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Informing hot flash treatment decisions for breast cancer survivors: a systematic review of randomized trials comparing active interventions

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Abstract

Patient-centered decision making about hot flash treatments often incorporates a balance of efficacy and side effects in addition to patient preference. This systematic review examines randomized controlled trials (RCTs) comparing at least two non-hormonal hot flash treatments in breast cancer survivors. In July 2015, PubMed, SCOPUS, CINAHL, Cochrane, and Web of Science databases were searched for RCTs comparing active, non-hormonal hot flash treatments in

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Compliance with ethical standards

Conflicts of interest The study complies with the current laws of the United States. The authors declare no conflicts of interest.

Informed consent This type of study is exempt from institutional review board review, and human consent is not required.

female breast cancer survivors. Thirteen trials were included after identifying 906 potential studies. Four trials were dose comparison studies of pharmacologic treatments citalopram, venlafaxine, gabapentin, and paroxetine. Hot flash reduction did not differ by tamoxifen or aromatase inhibitor use. Citalopram 10, 20, and 30 mg daily had comparable outcomes. Venlafaxine 75 mg daily improved hot flashes without additional side effects from higher dosing. Gabapentin 900 mg daily improved hot flashes more than 300 mg. Paroxetine 10 mg daily had fewer side effects than 20 mg. Among four trials comparing different pharmacologic treatments, venlafaxine alleviated hot flash symptoms faster than clonidine; participants preferred venlafaxine over gabapentin. Five trials compared pharmacologic to non-pharmacologic treatments. Acupuncture had similar efficacy to venlafaxine and gabapentin but may have longer durability after completing treatment and fewer side effects. We could not perform a pooled meta-analysis because outcomes were not reported in comparable formats. Clinical trial data on non-hormonal hot flash treatments provide comparisons of hot flash efficacy and other patient important outcomes to guide clinical management. Clinicians can use the information to help patients select hot flash interventions.

Keywords

Breast cancer; Hot flashes; Vasomotor symptoms; Treatment; Non-hormonal; Randomized; controlled trials

Introduction

Hot flashes are highly prevalent and persistent among breast cancer survivors [1]. Hot flashes are symptoms of estrogen deprivation that are exacerbated by anti-estrogen therapy used for breast cancer treatment [2, 3]. Furthermore, for pre-menopausal breast cancer patients, chemotherapy abruptly disrupts or permanently ceases ovarian function, leading to the onset of debilitating hot flashes [4, 5]. Breast cancer survivors who experience hot flashes report greater fatigue, poorer sleep quality, and worse quality of life [1, 6–8].

Compared to women without breast cancer, breast cancer survivors have more limited options for treating hot flashes. While menopausal hormone therapy can reduce hot flashes by up to 90 % [9], concerns that systemic estrogen exposure increases cancer recurrence rates in breast cancer survivors limit its use [10, 11]. Hence, a number of clinical trials have tested the efficacy of non-hormonal hot flash treatments in this population. Compared to placebo treatments, pharmacologic treatments including venlafaxine, citalopram, paroxetine, gabapentin, pregabalin, and clonidine significantly reduce hot flash frequency and scores in breast cancer survivors [12–17]. Non-pharmacologic treatments including acupuncture, yoga, and hypnosis have also shown promise in improving hot flashes [18–25]. Several systematic reviews have summarized outcome data comparing these interventions to placebo [26–29] and provide more precise estimates of the efficacy of particular interventions.

Among available pharmacologic and non-pharmacologic interventions, there is variability in hot flash treatment efficacy and side-effect profiles, which affect patient preferences for treatment. Women with breast cancer have multiple hot flash treatment options and must carefully weigh the benefits and side effects. Therefore, comparative studies of non-

hormonal hot flash treatments in breast cancer survivors are important for informing clinical care strategies. To support patient-centered decision making, we present a systematic review of randomized controlled trials (RCTs) comparing at least two non-hormonal hot flash treatments in breast cancer survivors.

