

Hot Flashes

Evidence Table

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
<b>Gabapentin: PEP Weight of Evidence Category: Likely to Be Effective</b>					
Biglia et al., 2009	Patients were randomized to gabapentin 900 mg/day or vitamin E 800 IU/day for 12 weeks.	<p><b>Sample characteristics:</b> Adult postmenopausal women with history of breast cancer experiencing eight or more hot flushes per day. N = 115; 60 women completed the study.</p> <p>Median age: 50 years old</p> <p>Inclusion: Previous breast cancer surgically treated one year prior; no evidence of systemic disease; eight or more hot flushes per day; postmenopausal status; adjuvant tamoxifen, aromatase inhibitors or gonadotropin releasing hormone (GnRH) analogs allowed if started at least two months prior.</p> <p>Exclusion: Use of any antidepressant treatment, progestagens, or other medication to treat hot flashes within three months; concomitant chemotherapy; uncontrolled hypertension; impaired renal or hepatic function or diabetes.</p> <p><b>Setting:</b> Oncology Department, University of Turin, Italy</p> <p><b>Study Design:</b> Non–placebo-controlled, non-blinded trial</p> <p><b>Purpose:</b> Assess efficacy and tolerability of gabapentin 900 mg/day compared to vitamin E for the control of vasomotor symptoms. Secondary objective to evaluate effect of the</p>	Hot flush diary completed daily; Pittsburgh Sleep Quality Index (PSQI); Menopause Rating Scale (MRS), and SF-36 Health Survey	Hot flush frequency and score decreased by 57.05% and 66.87%, respectively ( $p < 0.05$ ) in gabapentin group. Hot flush frequency and score were reduced by 10.02% and 7.28% respectively ( $p > 0.05$ ) in vitamin E group. Gabapentin effective in improving the quality of sleep (PSQI score reduction: 21.33%, $p < 0.05$ ).	Small sample size; high dropout rate

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Loprinzi et al., 2009	Randomized to placebo for 28 days versus gabapentin 300 mg at bedtime for 28 days versus gabapentin 300 mg at bedtime for 7 days then 300 mg twice a day for 7 days then 300 mg three times a day for 14 days.	<p>treatments on quality of sleep and other aspects of quality of life (QOL)</p> <p><b>Sample characteristics:</b> Men undergoing androgen deprivation therapy for prostate cancer with at least 14 hot flashes per week. N = 223; 214 completed the study. Mean age: 70 years old</p> <p><b>Inclusion:</b> Men with a history of prostate cancer on a program of androgen ablation hormone therapy four weeks prior study and planning continuation of therapy during study; bothersome hot flashes of at least 14 times per week with hot flashes present at least 1 month prior study entry; Antidepressant use at least one month prior study with continuation during study trial.</p> <p><b>Exclusion:</b> Renal insufficiency; concurrent therapies, including antineoplastic chemotherapy, androgens, estrogens, or progestational agents; previous therapy with gabapentin</p> <p><b>Setting:</b> Outpatient oncology centers</p> <p><b>Study design:</b> Double-blind, placebo-controlled.</p> <p><b>Purpose:</b> Efficacy and side-effects of three relatively low gabapentin doses in comparison to placebo</p>	Hot flash frequencies and severities were recorded daily for a baseline week and for four weeks while taking the study medication; symptom experience diaries completed weekly for five weeks; 30-item Profile of Mood States–Brief at end of baseline week and end of four weeks of treatment.	In comparison of the fourth treatment week to the baseline week, mean hot flash scores decreased in the placebo group by 4.1 units and in the three increasing dose gabapentin groups by 3.2, 4.6, and 7.0 units. No significant difference was reported in the three combined gabapentin arms versus placebo. Wilcoxon rank-sum p values for change in hot flash scores and frequencies after four weeks of treatment were 0.10 and 0.02 comparing the highest dose gabapentin arm to the placebo arm, respectively.	Short follow-up period
Pandya et al., 2005	Patients were randomized to	<b>Sample characteristics:</b> Women with breast cancer having an average of two	Hot flash diary one week prior to study, and during weeks 4	Decreases in hot flash severity score between baseline and	Long-term use of gabapentin not assessed.

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	<p>placebo, gabapentin 300 mg/day, or gabapentin 300 mg three times a day for eight weeks.</p>	<p>or more hot flashes per day (N = 420). Evaluable data for 371 patients at four weeks (119 placebo, 123 gabapentin 300 mg, and 129 gabapentin 900 mg) and 347 at eight weeks (113 placebo, 114 gabapentin 300 mg, 120 gabapentin 900 mg).  Mean age: 55 years old  <b>Inclusion:</b> Adult women with history of breast cancer and were having an average of two or more hot flashes per day; adjuvant tamoxifen use was permitted  <b>Exclusion:</b> Currently receiving chemotherapy; use of venlafaxine, clonidine, or anticonvulsants not permitted; pregnancy, breastfeeding, use of steroidal contraception, coronary insufficiency, recent history of myocardial infarction, symptomatic cardiac disease, peripheral or cerebrovascular disease, stroke, syncope, or symptomatic hypotension; hepatic dysfunction (aspartate aminotransferase concentration above twice the upper limit of normal or bilirubin concentration above the upper limit of normal), renal dysfunction (serum creatinine concentration above 1–25 times the upper limit of normal); allergy to gabapentin</p>	<p>and 8 of treatment. Symptom inventory pretreatment, weeks 4 and 8 of treatment.</p>	<p>weeks 4 and 8, respectively were: 21% and 15% in the placebo group; 33% and 31% in the group assigned gabapentin 300 mg; and 49% and 46% in the group assigned gabapentin 900 mg. The differences between the groups were significant (p = 0.0001 at four weeks and p = 0.007 at eight weeks by analysis of covariance for overall treatment effect. Gabapentin was effective in control of hot flashes at a dose of 900 mg/day but not at a dose of 300 mg/day.</p>	<p>Withdrawal rate of 12% at four weeks and 17% at eight weeks.</p>

