ONLINE EXCLUSIVE

Management of Androgen Deprivation Therapy–Associated Hot Flashes in Men With Prostate Cancer

Yousef Qan'ir, MS, Darrell DeDeaux, MNP, Paul A. Godley, MD, PhD, MPP, Deborah K. Mayer, PhD, RN, AOCN®, FAAN, and Lixin Song, PhD

PROBLEM IDENTIFICATION: To determine best practices for managing hot flashes associated with androgen deprivation therapy (ADT) in men with prostate cancer.

LITERATURE SEARCH: The CINAHL®, Embase®, PsycINFO®, PubMed®, and Scopus® databases were used to identify randomized controlled trials (RCTs) and quasiexperimental studies published between January 1994 and June 2018.

DATA EVALUATION: Using the *Cochrane Handbook for Systematic Reviews of Interventions*, the authors reviewed 15 studies examining the effects of pharmacologic or complementary and alternative medicine interventions on ADT-associated hot flashes in men with prostate cancer.

SYNTHESIS: Pharmacologic interventions (e.g., cyproterone, medroxyprogesterone, megestrol acetate) showed some promise for reducing hot flashes but were associated with side effects and risks. Acupuncture demonstrated potential benefit in reducing hot flashes without side effects.

IMPLICATIONS FOR RESEARCH: Evidence is insufficient to support interventions for ADT-associated hot flashes in men with prostate cancer. Future RCTs should be sufficiently powered, include a control group, and use standardized outcome measures.

KEYWORDS androgen deprivation therapy; complementary and alternative medicine; hot flashes
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More than 3 million men are living with or have survived prostate cancer. With an estimated 165,000 new individuals diagnosed with prostate cancer in 2018, 98.2% are expected to live for at least five years after diagnosis (National Cancer Institute, n.d.). Androgen deprivation therapy (ADT) is the first line of treatment for advanced-stage prostate cancer and can be administered before, during, or after radiation therapy (Nevedomskaya, Baumgart, & Haendler, 2018). ADT-associated side effects are well documented and include loss of libido, sexual dysfunction, fatigue, enlarged breasts, anemia, osteoporosis, mood symptoms, and hot flashes (Siddiqui & Krauss, 2018). The side effects of ADT may be debilitating and cause patients to stop ADT treatment (Crawford et al., 2019).

A hot flash is the intense sensation of heat accompanied by diaphoresis and flushing. These recurrent episodes can be transient or last as long as 20 minutes (Jones, Kohli, & Loprinzi, 2012). Hot flashes affect almost 80% of men with prostate cancer who undergo ADT (Vitolins et al., 2013), with nearly half of these patients continuing to experience them for five years following treatment. Most men reported that hot flashes still continued after cessation of treatment with the same frequency and duration as when treatment was initiated (Baum & Torti, 2007). The experience of hot flashes may lead to a decrease in quality of life (QOL) among men with prostate cancer and can result in early discontinuation of treatment (Ahmadi & Daneshmand, 2014). However, lack of evidence exists for best practices in managing ADT-associated hot flashes (Jones et al., 2012). In this integrative review, the effects of existing pharmacologic and complementary and alternative medicine (CAM) interventions on ADT-associated

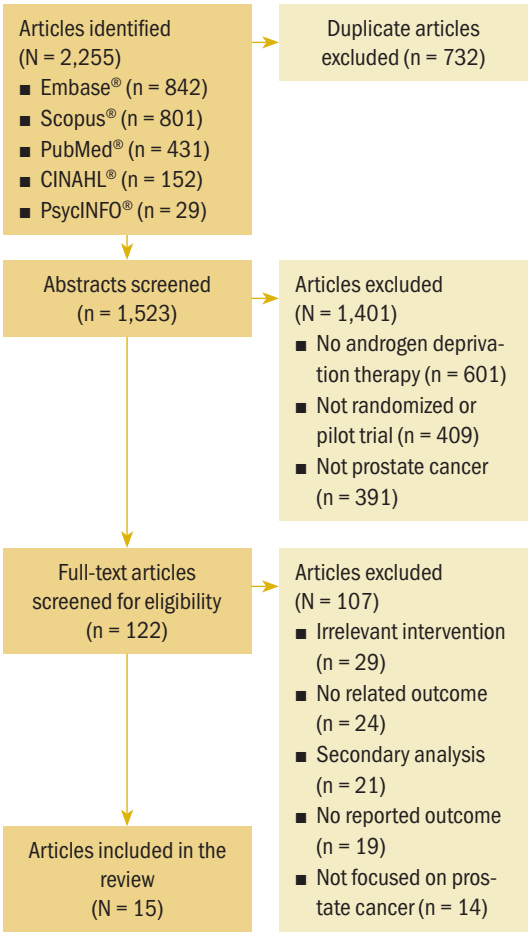
hot flashes among men with prostate cancer will be evaluated.