Methods

Search strategy

This systematic review was conducted in accordance with PRISMA guidelines [30]. In July 2015, we systematically searched the following databases: PubMed (1966–July 2015), SCOPUS (1966–July 2015), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1981–July 2015), COCHRANE (all years), and Web of Science (1900–July 2015). We screened the bibliographies of all included studies for additional references. We sought randomized controlled trials testing more than one active hot flash treatment in breast cancer survivors. We included studies on female breast cancer patients without age restriction and excluded studies on males, non-humans, and other female cancer patients. For types of interventions, we searched for the following prescription pharmacologic treatments: anti-depressants such as venlafaxine, citalopram, fluvoxamine, paroxetine, fluoxetine, sertraline, duloxetine, escitalopram; anti-epileptics such as gabapentin, pregabalin, gralise; and clonidine. We also searched for acupuncture, yoga, hypnosis, exercise, meditation, cognitive behavioral therapy, and physical therapy. In addition, we searched for non-prescription supplements such as vitamin E, black cohosh, homeopathy, and isoflavones. We excluded observational studies, case reports, and clinical trials where the hot flash intervention was only compared to placebo. The final PubMed search strategy is detailed in the Supplementary material 1.

Outcome measures

The primary outcomes of this review were hot flash frequency and scores (frequency $\times$ mean severity), treatment side effects, and patient preference for treatments.

Data collection

Four review authors (CJ, SS, IS, JG) independently screened the titles and abstracts of all search citations using the inclusion and exclusion criteria. Discrepancies among authors were resolved via consensus. Two of the three review authors (CJ, SS, or IS) independently abstracted data on included articles. Data extracted included participants, interventions, outcome and adverse effect measures, results, and risks of bias (randomization, allocation concealment, blinding, sample size, and analysis approach).

Risk of bias for all included studies was assessed independently by two review authors (CJ and IS) using the Cochrane risk of bias assessment tool [31]. Discrepancies were resolved by consensus. Studies were evaluated for the following: selection bias (random sequence generation and allocation concealment); performance blinding (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); reporting bias (selective reporting); and other bias. Each bias criterion was assigned a high, low, or unclear risk of bias rating. Additionally, we evaluated the quality of

each study using the following GRADE criteria: study limitations (i.e., risk of bias); consistency of effect; imprecision; indirectness; and publication bias [32]. RCTs were first classified as high quality. All studies were downgraded in quality for any of the following problems: serious limitation to study quality; important inconsistency; uncertainty about directness; imprecise or sparse data; or high probability of reporting bias.

Results

After searching PubMed ($n = 99$), SCOPUS ($n = 288$), CINAHL ($n = 59$), COCHRANE ($n = 106$), and Web of Science ($n = 351$) and hand-picking ($n = 3$), 906 articles were retrieved, leaving 637 articles after removing duplicates. Nineteen full-text articles were accessed, from which six were excluded, leaving 13 articles included in this review. These articles reported on prescription pharmacologic therapies including venlafaxine, citalopram, paroxetine, gabapentin, pregabalin, and clonidine, as well as vitamin E, acupuncture, hypnosis, and stellate ganglion block. No additional trials on other anti-depressants, anti-epileptics, non-prescription supplements, yoga, exercise, meditation, cognitive behavioral therapy, and physical therapy were identified. The PRISMA flow diagram details study selection results (Fig. 1) [30]. No article was excluded because of non-English language. Because of heterogeneity in both intervention and outcome measures, we were unable to pool estimates for a meta-analysis or derive strengths of recommendations based on the GRADE approach [32].

Dose comparisons of pharmacologic therapies

Four randomized controlled trials tested different doses of prescription pharmacologic treatments on hot flashes (Table 1, Supplementary material 2) [12, 14, 16, 17]. All trials were multi-centered and conducted in the United States. The populations were primarily comprised of breast cancer survivors, but also included menopausal women without a history of breast cancer or women concerned about taking estrogen for hot flashes [12, 14, 17]. Citalopram, venlafaxine, gabapentin, and paroxetine were each tested in one trial. Medication titration up to the final dose occurred for citalopram, venlafaxine, and gabapentin. In addition to hot flashes, the studies assessed mood symptoms and quality of life. Participants were also asked to report additional side effects, such as fatigue, pain, nausea, constipation, and sleep disturbance.