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<b>Venlafaxine: PEP Weight of Evidence Category: Likely to Be Effective</b>					
Buijs et al., 2009	<p>Comparison of venlafaxine versus clonidine for the treatment of hot flashes with regard to side effects, efficacy, QOL, and sexual functioning in patients with breast cancer.</p> <p>Patients randomly assigned to receive venlafaxine for eight weeks, followed by a wash out period of two weeks then eight weeks of clonidine or vice versa</p>	<p><b>Setting characteristics:</b> University community clinic oncology program.</p> <p><b>Study design:</b> Randomized, double-blind, placebo-controlled multi-institutional trial.</p> <p><b>Purpose:</b> Assess efficacy of gabapentin in controlling hot flashes in women with breast cancer.</p> <p><b>Sample:</b> N = 60 (30 assigned to venlafaxine and 30 to clonidine). Patients with a primary or metastatic breast cancer age 60 years or younger, allowed antitumor hormonal treatment if started one month prior and continued taking throughout treatment period.</p> <p><b>Study Design:</b> Double-blind, randomized, cross-over study.</p>	<p>Assessment took place before the start of each drug, then a 2, 8, 12, 18 weeks after treatment began.</p> <p>Six questionnaires were used to compare the drugs in terms of adverse events, efficacy, QOL, and sexual functioning. Daily diary on hot flashes, hot flash-related daily interface questionnaire, Medical outcomes study short form (SF-36), sexual activity questionnaire, and Zung Self-Rating Depression Scale.</p>	<p>40 patients completed all treatments, 12 patients only one treatment, 8 patients neither. Dropout rates during venlafaxine 15 out of 59 versus clonidine 5 out of 53. Withdrawal rates not affected by sequence of treatment.</p> <p>Efficacy: After eight weeks, no difference was seen between the two drugs with reduction of hot flash scores median 49% for venlafaxine and 55% for clonidine. The drug that the patient received first caused the greatest reduction in hot flash score.</p>	<p>Statistics: based on the testing used to calculate a number of patients needed to detect differences, the sample size was too small to detect difference, which may be the reason for no statistical difference found between the interventions.</p>
Carpenter, et al., 2007	<p>Examination of venlafaxine at two doses for efficacy in relation to physiologic and self-reported hot flashes and other</p>	<p>Low-dose study (n = 64) High-dose study (n = 20) Randomized, double-blind, placebo-controlled crossover trial.</p> <p>Breast cancer survivors were recruited</p>	<p>A psychologist verified absence of depressive symptoms using two measures: Structured clinical interview for the Diagnostic and Statistical Manual of</p>	<p>Venlafaxine resulted in modest hot flash reduction but only hot flash interference improved differentially at higher dose. Timing of effects varied by dose. Only women who</p>	<p>A placebo effect occurred for self-report of hot flashes but not for physiologic hot flash in the high- and low-dose studies. Main study limitations: racially and ethnically homogeneous</p>

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	<p>outcomes.</p> <p>Each study was 14 weeks; low dose consisted of 6 weeks at 37.5 mg of venlafaxine daily. The high-dose study consisted of 1 week of 37.5 mg of venlafaxine daily, 4 weeks of 75 mg daily, and one week of 37.5 mg daily. Weeks 1 and 2 provided baseline data. Weeks 3–14 included 6 weeks of treatment and 6 weeks of placebo.</p>	<p>between 2000–2004 with follow up continuing through 2005 from cancer clinics in the Southeast (low dose) and the Midwest (high dose). Must have been postmenopausal or using an approved method of birth control.</p>	<p>Mental Disorders and the 17-item Hamilton rating scale depression.</p> <p>Adherence to the treatment was assessed using capsule counts and weekly written verification. Physiologic hot flash frequency was evaluated using weekly 24-hour ambulatory sterna skin conductance monitoring and self-reported hot flash diaries. Weekly blood pressure monitoring and other tools were used for side effect monitoring.</p>	<p>experience a greater than 50% decrease in physiologic hot flashes also experienced a significant improvement in fatigue, sleep quality, and QOL. Although side effects were mild, most patients discontinued venlafaxine long term.</p>	<p>samples, limited treatment time, small sample size, lack of pharmacogenetic data. Also limitations regarding assessing hot flashes with self-reporting because it is subject to placebo effects.</p>
<p>Loibl et al., 2007</p>	<p>Randomized to receive 0.075 mg clonidine twice daily or venlafaxine 37.5 mg twice daily for four weeks then crossover.</p>	<p><b>Sample:</b> Women with breast cancer experiencing hot flashes at least 14 times per week (N = 80). 64 patients completed the study. Majority older than age 50. 40 randomized to each group. 33 received clonidine, 31 received venlafaxine 9 stopped early because of side-effects and 7 withdrew <b>Inclusion:</b> Adult women with primary breast cancer experiencing hot flashes at least 14 times per week or must have been seeking help for hot flashes. Hot</p>	<p>Self-reported one-week hot flash and other symptom questionnaire assessed one week before start of treatment and end of treatment. Hot flashes: frequency and severity Symptoms assessed: Loss of appetite, mouth dryness, nausea, tiredness, constipation, restless sleep, nervousness, sweating, dizziness, mood disorder,</p>	<p>At end of week 4, the median hot flash frequency dropped by 7.6 hot flashes per day for patients receiving venlafaxine and 4.85 hot flashes for those receiving clonidine (p = .025). Nausea was significantly greater with venlafaxine compared with clonidine. Mouth dryness, constipation, and restless sleep were reported more with clonidine but not significant difference.</p>	<p>Small sample size with less than 100 participants. Short follow-up period</p>

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		<p>flashes present at least four weeks before study entry. Predefined menopausal status was not required. Tamoxifen, gonadotropin-releasing agonists, and aldose reductase inhibitors were allowed as long as the patients had been on such therapy for at least a month and were planning to continue therapy during study. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.</p> <p><b>Exclusion:</b>            Previous treatment with venlafaxine and clonidine as well as estrogens, progestagens, or androgens for hot flashes            Current treatment with hypertensive or antidepressant agents, other nonhormonal agents for hot flashes such as black cohosh, isoflavones, and vitamin E.            Patients with hypertension or hypotension, peripheral or cardiovascular diseases, or symptomatic cardiac diseases.</p> <p><b>Setting:</b> University hospital setting.  <b>Study design:</b> Double-blind, randomized study. Randomized to receive 0.075 mg clonidine twice daily or venlafaxine 37.5 mg twice daily for 4 weeks then crossover.  <b>Purpose:</b> Compare venlafaxine to another nonhormonal agent in the</p>	<p>diarrhea, sleeplessness</p>		