Methods

Literature Search

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used for the integrative review process. Through a search of the CINAHL®, Embase®, PsycINFO®, PubMed®, and Scopus® databases, randomized controlled trials (RCTs) and quasiexperimental studies published in English were identified. A roughly 25-year span (1994–2018) was searched to maximize the number of studies available for review. Search terms were (*prostate cancer* OR *prostatic neoplasms*) AND (*androgen deprivation* OR *androgen suppression* OR *hormone* OR *gonadotropin*) AND (*hot flash* OR *hot flush* OR *vasomotor symptoms*). Medical subject heading (MeSH) terms related to pharmacologic action and alternative medicine were used, as were alternative vocabulary and syntax adjusted across databases. The authors also searched by hand to include as many studies as possible.

FIGURE 1. Flow Chart of Search Strategy and Selection Process



Two of the current authors individually reviewed and evaluated the articles by title and abstract to determine if they met the following inclusion criteria:

- Used RCT or quasiexperimental design
- Evaluated an intervention for treatment of ADT-associated hot flashes in men with prostate cancer
- Reported hot flash–related outcomes, such as change in hot flash score (HFS) or daily hot flash frequency (DHF); HFS is used to estimate the overall hot flash burden and is obtained by summing the daily number of hot flashes and multiplying this number by the severity of each hot flash, which is rated from 1 (not at all severe) to 10 (extremely severe).
- Included an intervention classified as pharmacologic or CAM

Studies were excluded if they had the following characteristics:

- The results were not stratified by cancer type when non–prostate cancer populations were included.
- Estrogen, estrogen derivatives, or combinations of medications were used in the intervention.

In the current review, studies of the effects of newer medications that are generally used as second-line therapies for management of hot flashes in men with prostate cancer (e.g., abiraterone, enzalutamide) were excluded. In studies using CAM, the authors focused on natural products (e.g., herbs) and mind and body practices (e.g., acupuncture), as recommended by the National Center for Complementary and Integrative Health. The authors obtained and reviewed the full texts of studies meeting the inclusion criteria.

Data Extraction and Data Synthesis

The *Cochrane Handbook for Systematic Reviews of Interventions* was used as a guide to properly extract appropriate data from the eligible studies (Higgins et al., 2011). Data on study design, sample size, intervention characteristics, baseline and outcome measures, and results were extracted. One author extracted the data, and three authors verified the extracted data; disagreements were resolved among members of the research team.

Using Cochrane risk of bias tool criteria, the authors assessed and rated each study's quality,

rating randomization, blinding of personnel and outcome assessment, allocation concealment, completeness of outcome data, and selective reporting as low, high, or unclear. A study was rated as having a low risk of bias if all criteria were met, a high risk of bias if at least one of the criteria was not met, or an unclear risk if at least one of the criteria was unclear (Higgins et al., 2011).

Results

From the authors' thorough search of five databases, 2,255 articles were identified (see Figure 1). After removing 732 duplicate articles, 1,523 abstracts were screened for study eligibility. A total of 1,401 articles in which ADT treatment was not used, study design was nonexperimental, or patients were not diagnosed with prostate cancer were excluded. The full articles of 122 potentially eligible studies were reviewed; of these, 107 were excluded because they did not use pharmacologic or CAM interventions as defined in this review, did not report hot flash–related study outcomes, were secondary analyses, or were not focused on prostate cancer. Overall, 15 studies (7 RCTs and 8 quasiexperimental studies) that met the eligibility criteria were included in the review (see Table 1).

Intervention Characteristics

The intervention period ranged from 4 to 12 weeks. Fourteen studies exclusively enrolled men, although one study enrolled men and women but reported intervention results stratified by gender (Loprinzi, Michalak, et al., 1994). Sample sizes ranged from 7 to 311 (median = 22, $\bar{X}$ = 64). Nine studies had a high risk of bias (Frisk, Spetz, Hjertberg, Petersson, & Hammar, 2009; Hammar et al., 1999; Loprinzi et al., 2004; Naoe et al., 2006; Quella et al., 1999; Rich, Porter, Ricks-Santi, Milshtein, & Corbin, 2017; Stefanopoulou, Yousaf, Grunfeld, & Hunter, 2015; Vandecasteele et al., 2012; Vitolins et al., 2013); four studies had an unclear risk of bias (Ashamalla, Jiang, Guirguis, Peluso, & Ashamalla, 2011; Beer et al., 2010; Loprinzi, Goldberg, et al., 1994; Loprinzi, Michalak, et al., 1994); and two had a low risk of bias (Irani, Salomon, Oba, Bouchard, & Mottet, 2010; Loprinzi et al., 2009). All studies had a low risk of bias regarding completeness of outcome data and selective reporting criteria (see Table 2); however, almost half of the studies had a high risk of bias regarding blinding of personnel, allocation concealment, and random sequence generation. The two studies with an overall low risk of bias were double-blind RCTs reporting the effects of pharmacologic interventions (Irani et al., 2010; Loprinzi et al., 2009).