Figure 2A and B depicts mean or median percent decreases from baseline hot flash scores and frequency, with 95 % confidence intervals, by study and medication dose. The 95 % confidence intervals for the paroxetine trial were derived by assuming an underlying normal distribution [17]. Table 2 summarizes if additional outcomes differed by medication dose. Citalopram (10, 20, or 30 mg daily), extended-release venlafaxine (75 or 150 mg daily), gabapentin (900 mg daily), and paroxetine (10 or 20 mg daily) decreased hot flash score and/or frequency significantly more than placebo. Hot flash, mood, and common adverse outcomes did not differ by citalopram 10, 20, or 30 mg daily dosing in a 6-week trial [12]. For extended-release venlafaxine, hot flash scores decreased more following 75 mg daily dosing than following 37.5 mg daily dosing but did not differ between the 75 and 150 mg daily dosing. In addition, the 150 mg dosing was associated with increased mouth dryness

[14]. In comparing gabapentin 300 or 900 mg daily dosing, hot flash outcomes were not statistically significantly different between the two doses [16]. However, while both doses decreased hot flash frequency compared to placebo, only the 900 mg dose significantly decreased hot flash scores compared to placebo. In addition, the higher 900 mg gabapentin dose did not incur more adverse outcomes than the 300 mg dose. Hot flash improvement did not differ between 10 and 20 mg of paroxetine daily, but higher paroxetine dose (20 mg daily) resulted in more nausea and study withdrawal [17]. In all studies, the effect of these pharmacologic treatments on hot flashes did not differ by whether participants were using tamoxifen and/or aromatase inhibitor.

Comparisons of different pharmacologic therapies

Four randomized controlled trials, two of which were crossover studies, compared the effect of different prescription pharmacologic therapies on hot flashes (Table 1; Supplementary material 2) [33–36]. The trials took place in Canada, Germany, and the Netherlands, and three were multi-centered. Three studies compared venlafaxine and clonidine, while one study compared venlafaxine and gabapentin. In addition to hot flashes, the studies assessed patient preference, mood, blood pressure changes, and additional side effects.

Table 3 summarizes whether hot flashes and additional outcomes differed by pharmacologic treatment type. Among the three studies comparing venlafaxine with clonidine, venlafaxine 75 mg daily was more effective than clonidine 0.15 mg daily in decreasing hot flash frequency and score in one study [36]; the other two studies showed no difference [33, 35]. Venlafaxine 75 mg daily did decrease hot flash symptoms more quickly than clonidine 0.1 mg daily in two studies [33, 36]. Patient reported preferences, and mood symptoms did not consistently favor venlafaxine. While clonidine modestly decreased blood pressure, venlafaxine was associated with more appetite loss, nausea, and constipation.

In a crossover trial comparing venlafaxine 75 mg daily and gabapentin 900 mg daily, hot flash improvements occurred by 4 weeks on treatment and were not different between the medications, but 68 % of evaluable participants preferred venlafaxine over gabapentin [34]. On venlafaxine, participants experienced more nausea and constipation; while on gabapentin, participants experienced more negative mood and dizziness.

Comparisons of non-pharmacologic and pharmacologic therapies

Five randomized controlled trials compared a non-pharmacologic with a pharmacologic hot flash treatment in women with breast cancer (Table 1; Supplementary material 2) [25, 37–40]. These trials took place in Egypt, Italy, and the United States and were single-center studies. Acupuncture was compared with gabapentin or venlafaxine in two trials [25, 40]. Gabapentin was compared with vitamin E or hypnosis in two trials [37, 38]. Pregabalin was compared with stellate ganglion block in one study [39]. In addition to measuring hot flashes, studies assessed additional side effects and quality of life.

Table 4 summarizes comparisons of hot flashes and additional outcomes from these studies. Acupuncture was compared to both gabapentin 900 mg daily and venlafaxine 75 mg daily. In these trials, the effect on hot flash frequency or score did not differ between acupuncture and gabapentin or venlafaxine during active treatment [25, 40]. However, after completing

active treatment, there was a greater rebound of hot flashes in women who used pharmacologic therapy than in women who underwent acupuncture. For example, hot flash frequency remained low for 4 weeks following the end of acupuncture, while women who stopped taking venlafaxine experienced significant rebound of hot flashes by 2 weeks [40]. At 16 weeks off treatment, the electroacupuncture group reported a 55 % improvement in hot flashes compared to 21 % in the gabapentin group [25]. Both pharmacologic therapies were also associated with more side effects than acupuncture.