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Biglia et al., 2005	<p>Evaluation of low-dose venlafaxine hydrochloride for the therapy of hot flashes in breast cancer survivors.</p> <p>The aim was to evaluate the efficacy and tolerability of a longer treatment (eight weeks) at a lower dose of venlafaxine (37.5 mg/day)</p>	<p>treatment of hot flashes in patients with breast cancer</p> <p><b>Sample:</b> N = 40 Patients attending the outpatient clinic for menopausal symptoms. All with a history of breast cancer without evidence of recurrence and no requirement of fulfilling menopausal status. Anti-estrogen therapy was allowed provided that it had been started at least four months before study entry and continued the next three months.</p> <p><b>Study Design:</b> open label study.</p> <p><b>Setting:</b> outpatient</p>	<p>Measures included: Hot flash diary and computation of daily hot flash scores. Weekly documentation of side effects experienced in diaries. A Beck Depression Inventory (BDI) was completed at baseline and at week 8. At weeks 4 and 8 a clinical visit to monitor blood pressure, assess side effects and hot flash frequency. A patient was excluded from study if blood pressure found to be diastolic above 95 or systolic above 160, or if important side effect occurred.</p>	<p>30 patients completed the first 4 weeks of treatment with reduction of hot flash frequency 39% compared to baseline. After eight weeks of treatment, a further significant reduction in hot flashes by 53% and a hot flash score of 59% was observed. Very few side effects reported, mainly nausea during first two weeks and mouth dryness. Only 23 women completed the BDI at week 8 with a reduction of 23% reported.</p>	<p>Was not blinded or placebo-controlled trial. No patient was withdrawn for blood pressure increase or major toxicity. Data on the safety of this therapy on breast cancer recurrence are reassuring.</p>
Loprinzi et al., 2000	<p>Assess more definitively the efficacy and toxicity of various doses of venlafaxine for treatment of hot flashes in the breast cancer survivor.</p> <p>Participants were assigned to placebo (n = 56), or venlafaxine 37.5 mg daily (n = 56), 75 mg daily (n = 55),</p>	<p><b>Sample :</b> N=221 Patients eligible for this trial were women who had a history of breast cancer or who were concerned about taking estrogen therapy for fear of developing breast cancer.</p> <p><b>Inclusion:</b> Troublesome hot flashes, occurring at least 14 times per week; hot flashes severe enough for the patient to desire therapeutic intervention, and present for at least one month prior to study entry, older than 18 years; life expectancy at least 6</p>	<p>The primary endpoint was a bivariate construct of average daily hot flash activity: the number of hot flashes and a score combining the number and severity of hot flashes.</p> <p>Use of hot flash diaries.</p> <p>Participants were stratified by age (younger than 50 versus older than 50), current tamoxifen use, duration of hot</p>	<p>The trial suggests that venlafaxine can alleviate hot flashes and that the most appropriate dose for this indication is 75 mg.</p> <p>Of the 229 which joined the study, 191 had data evaluable over the whole study period (50 from the placebo group, 49 from the venlafaxine 37.5 mg group, 43 from the venlafaxine 75 mg group, and 49 from the</p>	<p>Missing data were handled in several ways as a sensitivity analysis of the robustness of the results in relation to the missing data. Less than 10% of possible data were missing and the results were consistent across a series of analyses by various imputation methods.</p> <p>Results: The study does mention that 69% of participants were using tamoxifen. The study does</p>

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	or 150 mg daily (n = 54).	months; and ECOG performance status of 0–1. Anti-estrogens and aromatase inhibitors were allowed if they had been started four weeks prior to study entry and scheduled to continue for the next five weeks. Concomitant therapies not allowed were: antineoplastic chemotherapy, androgens, estrogens, progestins, antidepressants, clonidine, and Bellegral® (Novartis Pharmaceuticals) <b>Exclusion criteria:</b> Use of venlafaxine in the past, any antidepressant treatment within the preceding two years, pregnancy, breastfeeding, use of other medications to treat hot flashes within the past two weeks, uncontrolled hypertension. <b>Study design:</b> Double-blind, placebo-controlled, randomized trial	flashes (less than 9 versus more than 9 months) and frequency of hot flashes/day.  It was calculated that a sample size of 50 patients per group would provide 80% power to detect differences in average hot-flash activity of standard deviation (SD) 0–6 (1–2 hot flashes per day, a score of 3 units, or a 21% fall from baseline) with a type 1 error rate of 5%.	venlafaxine 150 mg group). After week 4 of treatment, median hot flash scores were reduced from baseline by 27%, 37%, 61%, and 61%, respectively, in the four groups.  Frequencies of some side effects (mouth dryness, decreased appetite, nausea, and constipation) were significantly higher in the venlafaxine 75 mg and 150 mg than in placebo group.	include the healthy population but, the majority was breast cancer survivors.  The study also makes mention that this may also be effective against hot flashes in men who have undergone androgen deprivation therapy for prostate cancer and references a study which investigated this intervention.

**Weight of Evidence Category: Effectiveness Not Established**

**Pharmacologic Interventions**

**Clonidine: PEP Weight of Evidence Category: Effectiveness Not Established**

Goldberg et al., 1994	Transdermal clonidine for alleviating tamoxifen-induced hot flashes in women with a history of breast cancer.  Intervention: four weeks of transdermal	<b>Sample characteristics:</b> women receiving tamoxifen for breast cancer experiencing hot flashes and requesting intervention; experiencing hot flashes for longer than one month and at least seven per week. 110 of the 116 completed the study Mean age: 54 Randomization stratified by age,	Daily self-administered patient questionnaires Weekly questionnaires Nurse assessment every two to three weeks for compliance, toxicity profile, and answer questions  Hot flash severity and	Statistically significant decrease in hot flashes (frequency and severity) (p < .0001) Clinically moderate decrease in frequency (20%) and severity (10%) Toxicities: dry mouth (p < .001), constipation (p < .02)	Small study size
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	clonidine (equivalent to a daily oral dose of 0.1mg), followed by four weeks of placebo patches or vice versa. Patches changed weekly.	duration of hot flash symptoms, and the average frequency and severity of hot flashes.  <b>Study design:</b> randomized, double-blind crossover prospective study	frequency and combined hot flash score		
Pandya et al., 2000	Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes  Intervention: oral clonidine hydrochloride 0.1 mg daily or placebo at bedtime for eight weeks.	<b>Sample characteristics:</b> Postmenopausal women with breast cancer on tamoxifen stratified by time since menopause (less than three years, more than three years), duration of tamoxifen use (less than one year; longer than one year), and baseline frequency of hot flashes (less than 10 per day, more than 10 per/day) N = 198; 149 completed study  Participants: 198 99 patients received clonidine and 99 received the placebo. Mean age : 71 years old <b>Inclusion:</b> Postmenopausal women who had been receiving adjuvant tamoxifen therapy for breast cancer for at least one month and reported at least one hot flash per day; Normal hepatic and renal function <b>Exclusion:</b> Premenopausal women and women receiving concurrent chemotherapy or endocrine therapy for breast cancer, hypertension therapy or concurrent treatment with monoamine	Daily hot flash diary for one week at baseline, during the weeks 4 and 8 during treatment and four weeks after the end of treatment.  Symptom checklist	149 of 198 completed 12 weeks of follow-up (73 in clonidine group and 76 in placebo group.)  Oral clonidine effective.  Mean decrease in hot flash frequency was greater in the clonidine group after week 4 (37% to 20%) and week 8 (38% to 24%). Clonidine group had more difficulty with sleep (41%–21%) Significant difference seen in mean change in QOL scale (p = 0.02) at 8 weeks.	Evaluation for eight weeks. No evaluation of long-term effectiveness.

