ONS HOT FLASHES SYMPTOM MANAGEMENT GUIDELINE

Supplementary Material

Table of Contents

---

1. Guideline panel member conflict of interest disclosures

Members	COI Disclosures
Marcelle Kaplan, MS, RN, CNS Oncology Nursing Consultant	**Consultant or Advisory:** Western Schools - compensated for writing chapters and serving as content editor of a CNE course titled "Oncology Nursing: 4th edition."
Jessica Bay Leibelt, MSN, NP-C, AOCNP® Nurse Practitioner Moffitt Cancer Center	No disclosures
Paz Fernández-Ortega, PhD, MSc, RN Nursing Research Coordinator and Associate Professor of Nursing Institut Català d'Oncologia	**Consultant or Advisory:** Vifor pharma
Dale Grimmer, MS, RN, AOCN®, CCRC Clinical Research Nurse Ascension St. Elizabeth Hospital	No disclosures
Suzanne Mahon, DNSc, RN, AGN-BC Professor, Department of Internal Medicine, Division of Hematology/Oncology; Oncology Professor, School of Nursing Saint Louis University	No disclosures
Laura B. Michaud, PharmD, BCOP, FASHP, CMQ Associate Director of Quality and Safety Division of Pharmacy University of Texas MD Anderson Cancer Center	**Honoraria:** University of Illinois (CE program), AiSM CE LLC (CE program), Jobson (CE manuscript)
Bernardo L. Rapoport, Dip in Med (UBA), MMed Consultant Medical Oncologist, Medical Oncology Centre Extraordinary Professor, Department of Immunology, Faculty of Health Sciences, University of Pretoria, South Africa	**Consultant or Advisory:** MSD, BMS, AstraZeneca, Sandoz, Roche South Africa, Tesaro (all compensated) **Honoraria:** MSD, BMS, AstraZeneca, Sandoz, Roche South Africa, Tesaro (all compensated) **Research Funding:** MSD, BMS, AstraZeneca, Sandoz, Roche South Africa, Tesaro (all compensated)
Valencia Robinson, EdS Patient Advocate Florida Breast Cancer Foundation	No disclosures

2. PICO questions

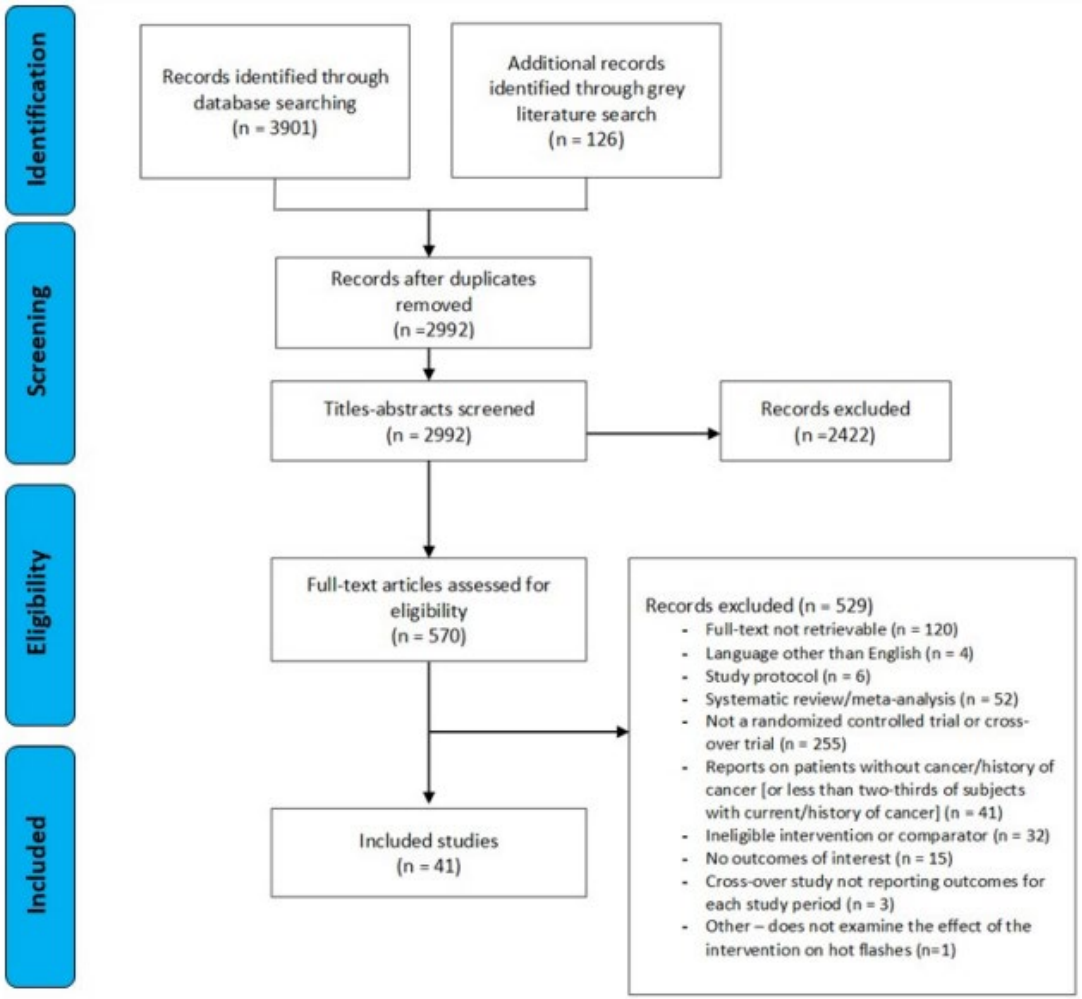
Population	Intervention(s)	Comparator	Outcomes
Women with Breast Cancer			
Women with drug- or surgery-induced hot flashes	Venlafaxine Paroxetine Clonidine	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes Quality of life (sleep/sleep quality in addition to global QOL from any validated scale) Depression Adverse events from intervention
Women with drug- or surgery-induced hot flashes	Sertraline Fluoxetine Escitalopram Duloxetine	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes Quality of life (sleep/sleep quality in addition to global QOL from any validated scale) Depression Adverse events from intervention
Men with Prostate Cancer			
Men with drug- or surgery-induced hot flashes	Paroxetine Clonidine	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes

			Quality of life (sleep/sleep quality in addition to global QOL from any validated scale) Depression Adverse events from intervention
	Sertraline Fluoxetine Escitalopram Duloxetine	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes Quality of life (sleep/sleep quality in addition to global QOL from any validated scale) Depression Adverse events from intervention
Men with drug- or surgery-induced hot flashes	Venlafaxine	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes Quality of life (sleep/sleep quality in addition to global QOL from any validated scale) Depression Adverse events from intervention

Women with Breast Cancer or Men with Prostate Cancer			
Women or men with drug- or surgery- induced hot flashes	Gabapentin Pregabalin	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes Quality of life (sleep/sleep quality in addition to global QOL from any scale) Depression Adverse events from intervention
Women or men with drug- or surgery- induced hot flashes	Herbal/dietary supplements (ingestible) (Soy, black cohosh, St. John's wort, melatonin, vitamin E)	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes Quality of life (sleep/sleep quality in addition to global QOL from any validated scale) Depression Tolerability of intervention Adverse events from intervention
Men or women with drug- or surgery- induced hot flashes	Hypnosis/relaxation therapy	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes Quality of life (sleep/sleep quality in addition to global QOL from any validated scale) Depression Adverse events from intervention

Men or women with drug- or surgery- induced hot flashes	Cognitive behavioral therapy	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes Quality of life (sleep/sleep quality in addition to global QOL from any validated scale) Depression Adverse events from intervention
Men or women with drug- or surgery- induced hot flashes	Physical activity (Exercise, yoga)	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes Quality of life (sleep/sleep quality in addition to global QOL from any validated scale) Depression Adverse events from intervention
Men or women with drug- or surgery- induced hot flashes	Acupuncture or electroacupuncture	Placebo, no treatment, or active comparator	Frequency of hot flashes (per 24 hours) Severity of hot flashes Quality of life (sleep/sleep quality in addition to global QOL from any validated scale) Depression Adverse events from intervention

3. PRISMA diagram (From Appendix 4 of 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*, E86–E106. https://doi.org/10.1188/20.ONF.E86-E106)



4. Summary of Findings table (From Appendix 12 of 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*, E86–E106. https://doi.org/10.1188/20.ONF.E86-E106)

Primary Outcomes	CoE	Classification	Intervention	RoM (95% CI) vs PLC
Hot flash composite score	Low (Low to very low)	May be among the most effective	Venlafaxine	**1.71 (1.05, 2.76)**
			Paroxetine	**2.83 (1.31, 6.09)**
			Clonidine	**2.13 (1.27, 3.54)**
			Electroacupuncture	**2.07 (1.01, 4.24)**
		May be no more effective than placebo	Gabapentin	1.43 (0.95, 2.12)
			Gabapentin + Antidepressants	1.34 (0.59, 3.01)
			Sertraline	1.58 (0.70, 3.41)
			Sham acupuncture	1.65 (0.83, 3.31)
			Melatonin	0.70 (0.05, 11.19)
		May be among the least effective	Vitamin E	0.14 (0.03, 0.58)
	High (Moderate to High)	Among the most effective	Venlafaxine	**2.48 (1.36, 4.32)**
		No more effective than placebo	Gabapentin	1.62 (0.92, 2.73)
Hot flash frequency	Low (Low to very low)	May be among the most effective	Paroxetine	**3.15 (1.29, 7.58)**
		May be among the least effective	Clonidine	1.62 (0.86, 2.98)
			Gabapentin + Antidepressants	1.80 (0.65, 4.65)
			Sertraline	1.67 (0.69, 3.94)
			Melatonin	1.03 (0.11, 8.90)
			Vitamin E	0.27 (0.06, 1.18)

*RoM: Ratio of Means (e.g. mean reduction of HF frequency in intervention / mean reduction of HF frequency in placebo)

5. Information by outcome on studies not able to be pooled in the network (From Appendix 11 of 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*, E86–E106. https://doi.org/10.1188/20.ONF.E86-E106)

The study team identified 41 publications (40 studies/RCTs) that informed the network meta-analysis of pharmacological, dietary supplements, physical, and psychological interventions.

Hot Flash Frequency:

Data from 11 RCTs contributed to the model for the outcome of frequency. Additional information from the 12 studies that reported on frequency but could not be pooled in the analysis are presented below.

Pharmacologic therapies:

Bordeleau 2010 – Gabapentin vs venlafaxine (n=66 overall; crossover study)

–This was a cross-over trial with 2-4 weeks in between study periods. The authors reported that with regard to hot flash frequency, the ratio of venlafaxine compared to gabapentin was 0.94 (95% CI not reported, but the p-value was reported to be >0.61). The authors also reported that 38 of 56 patients completing the study preferred venlafaxine over gabapentin; amongst them, 84.2% felt the frequency of hot flashes was reduced with venlafaxine. The authors concluded that breast cancer survivors prefer venlafaxine over gabapentin for treating hot flashes.

Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30)

–This study was for 12 weeks. Hot flashes were less frequent in the venlafaxine group in the initial 2 weeks of the study, but this early difference was not sustained at 12 weeks. No difference was noted between the soy and placebo groups throughout the study. The conclusion stated in by the authors was that neither soy nor venlafaxine effectively treated hot flashes over the 12-week study period. They noted the need for additional research for treatment of hot flashes in men with prostate cancer.

Loprinzi 2002 – Fluoxetine vs placebo (n=81; crossover trial)

–The first study period was 5 weeks followed by a second (cross-over) 4-week period. Findings include a decrease in hot flash frequency for patients in the fluoxetine group (3.4 HF per day, 42% decrease) and in the placebo group (2.5 HF per day, 31% decrease) (P=0.54). The conclusion stated by the authors was that the dose of fluoxetine studied resulted in a modest improvement in hot flashes.

Mao 2015 – Gabapentin (n=28) vs electroacupuncture (n=30) vs sham acupuncture (n=32) vs placebo (n=30)

– The study treatment was for 8 weeks with follow up at 24 weeks to assess sustainability of treatment. The mean (SD) daily frequency at baseline for electroacupuncture was 8.3 (5.6), and 6.3 (2.8) for the related sham group; the mean (SD) for the placebo gabapentin arm was 8.1 (5.4), while the related value for the gabapentin group was 6.8 (3.3). The conclusion stated by the authors was that a larger placebo effect, and a smaller nocebo effect, were seen with acupuncture than with medications for hot flashes. Detailed data with regard to frequency are not reported. It was noted that electroacupuncture may be more effective than gabapentin with fewer adverse effects for HF management.

Biglia 2016 – Escitalopram (n=30) vs duloxetine (n=28)

– In this study, HFF and HFS were self-reported at baseline and following 4 and 12 weeks of treatment. At 12 weeks, the total number of HFs per week decreased 49.8% in the duloxetine group (p=0.003) and in the escitalopram group they decreased 53% (P=0.001). The conclusion stated by the authors ws that both escitalopram and duloxetine had similar efficacy for the relief of HFs in survivors of breast cancer.

Dietary supplements:

Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30)

– This study was for 12 weeks. Hot flashes were less frequent in the venlafaxine group in the initial 2 weeks of the study, but this early difference was not sustained at 12 weeks. No difference was noted between the soy and placebo groups throughout the study. The conclusion stated in by the authors was that neither soy nor venlafaxine effectively treated hot flashes over the 12-week study period. They noted the need for additional research for treatment of hot flashes in men with prostate cancer.

Barton 1998 – Vitamin E (n=54) vs placebo (n=50) (crossover trial)

– This study compared vitamin E 800 IU to placebo. Following a 1-week lead-in, patients received 4 weeks of vitamin E followed by 4 weeks of placebo or the opposite schedule. At the first check at 4 weeks, no difference was found between interventions (decrease of 25% with vitamin E compared with 22% decrease with placebo, p=.90). Incorporating the second study period, a small but statistically significant advantage favoring Vitamin E was noted (suggesting approximately 1 less HF per day). The authors noted that while a significant reduction in HF frequency was seen with vitamin E, clinical relevance was small.

Quella 2000 – Soy (n=88) vs Placebo (n=88) (crossover trial)

– This study compared soy tablets to placebo. Following a 1-week lead-in patients received 4 weeks of soy followed by 4 weeks of placebo or the opposite schedule. The study was double blinded and patients self-reported HFF, hot flash intensity and side effects. Among patients receiving placebo, 36% reported that HF frequency was halved, compared with only 24% of patients receiving soy (*P* =0.01). The authors concluded that the soy product did not alleviate HFs in breast cancer survivors.

Van Patten 2002 – Soy (n=59) vs placebo (n=64)

–This study included a 4-week lead-in phase and 12-week treatment phase involving assignment to a soy or placebo beverage. There were no statistically significant differences between the soy and placebo groups in the mean reductions of daytime (-1.2 soy vs -1.8 placebo), nighttime (-0.5 soy vs -0.7 placebo) or 24-hr (-1.8 soy vs -2.5 placebo) HFs. The similar, and significant, reduction in hot flashes that was found in both groups was thought by the authors to be due to a strong placebo effect.

Acupuncture:

Frisk 2009 – Acupuncture (n=16) vs electroacupuncture (n=15)

– There was no significant difference between the acupuncture and electroacupuncture groups over time (p=0.25; ANOVA), however, hot flushes did decrease significantly in both groups and remained decreased at all time points, except for 12 months. The differences in hot flushes per 24 hours decreased from a median of 7.6 at baseline to 4.1 at 12 weeks in the electroacupuncture group and from a median of 5.7 to 3.4 at 12 weeks in the acupuncture group (p=0.001). The authors concluded that both electroacupuncture and acupuncture lowered number of HFs.

Hervik 2009 – Acupuncture (n=30) vs sham acupuncture (n=29)

–This study provided patients with twice weekly acupuncture or sham acupuncture for the first 5 weeks, and subsequently once per week for the next 5 weeks. Daytime HFs were significantly reduced in the acupuncture group (from baseline mean (SD) 9.5 (4.9) to 4.7 (3.7) at 10 weeks, which further

reduced to 3.2 (2.2) over the next 12 weeks), while no significant change was seen within the sham acupuncture group (from baseline mean (SD) 12.3 (7.3) to 11.7 (8.5) at 10 weeks, which increased back to 12.1 (8.3) over the next 12 weeks). Similar patterns were reported for nighttime HFs. The difference in acupuncture versus sham acupuncture was statistically significant for both daytime and nighttime HFs.

Liljegren 2012 – Acupuncture (n=42) vs sham acupuncture (n=42)

–Patients received treatment twice weekly for a duration of 5 weeks. The reductions in frequencies of HFs reached statistical significance at week 6 in both the acupuncture (from baseline mean (SD) 8.4 (5.5) to 5.7 (4.1) at 6 weeks) and sham acupuncture (from baseline 7.1 (4.4) to 4.5 (3.7) at 6 weeks) groups; however, the difference between groups was not statistically significant (mean difference 1.2, 95% CI -0.7 to 3.0; p=0.21).

Deng 2007 – Acupuncture (n=42) vs sham acupuncture (n=30)

– The protocol included twice weekly treatments for 4 weeks with evaluations at baseline, 6 weeks and 6 months. Patients in the sham group were crossed over to acupuncture at week 7. At week 6 no difference was noted between groups (95% CI, -0.7 to 2.4; p=0.3). At week 12 HFF reduced from 7.3 to 5.4 and treatment improvements were sustained at 6 months. Although HFF was reduced following acupuncture the reduction was not statistically significant.

Hot Flash Composite Score:

Data from 12 RCTs contributed to the model for the outcome of frequency. Additional information from the 12 studies that reported on frequency but could not be pooled in the analysis are presented below.

Pharmacologic therapies:

Boekhout 2011 – Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)

–Daily HF score was calculated as the sum of HF severity values experienced in a given day. At 12 weeks, venlafaxine and clonidine were both associated with lower median HF scores compared to placebo; the median (IQR) scores for the 3 groups were as follows: Placebo - median 10.9, IQR 7.4-15.8; Clonidine: median 7.5, IQR 2.0-10.8; Venlafaxine: median 7.6, IQR 4.0-110.4. It was also noted that when considering the entire 12-week study period, HF score reduction was greater overall with venlafaxine than clonidine due to an earlier start of benefits during the 12-week period. The study authors concluded that venlafaxine and clonidine are effective treatments in the management of HFs.

Bordeleau 2010 – Gabapentin vs venlafaxine (n=66 overall; crossover trial)

–Daily HF score was assessed as average HF severity that day x frequency of HFs that day. Treatment periods lasted 4 weeks, with 2-4 weeks washout in between. Findings performed to compare the intervention groups using a mixed modeling approach identified a venlafaxine to gabapentin ratio of 0.96 (near 1), suggesting little difference between intervention groups (p value >0.61); both groups were noted to have important reductions from baseline (from week 2 mean (SD) 18.7 (23.2) to 5.7 (4.6) for venlafaxine in the first study period; from 18.6 (15.4) to 6.5 (8.3) in the gabapentin group). Analyses were also performed to compare groups as based upon patients' preferred treatment; those that preferred venlafaxine (n=38) were reported to experience scores 41% lower, while those that preferred gabapentin (n=18) were reported to experience scores 47% lower.

Biglia 2016 – Escitalopram (n=30) vs duloxetine (n=28)

-HF score was assessed at both 4 and 12 weeks of treatment. Both treatments significantly reduced weekly HF scores (duloxetine, 53.6%, p=0.003 and escitalopram, 60.4%, p=0.001) but the difference between the groups was not statistically significant. The conclusion of the authors was that, at 12 weeks, both interventions were effective in the treatment of hot flashes.

Loprinzi 2002 – Fluoxetine vs placebo (n=81 total; crossover trial)

–HF score was calculated as the product of frequency x severity. In the first study period, HF scores decreased by a median of 4.7 units per day (36%) for those on placebo and by 6.4 units per day (50%) in those receiving fluoxetine, and the difference was not statistically significant between groups (P = 0.35). Table 3 shows the score at week 5. Subsequent cross-over analyses identified a significantly greater reduction with fluoxetine. The authors concluded that fluoxetine was associated with a modest improvement in HF score.

Dietary supplements:

Barton 1998 – Vitamin E vs placebo (n=104 total; crossover trial)

–HF score was calculated as the product of frequency x severity. After the first 4 weeks of therapy, the HF score decreased by 28% with vitamin E and 20% with placebo *(P* = 0.68). During the second treatment period, the mean hot-flash scores decreased by 0.03% and 25% in the placebo group and vitamin E group (P=0.24), respectively. A subsequent analysis encompassing the full crossover design suggested the presence of a small but statistically significant advantage of vitamin E over placebo.

Jacobson 2001 – Black cohosh (n=42) vs placebo (n=43)

–The HF score used was unclear in the study report. After 9 weeks, the HF score changed from baseline median 53.2 (IQR 25.3-71.3) to 31.0 (IQR 18.3-77.0) in the black cohosh group and from median 52.5 (IQR 28.9-93.0) to median 24.6 (IQR 16.4-64) in the placebo group; the difference was noted as not statistically significant, but no other data were provided.

Quella 2000 – Soy (n=87) vs placebo (n=88)

–Hot flash score was assessed using the formula of frequency x severity. Patients averaged approximately seven HFs per day during the baseline study week (SD 54.5), with an average HF score of 13 points (SD 59.0). The totals of patients reporting reductions in HF score of <25%, 25-50% and >50% were 44%, 21% and 35% in the soy group and 40%, 22% and 38% in the placebo group, respectively. The conclusions of the authors, based on the study data, was that soy did not significantly reduce hot flashes compared to placebo in this study.

Van Patten 2002 – Soy (n=78) vs placebo (n=79)

–HF score was assessed according to a formula that multiplied HFF by intensity for day and added it to HFF multiplied by intensity for night. This was calculated to be the HF score for 24 hours. The study reported there were no differences in hot flash related outcomes between groups: during the final 4 weeks of treatment, comparable changes from baseline in the soy group (mean (SD) change from baseline 18.0 (13.9) to final value 12.6 (13.4)) and placebo groups (mean (SD) change from baseline
18.9 (18.9) to final value 11.4 (11.3)) were observed.

Vitolins 2013 – Venlafaxine+soy protein (n=30) vs venlafaxine+milk protein (n=30) vs soy protein (n=30) vs milk protein (n=30) (prostate cancer trial)

–HF score calculated as the product of severity x frequency. No statistically significant differences were noted between soy and placebo throughout the study period. The venlafaxine group initially saw a decrease at 2 weeks, but this decrease was not sustained at 12 weeks. Results were reported as mean (SD) FH score at 12 weeks: venlafaxine and soy (-11.2, SD 10.9), venlafaxine and milk protein (-9.2, SD 7.2), placebo and soy (-13.6, SD 15.3), placebo and milk protein (-9.3, SD 8.5). The conclusion of the authors was that venlafaxine or soy were not effective in reducing hot flashes in men with prostate cancer on androgen deprivation therapy.

Acupuncture:

Bao 2014 – Acupuncture (n=25) vs sham acupuncture (n=26)

–HF score was determined using a 100-point visual analog scale (VAS) ≥ 20. The study presents comparison of median (IQR) scores between groups after 8 weeks of treatment. The chance in the sham acupuncture group wasn't statistically significant (from median (IQR) 20.5 (54.75) to 10 (47.25)),

while the change in the acupuncture group was significant (from median (IQR) 31 (67) to 14 (32.5)); the comparison of change between groups was not statistically significant (p=0.56). The authors reported no important differences between interventions.

