ONS Guidelines™ for Cancer Treatment–Related Hot Flashes in Women With Breast Cancer and Men With Prostate Cancer

Marcelle Kaplan, MS, RN, CNS, Pamela K. Ginex, EdD, RN, OCN®, Laura B. Michaud, PharmD, BCOP, FASHP, CMQ, Paz Fernández-Ortega, PhD, MSc, RN, Dale Grimmer, MS, RN, AOCN®, CCRC, Jessica Bay Leibelt, MSN, NP-C, AOCNP®, Suzanne Mahon, DNSc, RN, AOCN®, AGN-BC, Bernardo L. Rapoport, Dip in Med (UBA), MMed, Valencia Robinson, EdS, Christine Maloney, BA, Kerri A. Moriarty, MLS, Mark Vrabel, MLS, AHIP, ELS, and Rebecca L. Morgan, PhD, MPH

PURPOSE: Hot flashes are a common and troublesome side effect of surgery or endocrine therapy. They may lead to physical and psychological distress and negatively affect quality of life. This clinical practice guideline presents evidence-based recommendations for pharmacologic, behavioral, and natural health product interventions for treatment-related hot flashes in patients with breast or prostate cancer.

METHODOLOGIC APPROACH: An interprofessional panel of healthcare professionals with patient representation prioritized clinical questions and patient outcomes for the management of hot flashes. Systematic reviews of the literature were conducted. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach was used to assess the evidence and make recommendations.

FINDINGS: The panel agreed on 14 pharmacologic, behavioral, and natural health recommendations.

IMPLICATIONS FOR NURSING: Conditional recommendations include the use of antidepressants rather than no treatment, physical activity rather than no treatment, and the avoidance of gabapentin and dietary supplements in the treatment of hot flashes.

KEYWORDS hot flashes; breast cancer; prostate cancer; symptom management; antidepressants
***ONF, 47*(4), 374–399.**
DOI 10.1188/20.ONF.374-399

Hot flashes are a distressing and often prolonged side effect experienced by patients with cancer who are treated with hormone therapies or hormone-depleting surgeries. Hot flashes, also referred to as hot flushes or vasomotor symptoms, are recurrent sensations of intense heat and sweating on the face and upper body, which may be followed by chills. They occur suddenly and unpredictably, may be transient or persistent, and may be accompanied by heart palpitations and feelings of anxiety (Fisher et al., 2013; Jones et al., 2012; Reeves et al., 2018). Hot flashes have been described 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 frequency, intensity, and duration of hot flashes can affect sleep quality, energy, mood, and sexual function, and can be debilitating in women and men. Overall quality of life can diminish and lead to premature discontinuation of life-prolonging hormone therapies (Kadakia et al., 2012).

Hot flashes are reported to be much more frequent and severe in women treated for breast cancer than in women undergoing natural menopause (Carpenter, 2005; Kadakia et al., 2012). Estimates of the prevalence of hot flashes in women treated for breast cancer range from 51% to 81% (Fisher et al., 2013). In addition, almost 80% of men with prostate cancer treated with androgen deprivation therapies (ADTs) (i.e., drugs or orchiectomy) are reported to experience hot flashes, which can persist for years (Qan'ir et al., 2019).

Hot flashes are a subjective experience and, as such, self-reported hot flash diaries are considered adequate in clinical practice for patient report of this experience (Hanisch et al., 2009; Loprinzi & Barton, 2009). The use of these diaries to assess the frequency, severity, intensity, distress, and interference of hot flashes with daily activities has been validated in women with breast cancer via the Hot Flash Related Daily Interference Scale (Carpenter, 2001) and in men with prostate cancer via the Loprinzi and Sloan Self-Report Diary (Sloan et al., 2001). In reviewing results of hot flash intervention studies, it is important to consider the impact of the placebo effect. In several studies, the placebo intervention was reported to reduce hot flash frequency (HFF) and severity (HFS) between 25% and 55%, amounts greater than with the active comparators (Boekhout et al., 2006, 2011; Sloan et al., 2001; Vitolins et al., 2013).

The physiologic mechanisms underlying hot flashes are unclear, and most understanding comes from studies with menopausal women (Fisher et al., 2013; Shanafelt et al., 2002). In women treated for hormone-dependent breast cancer, it is hypothesized that the abrupt depletion of estrogen that occurs with chemotherapy-induced premature menopause, discontinuation of menopausal hormone therapy, and/or the prolonged use of estrogen suppression therapies (e.g., tamoxifen, aromatase inhibitor drugs) is responsible for precipitating the hot flashes (Fisher et al., 2013; Kaplan & Mahon, 2014). The initiation of hot flashes in men treated for prostate cancer is attributed to testosterone suppression associated with the use of ADTs (Qan'ir et al., 2019).

The endogenous plasma sex hormones (estrogen in women and testosterone in men), in conjunction with serotonin and norepinephrine neurotransmitters, are involved in regulating the core body temperature. Core temperature is regulated centrally in the hypothalamus and is maintained within a narrow physiologic range called the thermoneutral zone (Shanafelt et al., 2002). The abrupt withdrawal of endogenous sex hormones disrupts central thermoregulation mechanisms, resulting in small transitory elevations of the core temperature above the normal range, triggering the exaggerated heat loss mechanisms of profuse sweating and cutaneous vasodilation that are characteristic of hot flashes (Boekhout et al., 2006; Dalal & Zhukovsky, 2006; Morrow et al., 2011). Hormone therapies, such as estrogen replacement, although shown to be effective in managing hot flashes in postmenopausal women, are generally contraindicated in patients with a history of hormone-dependent cancer (Fisher et al., 2013). The efficacy of other treatment options for managing hot flash symptoms in women with breast cancer or men with prostate cancer are described in this guideline.

Aim and Objectives

The aim of this guideline is to provide evidence-based symptom management recommendations for patients with cancer who are experiencing drug- or surgery-induced hot flashes. The guideline incorporates the most recently published research on interventions for the management of hot flashes associated with cancer treatment. The target audience includes oncology healthcare professionals, patients, and decision makers. Policymakers interested in this guideline may include individuals and organizations developing local, national, or international protocols with a goal of improving management of adults with cancer who are experiencing hot flashes. The guideline is based on a systematic review and network meta-analysis (NMA) that explored the following research question: What are the nonhormonal pharmacologic, physical/behavioral, and natural health product interventions that minimize the frequency and severity of hot flashes and the negative impact on quality of life in patients with breast or prostate cancer?

Guideline Development Methods

The Oncology Nursing Society (ONS) vetted and appointed individuals to the ONS Guidelines™ panel. The membership of the interprofessional panel included oncology nurses at all levels of practice, a medical oncologist, an oncology pharmacist, and a patient representative. The panel was coordinated by the senior manager of evidence-based practice at ONS (P.G.), with collaboration from a methodologist with expertise in evidence appraisal and guideline development (R.L.M.). The evidence synthesis for this guideline was based on a recently completed rigorous systematic review and NMA (Hutton et al., 2020). The panel completed its work using online and web-based tools (www.gradepro.org) and a two-day, in-person meeting to review the evidence and formulate recommendations.

The panel developed and graded the recommendations and assessed the certainty in the supporting evidence according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (Guyatt, Oxman, Akl, et al., 2011; Guyatt, Oxman, Kunz, et al., 2011; Guyatt, Oxman, Sultan, et al., 2011). The guideline development process included panel formation, public comment, and internal review, which was guided by

policies and procedures derived from the Guideline International Network (GIN) McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and the National Academies of Science, Engineering, and Medicine (NASEM) criteria for trustworthy guidelines (Institute of Medicine, 2011; Schünemann et al., 2014).

Financial and intellectual disclosures of interest of all participants were collected and managed according to ONS policies and the recommendations of the NASEM and GIN (Institute of Medicine, 2011; Schünemann et al., 2015). Disclosures were recorded at the time of appointment and again at the recommendations meeting. The guideline panel had no

TABLE 1. GRADE Definitions on Strength of Recommendation and Guide to Interpretation

Strength of Recommendation	Wording in the Guideline	For the Patient	For the Clinician	For Policymakers	For Researchers
Strong	"The ONS Guidelines™ panel recommends . . ."	Most individuals in this situation would want the intervention and only a small proportion would not.	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	In most cases, the recommendation can be adopted as policy. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	This recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide information that alters the recommendation.
Conditional	"The ONS Guidelines panel suggests . . ."	Most individuals in this situation would want the suggested intervention, but many would not.	Different choices will be appropriate for different individuals. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with individuals when working toward a decision.	Policymaking will require substantial debate and involvement of various stakeholders.	This recommendation is likely to be strengthened by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional recommendation will help identify possible research gaps.
Research and/or knowledge gap	"The ONS Guidelines panel recommends the intervention only in the context of a clinical trial. . . ."	A discussion of benefits/harms and alternatives is warranted.	Clinicians should look for clinical trials testing this intervention, if individuals are interested.	–	Available evidence is insufficient to determine true effect, and this recommendation may be appropriate for research.

GRADE—Grading of Recommendations, Assessment, Development, and Evaluation; ONS—Oncology Nursing Society
Note. Based on information from Guyatt, Oxman, Akl, et al., 2011; Guyatt, Oxman, Kunz, et al., 2011; Guyatt, Oxman, Sultan, et al., 2011.

relevant conflicts of interests (no material interest in any commercial entity with a product that could be affected by the guidelines).

Formulation of Specific Clinical Questions and Determining Outcomes of Interest

The ONS Guidelines panel met remotely to discuss and prioritize clinical questions for this guideline. Panelists were instructed to identify questions that were clinically relevant, such as questions about hot flashes that patients with cancer were asking and that clinicians had uncertainty regarding the answers.

The panel considered the question of limiting to patients with cancer or expanding to include the general population, which would primarily include women with menopause-related hot flashes. Following discussion, several factors contributed to the panel's decision to focus on patients with cancer. Hormone replacement therapy is a primary therapy for hot flashes in the noncancer population, but is generally contraindicated in patients with cancer. Patients with cancer are often receiving other therapies that are critical to their treatment, and these other therapies need to be considered in the context of managing hot flashes. Men experiencing hot flashes following treatment for cancer is a unique population that is not, to the authors' knowledge, well represented in the research on hot flashes in the general population. In addition, the nature of chemical or surgical castration for the treatment for cancer is often abrupt and unavoidable. This may also be true for some patients without cancer, but it poses a unique situation for patients with cancer. Because of these considerations, the panel made the decision to focus the guideline questions on patients with cancer. In addition, the panel considered that, within the population of patients with cancer, the majority of evidence on hot flashes pertains to women with breast cancer, with a smaller amount focusing on men with prostate cancer. Patients with other types of cancer (e.g., gynecologic) and men with breast cancer may also experience hot flashes and may be indirectly informed by this guideline.

Questions were formulated according to the PICO (patient, intervention, comparator, and outcome) components. The guideline panel selected outcomes of interest for each question a priori. The panel discussed all possible outcomes and prioritized importance for patients and decision making using the GRADE approach (Guyatt, Oxman, Kunz, et al., 2011). The panel rated the following outcomes as critical for clinical decision making across the PICO components: HFF, HFS, quality of life (including sleep and sleep quality), depression, and adverse events from the intervention.

Synthesis of Evidence and Development of Recommendations

The evidence for this guideline was based on a systematic review and NMA of randomized controlled trials (RCTs) of interventions for hot flashes in women with breast cancer or men with prostate cancer conducted by researchers at the Ottawa Hospital Research Institute (Hutton et al., 2015, 2020). An NMA is a meta-analysis in which multiple treatments (three or more) are compared using direct comparisons of interventions within RCTs and indirect comparisons across distinct trials based on a common comparator (Dias & Caldwell, 2019).

Full results of the systematic review and NMA are reported elsewhere (Hutton et al., 2020) but, briefly, publication years ranged from 1998 to 2016, with sample sizes ranging from 24 to 422 (median = 88). Duration of treatment ranged from 4 to 52 weeks (median = 8 weeks, 39 of 40 studies were less than 12 weeks). Median age was 54 years (range = 45–70 years), with 90% of participants being women with breast cancer and 10% being men with prostate cancer. The types of breast and prostate cancer, postmenopausal status, years from menopause, time since diagnosis, and duration of hot flashes prior to randomization were largely unreported. In general, there was relatively limited evidence for many comparators and not all could be considered together in the NMA; therefore, the NMA and other methods of summary were performed. Pairwise comparisons generated from the NMA found that, among interventions in the network, most offered more benefits regarding HFF compared to placebo, and evidence to identify important differences between different active interventions was insufficient, although some of these studies were small and not powered to detect differences.