Pharmacologic Interventions

Eight studies examined the effects of pharmacologic interventions, including steroidal progestin (Irani et al., 2010; Loprinzi, Michalak, et al., 1994); serotonin and norepinephrine reuptake inhibitors (SNRIs) (Irani et al., 2010; Quella et al., 1999; Vitolins et al., 2013); selective serotonin reuptake inhibitors (SSRIs) (Loprinzi et al., 2004; Naoe et al., 2006); anticonvulsants (Loprinzi et al., 2009); and antihypertensives (Loprinzi, Goldberg, et al., 1994) on reducing hot flashes among men with prostate cancer. The efficacy of steroidal progestins, including megestrol acetate, cyproterone acetate, and medroxyprogesterone acetate, were evaluated in two RCTs (Irani et al., 2010; Loprinzi, Michalak, et al., 1994); these two studies produced similar results demonstrating significant reductions in HFS. Megestrol acetate reduced HFS by 85% compared to a placebo ($p < 0.001$) (Loprinzi, Michalak, et al., 1994). Cyproterone acetate reduced HFS by 100% ($p < 0.0001$) after two months when patients were given 75 mg daily for eight weeks and 37.5 mg daily for two weeks (Irani et al., 2010). Medroxyprogesterone reduced HFS by 97.3% ($p < 0.0001$) after two months when patients were given 20 mg daily for 10 weeks (Irani et al., 2010). However, no statistical difference was found in mean daily HFS between cyproterone and medroxyprogesterone at weeks 4, 8, and 12 ($p > 0.2$) (Irani et al., 2010).

The efficacy of venlafaxine (an SNRI) was evaluated in two RCTs (Irani et al., 2010; Quella et al., 1999). In Irani et al.'s (2010) study, two steroidal progestins (cyproterone and medroxyprogesterone) were each compared to a high dose of venlafaxine (75 mg daily). The median HFS improved for all three drugs at each time point ($p < 0.0001$) except between weeks four and eight for venlafaxine ($p = 0.4$). Compared to venlafaxine, the mean daily HFS of cyproterone improved at 4 ($p < 0.0001$), 8 ($p = 0.0122$), and 12 weeks ($p < 0.0001$); the mean daily HFS for medroxyprogesterone improved at 4, 8, and 12 weeks ($p < 0.0001$) (Irani et al., 2010). A multi-arm RCT by Vitolins et al. (2013) tested the effects of venlafaxine at 75 mg per day compared to milk protein powder, soy protein powder, and placebo after four weeks. The number of hot flashes decreased significantly within each arm ($p < 0.001$); however, no significant differences were noted between arms ($p > 0.05$) at week 4. Vitolins et al. (2013) also examined using soy protein powder alone or in combination with venlafaxine. After 12 weeks, there was a significant decrease in the number of hot flashes ($p < 0.001$) within both groups.

TABLE 1. Characteristics of Studies Included in Integrative Review (N = 15)

Study	Design and Sample	Treatment for Hot Flashes
Pharmacologic intervention		
Irani et al., 2010	RCT with 311 patients treated with gonadotropin-releasing hormone analogs	Treated with medroxyprogesterone (20 mg), cyproterone (100 mg), and venlafaxine (75 mg in weeks 1–8, 37.5 mg in weeks 9–10); all were given once per day.
Loprinzi et al., 2004	Single-arm pre-/post-test study with 26 patients	Treated with paroxetine; week 1 involved the completion of a hot flash diary, and paroxetine was administered in the following amounts for the remainder of the study: 12.5 mg in week 2; 25 mg in week 3; 37.5 mg in week 4; and 12.5, 25, or 37.5 mg in week 5; treatment was administered once per day.
Loprinzi et al., 2009	RCT with 223 patients	Treated with gabapentin; groups received 300 mg once a day in weeks 1–4; 300 mg once per day in week 1 and 300 mg twice per day in weeks 2–4; or 300 mg once per day in week 1, 300 mg twice per day in week 2, and 300 mg 3 times per day in weeks 3–4.
Loprinzi, Goldberg, et al., 1994	RCT with 78 patients treated with surgical or medical orchiectomy	Treated with transdermal clonidine; one group was given 0.1 mg in weeks 1–4 and placebo patch in weeks 5–8, and the other group was given placebo patch in weeks 1–4 and 0.1 mg in weeks 5–8. The placebo patch was worn all day.
Loprinzi, Michalak, et al., 1994	RCT with 66 patients treated with surgical or medical orchiectomy	Treated with megesterol acetate using gonadotropin-releasing hormone agonist; one group was given 20 mg in weeks 1–4 and placebo in weeks 5–8, and the other group was given placebo in weeks 1–4 and 20 mg in weeks 5–8; treatment was administered twice per day.
Naoe et al., 2006	Single-arm pre-/post-test study with 10 patients treated with castration, bicalutamide, bicalutamide and goserelin acetate, leuprorelin acetate, or bicalutamide and leuprorelin acetate	Treated with 10 mg paroxetine administered once per day for 4 weeks
Quella et al., 1999	Single-arm pre-/post-test study with 16 patients	Treated with 12.5 mg venlafaxine administered twice per day for 4 weeks
Vitolins et al., 2013	RCT with 120 patients treated with orchiectomy, luteinizing hormone-releasing hormone, or antiandrogen	Treated with 75 mg venlafaxine and 20 g milk protein powder administered once per day for 12 weeks
Complementary and alternative medicine intervention		
Ashamalla et al., 2011	Single-arm pre-/post-test study with 17 patients treated with monotherapy or combined hormonal deprivation therapy (adjunct to radiation therapy, radical prostatectomy, or brachytherapy)	Treated with 30 minutes of acupuncture administered twice weekly for 4 weeks