Frisk 2009 – Acupuncture (n=13) vs electroacupuncture (n=11) (prostate cancer trial)

–Daily HF distress calculated by summing individual HF distress (scored from 0-10). After 52 weeks of treatment, mean daily HF distress changed from baseline median 7.6 (IQR 4.7-8.3) to median 4.3 (IQR) 1.3 – 7.7 in the acupuncture group and from baseline median 8.2 (IQR 6.5-10.7) to median 5.5 (IQR 3.8-6.9) in the electroacupuncture group (p=0.65 between groups).

Lesi 2016 – Acupuncture + enhanced self-care (n=85) vs enhanced self-care (n=105)

–In this study, HF score was defined by calculating the average number of hot flashes that occurred daily during the week before assessment and then multiplying that by the average daily severity (mild, moderate or severe). After having comparable mean HF scores at baseline, the HF score at **week 12** was higher in the enhanced self-group (mean (SD) 22.70 (19.40)) than in the acupuncture + enhanced self-care group (11.34 (14.75); p<0.001 for the between-group difference of -11.36, 95% CI -16.39 to -6.33). Similar mean differences favoring the acupuncture + enhanced self-care group were seen at both 3-month (-7.86, 95% CI -12.99 to -2.73) and 6-month follow-up (-8.82, 95% CI -14.04 to -3.61). The conclusion of the authors was that that combination of acupuncture with enhanced self-care was effective for the management of hot flashes.

Hot Flash Severity:

Data from 10 RCTs reported on frequency but could not be pooled in the analysis are presented below.

Pharmacologic therapies:

Bordeleau 2010 – Gabapentin vs venlafaxine (n=66 overall; crossover trial)

–HF severity was assessed as 1=mild, 2=moderate, 3=severe, 4=severe, and were averaged per day. Study treatment periods lasted 4 weeks, with 2-4 weeks washout in between. Findings performed to compare the intervention groups using a mixed modeling approach identified a venlafaxine to gabapentin ratio of 1.02 (near 1), suggesting little difference between intervention groups (p value >0.61). Analyses were also performed to compare groups as based upon patients' preferred treatment; amongst those that preferred venlafaxine (n=38), 94.7% reported decreased HF severity, while amongst those that preferred gabapentin (n=18), 94.4% reported decreased HF severity.

Walker 2010 – Venlafaxine (n=25) vs acupuncture (n=25)

–Treatments were provided for 12 weeks, with outcomes measured up to 1-year post-treatment. The study reports that ANOVA analysis of patient data over time found no important differences between intervention groups with regard to changes in HF severity (p>0.05; detailed numeric data are not reported). Both groups experienced some improvement, with a subsequent return toward baseline values after the end of treatment. The authors suggested acupuncture may offer similar benefits as venlafaxine, with better tolerability.

Loibl 2007– Clonidine (n=40) vs venlafaxine (n=40)

–The duration of this study was 4 weeks of treatment. HF severity was scored as 1=mild, 2=moderate, 3=severe, 4=very severe. The mean HF severity at baseline week was 2.1 for clonidine and 1.9 for venlafaxine with a P-value of 0.78. Findings for this outcome are not clearly reported in the study report. Author conclusions appear to suggest benefits of venlafaxine over clonidine for reduction of HF frequency, but not HF severity.

Pandya 2000 – Clonidine (n=99) vs placebo (n=99)

–The study included a 1-week baseline period and follow-up at 4, 8 and 12 weeks; HFs were scored as 1=mild, 2=moderate, 3=severe, 4=very severe). Mean (SE) severity grades at baseline were 2.2 (0.1) and 2.1 (0.1) in the clonidine and placebo groups, respectively. The study reported % changes from

these baseline values; median reductions of -11.7%, -17.3% and -9.3% were reported at 4, 8 and 12 weeks in the clonidine group while corresponding values of -8.5%, -10.5% and -8.3% were observed with placebo. None of the differences reached statistical significance.

Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30) (prostate cancer study)

–The duration reported findings at 4, 8 and 12 weeks; The authors reported that HFS (rated as mild, moderate or severe) was not significantly different at any point in the study. Patients in the venlafaxine are had lower HFS during the first 4 weeks of the study but this was not sustained at 12 weeks.

Dietary supplements:

Chen 2014 – Melatonin (n=48) vs placebo (n=47)

–The study duration was 4 months, and HF severity was scored as 1=mild, 2=moderate, 3=severe, 4=very severe. The study denotes that there were no statistically significant differences between the groups with regard to changes in the numbers of mild, moderate and severe HFs experienced.

Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30) (prostate cancer study)

– The duration reported findings at 4, 8 and 12 weeks; The authors reported that HFS (rated as mild, moderate or severe) was not significantly different at any point in the study. Patients in the venlafaxine are had lower HFS during the first 4 weeks of the study but this was not sustained at 12 weeks.

Hernandez Munoz – Black cohosh (90) vs usual care (46)

–Patients were compared in terms of the % free of hot flashes, % still having moderate hot flashes (a few episodes of heat with discrete sweating), and % still having severe hot flashes (≥5 or more sudden episodes of heat are experienced during the day, accompanied by sweating, sleep disturbances, feeling of irritation and anxiety) at study end. At the 52-week conclusion of the study, the proportions of patients who were free of hot flashes/still endured moderate hot flashes/still endured severe hot flashes were different between those receiving black cohosh (46.7%, 28.9%, and 24.4%) compared to usual care (0%, 26.1%, and 73.9%).

Jacobson 2001 – Black cohosh (n=42) vs placebo (n=43)

–Patients completed HF diaries at 30 and 60 days, with an additional questionnaire at final follow-up. HF severity was scores as 1=mild, 2=moderate, 3=severe. The study notes that both groups experienced a decline in HF severity during the first month of study preparation. The differences between groups in intensity at the end of the study were described as not statistically significant, and no additional data were provided.

Barton 1998 – Vitamin E vs placebo (n=104 overall; crossover trial)

–Diaries were used to measure HFs (including mean daily HF severity) during the baseline week and the two subsequent 4-week treatment periods. The authors suggest there were few to no benefits of Vitamin E for HF severity.

Sleep measures:

The systematic review identified 5 RCTs that reported on sleep measures.

Pharmacologic therapies:

Boekhout 2011 – Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)

–**Groningen Sleep Quality Scale (GSQ)** was assessed. Sleep quality was not found to differ between the venlafaxine and clonidine intervention groups; no additional data or information was provided.

Stearns 2005 – Paroxetine (2 dose levels; 10mg, 20mg) vs placebo (crossover trial, n=151 overall)

–**The MOS Sleep Problems Index** was assessed. All three intervention groups (placebo, paroxetine 10mg and paroxetine 20mg) were associated with improvements of at least 10 points in the MOS Sleep Problems Index from baseline, however Paroxetine 10mg was associated with significantly greater improvement compared to placebo.

Biglia 2009 – Gabapentin (n=60) vs vitamin E (n=55)

–Based on findings from the **PSQI**, gabapentin demonstrated a statistically significant improvement in sleep quality from baseline; the gabapentin group incurred a mean global PSQI score reduction of 21.33% at twelve weeks and a mean absolute reduction of 1.67 (95% CI 0.90-2.43). The authors note that no significant change from baseline to twelve weeks was observed in women receiving Vitamin E. No numeric data for vitamin E is provided, nor is a statistical comparison between the gabapentin and vitamin E groups.

Dietary supplements:

Chen 2014 – Melatonin (n=48) vs placebo (n=47)

–The authors 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 sub-domains.

Acupuncture:

Bao 2014 – Acupuncture (n=23) vs sham acupuncture (n=24)

–Assessed sleep quality and sleep disturbance using **Pittsburgh Sleep Quality Index (PSQI)**, which has both an overall score and seven domain scores (sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbance; use of sleeping medications; daytime dysfunction) which were summed to form a total score out of 21. Comparison of median and IQR scores between groups at 4, 8 and 12 weeks found no differences between acupuncture and sham acupuncture.

Depression:

The systematic review identified 10 RCTs that reported on depression.

Pharmacologic therapies:

Boekhout 2011 – Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)

–**The HADS tool** was evaluated. After twelve weeks, depression scores were significantly higher in patients receiving venlafaxine than patients receiving clonidine (p=0.03), suggesting more depression. However, no additional numeric details are provided, and statistical comparisons with the placebo group are not detailed in the study report.

Loprinzi 2000 – Venlafaxine (n=165 across three dose groups) vs placebo (n=56)

–The **Beck Depression Inventory** was evaluated (once per week for 5 weeks). The study authors reported that at the end of the study, totals of 16/48 (33% (evaluable patients in the placebo group, and corresponding totals of 11/40 (23%), 9/43 (21%) and 13/49 (27%) in the venlafaxine 37.5mg, 75mg and 150mg groups had depression scores consistent with the presence of at least mild depression.

Walker 2010 – Venlafaxine (n=25) vs acupuncture (n=25)

–The **Beck Depression Index Primary Care (BDI-PC)** was evaluated. Both the venlafaxine group and the acupuncture group were associated with statistically significant reductions in depression after 12 months. The study report presents no detailed numeric data for changes within either group or

the comparison of changes between groups; a figure within the report indicates overlapping confidence intervals at final follow-up, suggesting no statistically significant difference between groups was present. Digitized data from a study figure suggest reductions from 10.1 (SE 0.9) to 8.3 (SE 1.1) and from 12.1 (SE 0.8) to 9.6 (SE 1.1) in the venlafaxine group after twelve months.

Stearns 2005 – Paroxetine vs placebo (n=151 overall; crossover with 2 paroxetine groups)

–The **CES-D scale** was evaluated. The study authors reported that after five weeks, there were no differences in the percentages of patients in the placebo and paroxetine groups who improved, worsened or stayed the same in terms of depressive symptoms.

Kimmick 2006 – Sertraline vs placebo (n=62 overall; crossover study)

–The **CES-D scale** was evaluated. After 12 weeks, mean CES-D score increased in the sertraline group (from 11.2 (SD 9.2) to 12.8 (SD 11.7)) and decreased in the placebo group (from 11.5 (SD 7.9) to 7.9 (SD 6.8)). The study reports no important differences between groups with regard to effects on depression were identified.

Loprinzi 2009 – Gabapentin (n=161 across 3 dose groups) vs placebo (n=54)

–The **POMS-B Scale** was evaluated. At 4 weeks, no significant differences were identified between the gabapentin and placebo groups and its subdomains, which included depression/dejection. No additional numeric data are provided in the study report.

Biglia 2016 – Duloxetine (n=28) vs escitalopram (n=30)

–**Both BDI and MADRS** were evaluated. A significant reduction of depression from baseline was observed in both groups after both 4 and 12 weeks, with no important differences identified between treatments. In the duloxetine group, the mean MADRS score changed from 12.9 at baseline to 5.6 after 12 weeks (a 56.6% reduction), and BDI changed from 4.9 to 3.6 in the same time period (a 26.5% reduction). The corresponding changes in the escitalopram group were from 19.4 to 11.1 (a 42.8% reduction) for MADRS and from 8.3 to 6.6 (a 20.5% reduction) for BDI.

Dietary supplements:

Chen 2014 – Melatonin (n=48) vs placebo (n=47)

–The **CES-D Scale** was evaluated. There was very little change in depression at four months from baseline in both the melatonin (mean change -0.2 (SD 4.6)) and placebo (mean change 0 (SD 5.4)) groups. No differences with respect to impact on depression were observed (p=0.66).

Jacobson 2001 – Black cohosh (n=42) vs placebo (n=43)

–The study reports evaluating changes in several menopausal symptoms, one of which was depression, though further details are not provided with regard to approach to measurement. The article denotes that while symptoms in general improved in both groups, there were no changes that were specifically impacted by treatment.

Acupuncture:

Bao 2014 – Acupuncture (n=23) vs sham acupuncture (n=24)

–The **Center for Epidemiologic Studies Depression (CES-D) Scale** was evaluated. After eight weeks, reported median (IQR) changes in both the acupuncture group (reduction from median 16 (IQR of 9) at baseline to median 10 (IQR of 10.5)) and sham acupuncture group (reduction from median 10.5 (IQR of 10) at baseline to 6 (IQR of 11.25)) showed important changes within each group that reached statistical significance, while the difference between groups did not (p=0.44).

Sexual Function:

The systematic review identified 4 RCTs on sexual function.

Pharmacologic therapies:

Boekhout 2011 - Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)

–Looked at changes in the **overall Sexual Activity Questionnaire (SAQ)**. The authors report there were no important differences noted for sexual function between the intervention groups; no detailed numeric data are provided to give further insights.

Loprinzi 2000 - Venlafaxine (n=165 across three dose groups) vs placebo (n=56)

–Looked at **libido change based on element 21 of the Beck Depression Index**. Improvements in libido were observed in the placebo group as well as patients receiving all doses of venlafaxine, however the authors do not report formal statistical comparisons to establish statistical significance nor clinical relevance of the between-group differences. Numeric values are also unreported, with only a line graph presented (one profile per group).

Stearns 2005 - Paroxetine vs placebo (n=151 overall)

–Looked at the **Medical Outcomes Study (MOS) Sexual Problems Index**. The study authors report that the following numbers of patients improved / stayed the same / worsened: Placebo = 9 (25%) / 21 (58%) / 6 (17%); Paroxetine 10mg = 3 (20%) / 10 (67%) / 2 (13%); Paroxetine 20mg = 4 (25%) / 7 (44%) / 5 (31%). Thus, there were no important gains associated with paroxetine.

Loprinzi 2002 - Fluoxetine vs placebo (n=81 overall)

–Looked at **libido change based on element 21 of the Beck Depression Index**. The study report noted that after five weeks of treatment, totals of 11 patients in the fluoxetine group and 9 in the placebo group had improved libido compared to baseline, while totals of 1 patient in the fluoxetine group and 3 in the placebo group had reduced libido compared to baseline. Fluoxetine thus appeared to offer some gains, though no formal statistical comparisons were performed.

Quality of Life:

The systematic review identified 15 RCTs that reported on quality of life.

Study and Year	Population	Tool used to Assess Study Participants	Time of assessment	Treatments compared	Significant difference between groups?
Bordeleau 2010	BC	Medical outcomes study SF-36	4 wks	Gabapentin, venlafaxine	NO
Wu 2009	BC	FACT-G	6 wks	Placebo, sertraline	NO
Loprinzi 2009	PC	Scored on scale ranging from 0-10	4 wks	Placebo, gabapentin	NO
Loprinzi 2007	BC	Weekly linear analog self -assessment questionnaire	4 wks	Gabapentin, gabapentin+antidepressant	NO
Kimmick 2006	BC	FACT-B	6 wks	Placebo, sertraline	NO
Loprinzi 2000	BC	Two single item global QoL questions	4 wks	Placebo, venlafaxine	YES
Pandya 2000	BC	Scored on scale ranging from 1-10	12 wks	Placebo, clonidine	NO
Stearns 2005	BC	EuroQol	4 wks	Placebo, sertraline	NO
Loprinzi 2002	BC	Global rating of health and well being (0-100)	4 wks	Placebo, fluoxetine	NO
Biglia 2009	BC	MRS; SF-36 (mental, physical)	12 wks	Gabapentin, vitamin E	UNCLEAR
MacGregor 2005	BC	EORTC QLQ30	12 wks	Placebo, soy	NO
Jacobson 2001	BC	Global rating of health and well being (0-100)	9 wks	Placebo, black cohosh	NO
Vitolins 2013	PC	FACT-P	12 wks	Venlafaxine, soy	NO
Bao 2014	BC	EuroQoL	8 wks	Sham acupuncture, acupuncture	NO
Walker 2010	BC	MenQOL tool	64 wks	Acupuncture, venlafaxine	NO

Loprinzi 2000 – Venlafaxine vs placebo

- From baseline to week 4, overall quality of life increased in the venlafaxine groups (average 3-point increase) and decreased in the placebo group (average of 3-point decrease). The difference in the venlafaxine groups was not significant.

Bordeleau 2010 – Venlafaxine vs gabapentin

- No difference was seen in QOL (measured by the MOS-SF36 QOL questionnaire) in the venlafaxine and gabapentin groups after 4 weeks of treatment.

Vitolins 2003 – Venlafaxine vs soy

-Between the venlafaxine and soy groups, no statistically significant differences were seen in the FACT-G or FACT-P subscales. For participants in the soy arm, statistically significant improvements were found in the emotional and functional subscales and in FACT-G and FACT-P total scores.

Adverse Events/Tolerability:

Outcomes reported (with available quantitative data) were as follows:

–***3 or more studies:*** constipation (n=8); headache (n=7); nausea (n=7); fatigue/sleepiness (n=6); diarrhea (n=4); dry mouth (n=4); weight gain (n=4); vomiting (n=4); appetite loss (n=3); abnormal sweating (n=3); insomnia/poor sleep (n=3); Grade 1-4 TEAEs/toxicities (n=3); mood change/moodiness (n=3); rash/itchiness (n=3)

–***1-2 studies:*** anxiety (n=2); bruising (n=2); hypertension/increased BP (n=2);vaginal bleeding/spotting (n=2); abdominal bloating (n=1); cramping (n=1); gas (n=1); undesirable appetite increase (n=1); appendectomy (n=1); arrhythmia (n=1); back pain (n=1); nightmares (n=1); blurred vision (n=1); depression (n=1)

Headache:

Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, electroacupuncture vs gabapentin, electroacupuncture vs placebo, gabapentin vs placebo, melatonin vs placebo, electroacupuncture vs sham acupuncture, gabapentin vs sham acupuncture, placebo vs sham acupuncture, placebo vs soy, acupuncture vs venlafaxine, placebo vs vitamin E.

Constipation:

Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, electroacupuncture vs gabapentin, electroacupuncture vs placebo, gabapentin vs placebo, electroacupuncture vs sham acupuncture, gabapentin vs sham acupuncture, placebo vs sham acupuncture, placebo vs soy, acupuncture vs venlafaxine, placebo vs venlafaxine, placebo vs vitamin E, clonidine vs venlafaxine, black cohosh vs placebo, clonidine vs placebo.

Fatigue:

Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, electroacupuncture vs gabapentin, electroacupuncture vs placebo, gabapentin vs placebo, electroacupuncture vs sham acupuncture, gabapentin vs sham acupuncture, placebo vs sham acupuncture, placebo vs venlafaxine, placebo vs vitamin E, clonidine vs venlafaxine, clonidine vs placebo.

Nausea:

Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, placebo vs soy, placebo vs venlafaxine, placebo vs vitamin E, clonidine vs placebo.

Precise estimate of harm based on small number of events for clonidine (6/41) vs venlafaxine (8/41): OR=0.33; 95% CI: 0.13, 0.81

6. Evidence Profiles (Developed using GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.)

- **Cognitive-behavioral therapy for patients**
- **Hypnosis or relaxation therapy for patients**
- **Physical activity for patients**
- **Venlafaxine for men**

Question: Should cognitive behavioral therapy rather than no treatment be used in patients with cancer who are experiencing drug or surgery-induced hot flashes?

Setting: Clinical care

Bibliography:

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*, 4124–4133. https://doi.org/10.1200/JCO.2012.41.8525

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 randomized controlled trial. *The Lancet Oncology, 13*, 309–318. https://doi.org/10.1016/S1470-2045(11)70364-3

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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	psychological interventions (such as cognitive behavioral therapy)	no treatment	Relative (95% CI)	Absolute (95% CI)		
Hot Flash Frequency (follow up: 32 weeks)												
1 [3]	randomized trials	serious [a]	not serious	serious [b]	serious [c]	none	33	35	-	MD **12.8 episodes fewer** (25.21 fewer to 3.86 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (follow up: 32 weeks; assessed with: Hospital Anxiety and Depression Scale (HADS))												
1 [3]	randomized trials	serious [a]	not serious	serious [b]	serious [d]	none	33	35	-	MD **0.52 points lower** (1.15 lower to 2.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of Life (follow up: 26 weeks; assessed with: depression subscale of the Women's Health Questionnaire (WHQ))												
1 [2]	randomized trials	not serious	not serious	serious [e]	serious [f,g]	none	47	49	-	MD **0.13 points lower** (0.22 lower to 0.05 lower)	⨁⨁◯◯ LOW	CRITICAL
Quality of Life (follow up: 6 months; assessed with: Habit and Pleasure subscales of the Sexual Activity Questionnaire (SAQ))												
1 [1]	randomized trials	serious [h]	not serious	serious [i]	serious [c]	none	Looked at both the Habit and Pleasure subscales of the Sexual Activity Questionnaire (SAQ). Data analyses identified a statistically significant improvement in sexual function (SAQ-Habit) in the CBT + exercise (n=58) group compared to the control group (n=54) at long-term follow-up (effect size 0.65,				⨁◯◯◯ VERY LOW	CRITICAL

							p=0.002). Supplemental per protocol analyses also identified important gains in SAQ-Pleasure in the CBT (n=55) and CBT + exercise groups.		

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Stefanopoulou 2015 demonstrates some concern with lack of blinding of participants and assessors, as well as incomplete outcome data, selective reporting, and analysis.
b. Stefanopoulou 2015 conducted among men only and may not be generalizable to the entire population.
c. Small sample reported.
d. The 95% CI includes the potential for benefit, as well as harm. Small sample reported.
e. Mann 2012 conducted among women only and may not be generalizable to the entire population.
f. The 95% CI may not include meaningful difference. Small sample reported.
g. Duijts 2012 compared CBT + exercise vs. exercise vs. CBT vs control among women with breast cancer experiencing treatment-induced menopausal symptoms and reported no statistical difference at 6 months; however, raw numbers were not reported.
h. Duijts 2012 introduced the potential of bias due to lack of blinding of outcome assessors and selective reporting.
i. Duijts conducted among women only and may not be generalizable to the entire population.

References

1. Duijts, Saskia FASFA, Marc van Beurden, Hester SAHSA Oldenburg, Myra S. Hunter, Jacobien M. Kieffer, Martijn M. Stuiver, Miranda A. Gerritsma et al. "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." J Clin Oncol 30, no. 33 (2012): 4124-4133.
2. Mann, Eleanor, Melanie J. Smith, Jennifer Hellier, Janet A. Balabanovic, Hisham Hamed, Elizabeth A. Grunfeld, and Myra S. Hunter. "Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomized controlled trial." The lancet oncology 13, no. 3 (2012): 309-318.
3. Stefanopoulou, Evgenia, Omar Yousaf, Elizabeth A. Grunfeld, and Myra S. Hunter. "A randomized controlled trial of a brief cognitive behavioural intervention for men who have hot flushes following prostate cancer treatment (MANCAN)." Psycho-Oncology 24, no. 9 (2015): 1159-1166.

Question: Should hypnosis or relaxation therapy rather than no treatment be used in patients with cancer who are experiencing drug or surgery-induced hot flashes?