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		<p>oxidase inhibitors; L-dopa, piribedil, tricyclic antidepressants, or sedatives; coronary insufficiency, recent history of myocardial infarction (within three months), symptomatic cardiac disease, peripheral or cerebrovascular disease, syncope, or symptomatic hypotension Allergy or adverse reaction to clonidine  <b>Setting characteristics:</b> community oncology clinic  <b>Study design:</b> randomized, double blind, placebo-controlled trial.  <b>Purpose:</b> evaluate effectiveness of oral clonidine for control of hot flashes associated with tamoxifen therapy in postmenopausal women with breast cancer.</p>			
<p><b>Estrogen Replacement: PEP Weight of Evidence Category: Effectiveness Not Established</b></p>					
<p>Gerber et al., 2000</p>	<p>Transdermal estrogen in men with hot flashes after hormonal therapy for prostate cancer.</p> <p>Intervention:                      Estrogen patch                      Low dose (0.05 mg)                      High dose (0.5 mg)</p> <p>Description of protocol:                      Week 1: daily log maintained, then four weeks at one dose, four weeks</p>	<p><b>Sample characteristics:</b> N = 12                      Men with advanced prostate cancer who were receiving leuprolide injections every one or three months; experiencing at least three hot flush episodes daily for at least three months.</p> <p><b>Study design:</b> Randomized multi-dose crossover trial. Randomized to low-dose or high-dose of transdermal estrogen, then switch after four week washout to other dose.</p>	<p>Treatment response assessed by daily logs. Questionnaires completed every four weeks, including visual analog assessment. Serum luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, and estradiol levels every four weeks.</p>	<p>Significant reduction in overall severity of hot flushes in both the low-dose and high-dose patches in 10 of the 12 men (83%).                      Significant decrease in daily frequency of hot flushes with high-dose patch.                      Overall moderate to major improvement in symptoms at both doses (p = 0.04)                      FSH levels decreased significantly with both doses; estradiol levels increased with both doses. No significant</p>	<p>Small sample size                      No placebo arm.                      Patients treated for only two nonconsecutive months</p>

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	washout, and four weeks at alternate dose			change in serum testosterone or LH.	
<b>Fluoxetine: PEP Weight of Evidence Category: Effectiveness Not Established</b>					
Loprinzi et al., 2002	Patients received four weeks of fluoxetine (20 mg/day orally) versus an identical-appearing placebo. For the next four weeks, patients were crossed over to the alternative arm.	<p><b>Sample characteristics:</b> Women with a history of breast cancer or a perceived increased risk of breast cancer (N = 81). 72 patients completed the study Mean age: older than 50 years.</p> <p><b>Inclusion:</b> Women with a history of breast cancer or a perceived increased risk of breast cancer; patients without current evidence of malignant disease; history of bothersome hot flashes (at least 14 per week) that were severe for patients to desire intervention; hot flashes present for at least one month Concomitant therapy of tamoxifen or raloxifene was permitted if patient was therapy for at least one month and was planning continuation of therapy during study.</p> <p><b>Exclusion:</b> Concomitant therapy with antineoplastic chemotherapy, androgens, estrogens, progestational drugs, or warfarin use Previous use of fluoxetine Antidepressant use for two years prior to study entry</p> <p><b>Setting:</b> Not identified</p> <p><b>Study design:</b> placebo-controlled, double-blind, cross-over clinical trial.</p>	Daily hot flash diary for nine weeks, toxicity questionnaire weekly. Beck Depression Inventory; Uniscale global QOL instrument at study entry and study completion.	At end of first treatment period (four weeks), hot flash scores (frequency x average severity) decreased 50% in fluoxetine arm versus 36% in the placebo arm. Cross-over analysis showed a significantly greater improvement in hot flash scores with fluoxetine than placebo (p = .02). More than half (54%) of the patients reported depressive symptoms of at least mild severity at baseline compared with only 30% of patients after the first treatment period and 21% after the second treatment period. After five weeks of treatment, QOL did not differ between groups. After cross-over, QOL showed a relative improvement trend for fluoxetine compared to placebo.	Age and tamoxifen use were not adjusted for as potential confounding factors.

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		<p><b>Purpose:</b> Assess efficacy of fluoxetine for treatment of hot flashes in women with a history of breast cancer or a concern regarding the use of estrogen because of a breast cancer risk.</p>			
<p><b>Mirtazapine: PEP Weight of Evidence Category: Effectiveness Not Established</b></p>					
<p>Biglia et al., 2007</p>	<p>Evaluate the efficacy and safety of mirtazapine 30 mg daily for 12 weeks to reduce hot flashes in women with a previous breast cancer and to assess the influence of the same treatment on sleep quality and other menopausal symptoms.</p> <p>Treatment was mirtazapine 15 mg/day at bedtime for one week, then 30 mg/day for the next 11 weeks.</p> <p>Primary end point was to compare hot flash score and frequency after 4, 8, and 12 weeks of treatment to the basal values.</p>	<p><b>Sample :</b> N = 40 consecutive postmenopausal women with a previous history of breast cancer</p> <p><b>Setting:</b> an outpatient treatment clinic for menopausal symptoms.</p> <p><b>Design/model:</b> pilot, open-label study</p>	<p>Sample size was calculated under the assumptions of the detection of a 50% reduction in hot flash frequency, with 80% power at a two-sided alpha level of 0.05. These assumptions using a dependant samples t-test required at least 20 evaluable patients.</p> <p><b>Tools:</b> Hot flash diary, hot flash score, MRS, PSQI, and the SF-36 Health Survey.</p>	<p>20 patients completed the study. After four weeks of treatment, a significant decrease of vasomotor symptom compared to baseline values was reported. The mean decrease in hot flash frequency was 46.9% and mean reduction in hot flash score was 49%. The benefit increased at week 8 when mean decrease in frequency/score was 56.5% and 62.16% respectively. The effects remained stable during the past month.</p>	<p>Small sample size. Out of 40 women enrolled in the study 13 (32.5%) had withdrawn from the study after signing consent and recording basal data and never began therapy; the reasons more frequently reported were the reluctance to assume antidepressant drugs or the fear that this drug may adversely affect cognitive function or cause side effects.</p> <p>Recommend study duplication in a larger blinded placebo controlled trial.</p> <p>Possible negative interaction between the antiproliferative effect of tamoxifen on the breast and mirtazapine. (Some studies showing fluoxetine and paroxetine as potent inhibitors of enzymes that play a role in tamoxifen metabolism, whereas venlafaxine has a weaker</p>