The evidence from that review was summarized and assessed in a GRADE evidence profile. Within the evidence profile, the body of evidence across each outcome is assessed based on the following factors that either decrease or increase one's certainty: risk of bias, inconsistency, indirectness, imprecision, publication bias, large magnitude of effect, dose-response gradient, or opposing residual confounding (Balshem et al., 2011; Guyatt, Oxman, Akl, et al., 2011; Guyatt, Oxman, Kunz, et al., 2011; Guyatt, Oxman, Sultan,

TABLE 2. Summary of Recommendations: ONS Guidelines™ for Hot Flashes in Patients With Cancer

Recommendation	Strength of Recommendation	Certainty of Evidence
Pharmacologic recommendations for women with breast cancer		
Recommendation 1: For women with breast cancer who are experiencing drug- or surgery-induced hot flashes, the ONS Guidelines panel suggests using venlafaxine, paroxetine, or clonidine rather than no treatment for the management of symptoms or (**Recommendation 2**) the panel suggests using sertraline, fluoxetine, escitalopram, or duloxetine rather than no treatment for the management of symptoms.[a]	Conditional	Low/Very low
Recommendation 3: Among these pharmaceuticals, the panel suggests using venlafaxine, paroxetine, or clonidine rather than sertraline, fluoxetine, escitalopram, or duloxetine for the management of symptoms.[a]	Conditional	Very low
Recommendation 4: Among venlafaxine, paroxetine, or clonidine, the panel suggests using venlafaxine or paroxetine rather than clonidine for the management of symptoms.[a] **Remarks:** Patients who have not responded to treatment with venlafaxine or paroxetine may wish to try clonidine to manage hot flash symptoms. Patients who have not responded to venlafaxine, paroxetine, or clonidine may wish to try these antidepressants: sertraline, fluoxetine, escitalopram, or duloxetine.[a]	Conditional	Low
Pharmacologic recommendations for men with prostate cancer		
Recommendation 5: For men with prostate cancer who are experiencing drug- or surgery-induced hot flashes, the panel suggests paroxetine or clonidine rather than no treatment for the management of symptoms or **(Recommendation 6)** the panel suggests sertraline, fluoxetine, escitalopram, or duloxetine rather than no treatment for the management of symptoms.	Conditional	Low/Very low
Recommendation 7: Among these pharmaceuticals, the panel suggests paroxetine or clonidine rather than sertraline, fluoxetine, escitalopram, or duloxetine for the management of symptoms. **Remarks:** Patients who have not responded to treatment with paroxetine or clonidine may wish to try the following antidepressants: sertraline, fluoxetine, escitalopram, or duloxetine.	Conditional	Very low
Recommendation 8: For men with cancer who are experiencing drug- or surgery-induced hot flashes, the panel recommends venlafaxine for the management of symptoms only in the context of a clinical trial.	No recommendation; knowledge gap	–
Pharmacologic recommendations for women with breast or men with prostate cancer		
Recommendation 9: For patients with cancer who are experiencing drug- or surgery-induced hot flashes, the panel suggests against gabapentin or pregabalin (gabapentinoids) for the management of symptoms.	Conditional	Very low
Nonpharmacologic recommendations for women with breast or men with prostate cancer		
Recommendation 10: For patients with cancer who are experiencing drug- or surgery-induced hot flashes, the panel suggests against herbal or dietary supplements (soy, black cohosh, St. John's wort, melatonin, vitamin E) for the management of symptoms.	Conditional	Very low
Recommendation 11: Among patients with cancer experiencing drug- or surgery-induced hot flashes, the panel recommends hypnosis or relaxation therapy only in the context of a clinical trial.	No recommendation; knowledge gap	–
Recommendation 12: Among patients with cancer experiencing drug- or surgery-induced hot flashes, the panel recommends cognitive behavioral therapy only in the context of a clinical trial.	No recommendation; knowledge gap	–

Continued on the next page

TABLE 2. Summary of Recommendations: ONS Guidelines™ for Hot Flashes in Patients With Cancer *(Continued)*

Recommendation	Strength of Recommendation	Certainty of Evidence
Nonpharmacologic recommendations for women with breast or men with prostate cancer *(continued)*		
Recommendation 13: Among patients with cancer experiencing drug- and surgery-induced hot flashes, the panel suggests physical activity interventions (exercise, yoga) rather than no treatment for the management of symptoms.	Conditional	Low
Recommendation 14: Among patients with cancer experiencing drug- or surgery-induced hot flashes, the panel recommends acupuncture and electroacupuncture only in the context of a clinical trial.	No recommendation; knowledge gap	–

[a] Paroxetine and fluoxetine are strong CYP2D6 inhibitors and may significantly interfere with tamoxifen metabolism and, therefore, are contraindicated in women taking tamoxifen.
ONS—Oncology Nursing Society

et al., 2011). In addition to the certainty of evidence, the panel formulated recommendations considering the balance of benefits and harms, patients' values and preferences, resource use, equity, acceptability, and feasibility. For each question, the panel entered judgments into the GRADE evidence-to-decision (EtD) framework using the GRADEpro Guideline Development Tool.

During a two-day, in-person meeting, the panel developed clinical recommendations based on the evidence summarized in the EtD framework. For each recommendation, the panel arrived at or came to a consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared intervention options, and the assumptions about the values and preferences associated with the decision. The panel also discussed the extent of the use of alternative treatment options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus vote based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the guideline panel.

Interpretation of Recommendations

The strength of the recommendations in this guideline is labeled as "strong" or "conditional." In some situations, the panel deemed the available evidence insufficient to determine a true effect and identified the area as an evidence gap. Table 1 provides the interpretation of the recommendations by patients, clinicians, healthcare policymakers, and researchers. The recommendations are then summarized in Table 2.

Document Review

Draft recommendations were reviewed and approved by all members of the guideline panel and then opened for public comment from December 6 to 20, 2019. In addition, a targeted peer review was conducted with three clinical or research experts on hot flashes. The goal of public comment and targeted peer review was to obtain direct feedback on the draft recommendations, as well as feedback to facilitate dissemination of the final guideline to practitioners. Following public comment and targeted peer review, the document was revised to address pertinent comments and clarify text where needed; however, no changes were made to the recommendations. The ONS Board of Directors reviewed and approved the guideline methodology and process. The guidelines were then submitted to the *Oncology Nursing Forum* for peer review.

How to Use These Guidelines

ONS Guidelines are intended to assist clinicians in making decisions about treatment interventions for common symptoms experienced by patients with cancer throughout the treatment trajectory. ONS Guidelines are intended to inform education, identify research gaps, and promote policy and advocacy. They may also be used by patients in collaboration with their healthcare team. ONS Guidelines are not medical advice and do not replace care by a cancer care clinician. Using a shared decision-making process, clinicians make decisions with patients, including discussion of patients' values and preferences with respect to their current situation. ONS Guidelines may not include all available treatments for an individual patient. Treatments described in the ONS Guidelines may not be appropriate for all patients

or in all scenarios. As scientific advances and new evidence become available, these ONS Guidelines may become outdated. The ONS Guidelines panel will monitor the evidence at least annually, or more frequently if needed, and plan to update every three years or sooner if the evidence warrants. Following these ONS Guidelines does not guarantee improvement or a successful outcome. ONS does not warrant or guarantee any products described.

Implementation of ONS Guidelines will be facilitated by forthcoming dissemination tools and patient education resources. The use of ONS Guidelines will also be facilitated by the links to the EtD frameworks and summary of findings tables in each section.

Recommendations, Key Evidence, and Qualifying Statements

The ONS Guidelines panel recommendations are grouped as pharmacologic, dietary, and behavioral (hypnosis/relaxation, cognitive behavioral therapy [CBT], physical activity, and acupuncture/electroacupuncture). For pharmacologic recommendations, distinctions were made for men or women with cancer, as appropriate. Each recommendation includes a description of the total analysis (NMA, pairwise meta-analysis, and narrative summaries) in the GRADE EtD frameworks. The narrative following each recommendation parallels the organization of the GRADE EtD. First, a summary of the evidence is presented, followed by a description of the benefits and harms considered by the panel members, including a statement about the certainty of the evidence. Additional factors from the EtD are then summarized. Lastly, a final summary of the recommendation is presented, considering any overarching remarks made by the panel. The EtD framework for each recommendation is provided in the supplementary material.

Women With Breast Cancer Who Are Experiencing Drug or Surgery-Induced Hot Flashes

Pharmacologic Interventions

Recommendations 1, 2, 3, and 4

For women with breast cancer who are experiencing drug- or surgery-induced hot flashes, the ONS Guidelines panel suggests using venlafaxine, paroxetine, or clonidine (conditional recommendation; low certainty of evidence) or sertraline, fluoxetine, escitalopram, or duloxetine (conditional recommendation; very low certainty of evidence) rather than no treatment for the management of symptoms.

Among these pharmaceuticals, the panel suggests using venlafaxine, paroxetine, or clonidine rather than sertraline, fluoxetine, escitalopram, or duloxetine for management of symptoms (conditional recommendation; very low certainty of evidence).

Among venlafaxine, paroxetine, or clonidine, the panel suggests using venlafaxine or paroxetine rather than clonidine for the management of symptoms (conditional recommendation; low certainty of evidence).

Remarks: Patients who have not responded to treatment with venlafaxine or paroxetine may wish to try clonidine to manage hot flash symptoms. Patients who have not responded to venlafaxine, paroxetine, or clonidine may wish to try these antidepressants: sertraline, fluoxetine, escitalopram, or duloxetine. Paroxetine and fluoxetine are strong CYP2D6 inhibitors and may significantly interfere with tamoxifen metabolism; therefore, they are contraindicated in women taking tamoxifen.

Summary of the Evidence

The authors identified a recently conducted systematic review and NMA that addressed these questions (Hutton et al., 2020). For the outcome of HFF, data from a total of 11 RCTs comparing 9 interventions (n = 1,403 participants) were available for the NMA. For the outcome of hot flash composite score (HFCS), data from a total of 12 RCTs comparing 11 interventions (n = 1,523 participants) were available for the NMA. For both HFF and HFCS, some head-to-head comparisons between active therapies were available, although most were assessed versus placebo. Of the studies included in the NMA, 90% reported on women with breast cancer and 10% reported on men with prostate cancer.

In addition to the studies in the NMA, the outcome of HFF for the comparison of pharmacologic interventions was informed by two trials, which could only be included in a narrative summary (Biglia et al., 2016; Loprinzi et al., 2002), and the outcome of HFCS was informed by three trials, also only included in a narrative summary (Biglia et al., 2016; Boekhout et al., 2011; Loprinzi et al., 2002). Individual RCTs identified from the same systematic review provided evidence for the outcomes of HFS, sleep measures, depression, sexual function, quality of life, and adverse events.

Benefits

Venlafaxine, paroxetine, and clonidine likely reduce HFCS compared to no treatment based on the NMA comparing 11 interventions from 12 RCTs among 1,523 participants (ratio of means [RoM] = 1.71; 95%

confidence interval [CI] [1.05, 2.76]; RoM = 2.83; 95% CI [1.31, 6.09]; RoM = 2.13; 95% CI [1.27, 3.54], respectively) (Hutton et al., 2020). Sertraline may reduce HFCS compared to no treatment, but the evidence was uncertain (RoM = 1.58; 95% CI [0.7, 3.41]). In addition to the studies included in the NMA, a study by Boekhout et al. (2011) assessed venlafaxine versus clonidine versus placebo in 2,012 women with breast cancer who were randomly assigned (2:2:1) to venlafaxine 75 mg, clonidine 0.1 mg, or placebo daily for 12 weeks. The authors found venlafaxine and clonidine to both be effective, with venlafaxine having a more immediate reduction in hot flash scores (median scores for placebo = 10.9, interquartile range [IQR] = 7.4–15.8; median scores for clonidine = 7.5, IQR = 2–10.8; median scores for venlafaxine = 7.6, IQR = 4–110.4). Biglia et al. (2016) assessed hot flashes in 34 survivors of breast cancer and randomized to duloxetine 60 mg daily or escitalopram 20 mg daily for 12 weeks. Participants completed a diary of HFF and HFS at baseline and after 4 and 12 weeks of treatment (Biglia et al., 2016). The authors reported a decrease in HFCS at the end of the study period with escitalopram and duloxetine (53.6% and 60.4% decrease, respectively) (Biglia et al., 2016). A crossover trial of fluoxetine compared to placebo included 81 women with breast cancer (Loprinzi et al., 2002). By the end of the initial treatment period, HFCS decreased 50% in the fluoxetine arm versus 36% in the placebo arm. Crossover analysis demonstrated a modest improvement with fluoxetine compared to placebo (p = 0.02) (Loprinzi et al., 2002).