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TABLE 1. Characteristics of Studies Included in Integrative Review (N = 15) *(Continued)*

Study	Design and Sample	Treatment for Hot Flashes
Complementary and alternative medicine intervention *(continued)*		
Beer et al., 2010	Single-arm pre-/post-test study with 22 patients treated with luteinizing hormone-releasing hormone agonist, antiandrogen, or luteinizing hormone-releasing hormone agonsit and ketoconazole	Treated with 30 minutes of acupuncture with 10-minute manual stimulation intervals; administered twice weekly in weeks 1–4 and once weekly in weeks 5–10
Frisk et al., 2009	RCT with 31 patients treated with castration through surgery or gonadotropin-releasing hormone analog	Treated with either 30 minutes of electrostimulated acupuncture or 30 minutes of traditional acupuncture; each was administered twice weekly in weeks 1–2 and once weekly in weeks 3–12.
Hammar et al., 1999	Single-arm pre-/post-test study with 7 patients treated with gonadotropin-releasing hormone analog	Treated with 30 minutes of acupuncture administered twice weekly in weeks 1–2 and once weekly in weeks 3–12
Rich et al., 2017	Single-arm pre-/post-test study with 16 patients	Treated with auricular electroacupuncture administered for 2 hours on and 2 hours off every other week for 96 hours for 6 weeks
Stefanopoulou et al., 2015	RCT with 73 patients treated with gonadotropin-releasing hormone/luteinizing hormone-releasing hormone agonists, leupropelin, and triptorelin, or antiandrogens (cyproterone acetate and bicalutamide)	Treated with 4-week cognitive behavioral therapy that included a booklet, a CD with relaxation and paced breathing exercises, and a telephone call (average length of 30 minutes; range = 20–40 minutes) from the clinical psychologist
Vandecasteele et al., 2012	Single-arm pilot study with 10 patients	Treated with *Salvia officinalis* (sage); one group completed a hot flash diary questionnaire in week 1 and was given 150 mg 3 times per day in weeks 2–9, and the other group completed a hot flash diary questionnaire in weeks 1–2 and was given 150 mg 3 times per day in weeks 3–10.
RCT—randomized controlled trial		

The effects of paroxetine (an SSRI), previously used to reduce hot flashes in women with menopause, were examined in two pilot studies of men with prostate cancer with ADT-associated hot flashes. Loprinzi et al. (2004) reported that patients' HFS decreased by 59% from baseline to week four after gradually increasing the paroxetine dosage from 12.5 mg to 37 mg per day during a five-week period. Naoe et al. (2006) reported significantly decreased mean DHF, from 3.5 to 2 ($p = 0.009$), and significantly decreased mean HFS, from 4.6 to 2 ($p = 0.0332$), after consistent use of paroxetine (10 mg per day) during a four-week period.

Loprinzi et al. (2009) evaluated the efficacy of the anticonvulsant gabapentin at target daily doses of 300 mg, 600 mg, and 900 mg per day among 223 eligible participants. After four weeks of treatment, the study results revealed no statistically significant differences in HFS between the experimental arms and the placebo arm ($p = 0.48$). However, there was a statistically significant difference in DHF between the 900 mg per day experimental arm and the placebo arm after four weeks of treatment ($p = 0.02$). Gabapentin was well tolerated with no apparent side effects (Loprinzi et al., 2009).

Loprinzi, Goldberg, et al. (1994) evaluated 78 men experiencing hot flashes following orchiectomy for the treatment of prostate cancer who received 0.1 mg of clonidine in the form of a patch worn all day. Findings did not show any significant differences

between clonidine and the placebo patch in the reduction of DHF (Loprinzi, Goldberg, et al., 1994).