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					effect and mirtazapine does not inhibit CYP2D6)
<p><b>Paroxetine: PEP Weight of Evidence Category: Effectiveness Not Established</b></p>					
Stearns et al., 2005	<p>Arm A: four weeks of paroxetine 10 mg/day followed by four weeks of placebo.            Arm B: four weeks of paroxetine 20 mg/day followed by four weeks of placebo.            Arm C: four weeks of placebo followed by four weeks of paroxetine 10 mg/day            Arm D: four weeks of placebo followed by four weeks of paroxetine 20 mg/day.</p>	<p><b>Sample characteristics:</b> Women with or without history of breast cancer having at least 14 hot flashes per week. 279 women were screened and 151 were randomly assigned. 107 patients completed study.            Mean age was 53 years. More than 80% had prior history of breast cancer and 60% were taking an antiestrogen.  <b>Inclusion:</b> Adult women with and without a prior history of breast cancer who could not or did not wish to take hormone therapy            History of troublesome hot flashes occurring at least 14 times per week lasting 1 month or longer;            ECOG performance status of 0–2            Creatinine and bilirubin less than two times normal level            Vitamin E use for at least one month prior to study entry and continued through study period;            Antiestrogen use for at least one month prior to study entry and continued through study period  <b>Exclusion:</b>            Concomitant use of cytotoxic chemotherapy, radiation therapy, estrogen or progesterone use, antidepressants, monoamine</p>	<p>Hot flash daily diary            QOL tools: The Center for Epidemiologic Studies Depression Scale; Hospital Anxiety and Depression Scale (seven anxiety items), Medical Outcomes Study (MOS) Sleep Problems Index, MOS Sexual Problems Index, Overall health-related QOL questionnaire.</p>	<p>Paroxetine significantly reduced hot flash frequency and composite score by 40.6% and 45.6%, respectively compared to 13.7% and 13.7% for placebo (p = .0006 and p = .0008, respectively).            Paroxetine 20 mg significantly reduced hot flash frequency and composite score by 51.7% and 56.1%, respectively compared to 26.6% and 28.8% for placebo (p = .002 and p = .004, respectively). Efficacy was similar between the two doses but women were less likely to discontinue low-dose paroxetine. Paroxetine 10 mg was associated with a significant improvement in sleep compared to placebo (p = .01).</p>	<p>Study attrition: 39 women did not complete 9 weeks of therapy; 26 women did not return diaries.</p>

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
		<p>oxidase inhibitors or treatments for hot flashes</p> <p><b>Setting characteristics:</b> Multi-institutional out-patient oncology clinics.</p> <p><b>Study design:</b> Stratified, randomized, double-blind, cross-over, placebo controlled trial.</p> <p>Stratified by age group (younger than 60 or older than 60) and antiestrogen use (yes or no).</p> <p><b>Purpose:</b> Assess efficacy of paroxetine 10 mg and 20 mg compared to placebo in reducing hot flashes in women with or without history of breast cancer.</p>			
Kelly et al., 2010	Postmenopausal women with breast cancer using tamoxifen therapy and a single SSRI antidepressant (paroxetine fluoxetine, sertraline, citalopram, fluvoxamine, or venlafaxine.)	<p><b>Sample Characteristics:</b> Women living in Ontario 66 years or older treated with tamoxifen for breast cancer between 1993 and 2005 who had overlapping treatment with a single SSRI. (24,430 women identified; 2,430 entered into study; mean age 74 years).</p> <p><b>Inclusion:</b> Postmenopausal women with breast cancer newly treated with tamoxifen (defined as no tamoxifen prescription in the preceding year) and a single SSRI antidepressant (paroxetine fluoxetine, sertraline, citalopram, fluvoxamine, or venlafaxine.)</p> <p><b>Exclusion:</b> Antidepressant use with duloxetine or escitalopram</p> <p><b>Setting:</b> Ontario Cancer Registry</p>	Total duration of tamoxifen therapy (index date: date tamoxifen was last dispensed plus an additional 60 days) and extent to which co-prescription of potentially interacting medications occurred during the course of treatment Primary outcome: death from breast cancer	Of 2,430 women treated with tamoxifen and single SSRI, 374 (15%) died of breast cancer during f/u. Absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen overlapping use of paroxetine were associated with 24%, 54%, & 91% increases in the risk of death from breast cancer. (p < 0.05) No such risk seen with other antidepressants	Reported study limitations include lack of information on breast cancer stage and lack of information on indication for antidepressant use.

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
		<p><b>Study Design:</b> Retrospective cohort study</p> <p><b>Purpose:</b> To characterize whether some SSRI antidepressants reduce tamoxifen's effectiveness by inhibiting its bioactivation by cytochrome P450 2D6 (CYP2D6).</p>			
<p><b>Progesterin Therapy: PEP Weight of Evidence Category: Effectiveness Not Established</b></p>					
Goodwin et al., 2008	<p>Southwest Oncology Group Study 9626: evaluation of 2 doses of megestrol for management of menopausal symptoms in women with breast cancer. Tests megestrol acetate at two doses versus placebo over six months. Randomized to placebo, megestrol 20 mg or megestrol 40 mg daily for three months. If success achieved-treatment continued for three additional months. If not-unblinded and given megestrol 20 mg daily</p>	<p><b>Study Design:</b> Phase III randomized placebo-controlled double blind trial.</p> <p><b>Sample characteristics:</b> Patients with T 1-3, N0-1 breast cancer following surgery, chemotherapy and at least four months of tamoxifen, if prescribed.</p> <p>Participants: 288 225 completed the trial</p>	<p>Initial evaluation: patients completed a seven-day patient daily log of hot flashes with reevaluation at three and six months.</p> <p>Primary endpoint: Differences in probability of hot flash success in three comparison groups</p> <p>Instruments: The patient report of menopausal symptoms The symptom log. National Cancer Institute Common Toxicity Criteria, version 2. Performance status assessed using ECOG scale</p>	<p>At three months, improvement was 14% with placebo, 65% with 20 mg, and 48% with 40 mg. Both doses were superior to placebo (p &lt; .0001). Duration of effectiveness continued at six months. Megestrol 40 mg was not superior to megestrol 20 mg.</p> <p>The recommended daily dose is 20 mg.</p>	<p>Not designed to evaluate long-term toxicities or relapse of symptoms with long-term use. Concern remains regarding the use of progestins in women with a history of breast cancer.</p>
<p><b>Megesterol: PEP Weight of Evidence Category: Effectiveness Not Established</b></p>					
Bertelli et	Intramuscular depot	<b>Study Design:</b> Randomized study	Primary endpoint was		Sample size-For an 80% power