Compared to vitamin E, gabapentin 900 mg daily significantly improved hot flashes (mean 63 % reduction in hot flash score at 4 weeks of treatment), while vitamin E did not [37]. Gabapentin use was also associated with improved sleep and quality of life. A small study comparing hypnotherapy to gabapentin 900 mg daily did not show differences in hot flash improvement between the two groups, but the study was terminated without full recruitment due to accrual difficulties [38]. Across studies, gabapentin treatment was related to more dizziness, drowsiness and fatigue; these side effects occurred in one-third of participants.

Finally, a single trial compared pregabalin 150 mg daily over 3 months with a single stellate ganglion block, a selective sympathetic blockade achieved by bupivacaine injection next to the stellate ganglion under fluoroscopy [39]. Both groups experienced similar initial decreases in hot flashes, but after the 3rd month, the stellate ganglion block group had fewer and less severe hot flashes compared to the pregabalin group. Women undergoing stellate ganglion block experienced transient Horner's syndrome for less than 18 h, and other adverse effects were minor.

Discussion

Hot flashes are reported by the majority of breast cancer survivors and adversely impact their quality of life. Due to concerns that estrogen exposure increases cancer recurrence rates in breast cancer survivors, menopausal hormonal therapy is not the recommended first-line hot flash treatment for breast cancer survivors [41]. This leaves breast cancer survivors with fewer hot flash treatment options compared to women without breast cancer. Among non-hormonal interventions, multiple pharmacologic and non-pharmacologic treatments improve hot flashes significantly more than placebo treatments in this population [12–25]. Relative to the larger number of clinical trials testing interventions against placebo treatment in breast cancer survivors, this systematic review identified a smaller number of randomized controlled trials in which two or more hot flash treatments with demonstrated efficacy were compared. These studies provide data to guide physician and patient choice of intervention by efficacy, side-effect profile and patient preference.

Pharmacologic therapy trials comparing different doses of citalopram, venlafaxine, gabapentin, and paroxetine showed that patients experienced improvements in hot flash frequency and/or score at all medication doses. In these clinical trial settings, dropout rates of less than 20 % were observed across studies, suggesting tolerability of treatments. For citalopram, hot flash efficacy and side-effect profiles did not vary among 10, 20, and 30 mg daily dosing, supporting starting treatment with the lowest dose. While higher doses of venlafaxine (75 mg daily) and gabapentin (900 mg daily) appeared to improve hot flash

symptoms to a greater extent than lower doses without incurring more adverse effects, these final doses followed upward titration from lower starting doses. Because symptom improvements occur quickly, as early as 1–2 weeks on medication, breast cancer survivors may be treated starting at lower doses and, in responders, not require upward titration. For paroxetine and venlafaxine, there were no additional gains in hot flash efficacy but additional side effects with increased dosing above paroxetine 10 mg daily or venlafaxine 75 mg daily.

Comparing different pharmacologic treatments, venlafaxine treatment resulted in faster reduction of hot flash symptoms compared to clonidine, and participants preferred venlafaxine over gabapentin. By side-effect profiles, venlafaxine was associated with increased gastrointestinal side effects including dry mouth, nausea, and constipation, but these symptoms did not result in patient preference of clonidine over venlafaxine. Taken together, venlafaxine may be a reasonable first medication to try to use for hot flash management among these three pharmacologic options.

When considering pharmacologic hot flash treatments, it is important to consider if a breast cancer survivor is also taking tamoxifen. Tamoxifen and aromatase inhibitor therapy did not alter the hot flash treatment efficacy of venlafaxine, citalopram, or paroxetine. However, some anti-depressants may interfere with tamoxifen metabolism by inhibiting the CYP2D6 enzyme that metabolizes tamoxifen to its more potent metabolite endoxifen. Paroxetine has been shown to have a strong interaction, while venlafaxine and gabapentin are not known to have an interaction with tamoxifen [42]. Hence, among effective pharmacologic hot flash treatments, breast cancer survivors taking tamoxifen should consider selecting medications that do not interact with tamoxifen.