Complementary and Alternative Medicine Interventions

The effects of a variety of CAM interventions (e.g., sage, acupuncture, cognitive behavioral therapy [CBT]) on ADT-associated hot flashes were the focus of seven studies. Vandecasteele et al. (2012) evaluated the effects of 150 mg of *Salvia officinalis* (sage) taken three times per day for 9–10 weeks in 10 men and employed the Moyad scoring scale to determine the frequency and severity of hot flashes. The Moyad scoring scale rates each hot flash as mild (1 point), moderate (2 points), or severe (3 points). Although a significant difference in weekly Moyad scores existed between baseline and week three (112 versus 59, respectively; $p < 0.05$), this disappeared after three weeks (see Table 3). One patient developed an acneiform rash in the final two weeks of his treatment but refused allergy testing; therefore, the investigators could not rule out definitive causal connection between the rash and the intake of sage (Vandecasteele et al., 2012).

CBT is a safe and effective intervention in improving psychosocial functioning and hot flashes and night sweats in women with menopause and/or breast cancer (Balabanovic, Ayers, & Hunter, 2012). Stefanopoulou et al. (2015) investigated a CBT intervention for men with prostate cancer experiencing ADT-associated hot flashes; this intervention included the use of a booklet and a CD to promote proper breathing and relaxation techniques. Compared to the usual care group, participants in the CBT intervention group reported significant reduction in frequency of hot flashes and night sweats ($p = 0.02$) at six weeks and in the hot flushes and night sweats (HFNS) problem-rating score ($p = 0.001$) after four weeks of treatment. The HFNS problem-rating score is a mean of three items assessing the extent to which hot flashes are problematic, are distressing,

TABLE 2. Risk of Bias Assessment by Study

Study	Random Sequence Generation	Allocation Concealment	Participant/ Personnel Blinding	Outcome Assessment Blinding	Risk of Bias
Frisk et al., 2009	Unclear	Unclear	High	Unclear	High
Hammar et al., 1999	High	High	High	Unclear	High
Irani et al., 2010	Low	Low	Low	Low	Low
Loprinzi et al., 2004	High	High	High	Unclear	High
Loprinzi et al., 2009	Low	Low	Low	Low	Low
Loprinzi, Goldberg, et al., 1994	Unclear	Unclear	Unclear	Low	Unclear
Loprinzi, Michalak, et al., 1994	Unclear	Low	Low	Low	Unclear
Naoe et al., 2006	High	High	High	Unclear	High
Quella et al., 1999	High	High	High	Unclear	High
Rich et al., 2017	High	High	High	Unclear	High
Stefanopoulou et al., 2015	Low	High	Low	Low	High
Vandecasteele et al., 2012	High	High	Unclear	Unclear	High
Vitolins et al., 2013	Unclear	Unclear	Unclear	Low	High

Note. All studies had low risk of bias regarding incomplete outcome data and selective reporting criteria. For the Ashamalla et al. (2011) and Beer et al. (2010) studies, all other categories for assessment were unclear.

and interfere with daily life; a scale ranging from 1 to 10 is used, with higher scores indicating more bothersome HFNS. Although improvements in hot flashes were maintained at 32 weeks, group differences did not reach significance (Stefanopoulou et al., 2015).

Five studies of the effects of acupuncture on ADT-associated hot flashes in men with prostate cancer tested the hypothesis that acupuncture affects endorphins that may be involved in vasomotor symptoms, such as hot flashes (Lee, Kim, Shin, Choi, & Ernst, 2009). In a pilot study, Hammar et al. (1999) found a statistically significant decrease in DHF from baseline to 6, 10, and 24 weeks ($p < 0.05$) among the six men who completed all 12 weeks of therapy. A pilot study led by Frisk et al. (2009) randomly assigned 31 men to receive either electrostimulated acupuncture (EA) or traditional acupuncture (TA) once a week for 12 weeks. DHF decreased significantly within the EA group ($p = 0.012$) and the TA group ($p = 0.001$) after four weeks of treatment; however, the within-group differences in DHF disappeared at 12-month follow-up. HFS decreased by 78% in the EA group and by 73% in the TA group after four weeks; the within-group differences remained significant at 12-month follow-up ($p = 0.016$) (Frisk et al., 2009).

In an open-label, single-arm, phase 2 pilot trial by Beer et al. (2010), 22 men received EA twice weekly for four weeks, then weekly for an additional six weeks. Participants' mean HFS decreased by 60% after four weeks and by 52% after eight weeks (Beer et al., 2010). Ashamalla et al. (2011) examined the long-term effects of acupuncture on ADT-associated hot flashes among 17 men with prostate cancer. The mean HFS of these patients decreased from 28.3 at baseline to 10.3 and to 7 after two and eight weeks of acupuncture treatment, respectively ($p = 0.0001$). Overall, HFS improved by 80% after eight months of acupuncture use ($p = 0.002$) (Ashamalla et al., 2011). Rich et al. (2017) investigated the effects of auricular electroacupuncture (AEA) on ADT-associated hot flashes among 10 men who received a microcurrent device placed behind the ear and three 96-hour sessions of AEA during a six-week period. Participants demonstrated a significant decrease in frequency of hot flashes ($p < 0.0001$) and number of daily hot flashes ($p = 0.005$), as well as a significant improvement in QOL ($p < 0.0001$) between baseline and six weeks of treatment (Rich et al., 2017).