Setting: Clinical care

Bibliography:

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*, 5022–5026. https://doi.org/10.1200/JCO.2008.16.6389

Fenlon, D. (1999). Relaxation therapy as an intervention for hot flashes in women with breast cancer. *European Journal of Oncology Nursing, 3*, 223–231. https://doi.org/10.1016/S1462-3889(99)81335-0

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

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*, 243–250. https://doi.org/10.1080/13697130500118050

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hypnosis or relaxation therapy	no treatment	Relative (95% CI)	Absolute (95% CI)		
Hot Flash Frequency (follow up: 5 weeks)												
1 [1]	randomized trials	serious [a]	not serious	not serious [b]	serious [c,d]	none	46	51	-	MD **5 lower** (0 to 10 lower)	⨁⨁◯◯ LOW	CRITICAL

Hot Flash Composite Score (assessed with: Hot Flash Related Daily Interference Scale)

1 [2]	randomized trials	serious [e]	not serious	not serious [f]	serious [c]	none	Patients in the hypnosis group demonstrated statistically significantly better improvement in HF score (from baseline mean (SD) 15.05 (13.75) to 4.84 (5.02)) compared to those in the control group (from baseline mean (SD) 17.17 (10.37) to 15.60 (10.71); p<.001). The authors concluded that hypnosis appears to reduce HFs in breast cancer survivors.				⊕⊕◯◯ LOW	CRITICAL

Hot Flash Severity (follow up: 3 months)

1 [1]	randomized trials	serious [a]	not serious	not serious [b]	serious [c,d]	none	46	51	-	MD **0.56 lower** (0.02 lower to 1.18 lower)	⊕⊕◯◯ LOW	CRITICAL

Depression (follow up: 5 weeks; assessed with: Center for Epidemiologic Studies Depression (CES-D) Scale)

1 [2]	randomized trials	serious [e]	not serious	serious [f]	serious [c,d]	none	Data suggested an important mean reduction in the hypnosis group (n=30; from 29.48 (SD 7.72) to 24.58 (SD 6.45)) compared to the waitlist group (n=30; 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).				⊕◯◯◯ VERY LOW	CRITICAL

Sleep Measures (follow up: 5 weeks; assessed with: Medical Outcomes Study (MOS) Sleep Problems Index)

1 [2]	randomized trials	serious [e]	not serious	not serious [f]	serious [c]	none	Hypnosis was associated with an improvement in sleep compared to the control group after five weeks treatment (F-test from an analysis of covariance reported; p <0.001), as well as in comparison to baseline levels within the group (MOS Sleep Index mean (SD) of 24.26 (8.17) at baseline and 13.71 (4.35) at follow-up).				⊕⊕◯◯ LOW	CRITICAL

Quality of Life (follow up: 13 weeks; assessed with: FACT-ES)[g]

1 [1]	randomized trials	serious [a]	not serious	not serious [b]	serious [c,h]	none	46	54	-	MD **1.5 points lower** (7 lower to 4.4 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Fenlon 2008 has some concerns with missing outcome reporting.
b. Fenlon 2008 compares relaxation to control among women with breast cancer.
c. Small sample reported.
d. The 95% CI may not include meaningful improvement.
e. Elkins 2008 demonstrates some concerns with missing outcome data.
f. Elkins 2008 compares hypnosis to control among women with breast cancer.
g. Functional Assessment of Cancer Therapy with the endocrine subscale
h. The 95% CI includes the potential for possible harm, as well as possible benefit.

References

1. Fenlon, Deborah R., Jessica L. Corner, and Joanne S. Haviland. "A randomized controlled trial of relaxation training to reduce hot flashes in women with primary breast cancer." Journal of pain and symptom management 35, no. 4 (2008): 397-405.
2. Elkins, Gary, Joel Marcus, Vered Stearns, Michelle Perfect, M. Hasan Rajab, Christopher Ruud, Lynne Palamara, and Timothy Keith. "Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors." Journal of Clinical Oncology 26, no. 31 (2008): 5022-5026.

Question: Should physical activity rather than no treatment be used in patients with cancer who are experiencing drug or surgery-induced hot flashes?

Setting: Clinical care

Bibliography:

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*, 1301–1309. https://doi.org/10.1007/s00520-009-0587-5

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*, 2175–2184. https://doi.org/10.1002/cncr.29330

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*, 4124–4133. https://doi.org/10.1200/JCO.2012.41.8525

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	behavioral interventions (such as exercise, yoga, tai chi)	no treatment	Relative (95% CI)	Absolute (95% CI)		
Depression (follow up: 24 weeks; assessed with: HADS)												
1 [1]	randomized trials	serious [a]	not serious	not serious [b,c]	serious [d,e]	none	19	21	-	MD 0.1 points higher (0.8 lower to 1 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of Life (follow up: 24 weeks; assessed with: FACT-B)												
1 [1]	randomized trials	serious [a]	not serious	not serious [b]	serious [d,f]	none	19	21	-	MD 12.6 points higher (4.2 higher to 21.1 higher)	⨁⨁◯◯ LOW	CRITICAL
Hot Flash Frequency - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Hot Flash Composite Score - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	behavioral interventions (such as exercise, yoga, tai chi)	no treatment	Relative (95% CI)	Absolute (95% CI)		
Hot Flash Severity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Sleep - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Sexual Function - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse events - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Cramer 2015 had a risk of bias due to blinding of participants and providers.

b. Cramer 2015 compares yoga to usual care among women with breast cancer.

c. Duijts 2012 compares exercise to usual care among women with breast cancer and narratively reports no difference between groups at 6 months.

d. Small sample reported.

e. The 95% CI includes the potential for possible harm, as well as possible benefit.

f. MID may fall between 4 and 7 points making this a meaningful increase.

g. Duijts 2012 presents a risk to bias based on lack of blinding of outcome assessors and selective outcome reporting.

References

1. Cramer, Holger, Sybille Rabsilber, Romy Lauche, Sherko Kümmel, and Gustav Dobos. "Yoga and meditation for menopausal symptoms in breast cancer survivors—a randomized controlled trial." Cancer 121, no. 13 (2015): 2175-2184.

Question: Should venlafaxine rather than no treatment be used in men with cancer who are experiencing drug or surgery-induced hot flashes?

Setting: Clinical care

Bibliography:

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*, 4092–4098. https://doi.org/10.1200/JCO.2012.48.1432

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	venlafaxine	no treatment	Relative (95% CI)	Absolute (95% CI)		
Hot Flash Frequency (follow up: 12 weeks)												
1	randomized trials	serious [a]	not serious	not serious [b]	very serious [c]	none	19	21	-	MD **0.7 events higher** (1.1 lower to 2.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Hot Flash Severity (follow up: 12 weeks)												
1	randomized trials	serious [a]	not serious	not serious [b]	very serious [d]	none	19	21	-	MD **0.1 lower** (0.56 lower to 0.36 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Hot Flash Composite Score												
1	randomized trials	serious [a]	not serious	not serious [b]	very serious [d]	none	19	21	-	MD **0.1 lower** (4.97 lower to 4.77 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of Life (follow up: 12 weeks; assessed with: FACT-P; Scale from: 0 to 156)[e]												
1	randomized trials	serious [a]	not serious	not serious [b]	very serious [d]	none	34	42	-	MD **2.3 points higher** (14.47 lower to 19.07 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Vitolins 2013 has concerns with blinding of outcome assessors and missing or incomplete data.

b. Vitolins 2013 compared venlafaxine with milk protein powder to placebo with milk protein powder.

c. The 95% CI includes the potential for possible harm, as well as possible benefit. Small sample reported.

d. The 95% CI includes the potential for possible benefit, as well as possible harm. Small sample reported.

e. Functional Assessment of Cancer Therapy-Prostate

7. Evidence-to-Decision frameworks (Developed using GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.)

- **Cognitive-behavioral therapy for patients**
- **Hypnosis for patients**
- **Physical activity for patients**
- **Various interventions—Pharmacologic, dietary supplements, acupuncture, electroacupuncture**

RECOMMENDATION

Should cognitive behavioral therapy rather than no treatment be used in patients with cancer who are experiencing drug- or surgery-induced hot flashes?	
POPULATION:	Women or men with cancer with drug- or surgery-induced hot flashes
INTERVENTION:	Psychological interventions (such as cognitive behavioral therapy)
COMPARISON:	No treatment
MAIN OUTCOMES:	Frequency of hot flashes (per 24 hours); severity of hot flashes; quality of life (sleep/sleep quality in addition to global QoL from any validated scale); depression; adverse events

SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation - Population perspective
BACKGROUND:	Hot flashes and night sweats may be side effects of cancer or its treatment. Hot flashes and night sweats affect quality of life in many patients with cancer. Treatment options that have been provided for persons experiencing hot flashes due to breast or prostate cancer include pharmacologic, psychological or behavioral interventions, as well as acupuncture and herbal supplements.
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Marcelle Kaplan, MS, RN, CNS, Jessica Bay Leibelt, MSN, NP-C, AOCNP®, Laura Boehnke Michaud, PharmD, BCOP, FASHP, CMQ, Paz Fernández-Ortega, PhD, MSc, RN, BPsych, Dale Grimmer, MS, RN, AOCN®, CCRC, Suzanne Mahon, RN, DNSC, AOCN®, AGN-BC, Bernardo L. Rapoport, Dip in Med (UBA), MMed, and Valencia Robinson, EdS. Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research suggests that hot flashes are experienced by 51%–81% of women with breast cancer and 69%–76% of men with prostate cancer (Fisher et al., 2013). Hot flashes can negatively impact quality of life and co-occur with mood and sleep disturbances (Fisher et al., 2013). The lack of tolerability of hot flash symptoms can lead to discontinuation of therapies used to prevent or treat cancer.	The panel decided to focus the discussion for this recommendation on Cognitive Behavioral Therapy (CBT).

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See table below	The panel determined the magnitude of the desirable outcomes to be small.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with psychological interventions (such as cognitive behavioral therapy)
Hot Flash Frequency follow up: 32 weeks	68 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean hot Flash Frequency was 0 episodes	MD 12.8 episodes fewer (25.21 fewer to 3.86 fewer)
Quality of life assessed with: Hospital Anxiety and Depression Scale (HADS) follow up: 32 weeks	68 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,c,d]	-	The mean quality of life was 0 points	MD 0.52 points lower (1.15 lower to 2.2 higher)
Quality of Life assessed with depression subscale of the Women's Health Questionnaire (WHQ) follow up: 26 weeks	96 (1 RCT)[2]	⨁⨁◯◯ LOW[e,f,g]	-	The mean quality of Life was 0 points	MD 0.13 points lower (0.22 lower to 0.05 lower)
Quality of Life assessed with: Habit and Pleasure	215 (1 RCT)[3]	⨁◯◯◯ VERY LOW[b,h,i]	-	Looked at both the Habit and Pleasure subscales of the Sexual Activity Questionnaire (SAQ). Data analyses identified a statistically significant	

subscales of the Sexual Activity Questionnaire (SAQ) follow up: 6 months				improvement in sexual function (SAQ-Habit) in the CBT + exercise (n=58) group compared to the control group (n=54) at long-term follow-up (effect size 0.65, p=0.002). Supplemental per protocol analyses also identified important gains in SAQ-Pleasure in the CBT (n=55) and CBT+exercise groups.

1. Stefanopoulou, Evgenia, Omar Yousaf, Elizabeth A. Grunfeld, and Myra S. Hunter. "A randomised controlled trial of a brief cognitive behavioural intervention for men who have hot flushes following prostate cancer treatment (MANCAN)." Psycho-Oncology 24, no. 9 (2015): 1159-1166.
2. Mann, Eleanor, Melanie J. Smith, Jennifer Hellier, Janet A. Balabanovic, Hisham Hamed, Elizabeth A. Grunfeld, and Myra S. Hunter. "Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial." The lancet oncology 13, no. 3 (2012): 309-318.
3. Duijts, Saskia FASFA, Marc van Beurden, Hester SAHSA Oldenburg, Myra S. Hunter, Jacobien M. Kieffer, Martijn M. Stuiver, Miranda A. Gerritsma et al. "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." J Clin Oncol 30, no. 33 (2012): 4124-4133.

a. Stefanopoulou 2015 conducted among men only and may not be generalizable to the entire population.
b. Small sample reported
c. Stefanopoulou 2015 demonstrates some concern with lack of blinding of participants and assessors, as well as incomplete outcome data, selective reporting, and analysis.
d. The 95% CI includes the potential for benefit, as well as harm. Small sample reported.
e. Mann 2012 conducted among women only and may not be generalizable to the entire population.
f. The 95% CI may not include meaningful difference. Small sample reported.
g. Duijts 2012 compared CBT+exercise vs. exercise vs. CBT vs control among women with breast cancer experiencing treatment-induced menopausal symptoms and reported no statistical difference at 6 months; however, raw numbers were not reported.
h. Duijts 2012 introduced the potential of bias due to lack of blinding of outcome assessors and selective reporting.
i. Duijts conducted among women only and may not be generalizable to the entire population

Undesirable Effects

How substantial are the undesirable anticipated effects?

<table>
<tr><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr>
<td>○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
● Don't know</td>
<td>
<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Certainty of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with no treatment</th><th>Risk difference with psychological interventions (such as cognitive behavioral therapy)</th></tr>
<tr><td>Hot Flash Frequency follow up: 32 weeks</td><td>68 (1 RCT)[1]</td><td>⨁◯◯◯ VERY LOW[a,b,c]</td><td>-</td><td>The mean hot Flash Frequency was 0 episodes</td><td>MD 12.8 episodes fewer (25.21 fewer to 3.86 fewer)</td></tr>
<tr><td>Quality of life assessed with: Hospital Anxiety and Depression Scale (HADS) follow up: 32 weeks</td><td>68 (1 RCT)[1]</td><td>⨁◯◯◯ VERY LOW[a,c,d]</td><td>-</td><td>The mean quality of life was 0 points</td><td>MD 0.52 points lower (1.15 lower to 2.2 higher)</td></tr>
<tr><td>Quality of Life assessed with: depression subscale of the Women's Health Questionnaire (WHQ) follow up: 26 weeks</td><td>96 (1 RCT)[2]</td><td>⨁⨁◯◯ LOW[e,f,g]</td><td>-</td><td>The mean quality of Life was 0 points</td><td>MD 0.13 points lower (0.22 lower to 0.05 lower)</td></tr>
<tr><td>Quality of Life assessed with: Habit and Pleasure subscales of the Sexual Activity</td><td>215 (1 RCT)[3]</td><td>⨁◯◯◯ VERY LOW[b,h,i]</td><td>-</td><td colspan="2">Looked at both the Habit and Pleasure subscales of the Sexual Activity Questionnaire (SAQ). Data analyses identified a statistically significant improvement in sexual function (SAQ-Habit) in the CBT + exercise (n=58) group</td></tr>
</table>
</td>
<td>CBT may have some adverse outcomes; however, the panel was not aware of this reported in the cancer literature. The panel decided that future recommendations could be informed by examining the general population for adverse events from CBT.</td>
</tr>
</table>

Questionnaire (SAQ) follow up: 6 months				compared to the control group (n=54) at long-term follow-up (effect size 0.65, p=0.002). Supplemental per protocol analyses also identified important gains in SAQ-Pleasure in the CBT (n=55) and CBT + exercise groups.	

1. Stefanopoulou, Evgenia, Omar Yousaf, Elizabeth A. Grunfeld, and Myra S. Hunter. "A randomised controlled trial of a brief cognitive behavioural intervention for men who have hot flushes following prostate cancer treatment (MANCAN)." Psycho-Oncology 24, no. 9 (2015): 1159-1166.
2. Mann, Eleanor, Melanie J. Smith, Jennifer Hellier, Janet A. Balabanovic, Hisham Hamed, Elizabeth A. Grunfeld, and Myra S. Hunter. "Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial." The lancet oncology 13, no. 3 (2012): 309-318.
3. Duijts, Saskia FASFA, Marc van Beurden, Hester SAHSA Oldenburg, Myra S. Hunter, Jacobien M. Kieffer, Martijn M. Stuiver, Miranda A. Gerritsma et al. "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." J Clin Oncol 30, no. 33 (2012): 4124-4133.

a. Stefanopoulou 2015 conducted among men only and may not be generalizable to the entire population.
b. Small sample reported
c. Stefanopoulou 2015 demonstrates some concern with lack of blinding of participants and assessors, as well as incomplete outcome data, selective reporting, and analysis.
d. The 95% CI includes the potential for benefit, as well as harm. Small sample reported.
e. Mann 2012 conducted among women only and may not be generalizable to the entire population.
f. The 95% CI may not include meaningful difference. Small sample reported.
g. Duijts 2012 compared CBT+exercise vs. exercise vs. CBT vs control among women with breast cancer experiencing treatment-induced menopausal symptoms and reported no statistical difference at 6 months; however, raw numbers were not reported.
h. Duijts 2012 introduced the potential of bias due to lack of blinding of outcome assessors and selective reporting.
i. Duijts conducted among women only and may not be generalizable to the entire population.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Hot flash symptoms among breast cancer survivors are reported with negative emotional perceptions and behavioral consequences. Often symptoms are concomitant with difficulty sleeping, fatigue, interruption in sexual relations, sleepiness, nervousness, and mood changes (Barton & Loprinzi, 2004). A qualitative study reported on the feelings identified by 35 women in regard to experiencing hot flashes following breast cancer (Hunter, Coventry, Mendes, & Grunfeld, 2009). Themes most commonly mentioned included negative beliefs about the perception when experiencing these symptoms in public. "Social anxiety/embarrassment" was the most commonly mentioned. Additionally, sleep quality and tiredness were commonly recognized as impacted by HF/NS.	The panel determine that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel noted the very low certainty in evidence and the closely balanced small benefits and unknown harms.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Alternative/Complementary, Psychological and Physical price examples accessed May 15, 2019** **Hypnosis/Relaxation Therapy** • $14.91: "Relaxation Techniques: Reduce Stress and Anxiety and Enhance Well-being" audio CD (https://www.amazon.com/Relaxation-Techniques-Anxiety-Enhance-Well-being/dp/1845900782) • $75 – $125 average price per hypnosis session (2017? American Association of Professional Hypnotherapists http://www.aaph.org/hypnosis-FAQ) **Acupuncture** • $60 - 120 average per session (https://www.acufinder.com/Acupuncture+Information/Detail/How+much+does+an+acupuncture+treatment+cost+) **Cognitive Behavioral Therapy** • $100 or more per hour, potentially (Anxiety and Depression Association of America: https://adaa.org/finding-help/treatment/low-cost-treatment.) **Exercise/Physical Activity** • $19.95: Dr. Scholl's Women's Aspire Medium and Wide Width Walking Shoe (https://www.walmart.com/ip/Women-s-Aspire-Medium-and-Wide-Width-Walking-Shoe/682850282?athcpid=682850282&athpgid=athenaItemPage&athcgid=null&athznid=PWVUB&athieid=v0&athstid=CS020&athguid=4f87b163-ed7-16abddb32a1c91&athena=true) • $50 per month average sports club dues in 2016 (https://money.cnn.com/2018/01/12/news/companies/planet-fitness/index.html) • $80 - $125 average for a one-hour personal training session in 2015 (https://www.angieslist.com/articles/what-factors-affect-cost-personal-trainer.htm) **Yoga** • $12.51: "Rodney Yee Complete Yoga for Beginners" DVD at Walmart.com (https://www.walmart.com/ip/Rodney-Yee-Complete-Yoga-for-Beginners/46606164) • $15 - $25 per hour average cost of yoga classes (https://lessons.com/costs/yoga-classes-cost) **Tai chi** • $9.88: "Tai chi for Beginners" DVD https://www.walmart.com/ip/Tai-Chi-for-Beginners-DVD/10779247 • $15 – $159 per hour for tai chi chuan lessons (https://takelessons.com/sports-and-fitness/tai-chi-chuan-lessons)	The panel agreed that the cost of CBT is greater than not providing that treatment.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	A search of the literature identified one study that examined the physical and psychosocial effects of breast cancer treatment differences between younger and older rural survivors based on menopausal status at diagnosis (Befort & Klemp, 2011). Younger women who are premenopausal at the time of breast cancer diagnosis report increased rates of menopausal side effects as well as more pronounced deficits in emotional and social functioning and cognitive performance. Women who were premenopausal at diagnosis were significantly more likely to experience numerous symptoms at the time of treatment and currently, including higher rates of hot flashes, vaginal dryness, loss of sexual desire, and weight gain. Negative physical and psychosocial sequelae of breast cancer were common in a rural population and were significantly worse for premenopausal women.	The panel agreed that because of the cost incurred by the intervention there may be increased health inequity, especially for those persons who are underinsured or uninsured.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	One study reported that a guided self-help cognitive behavioral intervention was well-received by men receiving androgen deprivation therapy experiencing hot flashes (Grunfeld, Hunter, & Yousaf, 2017).	The panel noted that CBT may be more acceptable with the overall cancer diagnosis rather than the hot flashes symptoms alone; however, it is probably generally acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel noted that the feasibility of providing CBT may vary depending on the length of the course of treatment, which would also relate to the cost of the CBT. The panel was concerned about having a standardized regimen of CBT to treat hot flashes symptoms.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

○	○	○	○	○

CONCLUSIONS

Recommendation

Among persons with cancer experiencing drug- or surgery-induced hot flashes, the Oncology Nursing Society guideline panel *recommends cognitive behavioral therapy only in the context of a clinical trial* (no recommendation, knowledge gap).

Justification

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 ONS Guideline 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.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Additional research on the components of CBT that are effective, cost effectiveness and sustainability of the effects of CBT

IN-TEXT CITED REFERENCES

Barton, D., & Loprinzi, C. L. (2004). Making sense of the evidence regarding nonhormonal treatments for hot flashes. *Clinical Journal of Oncology Nursing, 8*, 39–42. https://doi.org/10.1188/04.CJON.39-42

Befort, C.A., & Klemp, J. (2011). Sequelae of breast cancer and the influence of menopausal status at diagnosis among rural breast cancer survivors. *Journal of Women's Health, 20*, 1307–1313. https://doi.org/10.1089/jwh.2010.2308

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, 63*, 167–192. https://doi.org/10.3322/caac.21171

Grunfeld, E.A., Hunter, M.S., & Yousaf, O. (2017). Men's experience of a guided self-help intervention for hot flushes associated with prostate cancer treatment. *Psychology, Health & Medicine, 22*, 425–433. https://doi.org/10.1080/13548506.2016.1195504

Hunter, M.S., Coventry, S., Mendes, N., & Grunfeld, E.A. (2009). Menopausal symptoms following breast cancer treatment: a qualitative investigation of cognitive and behavioural responses. *Maturitas, 63*, 336–340. https://doi.org/10.1016/j.maturitas.2009.06.003

RECOMMENDATION

Should hypnosis or relaxation therapy rather than no treatment be used in patients with cancer who are experiencing drug- or surgery-induced hot flashes?