Non-pharmacologic treatments are important to consider in this population, because participants generally experience fewer side effects when compared to pharmacologic treatments. Acupuncture was compared to both venlafaxine and gabapentin, two effective pharmacologic treatments [25, 40]. In these two studies, hot flash treatment efficacy did not differ between acupuncture and the pharmacologic comparator while on active treatment. However, in this limited participant pool, women treated with acupuncture reported longer durability of hot flash efficacy that persisted after completing active treatment. Moreover, aside from bruising, participants undergoing acupuncture reported no other side effects, while participants randomized to pharmacologic treatments reported significant gastrointestinal and fatigue side effects. Larger comparative effectiveness trials in broader populations are needed to confirm these findings. Balancing hot flash treatment efficacy and side effects will be important to breast cancer survivors, especially for those patients who do not want to take another drug or who are not responding to a drug treatment.

Several limitations should be discussed. First, this systematic review was limited by the small number of randomized clinical trials comparing hot flash treatments. With exception of comparing venlafaxine to clonidine, there were no other pairs of treatments that were compared in more than one trial. Coupled to sample sizes smaller than 250 participants in all but two studies, there may be imprecision in the estimated effect, rendering the quality of the evidence moderate to very low (Supplementary material 2) [32]. It is unclear if data from hot

flash treatment trials in women without cancer, which draw from larger participant pools, may be generalized to breast cancer survivors. Several of the included studies in this systematic review and a separate pooled analysis support similar hot flash reductions in women with and without breast cancer [12, 14, 17, 38, 43]. In addition, despite fairly consistent collection of hot flash frequency and score data using hot flash diaries [44], studies did not consistently report outcomes in comparable formats, which prohibited pooling estimates in a meta-analysis. There was great variability in how hot flash outcomes were reported statistically. For example, among other inconsistencies in reporting, some studies reported outcomes in terms of means and standard deviations or standard errors, some reported means and 95 % confidence intervals, and some only reported the means without 95 % confidence intervals or standard deviations or standard errors, while others reported in terms of medians and ranges. Future studies should aim to report hot flash frequency and score results in a common measure so that their results can be compared directly. We would suggest that means and their associated SEs along with 95 % confidence intervals be reported if the data does not deviate from normal distribution severely; otherwise median, interquartile ranges along with 95 % confidence intervals should be reported.

For breast cancer survivors, there are a number of effective non-hormonal treatments for hot flashes. Based on current head-to-head trials, survivors and their healthcare providers should discuss the relative effectiveness and side-effect profiles of active treatments in order to determine the best clinical management approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Systematic review search strategy

Fig. 2. Mean or median % reductions with 95 % confidence intervals from baseline hot flash score (A) and hot flash frequency (B) following placebo or pharmacologic hot flash treatments