For the outcome of HFF, venlafaxine (RoM = 2.48; 95% CI [1.36, 4.32]) and paroxetine (RoM = 3.15; 95% CI [1.29, 7.58]) reduces and likely reduces, respectively, HFF compared to no treatment (Hutton et al., 2020). Sertraline may reduce HFF compared to no treatment, but the evidence is uncertain (RoM = 1.67; 95% CI [0.69, 2.73]). In addition, fluoxetine may reduce HFF when compared to no treatment, but the reduction may not be clinically meaningful (mean reduction in frequency over four weeks was 3.4 versus 2.5 hot flashes per day) (Loprinzi et al., 2002). Clonidine reduced HFF compared to placebo after four weeks of treatment (37% compared to 20%; 95% CI for the between-group difference [7%, 27%]) and at eight weeks of treatment (38% compared to 24%; 95% CI for the between-group difference [3%, 27%]) (Pandya et al., 2000).

For the secondary outcomes of sleep quality and depression, the results were inconsistent. Sleep quality was not significantly different among venlafaxine and clonidine treatment groups in the Boekhout et al. (2011) study. Paroxetine (at 10 mg daily dose) was associated with a significant improvement in sleep compared to placebo; however, it failed to demonstrate improvement at a dose of 20 mg daily (Stearns et al., 2005). Patients taking clonidine were more likely to report difficulty sleeping (41% compared to 21%, p = 0.02) in a study comparing clonidine to placebo (Pandya et al., 2000).

For the depression outcome, Boekhout et al. (2011) reported higher depression scores (indicating increased depression) in the venlafaxine group compared to the clonidine group (p = 0.03). In a study by Stearns et al. (2005), no differences were observed with different paroxetine doses (10 mg or 20 mg daily) or placebo in the distribution of patients who experienced improvement or worsening of depression scores (measured by the Center for Epidemiologic Studies Depression [CES-D] scale). A study by Loprinzi et al. (2000) on increasing doses of venlafaxine versus placebo found 33% of patients on placebo had depression scores consistent with at least mild depression, whereas patients on venlafaxine had lower percentages of depression scores (23% at 37.5 mg, 21% at 75 mg, and 27% at 150 mg).

Sexual function outcomes were mixed as well. No significant differences were found between treatment groups in two studies (Boekhout et al., 2011; Stearns et al., 2005), whereas a separate study identified improvements in libido scores for all groups (venlafaxine and placebo) during the four-week study (Loprinzi et al., 2000).

Patient preference and quality of life have also been investigated as important outcomes in the field of hot flash reduction. In a study comparing patient preference with gabapentin to venlafaxine, more patients preferred venlafaxine (68%) than gabapentin (32%) (Bordeleau et al., 2010). When compared to acupuncture, venlafaxine showed no additional effects on quality of life (measured with a menopause quality-of-life questionnaire), with both groups having improvements at post-treatment with a return toward baseline at 64-weeks follow-up (Walker et al., 2010). A statistically significant change was seen in quality-of-life scores with clonidine compared with placebo (0.3 points in the clonidine group, –0.2 points in the placebo group; p = 0.02), but this change is unlikely to be clinically meaningful (Pandya et al., 2000). Overall quality of life increased during a four-week period by an average of 3 points in the treatment groups (venlafaxine 37.5 mg, 75 mg, or 150 mg daily) compared to a decrease of

3 points in the placebo group (p = 0.02), with uncertain clinical significance (Loprinzi et al., 2000).

Harms and Burden

Antidepressants can cause a wide range of side effects which can be unpleasant for the patient and vary between drugs. Some of these include nausea, constipation, loss of sexual desire, fatigue, and dry mouth. Each individual antidepressant has a unique metabolic pathway, and consideration of other medications is always important when choosing treatment for hot flashes. Clonidine can cause orthostatic hypotension and should be used cautiously in patients taking other antihypertensives or who are particularly sensitive to reductions in blood pressure (e.g., patients who are dehydrated or frail).

Many antidepressants are extensively metabolized in the liver via the CYP450 enzyme system and may interact with other medications. Paroxetine is an antidepressant that is a strong inhibitor of the CYP2D6 enzyme system, which is partially responsible for the metabolism of tamoxifen to active metabolites (Kaplan & Mahon, 2013). Although controversial, at least one study has identified an increased risk of death from breast cancer with overlapping use of both paroxetine and tamoxifen (Kelly et al., 2010). Therefore, caution is recommended in the use of paroxetine in patients experiencing tamoxifen-induced hot flashes (Goetz et al., 2018; National Comprehensive Cancer Network [NCCN], 2019). In addition, fluoxetine is also a strong inhibitor of CYP2D6 and should be avoided in this clinical scenario (Indiana University, 2020). Many other drugs inhibit CYP2D6 to different degrees and may warrant caution for patients taking tamoxifen. Interaction checking is paramount in these patients to ensure clinically important drug interactions are avoided.

The study by Boekhout et al. (2011) identified that severe adverse events, including loss of appetite, were more frequent with venlafaxine versus clonidine (p = 0.003). A study comparing venlafaxine to clonidine identified common adverse events of mouth dryness, fatigue, and restless sleep among both groups (Loibl et al., 2007). In this study, nausea was more frequent in the venlafaxine group (p = 0.05), with mouth dryness, constipation, and restless sleep more common in patients on clonidine; these differences were not statistically significant (Loibl et al., 2007). However, premature discontinuation of medication occurred in two patients (5%) in the venlafaxine group and six patients (15%) in the clonidine group (p = 0.26). In a study comparing venlafaxine to acupuncture, Walker et al. (2010) found 18 reports of adverse events (i.e., nausea, headache, difficulty sleeping, dizziness) in the venlafaxine group compared to none in the acupuncture group ($p \leq 0.002$). For sertraline, a study by Kimmick et al. (2006) identified that 14 patients (44%) receiving sertraline reported side effects during the first six weeks of treatment compared to 7 patients (25%) receiving placebo. The events reported were similar to the known side effect profile of sertraline with nausea, fatigue/malaise, diarrhea, and anxiety/nervousness reported (Kimmick et al., 2006).

Certainty in the Evidence of Effects

The certainty in the estimates for antidepressants was judged as low and very low because of concerns with risk of bias and imprecision.

Other Evidence-to-Decision Criteria and Considerations

The panel assumed the adverse events related to the use of some pharmacologic interventions were underreported in the literature, leading to a more closely balanced net benefit for clonidine, sertraline, fluoxetine, escitalopram, and duloxetine. The panel assumed moderate costs to be associated with taking any pharmacologic intervention when compared with no treatment, and that the potential for health inequity may be increased for patients who are under- or uninsured. The panel assumed that pharmacologic interventions would be acceptable to a wide range of stakeholders and feasible to implement. Other EtD criteria were generally in favor of using any pharmacologic, with the desirable effects outweighing the undesirable consequences.

Conclusions

Several antidepressants have been evaluated in the literature for management of hot flashes with varying efficacy and tolerability. When considering which pharmacologic interventions to use first, the panel determined that there is very low certainty of net benefit in using venlafaxine, paroxetine, or clonidine rather than sertraline, fluoxetine, escitalopram, or duloxetine, and low certainty in the net benefit of using venlafaxine or paroxetine rather than clonidine.

Based on this evidence, the panel suggests venlafaxine or paroxetine as first-line therapy, followed by clonidine and then sertraline, fluoxetine, escitalopram, or duloxetine for the management of symptoms. Male patients with breast cancer were not included in these clinical trials; therefore,

evaluation and comments could not be made regarding this patient population. It is important to note that paroxetine and fluoxetine should be used with caution in women or men who are taking tamoxifen. Tolerability and the presence of other drug interactions should also be considered when choosing therapy for hot flashes.

Men With Prostate Cancer Who Are Experiencing Drug- or Surgery-Induced Hot Flashes

Pharmacologic Interventions

Recommendations 5, 6, and 7

For men with prostate cancer who are experiencing drug- or surgery-induced hot flashes, the ONS Guidelines panel suggests paroxetine or clonidine (conditional recommendation; low certainty of evidence) or sertraline, fluoxetine, escitalopram, or duloxetine (conditional recommendation; very low certainty of evidence) rather than no treatment for the management of symptoms.

Among these pharmaceuticals, the panel suggests paroxetine or clonidine rather than sertraline, fluoxetine, escitalopram, or duloxetine for the management of symptoms (conditional recommendation; very low certainty of evidence).

Remarks: Patients who have not responded to treatment with paroxetine or clonidine may wish to try these antidepressants: sertraline, fluoxetine, escitalopram, or duloxetine.

Summary of the Evidence

In addition to the studies in the NMA when comparing pharmacologic interventions, the outcome of HFF was informed by two trials, which could not be included in the NMA (Biglia et al., 2016; Loprinzi et al., 2002), and the outcome of HFCS was informed by three trials, which could not be included in the NMA (Biglia et al., 2016; Boekhout et al., 2011; Loprinzi et al., 2002). Individual RCTs identified from the same systematic review provided evidence for the outcomes of HFS, sleep measures, depression, sexual function, quality of life, and adverse events.

Benefits

Paroxetine and clonidine likely reduce HFCS compared to no treatment based on the NMA (RoM = 2.83; 95% CI [1.31, 6.09] and RoM = 2.13; 95% CI [1.27, 3.54], respectively) (Hutton et al., 2020). Sertraline may reduce HFCS compared to no treatment, but the evidence was uncertain (RoM = 1.58; 95% CI [0.7, 3.41]).

For the outcome of HFF, paroxetine (RoM = 3.15; 95% CI [1.29, 7.58]) likely reduces HFF compared to no treatment (Hutton et al., 2020). Sertraline may reduce HFF compared to no treatment, but the evidence is uncertain (RoM = 1.67; 95% CI [0.69, 2.73]). Data from studies including men regarding these pharmacologic interventions suggest that there was evidence supporting benefits in reducing HFF associated with fluoxetine (Loprinzi et al., 2002), escitalopram, and duloxetine (Biglia et al., 2016). In Loprinzi et al., (2002) fluoxetine decreased HFF by 42% compared to 31% with placebo. In Biglia et al., (2016) duloxetine and escitalopram were equivalent, with HFF decreased by 49.8% from baseline with duloxetine and 53% from baseline with escitalopram. HFS was assessed in a study by Loibl et al. (2007), and no differences were identified in mean severity or changes from baseline with clonidine compared to placebo. Overall, there was uncertainty of effects based on the small amounts of evidence available for clonidine. Although clonidine may offer some benefits related to HFS, the clinical relevance is unclear.

Additional outcomes, such as sleep and depression, were assessed in several studies including men. Stearns et al. (2005) used the Medical Outcomes Study (MOS) Sleep Problems Index and found that all three intervention groups (placebo, paroxetine 10 mg, and paroxetine 20 mg) were associated with improvements of at least 10 points on the MOS Sleep Problems Index from baseline; however, only paroxetine 10 mg was associated with significantly greater improvement compared to placebo.

Depression was assessed in four studies (Biglia et al., 2009; Boekhout et al., 2011; Kimmick et al., 2006; Stearns et al., 2005). Based mainly on these small, single-center studies, the following findings are noted: duloxetine and escitalopram reduced depression similarly, clonidine appears to offer some benefits in reducing depression, and no improvements in depression were observed with sertraline or paroxetine. The outcome of sexual function was assessed in three studies (Boekhout et al., 2011; Loprinzi et al., 2002; Stearns et al., 2005). In these studies, no benefits in sexual function were observed with either clonidine or paroxetine; evidence for fluoxetine was unclear based on study reporting.