Discussion

ADT-associated hot flashes affect as many as 80% of men with prostate cancer. However, hot flashes in men have received much less attention than and are understudied compared to hot flashes in women with breast cancer. In response to this gap in the research, the current authors reviewed 15 RCTs and quasiexperimental studies concerning the effects of classic pharmacologic and CAM interventions on ADT-associated hot flashes among men with prostate cancer. Pharmacologic and CAM interventions have demonstrated mixed and inconsistent effects on ADT-associated hot flashes. The quality and biases of these studies also varied significantly. The results of this review can supplement current practice guidelines, such as the Oncology Nursing Society's Putting Evidence Into Practice (PEP) resources, which have focused primarily on hot flashes in women with breast cancer.

Pharmacologic interventions using progestin, SSRIs, and SNRIs appeared to improve HFS and DHF, whereas interventions using an anticonvulsant (gabapentin) and an alpha-agonist antihypertensive (clonidine) did not appear to improve HFS and DHF. In addition, these pharmacologic interventions have associated side effects and adverse events. Irani et al. (2010) reported two adverse events, including an occurrence of dyspnea attributed to cyproterone and an occurrence of urticaria caused by medroxyprogesterone acetate. Cyproterone acetate is also associated with weight gain, fatigue, and enlarged breasts, and it can have hepatotoxic effects (Chitturi & Farrell, 2013; Verhagen et al., 2014). In a systematic review, Frisk (2010) suggested that medroxyprogesterone acetate might have side effects such as weight gain, muscle spasms, nausea, insomnia, depressed mood, and headache. Megestrol acetate is also associated with a rise in prostate-specific antigen levels and is a significant concern in prostate cancer (Sartor & Eastham, 1999).

Patients using paroxetine (an SSRI) have reported significant incidence of dry mouth and sleeping for an unusually long period of time (Naoe et al., 2006). In addition, four patients on paroxetine dropped out of

KNOWLEDGE TRANSLATION

- Evidence supporting treatment for hot flashes associated with androgen deprivation therapy among men with prostate cancer is lacking.
- Rigorous research and standardized measures are needed to evaluate the effects of interventions on hot flashes for men with prostate cancer.
- The current review added evidence to the Oncology Nursing Society's Putting Evidence Into Practice guideline for hot flashes.

TABLE 3. Intervention Results of Studies Included in Integrative Review (N = 15)

Study	Objective and Assessment	Findings
Pharmacologic intervention		
Irani et al., 2010	To compare the efficacy of cyproterone, medroxyprogesterone, and venlafaxine for preventing hot flashes; HFS was measured at baseline and at 4, 8, and 12 weeks.	The median HFS score for all three drugs at each time point improved ($p < 0.0001$) except between weeks 4 and 8 for venlafaxine ($p = 0.4$). When compared to venlafaxine, the mean daily HFS for cyproterone improved at 4 ($p < 0.0001$), 8 ($p = 0.0122$), and 12 weeks ($p < 0.0001$). The mean daily HFS for medroxyprogesterone improved at 4, 8, and 12 weeks ($p < 0.0001$).
Loprinzi et al., 2004	To evaluate the utility of treating hot flashes with paroxetine; HFS was measured at baseline and at 4 weeks.	DHF decreased by 50%, and HFS decreased by 59%.
Loprinzi et al., 2009	To study the efficacy and side effects of three relatively low gabapentin doses; HFS was measured at baseline and at 4 weeks.	No statistical significance was found for the change in HFS from baseline to 4 weeks between the placebo group and the 3 gabapentin intervention arms ($p = 0.48$). Statistical significance was found regarding change in DHF from baseline to week 4 in the 900 mg gabapentin arm ($p = 0.02$).
Loprinzi, Goldberg, et al., 1994	To determine if clonidine is helpful in alleviating hot flashes; HFS was measured at baseline and at 4 weeks.	When asked which 4-week period was better, 28% of patients chose clonidine, 21% chose placebo, and 51% could not tell a difference between the 2 periods. There was no difference in study arms regarding reduction of number of daily hot flashes.
Loprinzi, Michalak, et al., 1994	To assess the effectiveness and short-term toxicity of megestrol acetate to treat hot flashes; HFS was measured at baseline and at 4 weeks.	During the first 4 weeks, patients receiving megestrol acetate first (group 1) had an 85% reduction in HFS compared to a 21% reduction in HFS in patients receiving the placebo first (group 2) ($p < 0.001$).
Naoe et al., 2006	To evaluate a low dose of paroxetine to reduce the frequency and severity of hot flashes; severity of hot flash was measured at baseline and at 4 weeks.	Average DHF declined from 3.5 per day to 2 per day from baseline to week 4 ($p = 0.009$). The average severity of hot flashes declined from 4.6 to 2 from baseline to week 4 ($p = 0.322$).
Quella et al., 1999	To investigate whether venlafaxine can alleviate hot flashes; HFS was measured at baseline and at 4 weeks.	The average incidence of severe and very severe hot flashes decreased from 2.3 per day to 0.6 per day after the 4-week treatment ($p = 0.003$). Hot flashes reduced from 10 per day to 6 per day after 4 weeks.
Vitolins et al., 2013	To evaluate the effect of venlafaxine and soy on hot flashes; number of hot flashes was measured at baseline and at 4 weeks.	The daily number of hot flashes decreased in all study arms ($p < 0.001$). There was no difference in the number of hot flashes daily between study arms.
Complementary and alternative medicine intervention		
Ashamalla et al., 2011	To evaluate the use of acupuncture to alleviate hot flashes; HFS was measured at baseline and at 2 weeks, 6, weeks, and 8 months.	Mean initial HFS decreased to 10.3 at 2 weeks, 7.5 at 6 weeks, and 7 at 8 months ($p = 0.0001$ for all). Mean improvement in HFS was 68.4% at 2 weeks ($p = 0.001$), 89.2% at 6 weeks ($p = 0.0078$), and 80.3% at 8 months ($p = 0.002$).
Beer et al., 2010	To determine the effect of acupuncture on hot flash frequency and intensity; HFS was measured at baseline and after 2, 4, 6, and 10 weeks of treatment.	Mean HFS decreased by 60% after 4 weeks and by 52% after 8 weeks. After 4 weeks of treatment, 9 of 22 participants had at least a 50% reduction in HFS. HFRDIS score improved from 35.9 to 18.4 after 4 weeks ($p = 0.002$) and from 34.3 to 22.6 after 10 weeks ($p = 0.0003$).