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
al., 2002	<p>medroxyprogesterone versus oral Megestrol for the control of postmenopausal hot flashes in women with a history of breast cancer.</p> <p><u>Intervention:</u> <u>Group 1</u> received I.M. depot MPA (500mg on days 1, 14, and 28)</p> <p><u>Group 2</u> received oral Megesterol acetate (40mg po daily days 1-42)</p>	<p><b>Sample</b> Size: Group 1=37 Group 2=34</p> <p><u>Sample Population:</u> Eligible patients were postmenopausal females with a history of breast cancer, without evidence of relapse, whom had been suffering from hot flashes for at least 1 month prior to study entry.</p> <p><u>Major Inclusion/Exclusion Criteria:</u> -Concurrent adjuvant Tamoxifen 20mg/day was allowed if started at least 1 month before study entry and if the planned residual duration of treatment was at least 6 months. -No concurrent treatment with estrogens, androgens, progestins, corticosteroids, clonidine, veralipride, or ciclophenile was allowed. -Patients who had received adjuvant chemotherapy had to have concluded treatment for <math>\geq 2</math> months.</p> <p><b>Setting:</b> Not described</p>	<p>proportion of responding patients after 6 weeks of treatment (7 weeks after randomization). A patient was classified as a responder if she achieved <math>\geq 50\%</math> reduction in frequency of hot flashes and hot flash score.</p> <p>Frequency and severity of hot flashes monitored through self compiled diaries.</p> <p>Three main efficacy parameters:</p> <ol style="list-style-type: none"> <li>1. Changes in average number of hot flashes per day</li> <li>2. Average daily 'hot flash score' compared to baseline.</li> <li>3. Proportion of participants who obtained <math>\geq 50\%</math> reduction in frequency and reduction in HF score as compared to baseline score.</li> </ol>	<p>Mean number of hot flashes and hot flash score did not differ significantly at baseline between the two groups. Differences between the two groups at week six were not statistically significant either. Good control by both treatments is apparent.</p> <p><u>Response rate-</u> No significant difference between the proportion of responders between the two arms was observed (P=0.567)</p> <p>Overall 50 of 71 patients (70.4%, 95% CI 58-81%) achieved a response as previously defined (<math>\geq 50\%</math> reduction in hot flash frequency and hot flash score).</p> <p><u>Duration of response:</u> Maintenance of response in the group of 50 initial responders was assessed as 2- monthly follow up visits for 6 months after randomization. By patient report , a difference in the duration of response was observed: out of 28</p>	<p>and two sided 5% significance, 90 subjects were planned to detect such a difference. Only 71 accrued due to difficulties during patient accrual.</p> <p>After randomization, five patients in each group refused to start the assignment and withdrew from the study. Two more patients, both in group one were found ineligible (one for medical contraindication and one not postmenopausal) and withdrawn. Six patients did not provide complete diary recordings during treatment( five patients who dropped out before completion for side effects and one who was lost to follow-up).</p> <p>Treatment allocation was not double blinded because this would have required administration of I.M. Placebo in group 2 which was judged impractical</p>

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
				<p>responding patients in the MPA group, 25(89.3%) were still responding at 6 months. In the Megestrol group only 10 of the initial 22 responders (45.4%) were still in response after 6 months.</p>	
<p>Loprinzi et al., 1994</p>	<p>Study was done to assess efficacy and short-term toxicity of low-dose megestrol acetate as a treatment for hot flashes in women with breast cancer and in men who had undergone androgen-deprivation therapy for prostate cancer. Subjects were randomly assigned to receive megestrol for 4 weeks followed by placebo for 4 weeks or placebo for 4 weeks then megestrol for 4 weeks. Megestrol 20 mg twice a day was the dosage. Subjects received no medication for the first 7 days.</p>	<p><b>Study design:</b> Double blind randomized crossover trial</p> <p><b>Sample:</b> n = 163 completed the study</p> <p><u>Sample Characteristics</u> Women with a history of breast cancer and men who had undergone surgical or medical orchiectomy with hot flashes of at least 1 per month</p> <p>Women were stratified according to duration of hot flashes ( 9 months cut point). Men were stratified by medical or surgical orchiectomy and duration of androgen ablation</p>	<p>Hot flash diary with recording of number and severity of hot flashes each day.</p> <p>Recording of effects for appetite changes, fluid retention and vaginal problems</p>	<p>During the first 4 week medication period, megestrol was associated with decreased frequency of hot flashes for both men and women.</p> <p>Crossover analysis was not performed because of carryover effects of medication.</p>	<p>Insufficient washout period to allow for crossover analysis.</p>

**Sertraline: PEP Weight of Evidence Category: Effectiveness Not Established**

Hot Flashes

Evidence Table

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
Kimmick et al., 2006	<p>Patients randomized to receive 50 mg sertraline, each morning for six weeks, followed by six weeks of a placebo tablet each morning or to six weeks of a placebo followed by six weeks of sertraline.</p> <p>Before starting the medication, a one-week pretreatment period was included during which patients recorded baseline measurements of hot flashes with a daily diary.</p>	<p><b>Sample:</b> Adult women with localized breast cancer (stages 0–IIIB) who were receiving adjuvant tamoxifen therapy and had at least one hot flash per day. Normal hepatic function with total bilirubin of less than 2 mg/dl and aspartate aminotransferase (AST) greater than or equal to two times normal within six months of study entry.</p> <p><b>Exclusion:</b> Women who were pregnant or breastfeeding; had a history of seizure disorder; hepatic or renal insufficiency.</p> <p>Concurrent or planned therapy with estrogen, progestational agents, corticosteroids, androgens, or other antidepressant therapy.</p> <p>Monoamine oxidase inhibitors or other SSRI use had to have been discontinued at least 14 days before entering the study.</p> <p><b>Setting characteristics:</b> Oncology clinic in a tertiary care center</p> <p><b>Study design:</b> Randomized, double-blind, placebo-controlled, crossover study.</p> <p><b>Purpose:</b> To assess the effect of sertraline on the frequency and severity of hot flashes, mood status, and health-related QOL.</p>	<p>Daily hot flash diary to record hot flash frequency and severity.</p> <p>The Center for Epidemiologic Studies depression scale Functional Assessment of Cancer Therapy-Breast (FACT-B).</p> <p>Measurements assessed at baseline, 6 weeks, and 12 weeks.</p>	<p>The baseline daily hot flash frequency and score were 5.8 and 11.5. At the end of six weeks, frequency of hot flashes decreased by 50% in a greater proportion of those taking sertraline than those in the control group. In crossover analysis, sertraline was significantly more effective than placebo: (p= 0.03 ). Forty-eight percent preferred the sertraline period, 11% preferred the placebo period, and 41% had no preference (p = 0.006). Measures of depression and QOL were unchanged within treatment groups.</p>	<p>Small sample size less than 100. Unable to detect statistically significant difference in the effect of sertraline versus placebo on hot flashes at six weeks.</p>
Wu et al., 2009	<p>Week 1: baseline Week 2: single-blind placebo run-in; those</p>	<p><b>Sample characteristics:</b> Women aged 18 or older with personal or family history of carcinoma in situ or invasive</p>	<p>Hot flash diary to record number and severity of hot flashes per day</p>	<p>Hot flash frequencies and scores suggested greater decline but not statistically</p>	<p>Small sample size with reported insufficient statistical power to detect modest differences in hot</p>

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
	<p>reporting hot flash score reductions of greater than 50% were then excluded. The remaining women received placebo or sertraline 25 mg/day and titrated weekly as needed to a maximum of 100 mg/day for weeks 3–6.</p>	<p>breast cancer with reported hot flashes with a weekly hot flash score of greater than 15.            N = 57 (randomized eligible); N=53 (run-in phase); N=46 (assigned treatment); N = 41 completed treatment            Mean age: 55.8 years old            95% with breast cancer diagnosis  <b>Inclusion:</b> Adult women with personal or family history of carcinoma in situ or invasive breast cancer with reported hot flashes with a weekly hot flash score of greater than 15.  <b>Exclusion:</b> Progressive metastatic breast cancer, documented history of medication or treatment noncompliance, acute suicidal or homicidal ideation, any unstable clinically significant psychiatric condition including major depressive disorder, or concomitant use or use within 14 days of a monoamine oxidase inhibitor or another antidepressant drug, history of intolerable adverse reaction to sertraline, reduction of a weekly hot flash score by greater than 50% after placebo run-in.  <b>Setting:</b> university cancer center  <b>Study Design:</b> Randomized, double-blind, placebo-controlled  <b>Purpose:</b> Evaluate efficacy of sertraline for controlling hot flashes in women with or at high risk of breast cancer.</p>		<p>significant in the sertraline-treated group compared with the placebo group.</p>	<p>flashes between groups, and study design did not take into account the possibility of pharmacokinetic interaction between sertraline and tamoxifen</p>