For the outcome of generic quality of life, five studies (Kimmick et al., 2006; Loprinzi et al., 2002; Pandya et al., 2000; Stearns et al., 2005; Wu et al., 2009) used a variety of instruments to assess change in quality of life with clonidine, fluoxetine, and sertraline, and none identified a significant difference between groups.

Harms and Burdens

Many antidepressants are extensively metabolized in the liver via the CYP450 enzyme system and may interact with other medications. Each individual antidepressant has a unique metabolic pathway, and consideration of other medications is always important when choosing treatment for hot flashes. Many clinically relevant drug interactions exist with antidepressants and anticancer medications used to treat prostate cancer. Although these interactions have not been as well studied as those with tamoxifen, interaction checking is paramount in these patients to ensure clinically important drug interactions are avoided.

Antidepressants can cause a wide range of side effects which can be unpleasant for the patient, vary by drug, and may also vary by gender. Some of these include nausea, constipation, loss of sexual desire, fatigue, and dry mouth. Clonidine can cause orthostatic hypotension and should be used cautiously in patients taking other antihypertensives or who are particularly sensitive to decreases in blood pressure (patients who are dehydrated or frail). Many of the studies reviewed of patients with prostate cancer did not include a detailed assessment of adverse events to ascertain tolerability specific to men.

The panel recognized that most of the research on hot flashes in patients with cancer has been in women and extrapolated harms from the breast cancer literature, recognizing that the actual tolerability in men may differ. A study comparing venlafaxine to clonidine in women with breast cancer identified common adverse events of mouth dryness, fatigue, and restless sleep among both groups (Loibl et al., 2007). In this study, nausea was more frequent in the venlafaxine group ($p = 0.05$) with mouth dryness, constipation, and restless sleep more common in patients on clonidine; these differences were not statistically significant (Loibl et al., 2007). However, premature discontinuation of medication occurred in two patients (5%) in the venlafaxine group and six patients (15%) in the clonidine group ($p = 0.26$).

Certainty in the Evidence of Effects

In general, the evidence base was sparse, and trials involved relatively small numbers of patients and were judged to be at unclear or to have a high risk of bias. The quality of evidence supporting the use of antidepressants in men for the management of hot flashes was low. The panel acknowledged the indirectness in this evidence because the studies were conducted primarily in women with breast cancer. The panel considered that other antidepressants may be an option for men who are unable to tolerate or respond to paroxetine or clonidine. The panel also noted that a thorough discussion of potential side effects is important to guide a person's decision making.

Other Evidence-to-Decision Criteria and Considerations

The panel noted the lack of studies in men with hot flashes and considered the evidence in women to be indirect but relevant for decision making. The panel determined that the adverse events related to the use of some pharmacologic interventions were underreported in the literature, leading to a more closely balanced net benefit for clonidine, sertraline, fluoxetine, escitalopram, or duloxetine. The panel considered moderate costs to be associated with taking any pharmacologic intervention when compared with no treatment, and that the potential for health inequity may be increased for patients who are under- or uninsured. The panel decided that pharmacologic interventions would be acceptable to a wide range of stakeholders and feasible to implement. Other EtD criteria were generally in favor of using any pharmacologic, with the desirable effects outweighing the undesirable effects.

Conclusions

Hot flashes are prevalent among men with prostate cancer undergoing treatment with ADT, occurring in almost 80% of men (Vitolins et al., 2013). Despite this prevalence, there remains limited research evidence on interventions for hot flashes in men with prostate cancer. Male patients with breast cancer also experience hot flashes related to treatment and were not included in these trials. The panel issued a conditional recommendation for antidepressant interventions because of the low quality of evidence underpinning the statement. Based on the low quality and limitations of evidence, the panel made a conditional recommendation for paroxetine or clonidine over sertraline, fluoxetine, escitalopram, or duloxetine for the management of hot flashes in men with prostate cancer.

Venlafaxine

Recommendation 8

For men with cancer who are experiencing drug- or surgery-induced hot flashes, the ONS Guidelines panel recommends venlafaxine for the management of symptoms only in the context of a clinical trial (no recommendation; knowledge gap).

Summary of the Evidence

In addition to the studies in the NMA when comparing venlafaxine to no treatment for men with cancer, HFF and HFCS were also informed by several trials, which could not be included in the NMA (Boekhout et al., 2011; Bordeleau et al., 2010; Vitolins et al., 2013). Individual RCTs identified from the same systematic review provided evidence for the outcomes of HFS, sleep measures, depression, sexual function, quality of life, and adverse events. The majority of the evidence was in women with breast cancer, with only one study (Vitolins et al., 2013) assessing venlafaxine in men with prostate cancer.

Benefits

Venlafaxine likely reduces HFCS compared to no treatment based on the NMA (RoM = 1.71; 95% CI [1.05, 2.76]) (Hutton et al., 2020). For the outcome of HFF, venlafaxine reduces HFF compared to no treatment (RoM = 2.48; 95% CI [1.36, 4.32]). For the outcome of HFS, the review identified three studies, one in men with prostate cancer (Vitolins et al., 2013) and two in women with breast cancer (Loibl et al., 2007; Walker et al., 2010). Venlafaxine was compared to milk protein and soy with a decrease in HFS at weeks 1–4, but the difference was not significant at 12 weeks (Vitolins et al., 2013). No significant improvements were found in HFS when venlafaxine was compared to acupuncture (Walker et al., 2010) or clonidine (Loibl et al., 2007).

Other outcomes were assessed, with most finding no difference in sleep (Boekhout et al., 2011), depression (Loprinzi et al., 2000; Walker et al., 2010), and sexual function (Boekhout et al., 2011; Loprinzi et al., 2000). Boekhout et al. (2011) did identify that, after 12 weeks, depression scores were significantly higher in patients receiving venlafaxine than patients receiving clonidine ($p = 0.03$), suggesting more depression; however, no additional analyses were provided, and statistical comparisons with the placebo group were not detailed.

Quality of life was assessed in three studies. Two were in patients with breast cancer (Loprinzi et al., 2000; Walker et al., 2010) and one was in patients with prostate cancer (Vitolins et al., 2013). Only Loprinzi et al. (2000) found a benefit in quality of life when comparing venlafaxine to placebo.

Harms and Burdens

Venlafaxine was noted to have important side effects in several studies. Patients taking venlafaxine reported more frequent treatment-related adverse events for nausea ($p = 0.02$), constipation ($p = 0.04$), and severe appetite loss (Boekhout et al., 2011) in one study, and nausea ($p = 0.05$), mouth dryness, constipation, and restless sleep (Loibl et al., 2007) when compared to clonidine in women with a history of breast cancer. A study by Vitolins et al. (2013) comparing venlafaxine to soy protein in men with prostate cancer did not note a difference in toxicity among interventions, and the majority of toxicities that were reported were grade 0 or 1. When compared to acupuncture or placebo, patients receiving venlafaxine experienced more adverse events (Loprinzi et al., 2000; Walker et al., 2010).

Antidepressants can cause a wide range of side effects, which can be unpleasant for the patient. Some of these include nausea, constipation, loss of sexual desire, fatigue, and dry mouth. Most antidepressants are extensively metabolized in the liver and may interact with other drugs that are metabolized via similar pathways. Consideration of other medications is important when starting an antidepressant. Clonidine can cause orthostatic hypotension and should be used cautiously in patients taking other antihypertensives or who are particularly sensitive to decreases in blood pressure.

Certainty in the Evidence of Effects

The quality of evidence supporting venlafaxine in men for the management of hot flashes was low. Overall, the evidence was relatively sparse and included trials that had smaller patient samples with unclear or high risk of bias. The panel acknowledged the indirectness in this evidence in that the studies were conducted primarily in women with breast cancer, specifically the evidence informing the primary outcomes of HFCS and HFF. Interpretations must be made carefully given data sparsity and limitations of the trials. Additional research of interventions in men is needed.

Other Evidence-to-Decision Criteria and Considerations

The panel decided that venlafaxine did not show effectiveness in men with prostate cancer and that the undesirable effects were small. Overall, the panel judged that the balance of effects from venlafaxine does not favor either the intervention or the comparison.

Conclusions

Limited consistent evidence exists to support a recommendation for venlafaxine for the management of hot flashes in men with prostate cancer. Based on the low quality and indirectness of evidence, the panel made no recommendation for venlafaxine and identified this intervention as an evidence gap that warrants

additional research in the form of properly powered, well-designed RCTs with adequate endpoints.

Women With Breast Cancer or Men With Prostate Cancer Who Are Experiencing Drug- or Surgery-Induced Hot Flashes

Gabapentin or Pregabalin

Recommendation 9

For patients with cancer who are experiencing drug- or surgery-induced hot flashes, the ONS Guidelines panel suggests against gabapentin or pregabalin (gabapentinoids) for the management of symptoms (conditional recommendation; very low certainty of evidence).

Summary of the Evidence

In addition to the studies in the NMA, when comparing gabapentin or pregabalin to no treatment, the outcomes of HFF and HFCS were informed by two trials, which could not be included in the NMA but were narratively summarized (Bordeleau et al., 2010; Mao et al., 2015). Individual RCTs identified from the same systematic review provided evidence for the outcomes of HFS, sleep measures, depression, sexual function, quality of life, and adverse events.

Benefits

Based on results from the NMA, gabapentin may be no more effective than placebo for HFCS (RoM = 1.43; 95% CI [0.95, 2.12]; low/very low certainty of evidence) (Hutton et al., 2020). Similarly, gabapentin is no more effective than placebo for HFF (RoM = 1.62; 95% CI [0.92, 2.73]; high/moderate certainty of evidence). A study in women with breast cancer comparing gabapentin with venlafaxine reported a ratio of venlafaxine compared to gabapentin of 0.94 (95% CI not reported), suggesting little difference between intervention groups with participants preferring venlafaxine over gabapentin (Bordeleau et al., 2010). When compared to electroacupuncture, the authors noted that electroacupuncture may be more effective than gabapentin, with fewer adverse events for hot flash management (Mao et al., 2015).

For HFS, the findings are similar as with HFF and HFCS. Bordeleau et al. (2010) compared gabapentin to venlafaxine and identified a venlafaxine to gabapentin ratio of 1.02 (near 1), suggesting little difference between intervention groups ($p > 0.61$). Analyses were also performed to compare groups based on patients' preferred treatment; among those who preferred venlafaxine (n = 38), 94.7% reported decreased HFS, while among those who preferred gabapentin (n = 18), 94.4% reported decreased severity.

For the outcome of sleep, Biglia et al. (2009) evaluated gabapentin compared to vitamin E and found that gabapentin demonstrated a statistically significant improvement in sleep quality (measured with the Pittsburgh Sleep Quality Index [PSQI]) from baseline; the gabapentin group incurred a mean global PSQI score reduction of 21.33% at 12 weeks and a mean absolute reduction of 1.67 (95% CI [0.9, 2.43]). No significant difference was found in depression scores in one study comparing gabapentin to placebo (Loprinzi et al., 2009).

Quality of life and patient preference for gabapentin have been investigated in several studies. In a study comparing venlafaxine to gabapentin in women with breast cancer, 32% of patients preferred gabapentin compared to 68% of patients who preferred venlafaxine, even though both reduced hot flash scores to a similar extent (66% reduction in scores) (Bordeleau et al., 2010). Gabapentin slightly improved health-related quality of life compared to vitamin E in women with breast cancer (Biglia et al., 2009). In a study of men with prostate cancer who were experiencing hot flashes, Loprinzi et al. (2009) compared different doses of gabapentin to placebo and found that overall quality of life was not significantly different between the groups. Loprinzi et al. (2007) found no significant differences in quality of life when gabapentin was added to an antidepressant in women with inadequate hot flash control on an antidepressant.