POPULATION:	Women or men with cancer with drug- or surgery-induced hot flashes
INTERVENTION:	Hypnosis or relaxation therapy
COMPARISON:	No treatment
MAIN OUTCOMES:	Frequency of hot flashes (per 24 hours); severity of hot flashes; quality of life (sleep/sleep quality in addition to global QoL from any validated scale; depression; adverse events
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation - Population perspective
BACKGROUND:	Hot flashes and night sweats may be side effects of cancer or its treatment. Hot flashes and night sweats affect quality of life in many patients with cancer. Treatment options that have been provided for persons experiencing hot flashes due to breast or prostate cancer include pharmacologic, psychological or behavioral interventions, as well as acupuncture and herbal supplements.
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Marcelle Kaplan, MS, RN, CNS, Jessica Bay Leibelt, MSN, NP-C, AOCNP®, Laura Boehnke Michaud, PharmD, BCOP, FASHP, CMQ, Paz Fernández-Ortega, PhD, MSc, RN, BPsych, Dale Grimmer, MS, RN, AOCN®, CCRC, Suzanne Mahon, RN, DNSC, AOCN®, AGN-BC, Bernardo L. Rapoport, Dip in Med (UBA), MMed, and Valencia Robinson, EdS. Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research suggests that hot flashes are experienced by 51%–81% of women with breast cancer and 69%–76% of men with prostate cancer (Fisher et al., 2013). Hot flashes can negatively impact quality of life and co-occur with mood and sleep disturbances (Fisher et al., 2013). The lack of tolerability of hot flash symptoms can lead to discontinuation of therapies used to prevent or treat cancer.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	An NMA compared treatment options among persons with cancer who experienced hot flashes (Hutton et al., manuscript submitted for publication, 2020). This review identified 4 RCTs that reported on hypnosis or related interventions for persons with cancer experiencing hot flashes.	The panel determined the magnitude of the desirable outcomes to be small.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with hypnosis or relaxation therapy
Hot Flash Frequency follow up: 5 weeks	97 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,c,d]	-	The mean hot Flash Frequency was 0	MD 5 lower (0 to 10 lower)
Hot Flash Composite Score assessed with: Hot Flash Related Daily Interference Scale	60 (1 RCT)[2]	⨁⨁◯◯ LOW[c,e,f]	-	Patients in the hypnosis group demonstrated statistically significantly better improvement in HF score (from baseline mean (SD) 15.05 (13.75) to 4.84 (5.02)) compared to those in the control group (from baseline mean (SD) 17.17 (10.37) to 15.60 (10.71); p<.001). The authors concluded that hypnosis appears to reduce HFs in breast cancer survivors.	
Hot Flash Severity follow up: 3 months	97 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,c,d]	-	The mean hot Flash Severity was 0	MD 0.56 lower (0.02 lower to 1.18 lower)
Depression assessed with: Center for Epidemiologic Studies Depression (CES-D) Scale	60 (1 RCT)[2]	⨁◯◯◯ VERY LOW[c,d,e,f]	-	Data suggested an important mean reduction in the hypnosis group (n=30; from 29.48 (SD 7.72) to 24.58 (SD 6.45)) compared to the waitlist group (n=30; from 30.22 (SD 9.32) to 31.38 (SD 9.21)). The difference between groups was statistically	

follow up: 5 weeks				significant in favor of the hypnosis group (p<0.01).	
Sleep Measures assessed with: Medical Outcomes Study (MOS) Sleep Problems Index follow up: 5 weeks	60 (1 RCT)[2]	⨁⨁◯◯ LOW[c,e,f]	-	Hypnosis was associated with an improvement in sleep compared to the control group after five weeks treatment (F-test from an analysis of covariance reported; p <0.001), as well as in comparison to baseline levels within the group (MOS Sleep Index mean (SD) of 24.26 (8.17) at baseline and 13.71 (4.35) at follow-up).	
Quality of Life assessed with: FACT-ES follow up: 13 weeks[g]	100 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,c,h]	-	The mean quality of Life was 0 points	MD 1.5 points lower (7 lower to 4.4 higher)

1. Fenlon, Deborah R., Jessica L. Corner, and Joanne S. Haviland. "A randomized controlled trial of relaxation training to reduce hot flashes in women with primary breast cancer." Journal of Pain and Symptom Management 35, no. 4 (2008): 397-405.
2. Elkins, Gary, Joel Marcus, Vered Stearns, Michelle Perfect, M. Hasan Rajab, Christopher Ruud, Lynne Palamara, and Timothy Keith. "Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors." Journal of Clinical Oncology 26, no. 31 (2008): 5022-5026.

a. Fenlon 2008 has some concerns with missing outcome reporting.
b. Fenlon 2008 compares relaxation to control among women with breast cancer.
c. Small sample reported.
d. The 95% CI may not include meaningful improvement.
e. Elkins 2008 demonstrates some concerns with missing outcome data.
f. Elkins 2008 compares hypnosis to control among women with breast cancer.
g. Functional Assessment of Cancer Therapy with the endocrine subscale
h. The 95% CI includes the potential for possible harm, as well as possible benefit.

In addition to Elkin 2008 and Fenlon 2008, two studies reported on similar outcomes among patients receiving hypnosis or relaxation interventions.

Hot Flash Frequency

Fenlon 1999 – Relaxation (n=8) vs no treatment (n=8)

–The study was for one month and the median was 1-year post treatment with a range of 3 months to 5 years. When comparing the change in hot flushes between the two groups, there appeared to be a trend to reduce both the frequency of hot flushes and associated distress, but none of these differences were shown to be significant. There was an apparent increase in the amount of hot flushes and distress factor in the control group. This was not statistically significant. The authors concluded that a trend was seen for HFs and night sweats to be reduced, but the results did not achieve significance.

Nedstrand 2005 – Relaxation (n=19) vs electroacupuncture (n=19)

–This was a 12-week study comparing relaxation therapy with electroacupuncture. The number of daily HFs was registered in a logbook before and during treatment and after 3 and 6 months of follow-up. A significant change in HF frequency appeared after 4 weeks in both groups, and no further significant change was seen up to 6 months after the end of treatment. Thus, the decrease in number of flushes persisted even at 3- and 6-months follow-up. The authors concluded that there was thus a definite, albeit slow, decline in number of HFs over time. The authors suggested that applied relaxation and electro-acupuncture should be further evaluated as possible treatments for vasomotor symptoms.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	The systematic review identified 4 RCTs that reported on hypnosis or relaxation interventions for persons with cancer experiencing hot flashes.	The panel determined the magnitude of the undesirable outcomes to be trivial.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with hypnosis or relaxation therapy
Hot Flash Frequency follow up: 5 weeks	97 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,c,d]	-	The mean Hot Flash Frequency was 0	MD 5 higher (0 to 10 higher)
Hot Flash Composite Score assessed with:	60 (1 RCT)[2]	⨁⨁◯◯ LOW[c,e,f]	-	Patients in the hypnosis group demonstrated statistically significantly better improvement in HF score (from	

	Hot Flash Related Daily Interference Scale				baseline mean (SD) 15.05 (13.75) to 4.84 (5.02)) compared to those in the control group (from baseline mean (SD) 17.17 (10.37) to 15.60 (10.71); p<.001). The authors concluded that hypnosis appears to reduce HFs in breast cancer survivors.	
	Hot Flash Severity follow up: 3 months	97 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,c,d]	-	The mean hot Flash Severity was 0	MD 0.56 higher (0.02 higher to 1.18 higher)
	Depression assessed with: Center for Epidemiologic Studies Depression (CES-D) Scale follow up: 5 weeks	60 (1 RCT)[2]	⨁◯◯◯ VERY LOW[c,d,e,f]	-	Data suggested an important mean reduction in the hypnosis group (n=30; from 29.48 (SD 7.72) to 24.58 (SD 6.45)) compared to the waitlist group (n=30; 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).	
	Sleep Measures assessed with: Medical Outcomes Study (MOS) Sleep Problems Index follow up: 5 weeks	60 (1 RCT)[2]	⨁⨁◯◯ LOW[c,e,f]	-	Hypnosis was associated with an improvement in sleep compared to the control group after five weeks treatment (F-test from an analysis of covariance reported; p <0.001), as well as in comparison to baseline levels within the group (MOS Sleep Index mean (SD) of 24.26 (8.17) at baseline and 13.71 (4.35) at follow-up).	
	Quality of Life assessed with: FACT-ES follow up: 13 weeks[g]	100 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,c,h]	-	The mean Quality of Life was 0 points	MD 1.5 points lower (7 lower to 4.4 higher)

1. Fenlon, Deborah R., Jessica L. Corner, and Joanne S. Haviland. "A randomized controlled trial of relaxation training to reduce hot flashes in women with primary breast cancer." Journal of Pain and Symptom Management 35, no. 4 (2008): 397-405.
2. Elkins, Gary, Joel Marcus, Vered Stearns, Michelle Perfect, M. Hasan Rajab, Christopher Ruud, Lynne Palamara, and Timothy Keith. "Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors." Journal of Clinical Oncology 26, no. 31 (2008): 5022.

a. Fenlon 2008 has some concerns with missing outcome reporting.
b. Fenlon 2008 compares relaxation to control among women with breast cancer.
c. Small sample reported.
d. The 95% CI may not include meaningful improvement.
e. Elkins 2008 demonstrates some concerns with missing outcome data.
f. Elkins 2008 compares hypnosis to control among women with breast cancer.
g. Functional Assessment of Cancer Therapy with the endocrine subscale
h. The 95% CI includes the potential for possible harm, as well as possible benefit.

In addition to Elkin et al., 2008 and Fenlon, Corner, & Haviland, 2008, two studies reported on similar outcomes among patients receiving hypnosis or relaxation interventions.

Hot Flash Frequency

Fenlon 1999 – Relaxation (n=8) vs no treatment (n=8)

–The study was for one month and the median was 1-year post treatment with a range of 3 months to 5 years. When comparing the change in hot flushes between the two groups, there appeared to be a trend to reduce both the frequency of hot flushes and associated distress, but none of these differences were shown to be significant. There was an apparent increase in the amount of hot flushes and distress factor in the control group. This was not statistically significant. The authors concluded that a trend was seen for HFs and night sweats to be reduced, but the results did not achieve significance.

Nedstrand 2005 – Relaxation (n=19) vs electroacupuncture (n=19)

–This was a 12-week study comparing relaxation therapy with electroacupuncture. The number of daily HFs was registered in a logbook before and during treatment and after 3 and 6 months of follow-up. A significant change in HF frequency appeared after 4 weeks in both groups, and no further significant change was seen up to 6 months after the end of treatment. Thus, the decrease in number of flushes persisted even at 3- and 6-months follow-up. The authors concluded that there was thus a definite, albeit slow, decline in number of HFs over time. The authors suggested that applied relaxation and electro-acupuncture should be further evaluated as possible treatments for vasomotor symptoms.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty in the evidence was very low due to concerns with risk of bias, indirectness, and imprecision.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Hot flash symptoms among breast cancer survivors are reported with negative emotional perceptions and behavioral consequences. Often symptoms are concomitant with difficulty sleeping, fatigue, interruption in sexual relations, sleepiness, nervousness, and mood changes (Barton & Loprinzi, 2004). A qualitative study reported on the feelings identified by 35 women in regard to experiencing hot flashes following breast cancer (Hunter, Coventry, Mendes, & Grunfeld, 2009). Themes most commonly mentioned included negative beliefs about the perception when experiencing these symptoms in public. "Social anxiety/embarrassment" was the most commonly mentioned. Additionally, sleep quality and tiredness were commonly recognized as impacted by HF/NS.	The panel determine that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel noted the very low certainty in evidence, and the closely balanced net benefits and harms.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Alternative/Complementary, Psychological and Physical price examples accessed May 15, 2019** **Hypnosis/Relaxation Therapy** • $14.91: "Relaxation Techniques: Reduce Stress and Anxiety and Enhance Well-being" audio CD (https://www.amazon.com/Relaxation-Techniques-Anxiety-Enhance-Well-being/dp/1845900782) • $75 – $125 average price per hypnosis session (2017? American Association of Professional Hypnotherapists http://www.aaph.org/hypnosis-FAQ) **Acupuncture** • $60 - 120 average per session (https://www.acufinder.com/Acupuncture+Information/Detail/How+much+does+an+acupuncture+treatment+cost+) **Cognitive Behavioral Therapy** • $100 or more per hour, potentially (Anxiety and Depression Association of America: https://adaa.org/finding-help/treatment/low-cost-treatment.) **Exercise/Physical Activity** • $19.95: Dr. Scholl's Women's Aspire Medium and Wide Width Walking Shoe (https://www.walmart.com/ip/Women-s-Aspire-Medium-and-Wide-Width-Walking-Shoe/682850282?athcpid=682850282&athpgid=athenaItemPage&athcgid=null&athznid=PWVUB&athieid=v0&athstid=CS020&athguid=4f87b163-ed7-16abddb32a1c91&athena=true) • $50 per month average sports club dues in 2016 (https://money.cnn.com/2018/01/12/news/companies/planet-fitness/index.html) • $80 - $125 average for a one-hour personal training session in 2015 (https://www.angieslist.com/articles/what-factors-affect-cost-personal-trainer.htm) **Yoga** • $12.51: "Rodney Yee Complete Yoga for Beginners" DVD at Walmart.com (https://www.walmart.com/ip/Rodney-Yee-Complete-Yoga-for-Beginners/46606164) • $15 - $25 per hour average cost of yoga classes (https://lessons.com/costs/yoga-classes-cost) **Tai chi** • $9.88: "Tai chi for Beginners" DVD https://www.walmart.com/ip/Tai-Chi-for-Beginners-DVD/10779247 • $15 – $159 per hour for tai chi chuan lessons (https://takelessons.com/sports-and-fitness/tai-chi-chuan-lessons)	The panel agreed that the cost of providing hypnosis or relaxation therapy is greater than not providing those treatments; however, there may be some variability in the cost based on who provides the intervention, how it needs to be conducted, and what frequency. The panel noted that relaxation therapy might be a lower cost than hypnosis.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel agreed that because of the cost incurred by the intervention, there may be increased health inequity for those unable to access those services and a specialized provider or occupational therapist, as well as opportunity costs including childcare.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified.	The panel agreed that the acceptability of both interventions may vary based on the personal views of the providers and patients; however, the panel noted that relaxation therapy is non-invasive.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel decided that the initial access may be difficult because of the need for specialty providers, limited options (if any) for reimbursement, and need for a referral; however, some of the skills for relaxation can be taught and independently practiced by the patient.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Among persons with cancer experiencing drug- or surgery-induced hot flashes, the Oncology Nursing Society guideline panel *recommends hypnosis or relaxation therapy only in the context of a clinical trial* (no recommendation, knowledge gap).

Justification

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 ONS Guideline 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.

Subgroup considerations

No subgroup considerations.

Implementation considerations

Implementation considerations include standardization of the regimens and whether they can be self-taught or require a specialized clinician.

Monitoring and evaluation

Consistent and standardized outcomes and measurements across clinical trials are needed.

Research priorities

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

IN-TEXT CITED REFERENCES

Barton, D., & Loprinzi, C. L. (2004). Making sense of the evidence regarding nonhormonal treatments for hot flashes. *Clinical Journal of Oncology Nursing, 8*, 39–42. https://doi.org/10.1188/04.CJON.39-42

Fenlon, D. (1999). Relaxation therapy as an intervention for hot flushes in women with breast cancer. *European Journal of Oncology Nursing, 3*, 223–231. https://doi.org/10.1016/S1462-3889(99)81335-0

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, 63*, 167–192. https://doi.org/10.3322/caac.21171

Hunter, M.S., Coventry, S., Mendes, N., & Grunfeld, E.A. (2009). Menopausal symptoms following breast cancer treatment: A qualitative investigation of cognitive and behavioural responses. Maturitas, 63(4), 336-340. https://doi.org/10.1016/j.maturitas.2009.06.003

Hutton, B., Hersi, M., Cheng, W., Pratt, M., Quach, P., Yazdi, F., . . . Clemons, M. (2020). *Comparison of the effects of natural health products, pharmacologics, physical activity, psychologic therapy and combination interventions on hot flash frequency and intensity in patients with a history of breast and prostate cancer: A systematic review with meta-analyses*. Manuscript submitted for publication.

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*, 243–250. https://doi.org/10.1080/13697130500118050

RECOMMENDATION

Should physical activity rather than no treatment be used in patients with cancer who are experiencing drug- or surgery-induced hot flashes?	
POPULATION:	Women or men with cancer with drug- or surgery-induced hot flashes
INTERVENTION:	Physical activity
COMPARISON:	No treatment
MAIN OUTCOMES:	Frequency of hot flashes (per 24 hours); severity of hot flashes; quality of life (sleep/sleep quality in addition to global QoL from any validated scale; depression; adverse events
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation - Population perspective
BACKGROUND:	Hot flashes and night sweats may be side effects of cancer or its treatment. Hot flashes and night sweats affect quality of life in many patients with cancer. Treatment options that have been provided for persons experiencing hot flashes due to breast or prostate cancer include pharmacologic, psychological or behavioral interventions, as well as acupuncture and herbal supplements.
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Marcelle Kaplan, MS, RN, CNS, Jessica Bay Leibelt, MSN, NP-C, AOCNP®, Laura Boehnke Michaud, PharmD, BCOP, FASHP, CMQ, Paz Fernández-Ortega, PhD, MSc, RN, BPsych, Dale Grimmer, MS, RN, AOCN®, CCRC, Suzanne Mahon, RN, DNSC, AOCN®, AGN-BC, Bernardo L. Rapoport, Dip in Med (UBA), MMed, and Valencia Robinson, EdS. Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research suggests that hot flashes are experienced by 51%–81% of women with breast cancer and 69%–76% of men with prostate cancer (Fisher et al., 2013). Hot flashes can negatively impact quality of life and co-occur with mood and sleep disturbances (Fisher et al., 2013). The lack of tolerability of hot flash symptoms can lead to discontinuation of therapies used to prevent or treat cancer.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The systematic review identified 3 RCTs that reported on exercise or yoga vs standard of care for persons with cancer.	The narrative endpoints seemed to be positive, however, hard to quantify. Based on the outcomes in the table as well, the panel decided on a small benefit.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with behavioral interventions (such as exercise, yoga, tai chi)
Depression assessed with: HADS follow up: 24 weeks	40 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,c,d,e]	-	The mean depression was 0 points	MD 0.1 points higher (0.8 lower to 1 higher)
Quality of Life assessed with: FACT-B follow up: 24 weeks	40 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,d,f]	-	The mean quality of Life was 0 points	MD 12.6 points higher (4.2 higher to 21.1 higher)

1. Cramer, Holger, Sybille Rabsilber, Romy Lauche, Sherko Kümmel, and Gustav Dobos. "Yoga and meditation for menopausal symptoms in breast cancer survivors—a randomized controlled trial." Cancer 121, no. 13 (2015): 2175-2184.

a. Cramer 2015 had a risk of bias due to blinding of participants and providers.
b. Cramer 2015 compares yoga to usual care among women with breast cancer.
c. Duijts 2012 compares exercise to usual care among women with breast cancer and narratively reports no difference between groups at 6 months.
d. Small sample reported
e. The 95% CI includes the potential for possible harm, as well as possible benefit.
f. MID may fall between 4–7 points, making this a meaningful increase.

	Hot Flash Frequency ***Carson 2009 – Yoga (n=17) vs waitlist (n=20)*** –Study participants were enrolled in an 8-week yoga program or to wait-list control. Daily reports of hot flashes at baseline, post treatment, and 3 months after treatment were captured via an interactive telephone system. Patients' average daily frequency of hot flashes at baseline were 4.40 in the yoga group (range1.56 to 8.64) and 4.27 (range1.21 to 8.71) in the control group. Analyses conducted both after completion of treatment (Yoga from daily mean HF frequency 4.44 to 3.73 versus waitlist from 4.29 to 4.40) as well as 3 months later (Yoga from daily mean HF frequency 4.46 to 3.19 versus waitlist from 4.34 to 4.42) identified statistically significant reductions in HF frequency with yoga compared to control. ***Duijts 2012 – CBT + exercise (n=106) vs CBT (n=109) vs exercise (n=104) vs waitlist (n=103)*** –Self-report questionnaires were completed by patients at baseline, 12 weeks, and 6 months. Findings from intention to treat analyses based on overall model effects indicated statistically significant differences between groups in improvement over time for endocrine symptoms and perceived burden of HFs and night sweats, but not for frequency ratings of HFNS (hot flashes with night sweats). At 6 months, the mean change among women in the PE group was 0.24 (SE=1.58) when compared with the control group. Additionally, the mean change among women receiving PE and CBT was -3.27 (SE=1.71) when compared with the control group. **Hot Flash Composite Score** ***Carson 2009 – Yoga (n=17) vs waitlist control (n=17)*** –Hot flash total scores were computed as frequency × severity. Statistically significant improvements in the yoga group both post-treatment (yoga group: from mean score change 20.92 to 14.46 vs control group: mean score change from 23.01 to 25.81) and at 3-month follow-up. This pilot study provides promising support for the beneficial effects of a comprehensive yoga program for management of HFs and other menopausal symptoms. **Hot Flash Severity** ***Carson 2009 – Yoga (n=17) vs waitlist control (n=20)*** –The study lasted 8 weeks and included a 3-month follow-up; HF severity was scored on a scale from 0-9 (higher scores denoting higher severity). Findings identified significant improvements with yoga compared to the control group in daily HF severity (as well as frequency and score); in the yoga group, mean score improved from 4.16 to 3.21 post-treatment, while mean score in the control group shifted from 4.67 to 4.41 ($p<0.01$ for the difference between groups). Similar values were also observed 3 months after treatment. The authors suggested the study provides promising support for the beneficial effects of a comprehensive yoga program for HFs and other menopausal symptoms.	

	Sleep Measures ***Carson 2009 – Yoga (n=17) vs waitlist (n=20)*** –Measured **sleep disturbance on a scale from 0-9** (higher values denoted larger amounts). The yoga group was noted to have incurred significant post-treatment improvement in sleep disturbance compared to the control group (reduction from pre-treatment mean of 3.82 to 3.29 in the yoga group compared to pre- and post-treatment means of 4.21 and 4.37 in the control group; p <0.01, but no 95% CI reported). **Depression** In addition to the findings by Cramer 2015, one other study reported on the outcome of depression; however, effect estimates were not provided. ***Duijts 2012 – CBT + exercise (n=106) vs exercise (n=104) vs CBT (n=109) vs control (n=103)*** –The **HADS tool** was evaluated. The authors note that after 6 months of treatment, no important differences in psychological distress/depression were observed between groups. The trial report provides no additional data to detail this summary. **Sexual Function Measure** ***Duijts 2012 – CBT + exercise (n=106) vs exercise (n=104) vs CBT (n=109) vs waitlist (n=103)*** –Looked at both the **Habit and Pleasure subscales of the Sexual Activity Questionnaire (SAQ)**. Data analyses identified a statistically significant improvement in sexual function (SAQ-Habit) in the CBT + exercise group compared to the control group at long-term follow-up (effect size 0.65, p=0.002). Supplemental per protocol analyses also identified important gains in SAQ-Pleasure in the CBT and CBT + exercise groups. **Adverse Events/Tolerability** ***Cramer 2015 - Yoga (n=19) vs control (n=21)*** –4 adverse events (transient muscle soreness [n53] and unilateral hip pain [n51]) were temporarily and probably causally related to the yoga intervention. Six women (28.6%) in the usual care group also reported adverse events, including sciatica (n51), port pain (n51), elbow pain (n51), knee pain (n52), and panic attacks (n51).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	The systematic review identified 3 RCTs that reported on exercise or yoga vs standard of care for persons with cancer.	The panel determined the magnitude of the undesirable outcomes to be trivial.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with behavioral interventions (such as exercise, yoga, tai chi)
Depression assessed with: HADS follow up: 24 weeks	40 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,c,d,e]	-	The mean depression was 0 points	MD 0.1 points higher (0.8 lower to 1 higher)
Quality of Life assessed with: FACT-B follow up: 24 weeks	40 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,d,f]	-	The mean quality of Life was 0 points	MD 12.6 points higher (4.2 higher to 21.1 higher)

1. Cramer, Holger, Sybille Rabsilber, Romy Lauche, Sherko Kümmel, and Gustav Dobos. "Yoga and meditation for menopausal symptoms in breast cancer survivors—a randomized controlled trial." Cancer 121, no. 13 (2015): 2175-2184.

a. Cramer 2015 had a risk of bias due to blinding of participants and providers.
b. Cramer 2015 compares yoga to usual care among women with breast cancer.
c. Duijts 2012 compares exercise to usual care among women with breast cancer and narratively reports not difference between groups at 6 months.
d. Small sample reported.
e. The 95% CI includes the potential for possible harm, as well as possible benefit.
f. MID may fall between 4-7 points making this a meaningful increase.