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
<b>Stellate Ganglion Block: PEP Weight of Evidence Category: Effectiveness Not Established</b>					
Lipov et al., 2008	Pilot study to investigate safety and effectiveness of a stellate-ganglion block at the anterolateral aspect of the C6 vertebra on the right side under fluoroscopy.	<b>Sample</b> 13 breast cancer survivors <b>Design:</b> Pilot <b>Inclusion Criteria:</b> Breast cancer in remission, severe hot flashes, night awakenings	Participants recorded hot flashes in a daily diary by use of the Hot-Flash Score which was used 1 week before the procedure and then weekly after the procedure for 12 weeks.	The total number of hot flashes decreased from 79.4 mean episodes to 49.9 in the first two weeks, and continued to decrease during the follow-up period to 8.1 per week.  Night awakenings decreased from 19.5 mean episodes per week to 7.3 during treatment then to 1.4 per week during follow up.  Very severe hot flash episodes decreased to near zero at follow up.	No adverse events resulting from the stellate-ganglion block, although patients had temporary Horner's syndrome indicating the effectiveness of the block. Pilot study with a very small sample size
<b>Testosterone Replacement Therapy: PEP Weight of Evidence Category: Effectiveness Not Established</b>					
Agarwal & Oefelin, 2005	Testosterone replacement therapy (TRT) after primary treatment for prostate cancer.  Patients were placed on topical, transdermal, or intramuscular testosterone formulations and followed at regular	<b>Sample:</b> N = 10 Mean age: 63.4 years old <b>Study design:</b> Retrospective review of patients with organ confined prostate cancers that were subsequently treated for hypogonadism with testosterone replacement therapy.  Participants were identified between 1993 and 2003, with no evidence of disease by clinical and PSA criteria. They presented postoperatively with complaints of decreased libido, erectile	At each two month visit, the participants completed the hormone domain of the Extended Prostate Inventory Composite (EPIC) Health-Related QOL questionnaire without any assistance from a healthcare provider.	Median duration of treatment was 19 months. During the course of therapy no patient had a PSA recurrence.  The hormone domain of the EPIC questionnaire increased significantly from 38 to 49, primarily due to a reduction in hot flashes and an increase in energy level.	Study states no other human studies of the use of TRT after the treatment for prostate cancer.  A few case reports suggest that short-term TRT can cause an increase in PSA and convert an occult lesion into a clinically apparent one.  Baseline serum PSA and

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
	intervals (every two months) with determinations of serum total testosterone and prostate-specific antigen (PSA) level.	dysfunction, lack of energy, cognitive impairment, or hot flashes.			<p>digital rectal examination must be performed along with baseline serum free and total testosterone. Also patients must be followed more frequently especially if baseline prostate biopsy not performed.</p> <p>A large placebo-controlled, multicenter prospective trial to evaluate the feasibility of TRT in patients with hypogonadism after radical prostatectomy is indicated for further study.</p>
<p><b>Tibolone: PEP Weight of Evidence Category: Effectiveness Not Established</b></p>					
Kroiss et al., 2005.	<p>Tibolone</p> <p>Women were randomized to receive 20 mg/day tamoxifen plus 2.5 mg/day tibolone or placebo.</p>	<p><b>Sample characteristics:</b> Post-menopausal women less than or equal to 75 years of age with Stage IIB or less started on tamoxifen postoperatively. N = 70; 67 patients completed the study. Mean age: 58.</p> <p><b>Inclusion:</b> Post-menopausal women less than or equal to 75 years of age with newly diagnosed Stage IIb or lower breast cancer Surgical treatment with conservative therapy or modified radical mastectomy Receiving tamoxifen therapy</p>	<p><b>Primary end point:</b> Frequency and severity of hot flashes at three months.</p> <p>Daily hot flash diary to assess frequency and severity of hot flashes. Landgren scale to assess intensity of hot flashes and sweats. Questionnaire to assess interference of hot flashes and sweats with everyday life.</p>	<p>Daily diary showed no change in daily number of hot flashes with either tibolone or placebo (p = 0.219) after three months. Significant reduction in the severity of hot flashes with tibolone verses placebo (-0.4 versus 0.2, p = 0.031). Landgren scale showed a mean change in the number of hot flashes of -0.6 with tibolone and +1.1 with placebo after 12 months (p = 0.022). Endometrial biopsies were</p>	<p>Small sample size with less than 100 participants. The effect of tibolone on recurrence of breast cancer is unknown.</p>

**Hot Flashes  
Evidence Table**

**(Literature search completed through February 2010)**

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
		<p>Last menstrual period one year or more before the diagnosis of breast cancer            Serum estradiol concentration of less than or equal to 30 pg/mL  <b>Exclusion:</b> Other malignancies; prior hysterectomy or bilateral oophorectomy; endometrial hyperplasia/adenocarcinoma; cervical smear result showing moderate dysplasia or worse; cardiovascular, cerebrovascular, or thromboembolic disorders; uterine bleeding of unknown cause; severe liver disorders; drug or alcohol abuse in the previous 12 months; requirement for cancer therapy (other than tamoxifen therapy and radiotherapy); medication that may affect the metabolism of tibolone; use of steroids or tamoxifen in the six weeks prior to the study; hormonal implants at any time.  <b>Setting:</b> Outpatient, multicenter  <b>Design:</b> Double-blind, randomized, placebo-controlled, multicenter, pilot  <b>Purpose:</b> Assess the effects of tibolone versus placebo in postmenopausal women receiving tamoxifen measuring effects on hot flashes, endometrium, and serum lipid and lipoproteins</p>	<p>Endometrial biopsies at 6 and 12 months.            Monthly diary to assess incidence of bleeding or spotting throughout the study.            Serum lipid profile.</p>	<p>normal and vaginal bleeding similar in both groups.            Significant decrease in triglycerides (-23% versus 1.4%) and HDL (12% versus 19%) with tibolone versus placebo after 12 months.</p>	