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TABLE 3. Intervention Results of Studies Included in Integrative Review (N = 15) *(Continued)*

Study	Objective and Assessment	Findings
Complementary and alternative medicine intervention *(continued)*		
Frisk et al., 2009	To assess the changes in hot flashes after EA and TA; HFS was measured at baseline; at 4, 8, and 12 weeks; and at 6, 9, and 12 months.	After 12 weeks, median daily hot flashes decreased from 7.6 to 4.1 for the EA group ($p = 0.012$) and from 5.7 to 3.4 for the TA group ($p = 0.001$). HFS decreased by 78% for the EA group and by 73% for the TA group ($p = 0.001$).
Hammar et al., 1999	To examine if acupuncture could be used to treat hot flashes; number of hot flashes was measured at baseline and at 4, 6, 10, and 24 weeks.	After 6, 10, and 24 weeks, the number of hot flashes per week significantly decreased for patients receiving acupuncture ($p < 0.05$).
Rich et al., 2017	To determine the effect of auricular electroacupuncture on hot flashes; HFRDIS was used for assessment at baseline and weekly for 6 weeks.	HFRDIS scores reduced from 35.8 to 20.05 after 6 weeks ($p = 0.005$). Mean DHF reduced from 77.7 to 21 after 6 weeks ($p < 0.0001$).
Stefanopoulou et al., 2015	To evaluate CBT compared to usual care in treating hot flashes; HFNS problem-rating score was used for assessment at baseline and at 6 and 32 weeks.	Compared to usual care, CBT reduced HFNS daily frequency from 12.12 to 1.84 after 6 weeks of treatment ($p = 0.02$). CBT also reduced HFNS problem-rating score from 1.33 to 0.58 by treatment end ($p = 0.001$). Improvements in hot flashes were maintained at 32 weeks, but significant group differences did not exist.
Vandecasteele et al., 2012	To evaluate the efficacy and safety of sage in treating hot flashes; a hot flash diary questionnaire was used for assessment at baseline and weekly for 8 weeks.	*Salvia officinalis* was effective in reducing hot flashes ($p = 0.002$). Weekly Moyad score decreased from 112 to 59 after 3 weeks of treatment ($p = 0.024$).

CBT—cognitive behavioral therapy; DHF—daily hot flash frequency; EA—electrostimulated acupuncture; HFNS—hot flushes and night sweats; HFRDIS—Hot Flash Related Daily Interference Scale; HFS—hot flash score; TA—traditional acupuncture
Note. HFS is obtained by summing the daily number of hot flashes and multiplying this number by the severity of each hot flash (ranging from 1 [not at all] to 10 [extremely severe]); this is used to estimate the overall hot flash burden.
Note. The HFRDIS is a 10-item scale measuring the degree to which hot flashes interfere with 9 daily activities and overall quality of life. Participants rated the degree to which hot flashes interfered with each item during the previous week using a scale ranging from 0 (did not interfere) to 10 (completely interfered). A total score was computed by summing items.
Note. The HFNS problem-rating score is a mean of three items assessing the extent to which hot flashes are problematic, are distressing, and interfere with daily life; a 10-point scale ranging from 1 to 10 is used, with higher scores indicating more bothersome HFNS.
Note. The hot flash diary questionnaire was based on the Moyad scoring scale, which determines the frequency and severity of daily and weekly hot flashes. Patients rate each hot flash as mild (1 point), moderate (2 points), or severe (3 points). The points per day or per week are summed.