Table 1

Summary of Studies

Reference	Participants	Interventions	Outcome measures
<i>Dose comparisons of pharmacologic treatments</i>			
Barton et al. [12]	254 participants (87 breast cancer survivors) Postmenopausal 14 hot flashes/week for 1 month	6-week study 6 groups: - Citalopram 10 mg daily - Citalopram 20 mg daily - Citalopram 30 mg daily - Placebo 1 pill daily - Placebo 2 pills daily - Placebo 3 pills daily	Hot flash score and frequency Mood (POMS [45]) National Cancer Institute (NCI) Common Toxicity Criteria [46]
Loprinzi et al. [14]	229 participants (158 women on tamoxifen) Breast cancer history or concern about taking estrogen Age 18 4 hot flashes/week for 1 month	4-week study 4 groups: - Venlafaxine 37.5 mg daily - Venlafaxine 75 mg daily - Venlafaxine 150 mg daily - Placebo daily	Hot flash score and frequency Mood (Beck Depression Inventory [47]) Additional effects (study-specific questions) Quality of life (study-specific questions)
Pandya et al. [16]	420 participants with breast cancer Age 18 2 hot flashes/day	8-week study 3 groups: - Gabapentin 300 mg daily - Gabapentin 900 mg daily - Placebo daily	Hot flash score and frequency Additional effects (MD Anderson Symptom Inventory [48])
Stearns et al. [17]	151 participants (123 breast cancer survivors) Breast cancer history or concern about taking estrogen Age 18 2 hot flashes/day for 1 month	9-week study 4 groups: - Paroxetine 10 mg or 20 mg daily × 4 weeks, then placebo × 4 weeks - Placebo for 4 weeks, then paroxetine 10 or 20 mg daily for 4 weeks	Hot flash score and frequency Mood (CES-D [49], HADS [50]) Additional effects (MOS Sleep Problem Index, MOS Sexual Problems Index [51]) Quality of life (Euro QOL-LRS [52])
<i>Comparison of different pharmacologic treatments</i>			
Boekhout et al. [33]	102 participants with breast cancer Postmenopausal or on GnRH agonist Age 18 2 hot flashes/day	12-week study 3 groups: - Venlafaxine 75 mg daily - Clonidine 0.1 mg daily - Placebo daily	Hot flash score and frequency Mood (HADS [50]) Additional effects (study-specific questions, Groningen Sleep Quality Scale [53], Sexual Activity Questionnaire [54]) Patient preference Blood pressure/heart rate
Bordeleau et al. [34]	66 participants with breast cancer 14 hot flashes/week for 1 month	14-week study 2 groups: - Venlafaxine 75 mg daily, then washout, then gabapentin - Gabapentin 900 mg daily, then washout, then venlafaxine	Hot flash score and frequency Additional effects (study-specific questions) Quality of life (SF-36 [55])
Buijs et al. [35]	60 participants with breast cancer Age 60 14 hot flashes/week	18-week study 2 groups: - Venlafaxine 75 mg daily × 8 weeks, then washout, then clonidine - Clonidine 0.1 mg daily × 8 weeks, then washout, then venlafaxine	Hot flash score and frequency Mood (Zung Depression Scale [56]) Additional effects (study-specific questions, Sexual Activity Questionnaire [54]) Patient preference Blood pressure Quality of life (SF-36 [55])
Loibl et al. [36]	80 participants with breast cancer Age 18 14 hot flashes/week or seeking help for hot flashes	4-week study 2 groups: - Venlafaxine 75 mg daily - Clonidine 0.15 mg daily	Hot flash score and frequency Additional effects (study-specific questions)
<i>Comparisons of non-pharmacologic and pharmacologic treatments</i>			
Biglia et al. [37]	115 participants with breast cancer Postmenopausal or on GnRH agonist	12-week study 2 groups: - Gabapentin 900 mg daily - Vitamin E 800 IU daily	Hot flash score and frequency Additional effects (Pittsburgh Sleep Quality Index [57], Menopausal Rating Scale [58])

Reference	Participants	Interventions	Outcome measures
	8 hot flashes/day		Quality of life (SF-36 [55])
MacLaughlan David et al. [38]	27 participants with breast cancer or at increased risk of breast cancer Age 18 1 hot flash/day	8-week study 2 groups: - Gabapentin 900 mg daily - Three 1-hour hypnotic inductions (1 week apart) and home audio CD use	Hot flash score and frequency
Mao et al. [25]	120 participants with breast cancer 2 hot flashes/day for 1 month	8-week study, then 16-week follow up 4 groups: - Electroacupuncture 2 times weekly $\times$ 2 weeks, then weekly $\times$ 6 weeks - Sham acupuncture 2 times weekly $\times$ 2 weeks, then weekly $\times$ 6 weeks - Gabapentin 900 mg daily - Placebo daily	Hot flash score and frequency Additional events (study-specific questions)
Othman et al. [39]	40 participants with breast cancer Age 21 Hot flashes 1 month	12-week study 2 groups: - Pregabalin 150 mg daily - Stellate ganglion block-single episode	Hot flash score Additional effects (study-specific questions)
Walker et al. [40]	50 participants with breast cancer Age 18 14 hot flashes/week	12-week study, then 12-month follow up 2 groups: - Venlafaxine 75 mg daily - Acupuncture 2 times weekly $\times$ 4 weeks, then weekly $\times$ 8 weeks	Hot flash score and frequency Additional effects (NCI Common Toxicity Criteria [46]) Mood (Beck Depression Inventory [47]) Quality of life (MenQOL [59], SF-12 [60])

