supportive Care in Cancer, 25*(7), 2335–2347. https://doi.org/10.1007/s00520-017-3691-y

Van Patten, C.L., Olivotto, I.A., Chambers, G.K., Gelmon, K.A., Hislop, T.G., Templeton, E., . . . Prior, J.C. (2002). Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: A randomized, controlled clinical trial. *Journal of Clinical Oncology, 20*(6), 1449–1455. https://doi.org/10.1200/ JCO.2002.20.6.1449

Vitolins, M.Z., Griffin, L., Tomlinson, W.V., Vuky, J., Adams, P.T., Moose, D., . . . Shaw, E.G. (2013). Randomized trial to assess the impact of venlafaxine and soy protein on hot flashes and quality of life in men with prostate cancer. *Journal of Clinical Oncology, 31*(32), 4092–4098. https://doi.org/10.1200/ JCO.2012.48.1432

Walker, E.M., Rodriguez, A.I., Kohn, B., Ball, R.M., Pegg, J., Pocock, J.R., . . . Levine, R.A. (2010). Acupuncture versus venlafaxine for the management of vasomotor symptoms in patients with hormone receptor-positive breast cancer: A randomized controlled trial. *Journal of Clinical Oncology, 28*(4), 634–640. https://doi.org/ 10.1200/JCO.2009.23.5150

Williamson, P.R., Altman, D.G., Bagley, H., Barnes, K.L., Blazeby, J.M., Brookes, S.T., . . . Young, B. (2017). The COMET Handbook: Version 1.0. *Trials, 18*(Suppl 3), 280. https://doi.org/10.1186/s13063 -017-1978-4

Williamson, P.R., Altman, D.G., Blazeby, J.M., Clarke, M., Devane, D., Gargon, E., & Tugwell, P. (2012). Developing core outcome sets for clinical trials: Issues to consider. *Trials, 13*, 132. https://doi.org/ 10.1186/1745-6215-13-132

Wu, M.F., Hilsenbeck, S.G., Tham, Y.L., Kramer, R., Elledge, R.M., Chang, J.C., & Friedman, L.C. (2009). The efficacy of sertraline for controlling hot flashes in women with or at high risk of developing breast cancer. *Breast Cancer Research and Treatment, 118*(2), 369–375. https://doi.org/10.1007/s10549-009-0425-y

Zoberi, K., & Tucker, J. (2019). Primary care of breast cancer survivors. *American Family Physician, 99*(6), 370–375.