	Hot Flash Frequency ***Carson 2009 – Yoga (n=17) vs waitlist (n=20)*** –Study participants were enrolled in an 8-week yoga program or to wait-list control. Daily reports of hot flashes at baseline, post treatment, and 3 months after treatment were captured via an interactive telephone system. Patients' average daily frequency of hot flashes at baseline were 4.40 in the yoga group (range1.56 to 8.64) and 4.27 (range1.21 to 8.71) in the control group. Analyses conducted both after completion of treatment (Yoga from daily mean HF frequency 4.44 to 3.73 versus waitlist from 4.29 to 4.40) as well as 3 months later (Yoga from daily mean HF frequency 4.46 to 3.19 versus waitlist from 4.34 to 4.42) identified statistically significant reductions in HF frequency with yoga compared to control. ***Duijts 2012 – CBT + exercise (n=106) vs CBT (n=109) vs exercise (n=104) vs waitlist (n=103)*** –Self-report questionnaires were completed by patients at baseline, 12 weeks, and 6 months. Findings from intention to treat analyses based on overall model effects indicated statistically significant differences between groups in improvement over time for endocrine symptoms and perceived burden of HFs and night sweats, but not for frequency ratings of HFNS (hot flashes with night sweats). At 6 months, the mean change among women in the PE group was 0.24 (SE=1.58) when compared with the control group. Additionally, the mean change among women receiving PE and CBT was -3.27 (SE=1.71) when compared with the control group. **Hot Flash Composite Score** ***Carson 2009 – Yoga (n=17) vs waitlist control (n=17)*** –Hot flash total scores were computed as frequency × severity. Statistically significant improvements in the yoga group both post-treatment (yoga group: from mean score change 20.92 to 14.46 vs control group: mean score change from 23.01 to 25.81) and at 3-month follow-up. This pilot study provides promising support for the beneficial effects of a comprehensive yoga program for management of HFs and other menopausal symptoms. **Hot Flash Severity** ***Carson 2009 – Yoga (n=17) vs waitlist control (n=20)*** –The study lasted 8 weeks and included a 3-month follow-up; HF severity was scored on a scale from 0-9 (higher scores denoting higher severity). Findings identified significant improvements with yoga compared to the control group in daily HF severity (as well as frequency and score); in the yoga group,	

	mean score improved from 4.16 to 3.21 post-treatment, while mean score in the control group shifted from 4.67 to 4.41 (p<0.01 for the difference between groups). Similar values were also observed 3 months after treatment. The authors suggested the study provides promising support for the beneficial effects of a comprehensive yoga program for HFs and other menopausal symptoms. **Sleep Measures** ***Carson 2009 – Yoga (n=17) vs waitlist (n=20)*** –Measured **sleep disturbance on a scale from 0-9** (higher values denoted larger amounts). The yoga group was noted to have incurred significant post-treatment improvement in sleep disturbance compared to the control group (reduction from pre-treatment mean of 3.82 to 3.29 in the yoga group compared to pre- and post-treatment means of 4.21 and 4.37 in the control group; p <0.01, but no 95% CI reported). **Depression** In addition to the findings by Cramer 2015, one other study reported on the outcome of depression; however, effect estimates were not provided. ***Duijts 2012 – CBT + exercise (n=106) vs exercise (n=104) vs CBT (n=109) vs control (n=103)*** –The **HADS tool** was evaluated. The authors note that after 6 months of treatment, no important differences in psychological distress/depression were observed between groups. The trial report provides no additional data to detail this summary. **Sexual Function Measure** ***Duijts 2012 – CBT + exercise (n=106) vs exercise (n=104) vs CBT (n=109) vs waitlist (n=103)*** –Looked at both the **Habit and Pleasure subscales of the Sexual Activity Questionnaire (SAQ)**. Data analyses identified a statistically significant improvement in sexual function (SAQ-Habit) in the CBT + exercise group compared to the control group at long-term follow-up (effect size 0.65, p=0.002). Supplemental per protocol analyses also identified important gains in SAQ-Pleasure in the CBT and CBT + exercise groups. **Adverse Events/Tolerability** ***Cramer 2015 - Yoga (n=19) vs control (n=21)*** –4 adverse events (transient muscle soreness [n53] and unilateral hip pain [n51]) were temporarily and probably causally related to the yoga intervention. Six women (28.6%) in the usual care group also reported adverse events, including sciatica (n51), port pain (n51), elbow pain (n51), knee pain (n52), and panic attacks (n51).	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Hot flash symptoms among breast cancer survivors are reported with negative emotional perceptions and behavioral consequences. Often symptoms are concomitant with difficulty sleeping, fatigue, interruption in sexual relations, sleepiness, nervousness, and mood changes (Barton & Loprinzi, 2004). A qualitative study reported on the feelings identified by 35 women in regard to experiencing hot flashes following breast cancer (Hunter, Coventry, Mendes, & Grunfeld, 2009). Themes most commonly mentioned included negative beliefs about the perception when experiencing these symptoms in public. "Social anxiety/embarrassment" was the most commonly mentioned. Additionally, sleep quality and tiredness were commonly recognized as impacted by HF/NS. Hot flashes were among the most frequently mentioned symptoms with the highest interference ratings by men with non-metastatic castration-resistant prostate cancer and castration-resistant prostate cancer (Tomaszewski et al., 2017).	The panel determine that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel prioritized the QoL reported by patient-reported outcomes (PRO), measured by a validated tool over the weight on the trivial harm.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Alternative/Complementary, Psychological and Physical price examples accessed May 15, 2019** **Hypnosis/Relaxation Therapy** • $14.91: "Relaxation Techniques: Reduce Stress and Anxiety and Enhance Well-being" audio CD (https://www.amazon.com/Relaxation-Techniques-Anxiety-Enhance-Well-being/dp/1845900782) • $75 – $125 average price per hypnosis session (2017? American Association of Professional Hypnotherapists http://www.aaph.org/hypnosis-FAQ) **Acupuncture** • $60 - 120 average per session (https://www.acufinder.com/Acupuncture+Information/Detail/How+much+does+an+acupuncture+treatment+cost+) **Cognitive Behavioral Therapy** • $100 or more per hour, potentially (Anxiety and Depression Association of America: https://adaa.org/finding-help/treatment/low-cost-treatment.) **Exercise/Physical Activity** • $19.95: Dr. Scholl's Women's Aspire Medium and Wide Width Walking Shoe (https://www.walmart.com/ip/Women-s-Aspire-Medium-and-Wide-Width-Walking-Shoe/682850282?athcpid=682850282&athpgid=athenaItemPage&athcgid=null&athznid=PWVUB&athieid=v0&athstid=CS020&athguid=4f87b163-ed7-16abddb32a1c91&athena=true) • $50 per month average sports club dues in 2016 (https://money.cnn.com/2018/01/12/news/companies/planet-fitness/index.html) • $80 - $125 average for a one-hour personal training session in 2015 (https://www.angieslist.com/articles/what-factors-affect-cost-personal-trainer.htm) **Yoga** • $12.51: "Rodney Yee Complete Yoga for Beginners" DVD at Walmart.com (https://www.walmart.com/ip/Rodney-Yee-Complete-Yoga-for-Beginners/46606164) • $15 - $25 per hour average cost of yoga classes (https://lessons.com/costs/yoga-classes-cost) **Tai chi** • $9.88: "Tai chi for Beginners" DVD https://www.walmart.com/ip/Tai-Chi-for-Beginners-DVD/10779247 • $15 – $159 per hour for tai chi chuan lessons (https://takelessons.com/sports-and-fitness/tai-chi-chuan-lessons)	The panel agreed that the cost of providing behavioral therapy is greater than not providing those treatments.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	A search of the literature identified one study that examined the physical and psychosocial effects of breast cancer treatment differences between younger and older rural survivors based on menopausal status at diagnosis (Befort & Klemp, 2011). Younger women who are premenopausal at the time of breast cancer diagnosis report increased rates of menopausal side effects as well as more pronounced deficits in emotional and social functioning and cognitive performance. Women who were premenopausal at diagnosis were significantly more likely to experience numerous symptoms at the time of treatment and currently, including higher rates of hot flashes, vaginal dryness, loss of sexual desire, and weight gain. Negative physical and psychosocial sequelae of breast cancer were common in a rural population and were significantly worse for premenopausal women.	The panel agreed that exercise would have no impact on health equity but that yoga and tai chi may reduce equity because their availability may be limited in some areas.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel agreed that behavioral interventions would be widely acceptable.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel decided that behavioral interventions are widely feasible, however, recognized that patients may need of trainers for yoga or tai chi.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Among patients with cancer experiencing drug- and surgery-induced hot flashes, the Oncology Nursing Society guideline panel *suggests* physical activity interventions (exercise, yoga) over no treatment for management of symptoms. (Conditional recommendation, low certainty of evidence).

Justification

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.

Subgroup considerations

No subgroup considerations.

Implementation considerations

- Adapt the intervention to the limitations of the patient.
- Exercise may be more accessible than yoga.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

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

IN-TEXT CITED REFERENCES

Barton, D., & Loprinzi, C. L. (2004). Making sense of the evidence regarding nonhormonal treatments for hot flashes. *Clinical Journal of Oncology Nursing, 8*, 39–42. https://doi.org/10.1188/04.CJON.39-42

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*, 1301–1309. https://doi.org/10.1007/s00520-009-0587-5

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*, 2175–2184. https://doi.org/10.1002/cncr.29330

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*, 4124–4133. https://doi.org/10.1200/JCO.2012.41.8525

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, 63*, 167–192. https://doi.org/10.3322/caac.21171

Hunter, M.S., Coventry, S., Mendes, N., & Grunfeld, E.A. (2009). Menopausal symptoms following breast cancer treatment: a qualitative investigation of cognitive and behavioural responses. *Maturitas, 63*, 336–340. https://doi.org/10.1016/j.maturitas.2009.06.003

Tomaszewski, E.L., Moise, P., Krupnick, R.N., Downing, J., Meyer, M., Naidoo, S., & Holmstrom, S. (2017). Symptoms and impacts in non-metastatic castration-resistant prostate cancer: Qualitative study findings. *The Patient, 10*, 567–578. https://doi.org/10.1007/s40271-017-0227-y

RECOMMENDATION

Should interventions vs. other active interventions or standard of care be used for persons with cancer with drug- or surgery-induced hot flashes?	
POPULATION:	Persons with cancer with drug- or surgery-induced hot flashes
INTERVENTION:	Interventions
COMPARISON:	Other active interventions or standard of care
MAIN OUTCOMES:	Frequency of hot flashes (per 24 hours); severity of hot flashes; quality of life (sleep/sleep quality in addition to global QoL from any validated scale); depression; tolerability of intervention; adverse events
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation - population perspective
BACKGROUND:	Hot flashes and night sweats may be side effects of cancer or its treatment. Hot flashes and night sweats affect quality of life in many patients with cancer. Treatment options that have been provided for persons experiencing hot flashes due to breast or prostate cancer include pharmacologic, psychological or behavioral interventions, as well as acupuncture and herbal supplements.
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Marcelle Kaplan, MS, RN, CNS, Jessica Bay Leibelt, MSN, NP-C, AOCNP®, Laura Boehnke Michaud, PharmD, BCOP, FASHP, CMQ, Paz Fernández-Ortega, PhD, MSc, RN, BPsych, Dale Grimmer, MS, RN, AOCN®, CCRC, Suzanne Mahon, RN, DNSC, AOCN®, AGN-BC, Bernardo L. Rapoport, Dip in Med (UBA), MMed, and Valencia Robinson, EdS. Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Research suggests that hot flashes are experienced by 51%–81% of women with breast cancer and 69%–76% of men with prostate cancer (Fisher et al., 2013). Hot flashes can negatively impact quality of life and co-occur with mood and sleep disturbances (Fisher et al., 2013). The lack of tolerability of hot flash symptoms can lead to discontinuation of therapies used to prevent or treat cancer.	

Desirable Effects

How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	The study team identified 41 publications (40 studies/RCTs) that informed the network meta-analysis of pharmacological, dietary supplements, physical, and psychological interventions. **Hot Flash Frequency:** Data from 11 RCTs contributed to the model for the outcome of frequency. Additional information from the 12 studies that reported on frequency but could not be pooled in the analysis are presented below. **Pharmacologic therapies:** ***Bordeleau 2010 – Gabapentin vs venlafaxine (n=66 overall; crossover study)*** –This was a cross-over trial with 2-4 weeks in between study periods. The authors reported that with regard to hot flash frequency, the ratio of venlafaxine compared to gabapentin was 0.94 (95% CI not reported, but the p-value was reported to be >0.61). The authors also reported that 38 of 56 patients completing the study preferred venlafaxine over gabapentin; amongst them, 84.2% felt the frequency of hot flashes was reduced with venlafaxine. The authors concluded that breast cancer survivors prefer venlafaxine over gabapentin for treating hot flashes. ***Loprinzi 2002 – Fluoxetine vs placebo (n=81; crossover trial)*** –The first study period was 5 weeks followed by a second (cross-over) 4-week period. Study authors reported that the median hot flash frequency dropped by 3.4 hot flashes per day (42%) for patients while receiving fluoxetine and by 2.5 hot flashes per day (31%) while patients were receiving placebo in the first treatment period, respectively (P = 0.54). The authors concluded that this dose of fluoxetine resulted in a modest improvement in hot flashes. ***Mao 2015 – Gabapentin (n=28) vs electroacupuncture (n=30) vs sham acupuncture (n=32) vs placebo (n=30)*** –The study was for 8 weeks with additional evaluation at week 24 for durability of treatment effects. The mean (SD) daily frequency at baseline for electroacupuncture was 8.3 (5.6), and 6.3 (2.8) for the related sham group; the mean (SD) for the placebo gabapentin arm was 8.1 (5.4), while the related value for the gabapentin group was 6.8 (3.3). The authors concluded that acupuncture produced larger placebo and smaller nocebo effects than did pills for the treatment of hot flashes, however detailed data with regard to frequency are not reported. It was noted that electroacupuncture may be more effective than gabapentin with fewer adverse effects for HF management. ***Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30)*** –This study was for 12 weeks. There were no significant differences between the soy and placebo arms at any time; while participants in the venlafaxine arm tended to have fewer hot flashes during the initial 2 weeks, this early difference disappeared by 12 weeks. The authors concluded that neither soy protein nor venlafaxine were effective in treating hot flashes in men over a 12-week period, highlighting the need for additional investigations to identify treatments for hot flash management in men.	The panel considered each class of treatment separately based on the magnitude of the beneficial outcomes: Pharmacologic: Venlafaxine, paroxetine, clonidine: **Moderate** All others (gabapentin, sertraline, fluoxetine, escitalopram, duloxetine): **Small** No "others" showing benefit over placebo Venlafaxine not showing effectiveness among men (small study) Dietary supplements (soy, Black Cohosh, St. John's Wort, melatonin, Vitamin E): **Trivial** Electro-acupuncture: **Moderate** Non-electro acupuncture: **Small**

	Biglia 2016 – Escitalopram (n=30) vs duloxetine (n=28) –In this study, patients kept a diary of HF frequency and severity at baseline and after 4 and 12 weeks of treatment. The decrease, after 12 weeks of treatment, in the total number of HFs per week was 49.8% in the duloxetine group (P = 0.003) and 53% in the escitalopram group (P = 0.001). The author's concluded that escitalopram and duloxetine are both effective treatment for the relief of HFs in breast cancer survivors, with similar beneficial effect. **Dietary supplements:** ***Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30)*** –This study was for 12 weeks. There were no significant differences between the soy and placebo arms at any time; while participants in the venlafaxine arm tended to have fewer hot flashes during the initial 2 weeks, this early difference disappeared by 12 weeks. The authors concluded that neither soy protein nor venlafaxine were effective in treating hot flashes in men over a 12-week period, highlighting the need for additional investigations to identify treatments for hot flash management in men. ***Barton 1998 – Vitamin E (n=54) vs placebo (n=50) (crossover trial)*** –After a 1-week baseline period, patients received 4 weeks of vitamin E 800 IU daily, then 4 weeks of an identical appearing placebo, or vice versa. Diaries were used to measure potential toxicities and HFs during the baseline week and the two subsequent 4-week treatment periods. During the first study period after 4 weeks of therapy, HF frequency decreased 25% with vitamin E compared with 22% with placebo, finding no difference between interventions *(P* = .90). Incorporating the second study period, a small but statistically significant advantage favoring Vitamin E was noted (suggesting approximately 1 less HF per day). The authors noted that while a significant reduction in HF frequency was seen with vitamin E, clinical relevance was small. ***Quella 2000 – Soy (n=88) vs Placebo (n=88) (crossover trial)*** –The study included a 1-week baseline period with no therapy, followed by 4 weeks of either soy tablets or placebo. Patients then crossed over to the opposite arm in a double-blind manner for the last 4 weeks. Patients completed a daily questionnaire documenting HF frequency, intensity, and perceived side effects. Among patients receiving placebo, 36% reported that HF frequency was halved, compared with only 24% of patients receiving soy (*P* =0.01). The authors concluded that the soy product did not alleviate HFs in breast cancer survivors. ***Van Patten 2002 – Soy (n=59) vs placebo (n=64)*** –This study included a 4-week lead-in phase and 12-week treatment phase involving assignment to a soy or placebo beverage. There were no statistically significant differences between the soy and placebo groups in the mean reductions of daytime (-1.2 soy vs -1.8 placebo), night time (-0.5 soy vs -0.7 placebo) or 24-hr (-1.8 soy vs -2.5 placebo) HFs; however, presumably because of a strong placebo effect, both groups had significant reductions in hot flashes. The authors concluded that the soy beverage did not alleviate HFs any more than placebo. **Acupuncture:**	

	Frisk 2009 – Acupuncture (n=16) vs electroacupuncture (n=15) –The numbers of flushes per 24 hours decreased significantly in both groups from baseline to 4 wk of treatment and remained at this decreased level at all measuring points, except at 12 mo after start of treatment in the electroacupuncture group (when flushes tended to increase). There was no significant difference between the groups over time (p = 0.25; ANOVA). Hot flushes per 24 h decreased significantly, from a median of 7.6 (interquartile range [IQR], 6.0–12.3) at baseline in the electroacupuncture group to 4.1 (IQR, 2.0–6.5) (p = 0.012) after 12 weeks, and from 5.7 (IQR, 5.1–9.5) in the acupuncture group to 3.4 (IQR1.8–6.3) (p = 0.001). The authors concluded that both electroacupuncture and acupuncture lowered number of HFs. ***Hervik 2009 – Acupuncture (n=30) vs sham acupuncture (n=29)*** –This study provided patients with twice weekly acupuncture or sham acupuncture for the first 5 weeks, and subsequently once per week for the next 5 weeks. Daytime HFs were significantly reduced in the acupuncture group (from baseline mean (SD) 9.5 (4.9) to 4.7 (3.7) at 10 weeks, which further reduced to 3.2 (2.2) over the next 12 weeks), while no significant change was seen within the sham acupuncture group (from baseline mean (SD) 12.3 (7.3) to 11.7 (8.5) at 10 weeks, which increased back to 12.1 (8.3) over the next 12 weeks). Similar patterns were reported for nighttime HFs. The difference in acupuncture versus sham acupuncture was statistically significant for both daytime and nighttime HFs. ***Liljegren 2012 – Acupuncture (n=42) vs sham acupuncture (n=42)*** –Patients received treatment twice weekly for a duration of 5 weeks. The reductions in frequencies of HFs reached statistical significance at week 6 in both the acupuncture (from baseline mean (SD) 8.4 (5.5) to 5.7 (4.1) at 6 weeks) and sham acupuncture (from baseline 7.1 (4.4) to 4.5 (3.7) at 6 weeks) groups; however, the difference between groups was not statistically significant (mean difference 1.2, 95% CI -0.7 to 3.0; p=0.21). ***Deng 2007 – Acupuncture (n=42) vs sham acupuncture (n=30)*** –Interventions were given twice weekly for 4 consecutive weeks. HF frequency was evaluated at baseline, at 6 weeks, and at 6 months after initiation of treatment. Patients initially randomly assigned to the sham group were crossed over to acupuncture starting at week 7. In the principal analysis (week 6), acupuncture was associated with 0.8 fewer hot flashes per day than placebo, but the difference was not statistically significant (95% CI,-0.7 to 2.4; *P*=0.3). When participants in the sham acupuncture group were crossed over to the acupuncture group at week 7, HF frequency was reduced by approximately another 20% at week 12. HF frequency was reduced from 7.3 (SD 5.5) to 5.4 (SD 3.8), a difference of 1.9 hot flashes per day (95% CI -0.4 to 4.1). Treatment improvements were maintained at 6 months. The authors concluded HF frequency was reduced following acupuncture. However, compared with sham acupuncture, the reduction did not reach statistical significance. **<u>Hot Flash Composite Score:</u>** Data from 12 RCTs contributed to the model for the outcome of frequency. Additional information from the 12 studies that reported on frequency but could not be pooled in the analysis are presented below. **Pharmacologic therapies:** ***Biglia 2016 – Escitalopram (n=30) vs duloxetine (n=28)***	

	-HF score was assessed at both 4 and 12 weeks of treatment. At the end of the study period, the decrease in weekly HF score was 53.6% in the duloxetine group (P=0.003) and 60.4% in the escitalopram group (P=0.001). While both groups demonstrated a significant reduction from baseline, the difference between interventions was not statistically significant. The authors concluded that their data showed that a 12-week treatment both with escitalopram and duloxetine is effective for HF management. ***Boekhout 2011 – Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)*** –Daily HF score was calculated as the sum of HF severity values experienced in a given day. At 12 weeks, venlafaxine and clonidine were both associated with lower median HF scores compared to placebo; the median (IQR) scores for the 3 groups were as follows: Placebo - median 10.9, IQR 7.4-15.8; Clonidine: median 7.5, IQR 2.0-10.8; Venlafaxine: median 7.6, IQR 4.0-110.4. It was also noted that when considering the entire 12-week study period, HF score reduction was greater overall with venlafaxine than clonidine due to an earlier start of benefits during the 12-week period. The study authors concluded that venlafaxine and clonidine are effective treatments in the management of HFs. ***Bordeleau 2010 – Gabapentin vs venlafaxine (n=66 overall; crossover trial)*** –Daily HF score was assessed as average HF severity that day x frequency of HFs that day. Treatment periods lasted 4 weeks, with 2-4 weeks washout in between. Findings performed to compare the intervention groups using a mixed modeling approach identified a venlafaxine to gabapentin ratio of 0.96 (near 1), suggesting little difference between intervention groups (p value >0.61); both groups were noted to have important reductions from baseline (from week 2 mean (SD) 18.7 (23.2) to 5.7 (4.6) for venlafaxine in the first study period; from 18.6 (15.4) to 6.5 (8.3) in the gabapentin group). Analyses were also performed to compare groups as based upon patients' preferred treatment; those that preferred venlafaxine (n=38) were reported to experience scores 41% lower, while those that preferred gabapentin (n=18) were reported to experience scores 47% lower. ***Loprinzi 2002 – Fluoxetine vs placebo (n=81 total; crossover trial)*** –HF score was calculated as the product of frequency x severity. In the first study period, HF scores decreased by a median of 4.7 units per day (36%) for those on placebo and by 6.4 units per day (50%) in those receiving fluoxetine, and the difference was not statistically significant between groups (P = 0.35). Table 3 shows the score at week 5. Subsequent cross-over analyses identified a significantly greater reduction with fluoxetine. The authors concluded that fluoxetine was associated with a modest improvement in HF score. **Dietary supplements:** ***Barton 1998 – Vitamin E vs placebo (n=104 total; crossover trial)*** –HF score was calculated as the product of frequency x severity. After the first 4 weeks of therapy, the HF score decreased by 28% with vitamin E and 20% with placebo *(P* = 0.68). During the second treatment period, the mean hot-flash scores decreased by 0.03% and 25% in the placebo group and vitamin E group (P=0.24), respectively. A subsequent analysis encompassing the full crossover design suggested the presence of a small but statistically significant advantage of vitamin E over placebo. ***Jacobson 2001 – Black cohosh (n=42) vs placebo (n=43)*** –The HF score used was unclear in the study report. After 9 weeks, the HF score changed from baseline median 53.2 (IQR 25.3-71.3) to 31.0 (IQR 18.3-77.0) in the black cohosh group and from median 52.5 (IQR 28.9-93.0) to median 24.6 (IQR 16.4-64) in the placebo group; the difference was noted as not statistically significant, but no other data were provided.	