Harms and Burdens

Gabapentin can cause some adverse events and participant burden, which are important considerations in deciding on treatment. Gabapentin may cause dizziness, drowsiness, and confusion in some older adults and should be used cautiously. In a study comparing gabapentin to vitamin E, 28% of patients interrupted treatment with gabapentin because of side effects (primarily dizziness and somnolence) (Biglia et al., 2009). Rates of adverse events were highest with gabapentin (39.3%) when compared to placebo (20%) and electroacupuncture (16.7%) and sham acupuncture (3.1%) in women with breast cancer (Mao et al., 2015). In a study comparing venlafaxine to gabapentin with breast cancer survivors, no grade 3 or 4 treatment-emergent adverse events were reported by participants; however, patients on venlafaxine reported more nausea, appetite loss, and constipation, whereas patients on gabapentin reported more dizziness and increased appetite (Bordeleau et al., 2010). Loprinzi et al. (2007) added

gabapentin to an antidepressant in women who were experiencing uncontrolled hot flashes on an antidepressant and found that there was a temporary trend toward more dizziness in the gabapentin group.

Certainty in the Evidence of Effects

The panel had low to very low certainty in the evidence of effects related to the indirectness to men based on the evidence and the uncertainty of harms in men and women.

Other Evidence-to-Decision Criteria and Considerations

The panel judged the desirable and undesirable effects of gabapentin to be small, with a concern that adverse events may be underreported in the literature. The panel consensus was that the balance of effects does not favor gabapentin as an intervention for the treatment of hot flashes. The panel noted that gabapentin may require moderate resources because many insurers are not likely to cover it for this indication.

Conclusions

The panel acknowledged that, although there is limited evidence of benefit for gabapentinoids in the treatment of hot flashes, there may be moderate harms, particularly among patients with cancer. Based on this evidence, the panel issued a conditional recommendation suggesting against gabapentinoids for the management of hot flashes.

Dietary Supplements

Recommendation 10

For patients with cancer who are experiencing drug- or surgery-induced hot flashes, the ONS Guidelines panel suggests against herbal or dietary supplements (soy, black cohosh, St. John's wort, melatonin, vitamin E) for the management of symptoms (conditional recommendation; very low certainty of evidence).

Summary of the Evidence

In addition to the studies in the NMA, HFF was also informed by four trials, which could not be included in the NMA (Barton et al., 1998; Quella et al., 2000; Van Patten et al., 2002; Vitolins et al., 2013), all in women with breast cancer except for Vitolins et al. (2013), which was conducted in men with prostate cancer. For the outcome of HFCS, data from a total of 12 RCTs comparing 11 interventions (n = 1,523 participants) were available for the NMA. HFCS was also informed by five trials, which could not be included in the NMA (Barton et al., 1998; Jacobson et al., 2001; Quella et al., 2000; Van Patten et al., 2002; Vitolins et al., 2013), with Vitolins et al. (2013) the only study of prostate cancer.

Benefits

In general, there was relatively limited evidence for most comparators. For the outcome of HFCS, vitamin E may be among the least effective when compared to placebo (RoM = 0.14; 95% CI [0.03, 0.58]). Melatonin may be no more effective than placebo (RoM = 0.7; 95% CI [0.05, 11.19]). Pairwise comparisons generated from the NMA found that, among interventions in the network, there was insufficient evidence to identify important differences between other interventions. None identified a significant reduction in HFCS by soy, black cohosh, or vitamin E.

Vitamin E and melatonin may be among the least effective at reducing HFF (RoM = 0.27; 95% CI [0.06, 1.18] and RoM = 1.03; 95% CI [0.11, 8.9], respectively) (Hutton et al., 2020). Pairwise comparisons generated from the NMA found that, among interventions in the network, most offered more benefits regarding HFF in comparison to placebo and vitamin E, and there was insufficient evidence to identify important differences between different active interventions. HFF was also informed by four trials, which could not be included in the NMA (Barton et al., 1998; Quella et al., 2000; Van Patten et al., 2002; Vitolins et al., 2013), all in women with breast cancer except for Vitolins et al. (2013), which was conducted in men with prostate cancer. Soy was evaluated in three of the studies (Quella et al., 2000; Van Patten et al., 2002; Vitolins et al., 2013), with no benefit of soy found in any study. Barton (1998) investigated vitamin E compared to placebo and the authors noted that, although a reduction in HFF was seen with vitamin E, clinical relevance was small (approximately one less hot flash per day) and that participants did not prefer vitamin E to placebo.

In addition to the studies analyzed in the network, individual RCTs identified from the same systematic review provided evidence for the outcomes of HFS, sleep, depression, sexual function, quality of life, and adverse events (Hutton et al., 2020). HFS was reported in five studies (Barton et al., 1998; Chen et al., 2014; Hernández-Muñoz & Pluchino, 2003; Jacobson et al., 2001; Vitolins et al., 2013). Study-specific findings related to the impact of black cohosh on changes in HFS were mixed, with one study finding improvements compared to no treatment (Hernández-Muños & Pluchino, 2003) and another showing no benefit (Jacobson et al., 2001). There was

insufficient evidence of any important effects associated with vitamin E, melatonin, and soy (Barton et al., 1998; Chen et al., 2014; Vitolins et al., 2013).

Additional outcomes, such as sleep, depression, and quality of life, were assessed. For the outcome of sleep, Chen et al. (2014) observed significantly improved sleep quality in those taking melatonin compared to placebo in terms of PSQI global score, as well as the sleep quality, sleep duration, and daytime dysfunction subdomains. For the outcome of depression, there was no evidence that melatonin or black cohosh offered benefits over no treatment (Chen et al., 2014; Jacobson et al., 2001).

Harms and Burdens

Adverse events were minor, with only one study reporting serious adverse events (Jacobson et al., 2001). In a study of 85 women comparing black cohosh to placebo, the authors noted 3 serious adverse events (hysterectomy, cancer recurrence, and appendectomy) and 10 minor events among all participants. The studies that compared soy to placebo (MacGregor et al., 2005; Van Patten et al., 2002) reported mild gastrointestinal toxicity in both groups, with one study noting increased frequency and severity in the intervention group receiving soy (Van Patten et al., 2002).

Certainty in the Evidence of Effects

The quality of evidence supporting herbal or dietary supplements was low. Overall, the evidence was relatively sparse and included trials that had smaller patient samples with unclear or high risk of bias. In addition, variable reporting made the degree of homogeneity of study populations difficult to discern; therefore, interpretation and generalization of findings should be made cautiously.

Other Evidence-to-Decision Criteria and Considerations

The panel recognized the very low certainty of the evidence as well as concerns about implementability, reproducibility, lack of consistent good manufacturing practices and regulatory oversight for supplements, and lack of evidence around interactions between hormonal agents and herbal or dietary supplements. The beneficial effects were judged to be trivial with unknown undesirable effects. The balance of effects was judged to not favor the intervention or the comparison. Costs were considered to be negligible, and the panel thought that acceptability would vary among clinicians, patients, and payers.

Conclusions

The panel acknowledged that there is insufficient evidence to identify important differences between active interventions. Based on this evidence, the panel issued a conditional recommendation suggesting no treatment over herbal or dietary supplements for the management of hot flashes because of the very low quality of the evidence underpinning the statement, the lack of benefit, and unknown or potential harms.

Hypnosis or Relaxation Therapy

Recommendation 11

Among patients with cancer experiencing drug- or surgery-induced hot flashes, the ONS Guidelines panel recommends hypnosis or relaxation therapy only in the context of a clinical trial (no recommendation; knowledge gap).

Summary of the Evidence

The NMA identified four studies that addressed this question, all in women with breast cancer (Elkins et al., 2008; Fenlon, 1999; Fenlon et al., 2008; Nedstrand et al., 2005). Elkins et al. (2008) assessed weekly hypnosis for five weeks, and the other studies assessed either group or home-based relaxation therapy (Fenlon, 1999; Fenlon et al., 2008; Nedstrand et al., 2005). Sample sizes ranged from 8 to 76 per arm. Treatment duration was 4 to 12 weeks, with follow-up of 3 to 6 months in two studies and no follow-up in two studies.

Benefits

For the outcome of HFF, Fenlon et al. (2008) identified a median improvement of seven less hot flashes per week from relaxation therapy compared to an improvement of one less per week in the usual care group (median difference in improvement of 7 per week, 95% CI [4, 11]; $p < 0.001$). After three months, the corresponding improvements were 11 and 4 per week, respectively (median difference in improvement of 5 per week, 95% CI [0, 10]; $p = 0.06$). The severity of hot flashes in this study, recorded in a diary by the participants of every hot flash as it occurred, significantly declined during one month in the relaxation group compared with the control group ($p < 0.01$). The authors concluded that the study showed a small but statistically significant reduction in the incidence and severity of hot flashes associated with relaxation therapy. In Fenlon (1999), there appeared to be a trend for relaxation training to reduce both the frequency of hot flashes and

associated distress, but these differences were not found to be significant.

The Nedstrand et al. (2005) study was a 12-week comparison of relaxation therapy to electroacupuncture. A significant change in HFF appeared after four weeks in both groups, and no further significant change was seen as many as six months after the end of treatment. The authors concluded that there was a definite, albeit slow, decline in number of hot flashes over time. In Elkins et al. (2008), participants underwent five weeks of hypnosis sessions, with follow-up focused on HFF at baseline and postintervention. Analyses of covariance (ANCOVAs) (using pretest HFF as a covariate) identified a statistically significant improvement for the hypnosis group compared with the control group (detailed data not reported). Elkins et al. (2008) also assessed a composite of HFF and severity with the Hot Flash Related Daily Interference Scale. Patients in the hypnosis group demonstrated a statistically significant improvement in hot flash score (from baseline $\bar{X}$ score of 15.05 [SD = 13.75] to 4.84 [SD = 5.02]) compared to those in the control group (from baseline $\bar{X}$ score of 17.17 [SD = 10.37] to 15.6 [SD = 10.71]; $p < 0.001$). The authors concluded that hypnosis appears to reduce perceived hot flashes in breast cancer survivors.

Additional outcomes, such as sleep and depression, were assessed in one study (Elkins et al., 2008). Hypnosis was associated with an improvement in sleep compared to the control group after five weeks of treatment (F test from an ANCOVA reported; $p < 0.001$), as well as in comparison to baseline levels within the group (MOS Sleep Index $\bar{X}$ score of 24.26 [SD = 8.17] at baseline and 13.71 [SD = 4.35] at follow-up). For depressive symptoms (measured with the CES-D scale), data suggest an important mean reduction in the hypnosis group (from 29.48 [SD = 7.72] to 24.58 [SD = 6.45]) compared to the waitlist group (from 30.22 [SD = 9.32] to 31.38 [SD = 9.21]). The difference between groups was statistically significant in favor of the hypnosis group ($p < 0.01$). Based on this small study, improvements in sleep and depression were achieved with hypnosis compared with no treatment.

Harms and Burdens

None of the studies reported on treatment-related adverse events. Participant burden appears to be a concern, with 11 of 61 patients in the relaxation group and 10 of 64 in the control group withdrawing (Fenlon et al., 2008), and 5 of 19 in the relaxation group and 2 of 19 in the electroacupuncture group withdrawing during each study (Nedstrand et al., 2005).

Certainty in the Evidence of Effects

The quality of evidence supporting relaxation therapy or hypnosis was very low. Overall, the evidence was relatively sparse and included trials that had smaller patient samples with unclear or high risk of bias. Interpretations must be made carefully given data sparsity and limitations of the trials.

Other Evidence-to-Decision Criteria and Considerations

The panel noted that relaxation therapy and hypnosis have sustainability constraints requiring a specialty provider and may not be reimbursed by insurance. The panel judged the balance of effects to not favor either the intervention or the control and considered cost as a decision point. Clinicians and patients may have varying views of the acceptability of hypnosis or relaxation therapy. Implementation considerations include standardization of the regimens and whether they can be self-taught or require a specialized clinician.

Conclusions

Limited consistent evidence exists to support a recommendation for hypnosis or relaxation therapy for the management of hot flashes in patients with cancer. Based on the low quality and limitations of evidence, the panel made no recommendation for relaxation therapy or hypnosis and identified these interventions as an evidence gap that warrants additional research in the form of properly powered, well-designed RCTs with adequate endpoints.