Table 2

Comparisons of additional outcomes by different doses of pharmacologic treatments

Reference	Interventions	Mood	Quality of life	Additional side effects ^a	Time to hot flash improvement
Barton et al. [12]	Citalopram 10, 20 or 30 mg daily	↔	N/A	↔	↔
Loprinzi et al. [14]	Extended-release venlafaxine 37.5, 75 or 150 mg daily	↔	↔	Venlafaxine 150 mg: ↑ mouth dryness	↔
Pandya et al. [16]	Gabapentin 300 or 900 mg daily	↔	N/A	↔	↔
Stearns et al. [17]	Paroxetine 10 or 20 mg daily	↔	↔	Paroxetine 20 mg: ↑nausea, ↑ study withdrawal	↔

↔ no difference among groups, ↑ increased, ↓, decreased, N/A not assessed

^aOnly additional outcomes that were statistically significantly different among hot flash treatment groups are presented

Table 3

Comparisons of outcomes between different pharmacologic treatments

Reference	Interventions	Hot flashes	Mood	Quality of life	Patient preference	Blood Pressure	Additional side effects ^a	Time to hot flash improvement
Boekhout et al. [33]	Venlafaxine 75 mg or clonidine 0.1 mg daily	↔	Clonidine: ↑ anxiety Venlafaxine: ↑ depression	N/A	↔	↔	Venlafaxine: ↓ appetite	Favors venlafaxine (effect in 1-2 weeks) over clonidine (>4 weeks)
Bordeleau et al. [34]	Venlafaxine 75 mg or gabapentin 900 mg daily	↔	Venlafaxine (vs. gabapentin): ↓ negative mood	↔	Venlafaxine preferred	N/A	Venlafaxine: ↓ appetite, ↑ nausea and constipation Gabapentin: ↑ dizziness, ↑ appetite	↔
Buijs et al. [35]	Venlafaxine 75 mg or clonidine 0.1 mg daily	↔	Venlafaxine: ↓ depression	↔	↔	Clonidine: ↓ 5 mmHg systolic ↓ 3 mmHg diastolic	Venlafaxine: ↓ appetite, ↑ nausea and constipation ↑ study withdrawal Clonidine: ↑ pain, ↑ itching	↔
Loibl et al. [36]	Venlafaxine 75 mg daily or clonidine 0.15 mg daily	Favors venlafaxine	N/A	N/A	N/A	N/A	Venlafaxine: ↑ nausea	Favors venlafaxine

↔ no difference among groups, ↑ increased, ↓, decreased, N/A not assessed

^aOnly outcomes that were statistically significantly different among hot flash treatment groups are presented

Table 4

Comparison of outcomes of non-pharmacologic and pharmacologic treatments

Reference	Intervention	Hot flashes	Quality of life	Additional side effects ^a	Time to hot flash improvement
Biglia et al. [37]	Gabapentin 900 mg daily or vitamin E 800 IU daily	Favors gabapentin	Favors gabapentin	Gabapentin: ↑sleep quality, ↑dizziness	Favors gabapentin
MacLaughlan David et al. [38]	Gabapentin 900 mg daily or hypnotic inductions (weekly for 3 weeks)	↔	N/A	N/A	↔
Mao et al. [25]	Gabapentin 900 mg daily or electroacupuncture 1-2 times weekly	↔ during active treatment Electroacupuncture with longer durability of effect	N/A	Gabapentin: ↑dizziness, ↑fatigue, ↑drowsiness Electroacupuncture: ↑bruising	↔
Othman et al. [39]	Pregabalin 150 mg daily or stellate ganglion block once	Favors stellate ganglion block	N/A	Stellate ganglion block: Transient Horner's Syndrome Pregabalin: ↑dizziness	↔
Walker et al. [40]	Venlafaxine 75 mg daily or acupuncture 1-2 times weekly	↔ during active treatment Acupuncture with longer durability of effect	↔	Venlafaxine: ↑nausea, ↑headache, ↓sleep quality, ↑dizziness	↔

↔ no difference among groups, ↑ increased, ↓, decreased, N/A not assessed

^aOnly outcomes that were statistically significantly different among hot flash treatment groups are presented