	Quella 2000 – Soy (n=87) vs placebo (n=88) –Hot flash score was assessed using the formula of frequency x severity. Patients averaged approximately seven HFs per day during the baseline study week (SD 54.5), with an average HF score of 13 points (SD 59.0). The totals of patients reporting reductions in HF score of <25%, 25-50% and >50% were 44%, 21% and 35% in the soy group and 40%, 22% and 38% in the placebo group, respectively. The authors concluded that the available data strongly suggest that soy phytoestrogens do not substantially reduce HFs when compared with placebo ***Van Patten 2002 – Soy (n=78) vs placebo (n=79)*** –HF score was assessed according to: [hot flash frequency x intensity for day] + [hot flash frequency x intensity for night] for 24 hours. The study reported there were no differences in hot flash related outcomes between groups: during the final 4 weeks of treatment, comparable changes from baseline in the soy group (mean (SD) change from baseline 18.0 (13.9) to final value 12.6 (13.4)) and placebo groups (mean (SD) change from baseline 18.9 (18.9) to final value 11.4 (11.3)) were observed. ***Vitolins 2013 – Venlafaxine + soy protein (n=30) vs venlafaxine + milk protein (n=30) vs soy protein (n=30) vs milk protein (n=30) (prostate cancer trial)*** –HF score calculated as the product of severity x frequency. The study reported that there were no statistically significant differences between the soy and placebo arms at any time, and although participants in the venlafaxine arm tended to have fewer hot flashes during the initial 2 weeks, this early difference had disappeared by 12 weeks; mean (SD) 12-week HF score values were as follows: venlafaxine + soy protein – 11.2 (10.9); venlafaxine + milk protein – 9.2 (7.2); placebo + soy protein – 13.6 (15.3); placebo + milk protein – 9.3 (8.5). The authors concluded that in androgen-deprived men, neither venlafaxine nor soy proved effective in reducing HFs. **Acupuncture:** ***Bao 2014 – Acupuncture (n=25) vs sham acupuncture (n=26)*** –HF score was determined using a 100-point visual analog scale (VAS) ≥ 20. The study presents comparison of median (IQR) scores between groups after 8 weeks of treatment. The chance in the sham acupuncture group wasn't statistically significant (from median (IQR) 20.5 (54.75) to 10 (47.25)), while the change in the acupuncture group was significant (from median (IQR) 31 (67) to 14 (32.5)); the comparison of change between groups was not statistically significant (p=0.56). The authors reported no important differences between interventions. ***Frisk 2009 – Acupuncture (n=13) vs electroacupuncture (n=11) (prostate cancer trial)*** –Daily HF distress calculated by summing individual HF distress (scored from 0-10). After 52 weeks of treatment, mean daily HF distress changed from baseline median 7.6 (IQR 4.7-8.3) to median 4.3 (IQR) 1.3 – 7.7 in the acupuncture group and from baseline median 8.2 (IQR 6.5-10.7) to median 5.5 (IQR 3.8-6.9) in the electroacupuncture group (p=0.65 between groups). ***Lesi 2016 – Acupuncture + enhanced self-care (n=85) vs enhanced self-care (n=105)*** –The HF score was calculated by multiplying the mean number of daily hot flashes that occurred during the week before assessment by the mean daily severity (1, mild; 2, moderate; 3, severe). After having comparable mean HF scores at baseline, the HF score at **week 12** was higher in the enhanced self-group (mean (SD) 22.70 (19.40)) than in the acupuncture + enhanced self-care group (11.34 (14.75); p<0.001 for the between-group difference of -11.36, 95% CI -16.39 to -6.33). Similar mean differences favoring the acupuncture + enhanced self-care	

	group were seen at both 3-month (-7.86, 95% CI -12.99 to -2.73) and 6-month follow-up (-8.82, 95% CI -14.04 to -3.61). The authors concluded that acupuncture in association with enhanced self-care is an effective integrative intervention for managing HFs. **<u>Hot Flash Severity:</u>** Data from 10 RCTs reported on frequency but could not be pooled in the analysis are presented below. **Pharmacologic therapies:** ***Bordeleau 2010 – Gabapentin vs venlafaxine (n=66 overall; crossover trial)*** –HF severity was assessed as 1=mild, 2=moderate, 3=severe, 4=severe, and were averaged per day. Study treatment periods lasted 4 weeks, with 2-4 weeks washout in between. Findings performed to compare the intervention groups using a mixed modeling approach identified a venlafaxine to gabapentin ratio of 1.02 (near 1), suggesting little difference between intervention groups (p value >0.61). Analyses were also performed to compare groups as based upon patients' preferred treatment; amongst those that preferred venlafaxine (n=38), 94.7% reported decreased HF severity, while amongst those that preferred gabapentin (n=18), 94.4% reported decreased HF severity. ***Walker 2010 – Venlafaxine (n=25) vs acupuncture (n=25)*** –Treatments were provided for 12 weeks, with outcomes measured up to 1-year post-treatment. The study reports that ANOVA analysis of patient data over time found no important differences between intervention groups with regard to changes in HF severity (p>0.05; detailed numeric data are not reported). Both groups experienced some improvement, with a subsequent return toward baseline values after the end of treatment. The authors suggested acupuncture may offer similar benefits as venlafaxine, with better tolerability. ***Loibl 2007– Clonidine (n=40) vs venlafaxine (n=40)*** –The duration of this study was 4 weeks of treatment. HF severity was scored as 1=mild, 2=moderate, 3=severe, 4=very severe. The mean HF severity at baseline week was 2.1 for clonidine and 1.9 for venlafaxine with a P-value of 0.78. Findings for this outcome are not clearly reported in the study report. Author conclusions appear to suggest benefits of venlafaxine over clonidine for reduction of HF frequency, but not HF severity. ***Pandya 2000 – Clonidine (n=99) vs placebo (n=99)*** –The study included a 1-week baseline period and follow-up at 4, 8 and 12 weeks; HFs were scored as 1=mild, 2=moderate, 3=severe, 4=very severe). Mean (SE) severity grades at baseline were 2.2 (0.1) and 2.1 (0.1) in the clonidine and placebo groups, respectively. The study reported % changes from these baseline values; median reductions of -11.7%, -17.3% and -9.3% were reported at 4, 8 and 12 weeks in the clonidine group while corresponding values of -8.5%, -10.5% and -8.3% were observed with placebo. None of the differences reached statistical significance. ***Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30) (prostate cancer study)*** –The duration reported findings at 4, 8 and 12 weeks; HF severity was scored as 1=mild, 2=moderate and 3=severe. There were no significant differences in the comparison of soy and placebo at any time point. The venlafaxine arm tended to have lower HF severity values at weeks 1, 2, 3, and 4, though the difference was not significant at 12 weeks.	

	Dietary supplements: ***Chen 2014 – Melatonin (n=48) vs placebo (n=47)*** –The study duration was 4 months, and HF severity was scored as 1=mild, 2=moderate, 3=severe, 4=very severe. The study denotes that there were no statistically significant differences between the groups with regard to changes in the numbers of mild, moderate and severe HFs experienced. ***Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30) (prostate cancer study)*** –The duration reported findings at 4, 8 and 12 weeks; HF severity was scored as 1=mild, 2=moderate and 3=severe. There were no significant differences in the comparison of soy and placebo at any time point. The venlafaxine arm tended to have lower HF severity values at weeks 1, 2, 3, and 4, though the difference was not significant at 12 weeks. ***Hernandez Munoz – Black cohosh (90) vs usual care (46)*** –Patients were compared in terms of the % free of hot flashes, % still having moderate hot flashes (a few episodes of heat with discrete sweating), and % still having severe hot flashes (≥5 or more sudden episodes of heat are experienced during the day, accompanied by sweating, sleep disturbances, feeling of irritation and anxiety) at study end. At the 52-week conclusion of the study, the proportions of patients who were free of hot flashes/still endured moderate hot flashes/still endured severe hot flashes were different between those receiving black cohosh (46.7%, 28.9%, and 24.4%) compared to usual care (0%, 26.1%, and 73.9%). ***Jacobson 2001 – Black cohosh (n=42) vs placebo (n=43)*** –Patients completed HF diaries at 30 and 60 days, with an additional questionnaire at final follow-up. HF severity was scores as 1=mild, 2=moderate, 3=severe. The study notes that both groups experienced a decline in HF severity during the first month of study preparation. The differences between groups in intensity at the end of the study were described as not statistically significant, and no additional data were provided. ***Barton 1998 – Vitamin E vs placebo (n=104 overall; crossover trial)*** –Diaries were used to measure HFs (including mean daily HF severity) during the baseline week and the two subsequent 4-week treatment periods. The authors suggest there were few to no benefits of Vitamin E for HF severity. **Sleep measures:** The systematic review identified 5 RCTs that reported on sleep measures. **Pharmacologic therapies:** ***Boekhout 2011 – Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)*** –**Groningen Sleep Quality Scale (GSQ)** was assessed. Sleep quality was not found to differ between the venlafaxine and clonidine intervention groups; no additional data or information was provided.	

	Biglia 2009 – Gabapentin (n=60) vs vitamin E (n=55) –Based on findings from the **PSQI**, gabapentin demonstrated a statistically significant improvement in sleep quality from baseline; the gabapentin group incurred a mean global PSQI score reduction of 21.33% at twelve weeks and a mean absolute reduction of 1.67 (95% CI 0.90-2.43). The authors note that no significant change from baseline to twelve weeks was observed in women receiving Vitamin E. No numeric data for vitamin E is provided, nor is a statistical comparison between the gabapentin and vitamin E groups. ***Stearns 2005 – Paroxetine (2 dose levels; 10mg, 20mg) vs placebo (crossover trial, n=151 overall)*** –**The MOS Sleep Problems Index** was assessed. All three intervention groups (placebo, paroxetine 10mg and paroxetine 20mg) were associated with improvements of at least 10 points in the MOS Sleep Problems Index from baseline, however Paroxetine 10mg was associated with significantly greater improvement compared to placebo. **Dietary supplements:** ***Chen 2014 – Melatonin (n=48) vs placebo (n=47)*** –The authors 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 sub-domains. **Acupuncture:** ***Bao 2014 – Acupuncture (n=23) vs sham acupuncture (n=24)*** –Assessed sleep quality and sleep disturbance using **Pittsburgh Sleep Quality Index (PSQI)**, which has both an overall score and seven domain scores (sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbance; use of sleeping medications; daytime dysfunction) which were summed to form a total score out of 21. Comparison of median and IQR scores between groups at 4, 8 and 12 weeks found no differences between acupuncture and sham acupuncture. **Depression:** The systematic review identified 10 RCTs that reported on depression. **Pharmacologic therapies:** ***Biglia 2016 – Duloxetine (n=28) vs escitalopram (n=30)*** –**Both BDI and MADRS** were evaluated. A significant reduction of depression from baseline was observed in both groups after both 4 and 12 weeks, with no important differences identified between treatments. In the duloxetine group, the mean MADRS score changed from 12.9 at baseline to 5.6 after 12 weeks (a 56.6% reduction), and BDI changed from 4.9 to 3.6 in the same time period (a 26.5% reduction). The corresponding changes in the escitalopram group were from 19.4 to 11.1 (a 42.8% reduction) for MADRS and from 8.3 to 6.6 (a 20.5% reduction) for BDI. ***Boekhout 2011 – Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)***	

	–**The HADS tool** was evaluated. After twelve weeks, depression scores were significantly higher in patients receiving venlafaxine than patients receiving clonidine (p=0.03), suggesting more depression. However, no additional numeric details are provided, and statistical comparisons with the placebo group are not detailed in the study report. ***Loprinzi 2000 – Venlafaxine (n=165 across three dose groups) vs placebo (n=56)*** –The **Beck Depression Inventory** was evaluated (once per week for 5 weeks). The study authors reported that at the end of the study, totals of 16/48 (33%(evaluable patients in the placebo group, and corresponding totals of 11/40 (23%), 9/43 (21%) and 13/49 (27%) in the venlafaxine 37.5mg, 75mg and 150mg groups had depression scores consistent with the presence of at least mild depression. ***Loprinzi 2009 – Gabapentin (n=161 across 3 dose groups) vs placebo (n=54)*** –The **POMS-B Scale** was evaluated. At 4 weeks, no significant differences were identified between the gabapentin and placebo groups and its subdomains, which included depression/dejection. No additional numeric data are provided in the study report. ***Stearns 2005 – Paroxetine vs placebo (n=151 overall; crossover with 2 paroxetine groups)*** –The **CES-D scale** was evaluated. The study authors reported that after five weeks, there were no differences in the percentages of patients in the placebo and paroxetine groups who improved, worsened or stayed the same in terms of depressive symptoms. ***Kimmick 2006 – Sertraline vs placebo (n=62 overall; crossover study)*** –The **CES-D scale** was evaluated. After 12 weeks, mean CES-D score increased in the sertraline group (from 11.2 (SD 9.2) to 12.8 (SD 11.7)) and decreased in the placebo group (from 11.5 (SD 7.9) to 7.9 (SD 6.8)). The study reports no important differences between groups with regard to effects on depression were identified. ***Walker 2010 – Venlafaxine (n=25) vs acupuncture (n=25)*** –The **Beck Depression Index Primary Care (BDI-PC)** was evaluated. Both the venlafaxine group and the acupuncture group were associated with statistically significant reductions in depression after 12 months. The study report presents no detailed numeric data for changes within either group or the comparison of changes between groups; a figure within the report indicates overlapping confidence intervals at final follow-up, suggesting no statistically significant difference between groups was present. Digitized data from a study figure suggest reductions from 10.1 (SE 0.9) to 8.3 (SE 1.1) and from 12.1 (SE 0.8) to 9.6 (SE 1.1) in the venlafaxine group after twelve months. **Dietary supplements:** ***Chen 2014 – Melatonin (n=48) vs placebo (n=47)*** –The **CES-D Scale** was evaluated. There was very little change in depression at four months from baseline in both the melatonin (mean change -0.2 (SD 4.6)) and placebo (mean change 0 (SD 5.4)) groups. No differences with respect to impact on depression were observed (p=0.66). ***Jacobson 2001 – Black cohosh (n=42) vs placebo (n=43)***	

	–The study reports evaluating changes in several menopausal symptoms, one of which was depression, though further details are not provided with regard to approach to measurement. The article denotes that while symptoms in general improved in both groups, there were no changes that were specifically impacted by treatment. **Acupuncture:** ***Bao 2014 – Acupuncture (n=23) vs sham acupuncture (n=24)*** –**T**he **Center for Epidemiologic Studies Depression (CES-D) Scale** was evaluated. After eight weeks, reported median (IQR) changes in both the acupuncture group (reduction from median 16 (IQR of 9) at baseline to median 10 (IQR of 10.5)) and sham acupuncture group (reduction from median 10.5 (IQR of 10) at baseline to 6 (IQR of 11.25)) showed important changes within each group that reached statistical significance, while the difference between groups did not (p=0.44). **Sexual Function:** The systematic review identified 4 RCTs on sexual function. **Pharmacologic therapies:** ***Boekhout 2011 - Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)*** –Looked at changes in the **overall Sexual Activity Questionnaire (SAQ)**. The authors report there were no important differences noted for sexual function between the intervention groups; no detailed numeric data are provided to give further insights. ***Stearns 2005 - Paroxetine vs placebo (n=151 overall)*** –Looked at the **Medical Outcomes Study (MOS) Sexual Problems Index**. The study authors report that the following numbers of patients improved / stayed the same / worsened: Placebo = 9 (25%) / 21 (58%) / 6 (17%); Paroxetine 10mg = 3 (20%) / 10 (67%) / 2 (13%); Paroxetine 20mg = 4 (25%) / 7 (44%) / 5 (31%). Thus, there were no important gains associated with paroxetine. ***Loprinzi 2002 - Fluoxetine vs placebo (n=81 overall)*** –Looked at **libido change based on element 21 of the Beck Depression Index**. The study report noted that after five weeks of treatment, totals of 11 patients in the fluoxetine group and 9 in the placebo group had improved libido compared to baseline, while totals of 1 patient in the fluoxetine group and 3 in the placebo group had reduced libido compared to baseline. Fluoxetine thus appeared to offer some gains, though no formal statistical comparisons were performed. ***Loprinzi 2000 - Venlafaxine (n=165 across three dose groups) vs placebo (n=56)*** –Looked at **libido change based on element 21 of the Beck Depression Index**. Improvements in libido were observed in the placebo group as well as patients receiving all doses of venlafaxine, however the authors do not report formal statistical comparisons to establish statistical significance nor clinical relevance of the between-group differences. Numeric values are also unreported, with only a line graph presented (one profile per group).	

Quality of Life:

The systematic review identified 15 RCTs that reported on quality of life.

Study and Year	Population	Tool used to Assess Study Participants	Time of assessment	Treatments compared	Significant difference between groups?
Bordeleau 2010	BC	Medical outcomes study SF-36	4 wks	Gabapentin, venlafaxine	NO
Wu 2009	BC	FACT-G	6 wks	Placebo, sertraline	NO
Loprinzi 2009	PC	Scored on scale ranging from 0-10	4 wks	Placebo, gabapentin	NO
Loprinzi 2007	BC	Weekly linear analog self -assessment questionnaire	4 wks	Gabapentin, gabapentin+antidepressant	NO
Kimmick 2006	BC	FACT-B	6 wks	Placebo, sertraline	NO
Loprinzi 2000	BC	Two single item global QoL questions	4 wks	Placebo, venlafaxine	YES
Pandya 2000	BC	Scored on scale ranging from 1-10	12 wks	Placebo, clonidine	NO
Stearns 2005	BC	EuroQol	4 wks	Placebo, sertraline	NO
Loprinzi 2002	BC	Global rating of health and well being (0-100)	4 wks	Placebo, fluoxetine	NO
Biglia 2009	BC	MRS; SF-36 (mental, physical)	12 wks	Gabapentin, vitamin E	UNCLEAR
MacGregor 2005	BC	EORTC QLQ30	12 wks	Placebo, soy	NO
Jacobson 2001	BC	Global rating of health and well being (0-100)	9 wks	Placebo, black cohosh	NO
Vitolins 2013	PC	FACT-P	12 wks	Venlafaxine, soy	NO
Bao 2014	BC	EuroQoL	8 wks	Sham acupuncture, acupuncture	NO
Walker 2010	BC	MenQOL tool	64 wks	Acupuncture, venlafaxine	NO

Adverse Events/Tolerability:

Outcomes reported (with available quantitative data) were as follows:

–***3 or more studies:*** constipation (n=8); headache (n=7); nausea (n=7); fatigue/sleepiness (n=6); diarrhea (n=4); dry mouth (n=4); weight gain (n=4); vomiting (n=4); appetite loss (n=3); abnormal sweating (n=3); insomnia/poor sleep (n=3); Grade 1-4 TEAEs/toxicities (n=3); mood change/moodiness (n=3); rash/itchiness (n=3)

–***1-2 studies:*** anxiety (n=2); bruising (n=2); hypertension/increased BP (n=2);vaginal bleeding/spotting (n=2); abdominal bloating (n=1); cramping (n=1); gas (n=1); undesirable appetite increase (n=1); appendectomy (n=1); arrhythmia (n=1); back pain (n=1); nightmares (n=1); blurred vision (n=1); depression (n=1)

Headache:

Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, electroacupuncture vs gabapentin, electroacupuncture vs placebo, gabapentin vs placebo, melatonin vs placebo, electroacupuncture vs sham acupuncture, gabapentin vs sham acupuncture, placebo vs sham acupuncture, placebo vs soy, acupuncture vs venlafaxine, placebo vs vitamin E.