Cognitive Behavioral Therapy

Recommendation 12

Among patients with cancer experiencing drug- or surgery-induced hot flashes, the ONS Guidelines panel recommends CBT only in the context of a clinical trial (no recommendation; knowledge gap).

Summary of the Evidence

The NMA identified three studies that addressed this question, one in patients with prostate cancer (Stefanopoulou et al., 2015) and two in patients with breast cancer (Duijts et al., 2012; Mann et al., 2012). Stefanopoulou et al. (2015) included a guided self-help CBT intervention for four weeks, whereas Duijts et al. (2012) and Mann et al. (2012) included group CBT for six weeks in their studies.

Sample sizes ranged from 33 to 109 per arm, and all studies included long-term follow-up (from 24 to 32 weeks).

Benefits

For the outcome of HFF, the evidence with CBT was inconsistent. Duijts et al. (2012) did not find differences in frequency ratings of hot flashes and night sweats between groups of patients with breast cancer, but did see statistically significant improvements over time with CBT for endocrine symptoms and perceived burden of hot flashes and night sweats in this patient population. Mann et al. (2012) found that both groups (CBT and usual care) reported a nonsignificant fewer number of hot flashes and night sweats at 9 weeks (21% reduction in the CBT group and 24% reduction in the usual care group) and 26 weeks (38% reduction in both groups). The authors concluded that CBT and usual care resulted in a 38% reduction in hot flash night sweat frequency compared with baseline values, which represents no therapeutic benefit for this population of patients with breast cancer. For the guided self-help CBT program in patients with prostate cancer (Stefanopoulou et al., 2015), a significant difference between groups in incidence of weekly hot flashes with night sweats was found at six weeks, with greater reductions from baseline observed in the CBT group compared to the usual care group (adjusted $\bar{X}$ difference = 12.12; 95% CI [–22.39, –1.84]). The corresponding value at 32 weeks was –12.43 (95% CI [–28.38, 3.52]). For hot flashes (without night sweats), the adjusted mean differences did not reach statistical significance at either 6 weeks (–4.97; 95% CI [–13.09, 3.14]) or 32 weeks (–12.8; 95% CI [–25.21, –3.86]). The authors concluded that guided self-help CBT appears to be a safe and effective brief treatment for men who have problematic hot flashes with night sweats following prostate cancer treatment.

Additional outcomes such as sleep, depression, and sexual health were assessed in several studies. For sleep, Mann et al. (2012) used the sleep subscale of the Women's Health Questionnaire and found that women receiving CBT demonstrated significantly fewer sleep problems at both 9 weeks ($\bar{X}$ difference favoring CBT = –0.26; 95% CI [–0.39, –0.12]) and 26 weeks ($\bar{X}$ difference favoring CBT = –0.16; 95% CI [–0.29, –0.02]) of follow-up compared to the usual care group.

Mann et al. (2012) also used the Women's Health Questionnaire to assess depression and, at 26 weeks of follow-up, found a reduction in the CBT group (from $\bar{X}$ of 0.23 [SD = 0.16] to $\bar{X}$ of 0.13 [SD = 0.19]) to be significantly greater than the change in the usual care group (from $\bar{X}$ of 0.31 [SD = 0.27] to $\bar{X}$ of 0.28 [SD = 0.26]: $\bar{X}$ difference = –0.13; 95% CI [–0.22, –0.05]). A similar difference was also present earlier in the study at nine weeks. The Hospital Anxiety and Depression Scale (HADS) was used in two studies to assess depression. Stefanopoulou et al. (2015) found no differences between the CBT and usual care groups at either 6 weeks (adjusted $\bar{X}$ difference = –0.59; 95% CI [–1.94, 0.74]) or 32 weeks (adjusted $\bar{X}$ difference = –0.52, 95% CI [–1.15, 2.2]). Duijts et al. (2012) noted that, after six months of treatment, no important differences in psychological distress/depression were observed between CBT plus exercise, CBT alone, exercise alone, or a waitlist control. Based on these studies, conflicting evidence exists regarding the benefits of CBT versus usual care for improvement of depression in either the breast cancer or prostate cancer population.

For sexual health, Duijts et al. (2012) used the Habit and Pleasure subscales of the Sexual Activity Questionnaire (SAQ) and identified statistically significant improvements in sexual function in the CBT plus exercise group compared to the control group at long-term follow-up (effect size = 0.65). Supplemental per protocol analyses also identified important gains in SAQ–Pleasure in the CBT and CBT plus exercise groups.

Harms and Burdens

In the study by Duijts et al. (2012), participant burden appeared to be of concern. High levels of underadherence were observed for all three interventions (group CBT plus exercise, home-based exercise, CBT alone). Fifty-eight percent of the CBT group, 64% of the home-based exercise group, and 70% of the CBT plus exercise group did not meet criteria for adherence (Duijts et al., 2012). No study reported adverse events related to CBT or exercise.

Certainty in the Evidence of Effects

The quality of the evidence supporting CBT was very low. In general, the evidence base was relatively sparse; trials involved relatively small numbers of patients and were judged to be at unclear or high risk of bias. The degree of homogeneity of study populations is difficult to judge because of variable reporting. Interpretation of findings should, therefore, be made cautiously.

Other Evidence-to-Decision Criteria and Considerations

The panel noted that CBT has cost, feasibility, and accessibility constraints compared to other interventions. The panel assumed health equity would probably be reduced because of these constraints.

Conclusions

Limited consistent evidence exists to support a recommendation for CBT for the management of hot flashes in patients with cancer. Based on the very low quality and limitations of evidence, the panel made no recommendation for CBT and identified this intervention as an evidence gap that warrants additional research in the form of properly powered, well-designed RCTs with adequate endpoints.

Physical Activity

Recommendation 13

Among patients with cancer experiencing drug- and surgery-induced hot flashes, the ONS Guidelines panel suggests physical activity interventions (exercise, yoga) over no treatment for management of symptoms (conditional recommendation; low certainty of evidence).

Summary of the Evidence

The NMA identified three studies that addressed this question, all in women with breast cancer (Carson et al., 2009; Cramer et al., 2015; Duijts et al., 2012). Carson et al. (2009) investigated yoga alone, Cramer et al. (2015) investigated yoga plus meditation, and Duijts et al. (2012) investigated a home-based individually tailored exercise program alone, CBT alone, and a combination of CBT plus exercise. Each study included a long-term follow-up of outcomes (3 to 6 months postintervention). Sample sizes ranged from 17 to 109 per study arm, and treatment schedules, length of treatment (8 to 12 weeks), and follow-up (3 to 6 months) varied.

Benefits

For the outcome of HFF, there was evidence supporting benefits in reducing HFF associated with yoga. Carson et al. (2009) found statistically significant improvements in the yoga group both post-treatment (yoga group $\bar{X}$ score change from 20.92 to 14.46 versus control group $\bar{X}$ score change from 23.01 to 25.81) and at the three-month follow-up. For HFS, Carson et al. (2009) identified significant improvements with yoga compared to the control group in daily HFS, as well as frequency and score; in the yoga group, mean HFS improved from 4.16 to 3.21 post-treatment, whereas mean HFS in the control group decreased from 4.67 to 4.41 ($p < 0.01$ for the difference between groups). This pilot study provided promising support for the beneficial effects of a comprehensive yoga program for management of hot flashes in women with breast cancer. Duijts et al. (2012), in a larger trial with 422 participants, demonstrated no difference in HFF at 12 weeks or 6 months follow-up with home-based exercise (12 weeks $\bar{X}$ change = –0.7, effect size = 0.07, $p = 0.668$; 6 months $\bar{X}$ change = 0.24, effect size = 0.02, $p = 0.879$). Combining CBT with physical exercise demonstrated a larger intervention effect at 12 weeks, but the difference failed to reach statistical significance (effect size = 0.44, $p = 0.013$). At six months, this benefit was smaller and not statistically significant (effect size = 0.32, $p = 0.058$).

Additional outcomes, such as sleep, depression, and sexual function, were assessed in these studies. Carson et al. (2009) measured sleep disturbance on a scale from 0 to 9 (higher values denote more sleep disturbance). The yoga group had significant post-treatment improvement in sleep disturbance compared to the control group (reduction from pretreatment $\bar{X}$ of 3.82 to 3.29 in the yoga group compared to pre- and post-treatment $\bar{X}$ of 4.21 and 4.37 in the control group) ($p < 0.01$; 95% CI not reported). This study identified improvements in sleep disturbance attained with yoga compared to no therapy while noting that additional research of interventions in relation to impact on sleep measures is needed. Duijts et al. (2012) also evaluated the Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES) score as the primary endpoint of the trial and hot flash/night sweat problem rating, in addition to quality-of-life questionnaires, and found patients in the exercise group had a significant decrease in levels of endocrine symptoms (FACT-ES $\bar{X}$ change = 4.46 at 12 weeks and 2.67 at 6 months), and they showed an improvement in physical functioning ($\bar{X}$ change = 8.11 at 12 weeks and 7.26 at 6 months on the physical functioning subscale of the SF-36®).

Depression was measured in Cramer et al. (2015) and Duijts et al. (2012) with the HADS scale. Cramer et al. (2015) found no differences between the intervention groups for depression at 12 weeks ($\bar{X}$ difference = –0.7; 95% CI [–1.7, 0.3]) or 24 weeks ($\bar{X}$ difference = 0.1; 95% CI [–0.8, 1]). Changes from baseline were of small magnitude in each group. In the Duijts et al. (2012) study, no important differences in psychological distress or depression were observed between groups at six months. Based on this study, the authors concluded that exercise alone offered no benefits in psychological distress or depression compared to a waitlist control. For the outcome of sexual function, Duijts et al. (2012) included the habit and pleasure subscales of the SAQ and identified that exercise offered modest improvements compared to a waitlist control. An improvement in sexual function (SAQ–Habit) in the exercise group compared to the control group at long-term follow-up (effect size = 0.15) was noted.

Harms and Burdens

Overall, yoga and home-based physical activity were well tolerated and acceptable to patients. No serious adverse events were noted in the studies, with only Cramer et al. (2015) noting minor adverse events that were similar in both intervention and control groups. The adherence rate in the Dujits et al. (2012) study was very low for the intervention groups, including physical exercise.

Certainty in the Evidence of Effects

The quality of the evidence supporting physical activity interventions for the management of hot flashes was low. The panel recognized the low certainty of evidence, but noted a meaningful benefit to patients' quality of life, as documented by patient-reported outcomes and measured by a validated instrument. The panel also recognized that physical activity includes trivial harms and is accessible to patients.

Other Evidence-to-Decision Criteria and Considerations

The panel considered the resources required for physical activity interventions and judged them to be moderate. In addition, accessibility varies by location and training of instructors, so the impact on health equity was considered.

The panel determined that the balance of effects favors the intervention because of the meaningful benefits on quality of life, which were patient-reported outcomes measured by validated instruments. The panel judged that exercise was acceptable and feasible to most patients.

Conclusions

The panel determined that there was emerging evidence to support a recommendation of physical activity (yoga or general physical activity) for the management of hot flashes in patients with cancer. The panel acknowledged that studies did show a benefit from physical activity and that the adverse event profile was low. Based on this emerging evidence, the guideline panel made a conditional recommendation to suggest physical activity interventions (exercise, yoga) over no treatment for the management of hot flashes.

Acupuncture or Electroacupuncture

Recommendation 14

Among patients with cancer experiencing drug- or surgery-induced hot flashes, the ONS Guidelines panel recommends acupuncture and electroacupuncture only in the context of a clinical trial (no recommendation; knowledge gap).

Summary of the Evidence

The NMA identified eight studies that addressed this question, one in men (Frisk et al., 2009) and seven in women (Bao et al., 2014; Bokmand & Flyger, 2013; Deng et al., 2007; Hervik & Mjåland, 2009; Lesi et al., 2016; Liljegren et al., 2012; Mao et al., 2015). Five of the trials (Bao et al., 2014; Bokmand & Flyger, 2013; Deng et al., 2007; Hervik & Mjåland, 2009; Liljegren et al., 2012) compared acupuncture to sham acupuncture in women with a history of breast cancer, and the others compared acupuncture to electroacupuncture (Frisk et al., 2009), enhanced self-care (Lesi et al., 2016), and gabapentin (Mao et al., 2015). Sample sizes ranged from 15 to 105 per study arm and treatment schedules varied by frequency (once or twice a week) and length of treatment (4 to 12 weeks).