one study because of its perceived toxicities (Loprinzi et al., 2004). A pilot study reported the promising effects of venlafaxine in reducing HFS or DHF among men with prostate cancer (N = 16) (Quella et al., 1999). A later large-scale RCT (N = 120) found no differences in HFS among the patients who used venlafaxine, venlafaxine and soy protein powder, soy protein powder and placebo, or milk protein powder and placebo (Vitolins et al., 2013). Gabapentin produced moderate results at a high dose of 900 mg per day (Loprinzi et al., 2009). An RCT of 70 men receiving transdermal clonidine suggested only a minor trend in lowering HFS (Loprinzi, Goldberg, et al., 1994).

Among the CAM interventions reviewed, acupuncture significantly improved the HFS and/or DHF among men with prostate cancer. All five studies of acupuncture reported significant decreases in HFS but no side effects; however, these results should be interpreted using caution because of the lack of a placebo control (Ahmadi & Daneshmand, 2014). In a pilot study with 10 participants, Vandecasteele et al. (2012) reported that *Salvia officinalis* (sage) reduced HFS without improving QOL scores.

Limitations

The studies reviewed varied in scientific rigor and had a variety of biases. Most studies were underpowered in detecting the intervention effects because of their use of relatively small sample sizes ranging from 7 to 311 participants, with a median of 22. Fewer than half of the

studies (n = 7) were RCTs, which often lacked a placebo-controlled group. For example, the RCT with the largest sample size (N = 311) tested the effects of three different medications without a placebo group (Irani et al., 2010). Most studies examined the short-term effects of short-duration interventions, typically 4–12 weeks. Only three studies examined the intervention effects at 8 months and 12 months.

Although different strategies and databases were used in an attempt to include the most relevant literature, only seven RCTs were located and included; more than half of the studies reviewed used quasi-experimental designs, which may have significant biases. The use of different controls, treatment outcome measures, and types of interventions have made synthesis across studies challenging.

Implications for Research

Several implications for research exist. The underlying physiology of ADT-associated hot flashes in men with prostate cancer is poorly understood. Research clarifying this physiology may be useful in determining effective interventions, as suggested by Carpenter (2005) and Fisher et al. (2013). Rigorous research designs, such as sufficiently powered RCTs with well-controlled placebos, are needed to accurately assess the effects of different types of treatment regimens. The development and use of standardized measures of the effects of different interventions on hot flashes will allow findings to be compared across studies.

Implications for Nursing

ADT is a vital component of prostate cancer treatment; however, hot flashes are an expected but unfortunate side effect on patients' sleep, QOL, and adherence to treatment regimens. There is insufficient evidence to support effective treatment and/or intervention. Men with prostate cancer should be made aware of possible complications and side effects prior to the start of ADT; they should also understand that hot flashes are common and may be difficult to manage. Patients and healthcare providers should work together and be proactive to prevent or reduce side effects, including hot flashes, associated with ADT. The results of this review supplement the Oncology Nursing Society's PEP guidelines for hot flashes, which typically have focused on hot flashes in women with breast cancer.

Conclusion

Researchers have responded to the need for management of the troublesome hot flashes associated with ADT for men with prostate cancer. Although an increasing body of research into treatment options is developing, pharmacologic and CAM interventions have demonstrated mixed and inconsistent effects on ADT-associated hot flashes, and the quality and biases of studies vary widely. The results of this review add to the current literature about hot flashes in cancer (Fisher et al., 2013) and practice guidelines (Kligman & Younus, 2010), which have generally been focused on hot flashes in women with breast cancer.

Yousef Qan'ir, MS, is a PhD student research assistant in the School of Nursing at the University of North Carolina at Chapel Hill; **Darrell DeDeaux, MNP,** is a nurse practitioner at Campbell University Health Center in Lillington, NC; and **Paul A. Godley, MD, PhD, MPP,** was the Rush S. Dickson Distinguished Professor of Hematology/Oncology in the Department of Medicine and a medical oncologist in the Lineberger Comprehensive Cancer Center, **Deborah K. Mayer, PhD, RN, AOCN®, FAAN,** is a Frances Hill Fox Distinguished Professor of Nursing in the School of Nursing and the director of the Cancer Survivorship program in the Lineberger Comprehensive Cancer Center, and **Lixin Song, PhD,** is an associate professor and the Beerstecher-Blackwell Distinguished Term Scholar in the School of Nursing and in the Lineberger Comprehensive Cancer Center, all at the University of North Carolina at Chapel Hill. Song can be reached at lsong@unc.edu, with copy to ONFEditor@ons.org. (Submitted October 2018. Accepted February 11, 2019.)

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