	Constipation: Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, electroacupuncture vs gabapentin, electroacupuncture vs placebo, gabapentin vs placebo, electroacupuncture vs sham acupuncture, gabapentin vs sham acupuncture, placebo vs sham acupuncture, placebo vs soy, acupuncture vs venlafaxine, placebo vs venlafaxine, placebo vs vitamin E, clonidine vs venlafaxine, black cohosh vs placebo, clonidine vs placebo. **Fatigue:** Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, electroacupuncture vs gabapentin, electroacupuncture vs placebo, gabapentin vs placebo, electroacupuncture vs sham acupuncture, gabapentin vs sham acupuncture, placebo vs sham acupuncture, placebo vs venlafaxine, placebo vs vitamin E, clonidine vs venlafaxine, clonidine vs placebo. **Nausea:** Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, placebo vs soy, placebo vs venlafaxine, placebo vs vitamin E, clonidine vs placebo. Precise estimate of harm based on small number of events for clonidine vs venlafaxine: OR=0.33; 95% CI: 0.13, 0.81	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	The study team identified 41 publications (40 studies/RCTs) that informed the network meta-analysis of pharmacological, dietary supplements, physical, and psychological interventions. **Hot Flash Frequency:** Data from 11 RCTs contributed to the model for the outcome of frequency. Additional information from the 12 studies that reported on frequency but could not be pooled in the analysis are presented below. **Pharmacologic therapies:** ***Bordeleau 2010 – Gabapentin vs venlafaxine (n=66 overall; crossover study)*** –This was a cross-over trial with 2-4 weeks in between study periods. The authors reported that with regard to hot flash frequency, the ratio of venlafaxine compared to gabapentin was 0.94 (95% CI not reported, but the p-value was reported to be >0.61). The authors also reported that 38 of 56 patients completing the study preferred venlafaxine over gabapentin; amongst them, 84.2% felt the frequency of hot flashes was reduced with venlafaxine. The authors concluded that breast cancer survivors prefer venlafaxine over gabapentin for treating hot flashes.	The panel considered each class of treatment separately based on the magnitude of the harmful outcomes. In addition, the panel determined that across all treatments there were concerns about the harms/serious adverse events of the treatments being underreported. **Pharmacologic:** **Venlafaxine**, paroxetine, clonidine (not with prior dx of depression):

	Loprinzi 2002 – Fluoxetine vs placebo (n=81; crossover trial) –The first study period was 5 weeks followed by a second (cross-over) 4-week period. Study authors reported that the median hot flash frequency dropped by 3.4 hot flashes per day (42%) for patients while receiving fluoxetine and by 2.5 hot flashes per day (31%) while patients were receiving placebo in the first treatment period, respectively (P = 0.54). The authors concluded that this dose of fluoxetine resulted in a modest improvement in hot flashes. ***Mao 2015 – Gabapentin (n=28) vs electroacupuncture (n=30) vs sham acupuncture (n=32) vs placebo (n=30)*** –The study was for 8 weeks with additional evaluation at week 24 for durability of treatment effects. The mean (SD) daily frequency at baseline for electroacupuncture was 8.3 (5.6), and 6.3 (2.8) for the related sham group; the mean (SD) for the placebo gabapentin arm was 8.1 (5.4), while the related value for the gabapentin group was 6.8 (3.3). The authors concluded that acupuncture produced larger placebo and smaller nocebo effects than did pills for the treatment of hot flashes, however detailed data with regard to frequency are not reported. It was noted that electroacupuncture may be more effective than gabapentin with fewer adverse effects for HF management. ***Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30)*** –This study was for 12 weeks. There were no significant differences between the soy and placebo arms at any time; while participants in the venlafaxine arm tended to have fewer hot flashes during the initial 2 weeks, this early difference disappeared by 12 weeks. The authors concluded that neither soy protein nor venlafaxine were effective in treating hot flashes in men over a 12-week period, highlighting the need for additional investigations to identify treatments for hot flash management in men. ***Biglia 2016 – Escitalopram (n=30) vs duloxetine (n=28)*** –In this study, patients kept a diary of HF frequency and severity at baseline and after 4 and 12 weeks of treatment. The decrease, after 12 weeks of treatment, in the total number of HFs per week was 49.8% in the duloxetine group (P = 0.003) and 53% in the escitalopram group (P = 0.001). The author's concluded that escitalopram and duloxetine are both effective treatment for the relief of HFs in breast cancer survivors, with similar beneficial effect. **Dietary supplements:** ***Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30)*** –This study was for 12 weeks. There were no significant differences between the soy and placebo arms at any time; while participants in the venlafaxine arm tended to have fewer hot flashes during the initial 2 weeks, this early difference disappeared by 12 weeks. The authors concluded that neither soy protein nor venlafaxine were effective in treating hot flashes in men over a 12-week period, highlighting the need for additional investigations to identify treatments for hot flash management in men. ***Barton 1998 – Vitamin E (n=54) vs placebo (n=50) (crossover trial)*** –After a 1-week baseline period, patients received 4 weeks of vitamin E 800 IU daily, then 4 weeks of an identical appearing placebo, or vice versa. Diaries were used to measure potential toxicities and HFs during the baseline week and the two subsequent 4-week treatment periods. During the first study period after 4 weeks of therapy, HF frequency decreased 25% with vitamin E compared with 22% with placebo, finding no difference between interventions *(P* = .90). Incorporating the second study period, a small but statistically significant	**Venlafaxine**: change in tolerability over time - may be moderate to start, but small over time - **Small** (if patients then stay on the treatment - also delayed benefit) - start with smallest titration (37.5mg) **Paroxetine**: **Small** (possibly dose-response - start with smallest titration) (note in feasibility - drug interactions) **Clonidine**: side effects include headache and hypertension – **Moderate** Additional information informed by 1 study using transdermal patch (Loprinzi 1994) **Anti-depressants** (without dx of depression) (sertraline, fluoxetine, escitalopram, duloxetine): **Small** (however, the panel thinks that the AEs are underreported in the literature) **Gabapentin**: **Small** (however, the panel thinks that the AEs are underreported in the literature) **Dietary supplements** (soy, Black Cohosh, St. Johns Wort, melatonin, Vitamin E): **Don't know** **Electro-acupuncture: Small**

	advantage favoring Vitamin E was noted (suggesting approximately 1 less HF per day). The authors noted that while a significant reduction in HF frequency was seen with vitamin E, clinical relevance was small. ***Quella 2000 – Soy (n=88) vs Placebo (n=88) (crossover trial)*** –The study included a 1-week baseline period with no therapy, followed by 4 weeks of either soy tablets or placebo. Patients then crossed over to the opposite arm in a double-blind manner for the last 4 weeks. Patients completed a daily questionnaire documenting HF frequency, intensity, and perceived side effects. Among patients receiving placebo, 36% reported that HF frequency was halved, compared with only 24% of patients receiving soy (*P* =0.01). The authors concluded that the soy product did not alleviate HFs in breast cancer survivors. ***Van Patten 2002 – Soy (n=59) vs placebo (n=64)*** –This study included a 4-week lead-in phase and 12-week treatment phase involving assignment to a soy or placebo beverage. There were no statistically significant differences between the soy and placebo groups in the mean reductions of daytime (-1.2 soy vs -1.8 placebo), night time (-0.5 soy vs -0.7 placebo) or 24-hr (-1.8 soy vs -2.5 placebo) HFs; however, presumably because of a strong placebo effect, both groups had significant reductions in hot flashes. The authors concluded that the soy beverage did not alleviate HFs any more than placebo. **Acupuncture:** ***Frisk 2009 – Acupuncture (n=16) vs electroacupuncture (n=15)*** –The numbers of flushes per 24 hours decreased significantly in both groups from baseline to 4 wk of treatment and remained at this decreased level at all measuring points, except at 12 mo after start of treatment in the electroacupuncture group (when flushes tended to increase). There was no significant difference between the groups over time (p = 0.25; ANOVA). Hot flushes per 24 h decreased significantly, from a median of 7.6 (interquartile range [IQR], 6.0–12.3) at baseline in the electroacupuncture group to 4.1 (IQR, 2.0–6.5) (p = 0.012) after 12 weeks, and from 5.7 (IQR, 5.1–9.5) in the acupuncture group to 3.4 (IQR1.8–6.3) (p = 0.001). The authors concluded that both electroacupuncture and acupuncture lowered number of HFs. ***Hervik 2009 – Acupuncture (n=30) vs sham acupuncture (n=29)*** –This study provided patients with twice weekly acupuncture or sham acupuncture for the first 5 weeks, and subsequently once per week for the next 5 weeks. Daytime HFs were significantly reduced in the acupuncture group (from baseline mean (SD) 9.5 (4.9) to 4.7 (3.7) at 10 weeks, which further reduced to 3.2 (2.2) over the next 12 weeks), while no significant change was seen within the sham acupuncture group (from baseline mean (SD) 12.3 (7.3) to 11.7 (8.5) at 10 weeks, which increased back to 12.1 (8.3) over the next 12 weeks). Similar patterns were reported for nighttime HFs. The difference in acupuncture versus sham acupuncture was statistically significant for both daytime and nighttime HFs. ***Liljegren 2012 – Acupuncture (n=42) vs sham acupuncture (n=42)*** –Patients received treatment twice weekly for a duration of 5 weeks. The reductions in frequencies of HFs reached statistical significance at week 6 in both the acupuncture (from baseline mean (SD) 8.4 (5.5) to 5.7 (4.1) at 6 weeks) and sham acupuncture (from baseline 7.1 (4.4) to 4.5 (3.7) at 6 weeks) groups; however, the difference between groups was not statistically significant (mean difference 1.2, 95% CI -0.7 to 3.0; p=0.21).	**Non-electro Acupuncture: Trivial**

	Deng 2007 – Acupuncture (n=42) vs sham acupuncture (n=30) –Interventions were given twice weekly for 4 consecutive weeks. HF frequency was evaluated at baseline, at 6 weeks, and at 6 months after initiation of treatment. Patients initially randomly assigned to the sham group were crossed over to acupuncture starting at week 7. In the principal analysis (week 6), acupuncture was associated with 0.8 fewer hot flashes per day than placebo, but the difference was not statistically significant (95% CI,-0.7 to 2.4; *P*=0.3). When participants in the sham acupuncture group were crossed over to the acupuncture group at week 7, HF frequency was reduced by approximately another 20% at week 12. HF frequency was reduced from 7.3 (SD 5.5) to 5.4 (SD 3.8), a difference of 1.9 hot flashes per day (95% CI -0.4 to 4.1). Treatment improvements were maintained at 6 months. The authors concluded HF frequency was reduced following acupuncture. However, compared with sham acupuncture, the reduction did not reach statistical significance. **<u>Hot Flash Composite Score:</u>** Data from 12 RCTs contributed to the model for the outcome of frequency. Additional information from the 12 studies that reported on frequency but could not be pooled in the analysis are presented below. **Pharmacologic therapies:** ***Biglia 2016 – Escitalopram (n=30) vs duloxetine (n=28)*** -HF score was assessed at both 4 and 12 weeks of treatment. At the end of the study period, the decrease in weekly HF score was 53.6% in the duloxetine group (P=0.003) and 60.4% in the escitalopram group (P=0.001). While both groups demonstrated a significant reduction from baseline, the difference between interventions was not statistically significant. The authors concluded that their data showed that a 12-week treatment both with escitalopram and duloxetine is effective for HF management. ***Boekhout 2011 – Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)*** –Daily HF score was calculated as the sum of HF severity values experienced in a given day. At 12 weeks, venlafaxine and clonidine were both associated with lower median HF scores compared to placebo; the median (IQR) scores for the 3 groups were as follows: Placebo - median 10.9, IQR 7.4-15.8; Clonidine: median 7.5, IQR 2.0-10.8; Venlafaxine: median 7.6, IQR 4.0-110.4. It was also noted that when considering the entire 12-week study period, HF score reduction was greater overall with venlafaxine than clonidine due to an earlier start of benefits during the 12-week period. The study authors concluded that venlafaxine and clonidine are effective treatments in the management of HFs. ***Bordeleau 2010 – Gabapentin vs venlafaxine (n=66 overall; crossover trial)*** –Daily HF score was assessed as average HF severity that day x frequency of HFs that day. Treatment periods lasted 4 weeks, with 2-4 weeks washout in between. Findings performed to compare the intervention groups using a mixed modeling approach identified a venlafaxine to gabapentin ratio of 0.96 (near 1), suggesting little difference between intervention groups (p value >0.61); both groups were noted to have important reductions from baseline (from week 2 mean (SD) 18.7 (23.2) to 5.7 (4.6) for venlafaxine in the first study period; from 18.6 (15.4) to 6.5 (8.3) in the gabapentin group). Analyses were also performed to compare groups as based upon patients' preferred treatment; those that preferred venlafaxine (n=38) were reported to experience scores 41% lower, while those that preferred gabapentin (n=18) were reported to experience scores 47% lower.	

	Loprinzi 2002 – Fluoxetine vs placebo (n=81 total; crossover trial) –HF score was calculated as the product of frequency x severity. In the first study period, HF scores decreased by a median of 4.7 units per day (36%) for those on placebo and by 6.4 units per day (50%) in those receiving fluoxetine, and the difference was not statistically significant between groups (P = 0.35). Table 3 shows the score at week 5. Subsequent cross-over analyses identified a significantly greater reduction with fluoxetine. The authors concluded that fluoxetine was associated with a modest improvement in HF score. **Dietary supplements:** ***Barton 1998 – Vitamin E vs placebo (n=104 total; crossover trial)*** –HF score was calculated as the product of frequency x severity. After the first 4 weeks of therapy, the HF score decreased by 28% with vitamin E and 20% with placebo *(P* = 0.68). During the second treatment period, the mean hot-flash scores decreased by 0.03% and 25% in the placebo group and vitamin E group (P=0.24), respectively. A subsequent analysis encompassing the full crossover design suggested the presence of a small but statistically significant advantage of vitamin E over placebo. ***Jacobson 2001 – Black cohosh (n=42) vs placebo (n=43)*** –The HF score used was unclear in the study report. After 9 weeks, the HF score changed from baseline median 53.2 (IQR 25.3-71.3) to 31.0 (IQR 18.3-77.0) in the black cohosh group and from median 52.5 (IQR 28.9-93.0) to median 24.6 (IQR 16.4-64) in the placebo group; the difference was noted as not statistically significant, but no other data were provided. ***Quella 2000 – Soy (n=87) vs placebo (n=88)*** –Hot flash score was assessed using the formula of frequency x severity. Patients averaged approximately seven HFs per day during the baseline study week (SD 54.5), with an average HF score of 13 points (SD 59.0). The totals of patients reporting reductions in HF score of <25%, 25-50% and >50% were 44%, 21% and 35% in the soy group and 40%, 22% and 38% in the placebo group, respectively. The authors concluded that the available data strongly suggest that soy phytoestrogens do not substantially reduce HFs when compared with placebo ***Van Patten 2002 – Soy (n=78) vs placebo (n=79)*** –HF score was assessed according to: [hot flash frequency x intensity for day] + [hot flash frequency x intensity for night] for 24 hours. The study reported there were no differences in hot flash related outcomes between groups: during the final 4 weeks of treatment, comparable changes from baseline in the soy group (mean (SD) change from baseline 18.0 (13.9) to final value 12.6 (13.4)) and placebo groups (mean (SD) change from baseline 18.9 (18.9) to final value 11.4 (11.3)) were observed. ***Vitolins 2013 – Venlafaxine + soy protein (n=30) vs venlafaxine + milk protein (n=30) vs soy protein (n=30) vs milk protein (n=30) (prostate cancer trial)*** –HF score calculated as the product of severity x frequency. The study reported that there were no statistically significant differences between the soy and placebo arms at any time, and although participants in the venlafaxine arm tended to have fewer hot flashes during the initial 2 weeks, this early difference had disappeared by 12 weeks; mean (SD) 12-week HF score values were as follows: venlafaxine + soy protein – 11.2 (10.9); venlafaxine + milk protein – 9.2 (7.2); placebo + soy protein – 13.6 (15.3); placebo + milk protein – 9.3 (8.5). The authors concluded that in androgen-deprived men, neither venlafaxine nor soy proved effective in reducing HFs.	

	Acupuncture: ***Bao 2014 – Acupuncture (n=25) vs sham acupuncture (n=26)*** –HF score was determined using a 100-point visual analog scale (VAS) ≥ 20. The study presents comparison of median (IQR) scores between groups after 8 weeks of treatment. The chance in the sham acupuncture group wasn't statistically significant (from median (IQR) 20.5 (54.75) to 10 (47.25)), while the change in the acupuncture group was significant (from median (IQR) 31 (67) to 14 (32.5)); the comparison of change between groups was not statistically significant (p=0.56). The authors reported no important differences between interventions. ***Frisk 2009 – Acupuncture (n=13) vs electroacupuncture (n=11) (prostate cancer trial)*** –Daily HF distress calculated by summing individual HF distress (scored from 0-10). After 52 weeks of treatment, mean daily HF distress changed from baseline median 7.6 (IQR 4.7-8.3) to median 4.3 (IQR) 1.3 – 7.7 in the acupuncture group and from baseline median 8.2 (IQR 6.5-10.7) to median 5.5 (IQR 3.8-6.9) in the electroacupuncture group (p=0.65 between groups). ***Lesi 2016 – Acupuncture + enhanced self-care (n=85) vs enhanced self-care (n=105)*** –The HF score was calculated by multiplying the mean number of daily hot flashes that occurred during the week before assessment by the mean daily severity (1, mild; 2, moderate; 3, severe). After having comparable mean HF scores at baseline, the HF score at **week 12** was higher in the enhanced self group (mean (SD) 22.70 (19.40)) than in the acupuncture + enhanced self-care group (11.34 (14.75); p<0.001 for the between-group difference of -11.36, 95% CI -16.39 to -6.33). Similar mean differences favoring the acupuncture + enhanced self-care group were seen at both 3-month (-7.86, 95% CI -12.99 to -2.73) and 6-month follow-up (-8.82, 95% CI -14.04 to -3.61). The authors concluded that acupuncture in association with enhanced self-care is an effective integrative intervention for managing HFs. **<u>Hot Flash Severity:</u>** Data from 10 RCTs reported on frequency but could not be pooled in the analysis are presented below. **Pharmacologic therapies:** ***Bordeleau 2010 – Gabapentin vs venlafaxine (n=66 overall; crossover trial)*** –HF severity was assessed as 1=mild, 2=moderate, 3=severe, 4=severe, and were averaged per day. Study treatment periods lasted 4 weeks, with 2-4 weeks washout in between. Findings performed to compare the intervention groups using a mixed modeling approach identified a venlafaxine to gabapentin ratio of 1.02 (near 1), suggesting little difference between intervention groups (p value >0.61). Analyses were also performed to compare groups as based upon patients' preferred treatment; amongst those that preferred venlafaxine (n=38), 94.7% reported decreased HF severity, while amongst those that preferred gabapentin (n=18), 94.4% reported decreased HF severity. ***Walker 2010 – Venlafaxine (n=25) vs acupuncture (n=25)*** –Treatments were provided for 12 weeks, with outcomes measured up to 1 year post-treatment. The study reports that ANOVA analysis of patient data over time found no important differences between intervention groups with regard to changes in HF severity (p>0.05; detailed numeric data are not reported). Both groups experienced some improvement, with a subsequent return toward baseline values after the end of treatment. The authors suggested acupuncture may offer similar benefits as venlafaxine, with better tolerability.	

	Loibl 2007– Clonidine (n=40) vs venlafaxine (n=40) –The duration of this study was 4 weeks of treatment. HF severity was scored as 1=mild, 2=moderate, 3=severe, 4=very severe. The mean HF severity at baseline week was 2.1 for clonidine and 1.9 for venlafaxine with a P-value of 0.78. Findings for this outcome are not clearly reported in the study report. Author conclusions appear to suggest benefits of venlafaxine over clonidine for reduction of HF frequency, but not HF severity. ***Pandya 2000 – Clonidine (n=99) vs placebo (n=99)*** –The study included a 1-week baseline period and follow-up at 4, 8 and 12 weeks; HFs were scored as 1=mild, 2=moderate, 3=severe, 4=very severe). Mean (SE) severity grades at baseline were 2.2 (0.1) and 2.1 (0.1) in the clonidine and placebo groups, respectively. The study reported % changes from these baseline values; median reductions of -11.7%, -17.3% and -9.3% were reported at 4, 8 and 12 weeks in the clonidine group while corresponding values of -8.5%, -10.5% and -8.3% were observed with placebo. None of the differences reached statistical significance. ***Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30) (prostate cancer study)*** –The duration reported findings at 4, 8 and 12 weeks; HF severity was scored as 1=mild, 2=moderate and 3=severe. There were no significant differences in the comparison of soy and placebo at any time point. The venlafaxine arm tended to have lower HF severity values at weeks 1, 2, 3, and 4, though the difference was not significant at 12 weeks. **Dietary supplements:** ***Chen 2014 – Melatonin (n=48) vs placebo (n=47)*** –The study duration was 4 months, and HF severity was scored as 1=mild, 2=moderate, 3=severe, 4=very severe. The study denotes that there were no statistically significant differences between the groups with regard to changes in the numbers of mild, moderate and severe HFs experienced. ***Vitolins 2013 – Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30) (prostate cancer study)*** –The duration reported findings at 4, 8 and 12 weeks; HF severity was scored as 1=mild, 2=moderate and 3=severe. There were no significant differences in the comparison of soy and placebo at any time point. The venlafaxine arm tended to have lower HF severity values at weeks 1, 2, 3, and 4, though the difference was not significant at 12 weeks. ***Hernandez Munoz 2003 – Black cohosh (90) vs usual care (46)*** –Patients were compared in terms of the % free of hot flashes, % still having moderate hot flashes (a few episodes of heat with discrete sweating), and % still having severe hot flashes ($\geq$5 or more sudden episodes of heat are experienced during the day, accompanied by sweating, sleep disturbances, feeling of irritation and anxiety) at study end. At the 52-week conclusion of the study, the proportions of patients who were free of hot flashes/still endured moderate hot flashes/still endured severe hot flashes were different between those receiving black cohosh (46.7%, 28.9%, and 24.4%) compared to usual care (0%, 26.1%, and 73.9%).	

	Jacobson 2001 – Black cohosh (n=42) vs placebo (n=43) –Patients completed HF diaries at 30 and 60 days, with an additional questionnaire at final follow-up. HF severity was scores as 1=mild, 2=moderate, 3=severe. The study notes that both groups experienced a decline in HF severity during the first month of study preparation. The differences between groups in intensity at the end of the study were described as not statistically significant, and no additional data were provided. ***Barton 1998 – Vitamin E vs placebo (n=104 overall; crossover trial)*** –Diaries were used to measure HFs (including mean daily HF severity) during the baseline week and the two subsequent 4-week treatment periods. The authors suggest there were few to no benefits of Vitamin E for HF severity. **Sleep measures:** The systematic review identified 5 RCTs that reported on sleep measures. **Pharmacologic therapies:** ***Boekhout 2011 – Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)*** –**Groningen Sleep Quality Scale (GSQ)** was assessed. Sleep quality was not found to differ between the venlafaxine and clonidine intervention groups; no additional data or information was provided. ***Biglia 2009 – Gabapentin (n=60) vs vitamin E (n=55)*** –Based on findings from the **PSQI**, gabapentin demonstrated a statistically significant improvement in sleep quality from baseline; the gabapentin group incurred a mean global PSQI score reduction of 21.33% at twelve weeks and a mean absolute reduction of 1.67 (95% CI 0.90-2.43). The authors note that no significant change from baseline to twelve weeks was observed in women receiving Vitamin E. No numeric data for vitamin E is provided, nor is a statistical comparison between the gabapentin and vitamin E groups. ***Stearns 2005 – Paroxetine (2 dose levels; 10mg, 20mg) vs placebo (crossover trial, n=151 overall)*** –**The MOS Sleep Problems Index** was assessed. All three intervention groups (placebo, paroxetine 10mg and paroxetine 20mg) were associated with improvements of at least 10 points in the MOS Sleep Problems Index from baseline, however Paroxetine 10mg was associated with significantly greater improvement compared to placebo. **Dietary supplements:** ***Chen 2014 – Melatonin (n=48) vs placebo (n=47)*** –The authors 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 sub-domains. **Acupuncture:**	

	Bao 2014 – Acupuncture (n=23) vs sham acupuncture (n=24) –Assessed sleep quality and sleep disturbance using **Pittsburgh Sleep Quality Index (PSQI)**, which has both an overall score and seven domain scores (sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbance; use of sleeping medications; daytime dysfunction) which were summed to form a total score out of 21. Comparison of median and IQR scores between groups at 4, 8 and 12 weeks found no differences between acupuncture and sham acupuncture. **Depression:** The systematic review identified 10 RCTs that reported on depression. **Pharmacologic therapies:** ***Biglia 2016 – Duloxetine (n=28) vs escitalopram (n=30)*** –**Both BDI and MADRS** were evaluated. A significant reduction of depression from baseline was observed in both groups after both 4 and 12 weeks, with no important differences identified between treatments. In the duloxetine group, the mean MADRS score changed from 12.9 at baseline to 5.6 after 12 weeks (a 56.6% reduction), and BDI changed from 4.9 to 3.6 in the same time period (a 26.5% reduction). The corresponding changes in the escitalopram group were from 19.4 to 11.1 (a 42.8% reduction) for MADRS and from 8.3 to 6.6 (a 20.5% reduction) for BDI. ***Boekhout 2011 – Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)*** –**The HADS tool** was evaluated. After twelve weeks, depression scores were significantly higher in patients receiving venlafaxine than patients receiving clonidine (p=0.03), suggesting more depression. However, no additional numeric details are provided, and statistical comparisons with the placebo group are not detailed in the study report. ***Loprinzi 2000 – Venlafaxine (n=165 across three dose groups) vs placebo (n=56)*** –The **Beck Depression Inventory** was evaluated (once per week for 5 weeks). The study authors reported that at the end of the study, totals of 16/48 (33%(evaluable patients in the placebo group, and corresponding totals of 11/40 (23%), 9/43 (21%) and 13/49 (27%) in the venlafaxine 37.5mg, 75mg and 150mg groups had depression scores consistent with the presence of at least mild depression. ***Loprinzi 2009 – Gabapentin (n=161 across 3 dose groups) vs placebo (n=54)*** –The **POMS-B Scale** was evaluated. At 4 weeks, no significant differences were identified between the gabapentin and placebo groups and its subdomains, which included depression/dejection. No additional numeric data are provided in the study report. ***Stearns 2005 – Paroxetine vs placebo (n=151 overall; crossover with 2 paroxetine groups)*** –The **CES-D scale** was evaluated. The study authors reported that after five weeks, there were no differences in the percentages of patients in the placebo and paroxetine groups who improved, worsened or stayed the same in terms of depressive symptoms.	