Benefits

For reducing HFF, there was limited evidence supporting acupuncture and electroacupuncture when compared to sham acupuncture. Hervik and Mjåland (2009) and Bokmand and Flyger (2013) identified statistically significant improvements with acupuncture when compared to sham acupuncture, whereas, in the other studies (Bao et al., 2014; Deng et al., 2007; Liljegren et al., 2012), results were equivocal. In the Hervik and Mjåland (2009) study, daytime hot flashes were significantly reduced in the acupuncture group (from a baseline $\bar{X}$ of 9.5 (SD = 4.9) to 4.7 (SD = 3.7) at 10 weeks, which further reduced to 3.2 (SD = 2.2) during the next 12 weeks), whereas no significant change was seen within the sham acupuncture group (from a baseline $\bar{X}$ of 12.3 [SD = 7.3] to 11.7 [SD = 8.5] at 10 weeks, which increased to 12.1 [SD = 8.3] during the next 12 weeks). Similar patterns were reported for nighttime hot flashes. The difference in acupuncture versus sham acupuncture was statistically significant for both daytime and nighttime HFS (Hervik & Mjåland, 2009). In the Bokmand and Flyger (2013) study, 52% of patients in the acupuncture group experienced a significant reduction in hot flashes compared with 24% in the sham acupuncture group ($p < 0.05$). In the equivocal studies, Liljegren et al. (2012) found 42% of patients who received true acupuncture reported improvements in hot flashes compared to 47% in a sham acupuncture group. In the Deng et al. (2007) study, acupuncture was associated with 0.8 fewer hot flashes per day compared to sham acupuncture. Bao et al. (2014) found significant

improvements in real acupuncture and sham acupuncture for quality of life, daily interference of hot flashes, and menopausal symptoms.

Additional outcomes, such as sleep and depression, were assessed in one study. Bao et al. (2014) assessed sleep quality and sleep disturbance using the PSQI and found no difference between acupuncture and sham acupuncture groups at 4, 8, and 12 weeks. The same study also assessed depression with the CES-D scale. After eight weeks, reported median changes in both the acupuncture group (reduction from median of 16 [IQR = 9] at baseline to a median of 10 [IQR = 10.5]) and sham acupuncture group (reduction from median of 10.5 [IQR = 10] at baseline to 6 [IQR = 11.25]) showed important changes within each group that reached statistical significance, whereas the difference between groups did not ($p = 0.44$). For depression, acupuncture and sham acupuncture both improved depressive symptoms, with little difference between the two interventions (Bao et al., 2014).

Several studies comparing acupuncture to active control could not be included in the NMA but were considered separately. Lesi et al. (2016) compared acupuncture with and without enhanced self-care (including diet, physical exercise, and psychological support). After having comparable mean hot flash scores at baseline, the score at week 12 was higher in the enhanced self-care group ($\bar{X}$ = 22.7 [SD = 19.4]) than in the acupuncture and enhanced self-care group ($\bar{X}$ = 11.34 [SD = 14.75], $p < 0.001$). Similar mean differences favoring the acupuncture and enhanced self-care group were seen at both three-month (–7.86; 95% CI [–12.99, –2.73]) and six-month follow-ups (–8.82; 95% CI [–14.04, –3.61]). The authors concluded that acupuncture combined with enhanced self-care is an effective intervention for managing hot flashes. Mao et al. (2015) compared patients with breast cancer experiencing bothersome hot flashes (at least twice a day) to electroacupuncture or gabapentin with a sham/placebo control for each. At week 8, participants in the two active treatment groups (electroacupuncture and gabapentin) experienced 47.8% and 39.4% improvement in hot flashes, respectively, when compared with baseline, whereas participants in the sham acupuncture and placebo medication groups experienced 45% and 22.3% improvement, respectively. At 24 weeks from random assignment, group differences were observed, with the electroacupuncture group having the largest long-term effect (–8.5 change from baseline), followed by sham acupuncture (–6.1 change from baseline), medication placebo (–4.6 change from baseline), and gabapentin (–2.8 change from baseline) ($p < 0.001$) (Mao et al., 2015). In men with prostate cancer and hot flashes, Frisk et al. (2009) compared acupuncture to electroacupuncture and found the numbers of hot flashes per 24 hours decreased significantly in both groups from baseline to 4 weeks of treatment and remained

FIGURE 1. Research Priorities and Rationales Identified by the ONS Guidelines™ Panel

Recommended Methods for Research on Hot Flashes

Priority: Methodology recommendations

- Develop validated tools to assess hot flashes.
- Design rigorous research studies (randomized controlled trials with well-controlled placebo groups).
- Assess hot flash interventions for secondary endpoints, such as sleep.
- Identify the appropriate duration of treating hot flashes with antidepressant drugs and how to taper when stopping.
- Follow study participants for sufficiently long periods to assess if benefits are sustained, and to determine any long-term side effects.
- Report outcomes (depression, sleep, sexual function, quality of life) consistently across studies with validated measures.
- Initiate research studies for managing hot flashes in patients with cancer diagnoses other than breast or prostate cancer.

Interventions for Hot Flashes Requiring Additional Research

Physical activity

- Evidence is emerging on physical activity as an intervention to treat hot flashes. Because this is within the scope of nursing and easy to implement at the clinical level, additional research is warranted.

Men experiencing hot flashes

- Additional research is needed on pharmacologic and nonpharmacologic interventions for men experiencing hot flashes.
- Research to understand the underlying physiology of androgen deprivation therapy–associated hot flashes in men with cancer is warranted.

Cognitive behavioral therapy

- Additional research is needed on the components of cognitive behavioral therapy that are effective, show cost effectiveness, and show sustainability.

Hypnosis/relaxation therapy

- Additional research to compare hypnosis/relaxation therapy to no or other therapies. Studies in both men and women would be important.

ONS—Oncology Nursing Society

SUPPLEMENTARY MATERIAL AVAILABLE ONLINE

Additional supplementary material for this article can be accessed at https://bit.ly/2x0s94v. Items include a summary of findings table, information by outcome on studies not pooled into this analysis, evidence profiles, and evidence-to-decision framework tables.

at this decreased level until 12 months after the start of treatment in the electroacupuncture group (when hot flashes tended to increase). There was no significant difference between the groups over time ($p = 0.25$; ANOVA) (Frisk et al., 2009).

Harms and Burdens

Acupuncture and electroacupuncture were well tolerated in the reported studies. No serious adverse events were reported. For studies that did report adverse events, only minor or very minor events were reported. Because these interventions are generally not a covered procedure with most insurance for this indication, the out-of-pocket expense of these interventions may be burdensome.

Certainty in the Evidence of Effects

The quality of evidence supporting acupuncture or electroacupuncture was very low because of imprecision and risk of bias. Overall, the evidence was inconsistent and included trials that had smaller patient samples with unclear or high risk of bias. In addition, variable reporting made the degree of homogeneity of study populations difficult to judge; therefore, interpretation of findings should be made cautiously.

Other Evidence-to-Decision Criteria and Considerations

The panel considered the resources required for acupuncture or electroacupuncture and judged them to be moderate. In addition, accessibility varies by location and training of acupuncturists and the impact on health equity was considered. Acupuncture or electroacupuncture would be contraindicated in patients who are immunocompromised and, therefore, may not be feasible for all patients.

Conclusions

The panel determined that there was limited consistent evidence to support a recommendation of acupuncture or electroacupuncture for the management of hot flashes in patients with cancer. The panel acknowledged that some studies did show a benefit from acupuncture and that the adverse event profile was low. Based on the inconsistent evidence, the guideline panel made no recommendation for acupuncture or electroacupuncture and identified this area as an evidence gap that warrants additional research in the form of properly powered, well-designed RCTs with adequate endpoints.

Discussion

Other Guidelines on Hot Flashes

Several national guidelines exist for hot flashes, some for patients with cancer and some for a general population of women. The methodology of evidence synthesis and appraisal vary among them. For pharmacologic recommendations, there is consensus among the guidelines that antidepressants (selective serotonin reuptake inhibitors [SSRIs]) are effective for women with or without cancer or men with cancer who are experiencing hot flashes.

Discrepancy among guideline recommendations exists with venlafaxine for men with cancer and for gabapentin or pregabalin for men or women. NCCN (2019) survivorship guidelines and the American Cancer Society (Skolarus et al., 2014) both recommend venlafaxine for men with cancer, whereas the ONS Guidelines panel recommends it only in the context of a clinical trial. Other guidelines (NCCN, 2019; North American Menopause Society, 2017; Runowicz et al., 2016; Skolarus et al., 2014) recommend gabapentin or pregabalin for hot flashes for men or women (with cancer or in a general population), whereas the ONS Guidelines panel did not recommend gabapentinoids. The ONS Guidelines panel considered the side effect profile of gabapentinoids when making this decision. The studies reviewed for this guideline, as well as recent reports, identify serious side effects of gabapentinoids, including breathing difficulties, for patients on other medications that depress the central nervous system, such as opioid pain medicines or in patients with comorbidities such as chronic obstructive pulmonary disease as well as in older adults (U.S. Food and Drug Administration, 2019). The ONS Guidelines panel considered that many patients with cancer are older, have comorbidities, and may be on concurrent medications that would place them at risk for side effects from gabapentinoids. With other options available, the panel made the decision not to recommend gabapentinoids.

For dietary interventions, consensus was consistent among guidelines that dietary interventions were not recommended (Cobin & Goodman, 2017; North American Menopause Society, 2017), including the

ONS Guidelines panel recommendation. The ONS Guidelines panel recommended hypnosis/relaxation therapy, CBT, and acupuncture or electroacupuncture only in the context of a clinical trial. The NCCN (2019) and the North American Menopause Society (2017) both recommend hypnosis/relaxation therapy as well as CBT, with the evidence base for NCCN in patients with cancer and the North American Menopause Society in a general population of women. For physical activity, the ONS Guidelines panel recommends physical activity/yoga for men and women with cancer, which is consistent with the NCCN survivorship guidelines (NCCN, 2019) and American Society of Clinical Oncology breast cancer survivorship guidelines (Runowicz et al., 2016), but differs from the North American Menopause Society (2017), which does not recommend physical activity or yoga for hot flashes for women in a general population.

The other guidelines on hot flashes differed in scope and methods from the current ONS Guidelines. Apparent in the current review, as well as in other guidelines, is the lack of evidence with which to base clinical decisions, particularly for men with cancer treatment–related hot flashes and for men or women who are interested in nonpharmacologic interventions for the treatment of hot flashes. Therefore, the ONS Guidelines panel used the GRADE approach to consider additional dimensions that inform healthcare decision-making: patients' values and preferences, resource use, equity, acceptability, and feasibility. Many of the studies included short observation periods, and the long-term efficacy as well as toxicities of these interventions are not well known. The ONS Guidelines panel identified gaps in evidence during the development of this guideline. Several priorities for future research were identified and are listed in Figure 1.

Clinical Implications

Hot flashes as a result of surgery or systemic therapy for cancer are a common and often distressing side effect for patients. This ONS Guidelines panel employed a rigorous methodology to evaluate the research literature and considered relevant factors to make informed recommendations for treatment. The clinical implications include:

- Patients often experience hot flashes for a long time before seeking treatment.
- Clinicians need to assess for hot flashes in patients who are at risk and discuss treatment options.
- Patients should be informed that evidence-based interventions to treat hot flashes in patients with cancer exist, and patients who are experiencing this distressing side effect have options to consider.

Medications, particularly antidepressants, are an appropriate consideration for many, but not all patients. These medications do have associated side effects and adverse events. Although most antidepressants studied have reasonable side effect profiles, medication interactions and patient history are important components of a shared decision-making process to identify the appropriate treatment. Antidepressants may not work immediately, and patients may need to take them for six to eight weeks to see a benefit. Clinicians should support and educate patients about the duration of time needed to see benefit and encourage patients not to stop treatment too soon. Although antidepressants can be effective, paroxetine and some other SSRIs that inhibit CYP2D6 are contraindicated in women and men who are treated with tamoxifen. The ONS Guidelines panel did not recommend gabapentinoids because of the limited benefit and side effect profile. As the evidence continues to evolve, guideline panels will continue to review the relevant literature to make evidence-based recommendations to support clinical practice.