	Kimmick 2006 – Sertraline vs placebo (n=62 overall; crossover study) –The **CES-D scale** was evaluated. After 12 weeks, mean CES-D score increased in the sertraline group (from 11.2 (SD 9.2) to 12.8 (SD 11.7)) and decreased in the placebo group (from 11.5 (SD 7.9) to 7.9 (SD 6.8)). The study reports no important differences between groups with regard to effects on depression were identified. ***Walker 2010 – Venlafaxine (n=25) vs acupuncture (n=25)*** –The **Beck Depression Index Primary Care (BDI-PC)** was evaluated. Both the venlafaxine group and the acupuncture group were associated with statistically significant reductions in depression after 12 months. The study report presents no detailed numeric data for changes within either group or the comparison of changes between groups; a figure within the report indicates overlapping confidence intervals at final follow-up, suggesting no statistically significant difference between groups was present. Digitized data from a study figure suggest reductions from 10.1 (SE 0.9) to 8.3 (SE 1.1) and from 12.1 (SE 0.8) to 9.6 (SE 1.1) in the venlafaxine group after twelve months. **Dietary supplements:** ***Chen 2014 – Melatonin (n=48) vs placebo (n=47)*** –The **CES-D Scale** was evaluated. There was very little change in depression at four months from baseline in both the melatonin (mean change -0.2 (SD 4.6)) and placebo (mean change 0 (SD 5.4)) groups. No differences with respect to impact on depression were observed (p=0.66). ***Jacobson 2001 – Black cohosh (n=42) vs placebo (n=43)*** –The study reports evaluating changes in several menopausal symptoms, one of which was depression, though further details are not provided with regard to approach to measurement. The article denotes that while symptoms in general improved in both groups, there were no changes that were specifically impacted by treatment. **Acupuncture:** ***Bao 2014 – Acupuncture (n=23) vs sham acupuncture (n=24)*** –The **Center for Epidemiologic Studies Depression (CES-D) Scale** was evaluated. After eight weeks, reported median (IQR) changes in both the acupuncture group (reduction from median 16 (IQR of 9) at baseline to median 10 (IQR of 10.5)) and sham acupuncture group (reduction from median 10.5 (IQR of 10) at baseline to 6 (IQR of 11.25)) showed important changes within each group that reached statistical significance, while the difference between groups did not (p=0.44). **Sexual Function:** The systematic review identified 4 RCTs on sexual function. **Pharmacologic therapies:** ***Boekhout 2011 - Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)***	

	–Looked at changes in the **overall Sexual Activity Questionnaire (SAQ)**. The authors report there were no important differences noted for sexual function between the intervention groups; no detailed numeric data are provided to give further insights. ***Stearns 2005 - Paroxetine vs placebo (n=151 overall)*** –Looked at the **Medical Outcomes Study (MOS) Sexual Problems Index**. The study authors report that the following numbers of patients improved / stayed the same / worsened: Placebo = 9 (25%) / 21 (58%) / 6 (17%); Paroxetine 10mg = 3 (20%) / 10 (67%) / 2 (13%); Paroxetine 20mg = 4 (25%) / 7 (44%) / 5 (31%). Thus, there were no important gains associated with paroxetine. ***Loprinzi 2002 - Fluoxetine vs placebo (n=81 overall)*** –Looked at **libido change based on element 21 of the Beck Depression Index**. The study report noted that after five weeks of treatment, totals of 11 patients in the fluoxetine group and 9 in the placebo group had improved libido compared to baseline, while totals of 1 patient in the fluoxetine group and 3 in the placebo group had reduced libido compared to baseline. Fluoxetine thus appeared to offer some gains, though no formal statistical comparisons were performed. ***Loprinzi 2000 - Venlafaxine (n=165 across three dose groups) vs placebo (n=56)*** –Looked at **libido change based on element 21 of the Beck Depression Index**. Improvements in libido were observed in the placebo group as well as patients receiving all doses of venlafaxine, however the authors do not report formal statistical comparisons to establish statistical significance nor clinical relevance of the between-group differences. Numeric values are also unreported, with only a line graph presented (one profile per group). **Quality of Life:** The systematic review identified 15 RCTs that reported on quality of life.	

Study and Year	Population	Tool used to Assess Study Participants	Time of assessment	Treatments compared	Significant difference between groups?
Bordeleau 2010	BC	Medical outcomes study SF-36	4 wks	Gabapentin, venlafaxine	NO
Wu 2009	BC	FACT-G	6 wks	Placebo, sertraline	NO
Loprinzi 2009	PC	Scored on scale ranging from 0-10	4 wks	Placebo, gabapentin	NO
Loprinzi 2007	BC	Weekly linear analog self -assessment questionnaire	4 wks	Gabapentin, gabapentin+antidepressant	NO
Kimmick 2006	BC	FACT-B	6 wks	Placebo, sertraline	NO
Loprinzi 2000	BC	Two single item global QoL questions	4 wks	Placebo, venlafaxine	YES
Pandya 2000	BC	Scored on scale ranging from 1-10	12 wks	Placebo, clonidine	NO
Stearns 2005	BC	EuroQol	4 wks	Placebo, sertraline	NO
Loprinzi 2002	BC	Global rating of health and well being (0-100)	4 wks	Placebo, fluoxetine	NO
Biglia 2009	BC	MRS; SF-36 (mental, physical)	12 wks	Gabapentin, vitamin E	UNCLEAR
MacGregor 2005	BC	EORTC QLQ30	12 wks	Placebo, soy	NO
Jacobson 2001	BC	Global rating of health and well being (0-100)	9 wks	Placebo, black cohosh	NO
Vitolins 2013	PC	FACT-P	12 wks	Venlafaxine, soy	NO
Bao 2014	BC	EuroQoL	8 wks	Sham acupuncture, acupuncture	NO
Walker 2010	BC	MenQOL tool	64 wks	Acupuncture, venlafaxine	NO

Adverse Events/Tolerability:

Outcomes reported (with available quantitative data) were as follows:

–***3 or more studies:*** constipation (n=8); headache (n=7); nausea (n=7); fatigue/sleepiness (n=6); diarrhea (n=4); dry mouth (n=4); weight gain (n=4); vomiting (n=4); appetite loss (n=3); abnormal sweating (n=3); insomnia/poor sleep (n=3); Grade 1-4 TEAEs/toxicities (n=3); mood change/moodiness (n=3); rash/itchiness (n=3)

–***1-2 studies:*** anxiety (n=2); bruising (n=2); hypertension/increased BP (n=2);vaginal bleeding/spotting (n=2); abdominal bloating (n=1); cramping (n=1); gas (n=1); undesirable appetite increase (n=1); appendectomy (n=1); arrhythmia (n=1); back pain (n=1); nightmares (n=1); blurred vision (n=1); depression (n=1)

Headache:

Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, electroacupuncture vs gabapentin, electroacupuncture vs placebo, gabapentin vs placebo, melatonin vs placebo, electroacupuncture vs sham acupuncture, gabapentin vs sham acupuncture, placebo vs sham acupuncture, placebo vs soy, acupuncture vs venlafaxine, placebo vs vitamin E.

Constipation:

	Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, electroacupuncture vs gabapentin, electroacupuncture vs placebo, gabapentin vs placebo, electroacupuncture vs sham acupuncture, gabapentin vs sham acupuncture, placebo vs sham acupuncture, placebo vs soy, acupuncture vs venlafaxine, placebo vs venlafaxine, placebo vs vitamin E, clonidine vs venlafaxine, black cohosh vs placebo, clonidine vs placebo. **Fatigue:** Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, electroacupuncture vs gabapentin, electroacupuncture vs placebo, gabapentin vs placebo, electroacupuncture vs sham acupuncture, gabapentin vs sham acupuncture, placebo vs sham acupuncture, placebo vs venlafaxine, placebo vs vitamin E, clonidine vs venlafaxine, clonidine vs placebo. **Nausea:** Imprecise estimates of harms based on small number of events for the following comparisons: Sertraline vs placebo, placebo vs soy, placebo vs venlafaxine, placebo vs vitamin E, clonidine vs placebo. Precise estimate of harm based on small number of events for clonidine vs venlafaxine: OR=0.33; 95% CI: 0.13, 0.81	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies		The panel agreed on the following judgments: **Pharmacologic**: **Venlafaxine** for women: **Low** (based on risk of bias, and based on uncertainty of harms - possible under-reporting of harms) **Venlafaxine** for men: **Low** (based on risk of bias and imprecision, and based on uncertainty of harms - possible under-reporting of harms) **Paroxetine**: **Low** (based on risk of bias and imprecision, and based on uncertainty of

		harms - possible under-reporting of harms) Indirectness to men based on the evidence - **Very Low** **Clonidine**: **Low** (based on risk of bias and imprecision, and based on uncertainty of harms - possible under-reporting of harms) Indirectness to men based on the evidence - **Very Low** **Dietary supplements**: **Very Low** (driven by evidence of potential harms) **Acupuncture**: **Low** (imprecision and risk of bias)

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Hot flash symptoms among breast cancer survivors are reported with negative emotional perceptions and behavioral consequences. Often symptoms are concomitant with difficulty sleeping, fatigue, interruption in sexual relations, sleepiness, nervousness, and mood changes (Barton & Loprinzi, 2004). A qualitative study reported on the feelings identified by 35 women in regard to experiencing hot flashes following breast cancer (Hunter, Coventry, Mendes, & Grunfeld, 2009). Themes most commonly mentioned included negative beliefs about the perception when experiencing these symptoms in public. "Social anxiety/embarrassment" was the most commonly mentioned. Additionally, sleep quality and tiredness were commonly recognized as impacted by HF/NS. One study explored the willingness of 25 breast cancer survivors to commit to an additional medical intervention (i.e., acupuncture) to treat their hot flash symptoms (Mao et al., 2012). Respondents indicated that their acceptance of acupuncture would be dependent on (1) expected therapeutic effects (e.g., pain relief, energy); (2) practical concerns (e.g., fear of needles, practitioner experience, time commitment); and (3) source of decision support/validation (e.g., family members, physicians, self). In addition, their acceptance of acupuncture would vary based on their beliefs of acupuncture as a natural alternative to medications, and (2) assessing the degree of HFs as bothersome enough in the context of other medical comorbidities to trigger the need for therapy.	The panel determined that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel agreed on the following judgments: Venlafaxine women: **Favors intervention** Venlafaxine men: **Does not favor either** Paroxetine women: **Favors intervention** (NOT tamoxifen) Paroxetine men: **Don't know** Clonidine women: **Probably favors intervention** Clonidine men: **Does not favor either** Other antidepressants: **Does not favor** Gabapentin: **Does not favor** Dietary supplement: **Does not favor either the intervention or the comparison** Vitamin E - **Probably favors the comparison** Electroacupuncture: **Probably favors intervention** Acupuncture: **Does not favor**

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	GoodRx: www.goodrx.com. Accessed May 9, 2019	The panel agreed on the following judgments: Pharmacologic: Wide range based on dose, frequency, delivery - **Moderate** Dietary supplements: **Negligible cost/savings** Acupuncture: **Moderate**

Drug	Pittsburgh-area Price	Average Retail Price
Venlafaxine 75 mg—60 tablets	Walmart: $9.00	$91.24
Gabapentin 300 mg—90 capsules	Walmart: $11.50 w/ GoodRx discount card	$79.48
Pregabalin 75 mg—60 capsules	Multiple pharmacies: $460.14 w/ GoodRx discount card. Has eligibility rules. Pfizer offers a Lyrica co-pay card. Co-pay becomes $4/mo., subject to a $2,100 maximum benefit per year. Up to 12 uses. Expires 12/31/20.	None listed
Clonidine 0.1 mg—60 tablets	Multiple pharmacies: $7.50 w/ GoodRx discount card	$18.65
Oxybutynin 5 mg—60 tablets	Walgreens: $18.47 w/ GoodRx coupon	$42.61

Walmart.com accessed May 10, 2019			
Black Cohosh	Enzymatic Therapy's Remifemin Menopause Relief Tablets, 20 mg Black Cohosh Extract per tablet, 60 ct.	$12.79	
Soy	Spring Valley Soy Isoflavones Tablets, 40 mg soy isoflavones per tablet, 60 Ct	$5.94	
Flaxseed	Spring Valley Cold-Milled Organic Ground Flax Seeds, 16 Oz	$5.94	
Vitamin E	Spring Valley Vitamin E Supplement, 400IU, 500 Softgel Capsules	$11.48	
Vitamin C	Spring Valley Vitamin C Tablets, 500 mg, 250 Ct	$5.94	
Vitamin B12	Spring Valley Vitamin B12 Tablets, 2500 mcg, 60 Ct	$5.94	
Red Clover	Nature's Way Red Clover Blossom / Herb 400 mg, 100 Ct	$8.00	
Saw Palmetto	Spring Valley Whole Herb Saw Palmetto Capsules, 450 mg, 200 Ct	$9.88	
St. John's Wort	Spring Valley Standardized Extract St. John's Wort Capsules, 300 mg, 150 count	$7.88	

Alternative/Complementary, Psychological and Physical price examples accessed May 15, 2019	
Hypnosis/Relaxation Therapy	• $14.91: "Relaxation Techniques: Reduce Stress and Anxiety and Enhance Well-being" audio CD (https://www.amazon.com/Relaxation-Techniques-Anxiety-Enhance-Well-being/dp/1845900782) • $75 – $125 average price per hypnosis session (2017? American Association of Professional Hypnotherapists http://www.aaph.org/hypnosis-FAQ)
Acupuncture	• $60 - 120 average per session (https://www.acufinder.com/Acupuncture+Information/Detail/How+much+does+an+acupuncture+treatment+cost+)
Cognitive Behavioral Therapy	• $100 or more per hour, potentially (Anxiety and Depression Association of America: https://adaa.org/finding-help/treatment/low-cost-treatment.)
Exercise/Physical Activity	• $19.95: Dr. Scholl's Women's Aspire Medium and Wide Width Walking Shoe (https://www.walmart.com/ip/Women-s-Aspire-Medium-and-Wide-Width-Walking-Shoe/682850282?athcpid=682850282&athpgid=athenaItemPage&athcgid=null&athznid=PWVUB&athieid=v0&athstid=CS020&athguid=4f87b163-ed7-16abddb32a1c91&athena=true) • $50 per month average sports club dues in 2016 (https://money.cnn.com/2018/01/12/news/companies/planet-fitness/index.html) • $80 - $125 average for a one-hour personal training session in 2015 (https://www.angieslist.com/articles/what-factors-affect-cost-personal-trainer.htm)
Yoga	• $12.51: "Rodney Yee Complete Yoga for Beginners" DVD at Walmart.com (https://www.walmart.com/ip/Rodney-Yee-Complete-Yoga-for-Beginners/46606164) • $15 - $25 per hour average cost of yoga classes (https://lessons.com/costs/yoga-classes-cost)
Tai chi	• $9.88: "Tai chi for Beginners" DVD https://www.walmart.com/ip/Tai-Chi-for-Beginners-DVD/10779247 • $15 – $159 per hour for tai chi chuan lessons (https://takelessons.com/sports-and-fitness/tai-chi-chuan-lessons)

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	A search of the literature identified one study that examined the physical and psychosocial effects of breast cancer treatment differences between younger and older rural survivors based on menopausal status at diagnosis (Befort & Klemp, 2011). Younger women who are premenopausal at the time of breast cancer diagnosis report increased rates of menopausal side effects as well as more pronounced deficits in emotional and social functioning and cognitive performance. Women who were premenopausal at diagnosis were significantly more likely to experience numerous symptoms at the time of treatment and currently, including higher rates of hot flashes, vaginal dryness, loss of sexual desire, and weight gain. Negative physical and psychosocial sequelae of breast cancer were common in a rural population and were significantly worse for premenopausal women.	The panel agreed on the following judgments: Pharmacologic: **Probably reduced** (panel noted potential inequity for persons who are underinsured and uninsured) Dietary supplements: **Probably increased** Acupuncture: **Probably reduce equity**

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	One study explored the willingness of 25 breast-cancer survivors to commit to an additional medical intervention (i.e., acupuncture) to treat their hot flash symptoms (Mao et al., 2012). Respondents indicated that their acceptance of acupuncture would be dependent on (1) expected therapeutic effects (e.g., pain relief, energy); (2) practical concerns (e.g., fear of needles, practitioner experience, time commitment); and (3) source of decision support/validation (e.g., family members, physicians, self). In addition, their acceptance of acupuncture would vary based on their beliefs of acupuncture as a natural alternative to medications, and (2) assessing the degree of HFs as bothersome enough in the context of other medical comorbidities to trigger the need for therapy.	The panel agreed on the following judgments: Pharmacologic: **Probably yes** (some patients would prefer to not use pharm), clinicians acceptable, payers acceptable Dietary Supplements: **Probably no** (clinicians - not acceptable, patients - may be acceptable, payers - not acceptable) Acupuncture: **Varies**

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel agreed on the following judgments: Pharmacologic: Venlafaxine women: **Yes** Caveat: Suicidal ideation, QT prolongation, consider with other medications taken Venlafaxine men: **Yes** Caveat: Suicidal ideation, QT prolongation, consider with other medications taken Paroxetine: **Yes** Caveat is for patients taking tamoxifen cannot take it. Clonidine: **Yes** Caveat - caution among patients taking other hypertension medication or with a baseline risk of hypotension Antidepressants (other): **Yes** Caveat: Suicidal ideation, QT prolongation, consider with other medications taken Gabapentin: **Yes** Caveat: Suicidal ideation, consider with other medications taken, not prescribed in older adults Dietary supplements: **Probably no** (readily

		available; however, the ingredients/regimen/dosing are not standardized and also may have potentially dangerous interactions with hormone-dependent cancer as a result of contamination or ingredients) Acupuncture: **Probably no** Caveats: Immunosuppressed (not feasible), variable accessibility and standards and specialized training for hot flash treatment - need of specialized training (and equipment for electro acupuncture) and standardized regimen

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Pharmacologic recommendations for women:

For women with breast cancer who are experiencing drug- or surgery-induced hot flashes the Oncology Nursing Society guideline 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 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 management of symptoms (conditional recommendation, low certainty of evidence ⊕⊕◯◯).

Remarks: Persons 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.**

Pharmacologic recommendations for men:

For men with prostate cancer who are experiencing drug- or surgery-induced hot flashes the Oncology Nursing Society guideline 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 management of symptoms.

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

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

Venlafaxine recommendation for men:

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

Gabapentin or pregabalin for women or men:

For patients with cancer who are experiencing drug- or surgery-induced hot flashes the Oncology Nursing Society guideline panel *suggests* no treatment rather than gabapentin or pregabalin (gabapentinoids) for management of symptoms (conditional recommendation, very low certainty of evidence ⊕◯◯◯).

Dietary supplements for women or men:

For patients with cancer who are experiencing drug- or surgery-induced hot flashes the Oncology Nursing Society guideline panel *suggests* no treatment rather than herbal or dietary supplements (soy, Black Cohosh, St. John's Wort, melatonin, vitamin E) for management of symptoms (conditional recommendation, very low certainty of evidence ⊕◯◯◯).

Acupuncture or electroacupuncture for women or men:

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

Justification

Pharmacologic for women:

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 ONS Guideline panel suggests venlafaxine or paroxetine as first-line therapy, followed by clonidine and then sertraline, fluoxetine, escitalopram, or duloxetine for 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**.**

Pharmacologic for men:

Hot flashes are prevalent among men with prostate cancer undergoing treatment with androgen deprivation therapy (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 ONS Guideline 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 ONS 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 for men:

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 guideline 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.

Gabapentin or pregabalin for women or men:

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 ONS Guideline panel issued a conditional recommendation suggesting against gabapentinoids for the management of hot flashes.

Dietary supplements for women or men:

The panel acknowledged that there is insufficient evidence to identify important differences between active interventions. Based on this evidence, the ONS Guideline 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.

Acupuncture or electroacupuncture for women or men:

The ONS 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.

Subgroup considerations

The panel considered each treatment option as a potential subgroup when making the recommendations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- Additional research is needed on pharmacologic interventions for men with hot flashes.
- Identify the appropriate duration of treatment with antidepressants for hot flashes and how to taper when stopping.

IN-TEXT CITED REFERENCES

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*, 381–389. https://doi.org/10.1002/cncr.28352

Barton, D., & Loprinzi, C. L. (2004). Making sense of the evidence regarding nonhormonal treatments for hot flashes. *Clinical Journal of Oncology Nursing, 8*, 39–42. https://doi.org/10.1188/04.CJON.39-42

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*, 495–500. https://doi.org/10.1200/JCO.1998.16.2.495

Befort, C.A., & Klemp, J. (2011). Sequelae of breast cancer and the influence of menopausal status at diagnosis among rural breast cancer survivors. *Journal of Women's Health, 20*, 1307–1313. https://doi.org/10.1089/jwh.2010.2308

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*, 310–318. https://doi.org/10.1080/13697130902736921

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*, e12484. https://doi.org/10.1111/ecc.12484

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*), 3862–3868. https://doi.org/10.1200/JCO.2010.33.1298

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*, 5147–5152. https://doi.org/10.1200/JCO.2010.29.9230

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*, 381–388. https://doi.org/10.1007/s10549-014-2944-4

Deng, G., Vickers, A., Yeung, S., D'Andrea, G. M., Xiao, H., Heerdt, A. S., … Cassileth, B. (2007). Randomized, controlled trial of acupuncture for the treatment of hot flashes in breast cancer patients. *Journal of Clinical Oncology, 25*), 5584–5590. https://doi.org/10.1200/JCO.2007.12.0774

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, 63*, 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*, 156–163. https://doi.org/10.1016/j.eururo.2008.02.002

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.

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. https://doi.org/10.1007/s10549-008-0210-3

Hunter, M.S., Coventry, S., Mendes, N., & Grunfeld, E.A. (2009). Menopausal symptoms following breast cancer treatment: A qualitative investigation of cognitive and behavioural responses. *Maturitas, 63*, 336–340. https://doi.org/10.1016/j.maturitas.2009.06.003

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*, 2739–2745. https://doi.org/10.1200/JCO.2001.19.10.2739

Kimmick, G.G., Lovato, J., McQuellon, R., Robinson, E., & Muss, H.B. (2006). Randomized, double-blind, placebo-controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. *The Breast Journal, 12*, 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*, 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*, 689–693. https://doi.org/10.1093/annonc/mdl478

Loprinzi, C.L., Dueck, A.C., Khoyratty, B.S., Barton, D.L., Jafar, S., Rowland, K.M., … Fitch, T.R. (2009). A phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB). *Annals of Oncology, 20*, 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*, 308–312. https://doi.org/10.1200/JCO.2006.07.5390

Loprinzi, C.L., Kugler, J.W., Sloan, J.A., Mailliard, J.A., LaVasseur, B.I., Barton, D.L., … Christensen, B. J. (2000). Venlafaxine in management of hot flashes in survivors of breast cancer: A randomised controlled trial. *Lancet, 356*, 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*, 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*, 708–714. https://doi.org/10.1016/j.ejca.2005.01.005

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*, 3615–3620. https://doi.org/10.1200/JCO.2015.60.9412

Mao, J.J., Leed, R., Bowman, M.A., Desai, K., Bramble, M., Armstrong, K., & Barg, F. (2012). Acupuncture for hot flashes: decision making by breast cancer survivors. *Journal of the American Board Family Medicine, 25*, 323–332. 10.3122/jabfm.2012.03.110165

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*, 788–793. https://doi.org/10.7326/0003-4819-132-10-200005160-00004

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*, 1068–1074. https://doi.org/10.1200/JCO.2000.18.5.1068

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*, 6919–6930. https://doi.org/10.1200/JCO.2005.10.081

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*, 1449–1455. https://doi.org/10.1200/JCO.2002.20.6.1449

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

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

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*, 369–375. https://doi.org/10.1007/s10549-009-0425-y