Although most of the research on hot flashes in patients with cancer has been in women with breast cancer or men with prostate cancer, patients with other cancer diagnoses may experience this side effect and clinicians should assess patients at risk and offer interventions as appropriate. Nurses and other healthcare professionals need to know which patients are at risk for hot flashes and assess if hot flashes are present as well as their degree of frequency, severity, and level of interference with quality of life.

Marcelle Kaplan, MS, RN, CNS, is an oncology nursing consultant in Merrick, NY; **Pamela K. Ginex, EdD, RN, OCN®,** is the senior manager of evidence-based practice and inquiry at the Oncology Nursing Society in Pittsburgh, PA; **Laura B. Michaud, PharmD, BCOP, FASHP, CMQ,** is the associate director of quality and safety in the Division of Pharmacy at the University of Texas MD Anderson Cancer Center in Pearland; **Paz Fernández-Ortega, PhD, MSc, RN,** is a nursing research coordinator and an associate professor of nursing at the Institut Català d'Oncologia in Barcelona, Spain; **Dale Grimmer, MS, RN, AOCN®, CCRC,** is a clinical research nurse at Ascension St. Elizabeth Hospital in Neenah, WI; **Jessica Bay Leibelt, MSN, NP-C, AOCNP®,** is a nurse practitioner at Moffitt Cancer Center in St. Petersburg, FL; **Suzanne Mahon, DNSc, RN, AOCN®, AGN-BC,** is a professor in the Department of Internal Medicine in the Division

of Hematology/Oncology and an oncology professor in the School of Nursing at Saint Louis University in MO; **Bernardo L. Rapoport, Dip in Med (UBA), MMed,** is a consultant medical oncologist at the Medical Oncology Centre in Rosebank, South Africa, and an extraordinary professor in the Department of Immunology, Faculty of Health Sciences, at the University of Pretoria in Pretoria, South Africa; **Valencia Robinson, EdS,** is a patient advocate at the Florida Breast Cancer Foundation in Daytona Beach; **Christine Maloney, BA,** was, at the time of this writing, an archivist, **Kerri A. Moriarty, MLS,** is a research specialist, and **Mark Vrabel, MLS, AHIP, ELS,** was, at the time of this writing, an information resources supervisor, all at the Oncology Nursing Society; and **Rebecca L. Morgan, PhD, MPH,** is an assistant professor in the Department of Health Research Methods, Evidence and Impact at McMaster University in Hamilton, Canada. Ginex can be reached at pginex@ons.org, with copy to ONFEditor@ons.org. (Submitted January 2020. Accepted January 21, 2020.)

The authors gratefully acknowledge Brian Hutton, MSc, PhD, and his team at the Ottawa Hospital Research Institute for their collaboration and assistance in using the network meta-analysis data for this guideline. The authors also thank Behnam Sadeghirad, PhD, PharmD, MPH, for his help in preparing the network meta-analysis for presentation at the guideline panel meeting.

Development of this guideline was wholly funded by the Oncology Nursing Society, a nonprofit organization that represents oncology nurses. ONS staff supported panel appointment and coordinated meetings but had no role in guideline question identification or voting on recommendations. Members of the guideline panel received travel reimbursement to attend one in-person meeting at ONS headquarters in Pittsburgh, PA. No honoraria were provided.

Kaplan, Ginex, Michaud, Mahon, Rapoport, Robinson, and Morgan contributed to the conceptualization and design. Kaplan, Ginex, Fernández-Ortega, Mahon, Robinson, Maloney, Moriarty, and Morgan contributed to the data collection. Ginex, Fernández-Ortega, and Morgan provided statistical support. Kaplan, Ginex, Fernández-Ortega, Grimmer, Bay, Mahon, Moriarty, and Morgan provided the analysis. Kaplan, Ginex, Michaud, Fernández-Ortega, Grimmer, Mahon, Rapoport, Robinson, Vrabel, and Morgan contributed to the manuscript preparation.

REFERENCES

Balshem, H., Helfand, M., Schünemann, H.J., Oxman, A.D., Kunz, R., Brozek, J., . . . Norris, S. (2011). GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology, 64*(4), 401–406. https://doi.org/10.1016/j.jclinepi.2010.07.015

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.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

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.

Carpenter, J.S. (2001). The Hot Flash Related Daily Interference Scale: A tool for assessing the impact of hot flashes on quality of life following breast cancer. *Journal of Pain and Symptom Management, 22*(6), 979–989.

Carpenter, J.S. (2005). State of the science: Hot flashes and cancer, part 1: Definition, scope, impact, physiology, and measurement. *Oncology Nursing Forum, 32*(5), 959–968. https://doi.org/10.1188/05.ONF.959-968

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

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.

Cobin, R.H., & Goodman, N.F. (2017). American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause—2017 update. *Endocrine Practice, 23*(7), 869–880. https://doi.org/10.4158/EP171828.PS

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

Dalal, S., & Zhukovsky, D.S. (2006). Pathophysiology and management of hot flashes. *Journal of Supportive Oncology, 4*(7), 315–320, 325.

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. & Caldwell, D.M. (2019). Network meta-analysis explained. *Archives of Disease in Childhood–Fetal and Neonatal Edition, 104,* F8–F12. https://doi.org/10.1136/archdischild-2018-315224

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*(22), 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. *Journal of Clinical Oncology, 26*(31), 5022–5026. https://doi.org/10.1200/JCO.2008.16.6389

Fenlon, D. (1999). Relaxation therapy as an intervention for hot flushes in women with breast cancer. *European Journal of Oncology Nursing, 3*(4), 223–231.

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.jpainsymman.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 treatment of hot flashes in cancer. *CA: A Cancer Journal for Clinicians, 63*(3), 167–192. https://doi.org/10.3322/caac.21171

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

Goetz, M.P., Sangkuhl, K., Guchelaar, H.J., Schwab, M., Province, M., Whirl-Carrillo, M., . . . Klein, T.E. (2018). Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and tamoxifen therapy. *Clinical Pharmacology and Therapeutics, 103*(5), 770–777. https://doi.org/10.1002/cpt.1007

Guyatt, G., Oxman, A.D., Akl, E.A., Kunz, R., Vist, G., Brozek, J., . . . Norris, S. (2011). GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology, 64*(4), 383–394. https://doi.org/10.1016/j.jclinepi.2010.04.026

Guyatt, G.H., Oxman, A.D., Kunz, R., Atkins, D., Brozek, J., Vist, G., . . . Schünemann, H.J. (2011). GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology, 64*(4), 395–400. https://doi.org/10.1016/j.jclinepi.2010.09.012

Guyatt, G.H., Oxman, A.D., Sultan, S., Glasziou, P., Akl, E.A., Alonso-Coello, P., . . . Schünemann, H.J. (2011). GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology, 64*(12), 1311–1316. https://doi.org/10.1016/j.jclinepi.2011.06.004

Hanisch, L.J., Palmer, S.C., Marcus, S.C., Hantsoo, L., Vaughn, D.J., & Coyne, J.C. (2009). Comparison of objective and patient-reported hot flash measures in men with prostate cancer. *Journal of Supportive Oncology, 7*(4), 131–135.

Hernández-Muñoz, G., & Pluchino, S. (2003). Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer. *Maturitas, 44*(Suppl. 1), 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,* 311–316.

Hutton, B., Hersi, M., Cheng, W., Pratt, M., Barbeau, P., Mazzarello, S., . . . Clemons, M. (2020). Comparing interventions for management of hot flashes in patients with breast and prostate cancer: A systematic review with meta-analyses. *Oncology Nursing Forum, 47*(4), 1–21.

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 pharmacologics 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

Indiana University. (2020). Drug interactions Flockhart Table™. https://drug-interactions.medicine.iu.edu/MainTable.aspx

Institute of Medicine. (2011). *Clinical practice guidelines we can trust*. National Academies Press. https://nap.edu/catalog/13058/clinical-practice-guidelines-we-can-trust

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.

Jones, J.M., Kohli, M., & Loprinzi, C.L. (2012). Androgen deprivation therapy–associated vasomotor symptoms. *Asian Journal of Andrology, 14*(2), 193–197. https://doi.org/10.1038/aja.2011.101

Kadakia, K.C., Loprinzi, C.L., & Barton, D.L. (2012). Hot flashes: The ongoing search for effective interventions. *Menopause, 19*(7), 719–721. https://doi.org/10.1097/gme.0b013e3182578d31

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.M. (2013). Tamoxifen benefits and CYP2D6 testing in women with hormone receptor-positive breast cancer. *Clinical Journal of Oncology Nursing, 17*(2), 174–179. https://doi.org/10.1188/13.CJON.174-179

Kelly, C.M., Juurlink, D.N., Gomes, T., Duong-Hua, M., Pritchard, K.I., Austin, P.C., & Paszat, L.F. (2010). Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: A population based cohort study. *BMJ, 340*, c693. https://doi.org/10.1136/bmj.c693

Kimmick, G.G., Lovato, J., McQuellon, R., Robinson, E., & Muss, H.B. (2006). Randomized, double-blind, placebo-controlled, crossover study of sertraline 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

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

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*, 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., & Barton, D.L. (2009). Gadgets for measuring hot flashes: Have they become the gold standard? *Journal of Supportive Oncology, 7*(4), 136–137.

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., Nelimark, R.A., . . . 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.

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

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.

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

Morrow, P.K.H., Mattair, D.N., & Hortobagyi, G.N. (2011). Hot flashes: A review of pathophysiology and treatment modalities. *Oncologist, 16*(11), 1658–1664.

National Comprehensive Cancer Network. (2019). *NCCN Clinical Practice Guidelines in Oncology* (*NCCN Guidelines®*): *Survivorship* [version 2.2019]. https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf

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

North American Menopause Society. (2017). The 2017 hormone therapy position statement of the North American Menopause Society. *Menopause, 24*(7), 728–753.

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.

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.

Reeves, K.W., Pennell, M., Foraker, R.E., Crandall, C.J., Stefanick, M., & Paskett, E.D. (2018). Predictors of vasomotor symptoms among breast cancer survivors. *Journal of Cancer Survivorship, 12*(3), 379–387. https://doi.org/10.1007/s11764-018-0677-9

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. *Journal of Clinical Oncology, 34*(6), 611–635. https://doi.org/10.1200/JCO.2015.64.3809

Schünemann, H.J., Al-Ansary, L.A., Fortand, F., Kersten, S., Komauainen, J., Kopp, I.B., . . . Qaseem, A. (2015). Guidelines International Network: Principles for disclosure of interests and management of conflicts in guidelines. *Annals of Internal Medicine, 163*(7), 548–553. https://doi.org/10.7326/M14-1885

Schünemann, H.J., Wiercioch, W., Etxeandia, I., Flavigna, M., Santesso, N., Mustafa, R., . . . Akl, E.A. (2014). Guidelines 2.0: Systematic development of a comprehensive checklist for a successful guideline enterprise. *Canadian Medical Association Journal, 186*(3), E123–E142. https://doi.org/10.1503/cmaj.131237

Shanafelt, T.D., Barton, D.L., Adjei, A.A., & Loprinzi, C.L. (2002). Pathology and treatment of hot flashes. *Mayo Clinic Proceedings, 77*(11), 1207–1218. https://doi.org/10.4065/77.11.1207

Skolarus, T.A., Wolf, A.M.D., Erb, N.L., Brooks, D.D., Rivers, B., Underwood, W., . . . Cowens-Alvarado, R.L. (2014). American Cancer Society prostate cancer survivorship care guidelines. *CA: A Cancer Journal for Clinicians, 64*(4), 225–249.

Sloan, J.A., Loprinzi, C.L., Novotny, P.J., Barton, D.L., LaVasseur, B.I., & Windschitl, H. (2001). Methodologic lessons learned from hot flash studies. *Journal of Clinical Oncology, 19*(23), 4280–4290. https://doi.org/10.1200/JCO.2001.19.23.4280

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

U.S. Food and Drug Administration. (2019). 12-19-2019 FDA drug safety communication. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). https://bit.ly/2JzHJqm

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.

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.

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.

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