**Weight of Evidence Category: Effectiveness Not Established**  
**Nonpharmacologic Interventions**

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
<b>Acupuncture: PEP Weight of Evidence Category: Effectiveness Not Established</b>					
Deng et al., 2007	Compare the immediate and long-term effects of true acupuncture versus sham acupuncture on hot flash frequency in women with breast cancer.	<b>Sample:</b> 72 women with breast cancer experiencing three or more hot flashes per day <b>Design:</b> randomly assigned to receive either true or sham acupuncture	Primary outcome measurement was hot flash frequency Participants completed a hot flash diary for one day at days 7, 14, 21, 28, and 35	The mean number of hot flashes per day was reduced from 8.7 to 6.2 in the true acupuncture group. The mean number of daily hot flashes was reduced from 10.0 to 7.6 in the sham group.  The true acupuncture was associated with 0.8 fewer hot flashes per day when compared to the sham at six weeks. This difference was not statistically significant.  During the cross over phase, participants in the sham group who received true acupuncture reported a further reduction in the frequency of hot flashes was seen.  The overall reduction in hot flash frequency persisted for up to 6 months after the completion of treatment.	<b>Limitations:</b> Reliance on self-report instruments and recall. No physiologic measurements were used.  Study may not have been of a sufficiently long duration.  Modest sample size.
Filshie et al., 2005	Describe the effects of acupuncture and self-acupuncture on hot flash frequency and intensity	<b>Sample:</b> 182 females ages 35 to 83 and 12 men ages 49 to 79 years of age <b>Design:</b> retrospective audit of electronic charts	Primary outcome measurement was hot flash frequency and intensity Participants used both traditional acupuncture and self-acupuncture.	The average pre treatment hot flash count was 16 per day. When acupuncture was added the chart audit	<b>Limitations:</b> Data was not collected prospectively; study relied on data available in the chart.  Data was missing in 27

Hot Flashes

Evidence Table

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
				showed that 114 (79%) subjects achieved a 50% or greater reduction in hot flashes.	charts Study was not of a long duration – 24 weeks
Frisk et al., 2008	To evaluate the effects of electro-acupuncture (EA) and hormone therapy (HT) on vasomotor symptoms in women with a history of breast cancer.	<b>Sample:</b> Forty-five women were randomized to EA (n = 27) for 12 weeks or HT (n = 18) for 24 months <b>Design:</b> Randomized, controlled study was part of an international, multicenter study, HABITS19, involving patients from three centers in Sweden between April 1998 and December 2002.	The patients were monitored with daily entries made in a log book, recording the numbers of hot flashes during day and night, and how disturbing they were (range 0 for no distress to 10 for worst possible distress) The log books were completed daily for 1–3 weeks before treatment, continuously during the first 12 weeks of treatment and thereafter for 1 week per month, altogether 24 months. The measuring points were baseline, the 12th week of treatment, and at 1 week at 6, 9, 12, 18 and 24 months after start of treatment.	In 19 women who completed 12 weeks of EA, the median number of hot flashes per 24 hours decreased from 9.6 at baseline to 4.3 at 12 weeks of treatment At 12 months after start of treatment, 14 women with only the initial 12 weeks of EA had a median number of flashes per 24 hours of 4.9, and at 24 months seven, women with no other treatment than EA had 2.1 flashes per 24 hours.	Small sample size Relatively large attrition rate
Hammar et al., 1999	Evaluate acupuncture treatment 30 minutes twice weekly for 2 weeks and once a week for 10 weeks	<b>Sample:</b> Seven men with vasomotor symptoms due to castration	Hot flashes were recorded in logbooks	Of the seven men, six completed at least 10 weeks of acupuncture therapy, and all had a substantial decrease in the number of hot flashes (average 70% after 10 weeks). At three months after the last	Very small sample size. Small duration of study. Convenience sample

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
				treatment, the number of flashes was 50% lower than before therapy. Therapy was discontinued after 10 weeks because of a femoral neck fracture in one man and after three weeks due to severe back pain in one subject.	
Harding et al., 2008	To evaluate the role of auricular acupuncture (AA) in men receiving luteinizing-hormone releasing hormone (LHRH) analogues for prostate cancer on hot flash incidence and severity	<b>Sample:</b> 60 consecutive patients with prostate cancer and on LHRH agonist treatment (median age 74 years) receiving weekly AA for 10 weeks.	Recorded the frequency of hot flash episodes both during the day and at night at 0, 4 and 10 weeks. Participants were asked to grade the intensity of their hot flashes on a 0–6 scale, with 6 representing maximum intensity and recorded these data at 0, 4, and 10 weeks.	95% of patients reported a decrease in the severity of symptoms, from a mean of 5.0 to 2.1 (Student's test, $p < 0.01$ ).	Convenience sample No control group
Hervik & Mjåland, 2009	Examine the efficacy of acupuncture in women with breast cancer experiencing hot flashes as a result of anti-estrogen medication	<b>Sample:</b> 59 women with breast cancer <b>Design:</b> prospective, controlled. Trial randomized to either 10 weeks of traditional Chinese acupuncture or sham acupuncture.	Mean number of hot flashes at day and night were recorded prior to treatment, during the treatment period, and during the 12 weeks following treatment. Kupperman index was completed at baseline, at the end of the treatment period, and at 12 weeks following treatment.	During the treatment period the mean number of hot flashes at day and night was significantly reduced by 50% and almost 60%, respectively from baseline in the acupuncture group, and was further reduced by 30% both at day and night during the next 12 weeks. In the sham acupuncture group, a significant reduction of 25% in hot flashes at day was seen during treatment, but was reversed during the following	May have been a placebo effect. Need to have longer studies to see if effect continues Small sample size

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
				<p>12 weeks. No reduction was seen in hot flashes at night. Kupperman Index was reduced by 44% from baseline to the end of the treatment period in the acupuncture group, and largely maintained 12 weeks after treatment ended. No corresponding changes were seen in the sham acupuncture group.</p>	
<p>Nedstrand et al., 2005</p>	<p>Randomized to treatment with electro-acupuncture (n = 19) or applied relaxation (n = 19) during 12 weeks.</p>	<p><b>Sample:</b> of 38 postmenopausal women from Sweden <b>Study Design:</b> Randomized trial</p>	<p>The number of hot flashes was registered daily in a logbook before and during treatment and after 3 and 6 months of follow-up.</p>	<p>Thirty-one women completed 12 weeks of treatment and 6 months of follow-up. After 12 weeks of applied relaxation, the number of flashes/24 h had decreased from 9.2 at baseline to 4.5 and to 3.9 at 6 months follow-up. The flashes/24 h were reduced from 8.4 to 4.1 after 12 weeks of treatment with electro-acupuncture and to 3.5 after 6 months follow-up (n = 17). In both groups, the mean Kupperman Index score was significantly reduced after treatment and remained unchanged 6 months after end of treatment.</p>	<p>Small sample size Method to evaluate hot flash log books was not described High attrition rate</p>
<p>Towlerton et al., 1999</p>	<p>Pilot study of the placement of semipermanent</p>	<p>Sample: 12 breast cancer patients on Tamoxifen</p>	<p>Not reported</p>	<p>8 of 12 women reported a decrease in hot flashes</p>	<p>Letter to the editor—limited data</p>

Hot Flashes

Evidence Table

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
	acupuncture studs				
Walker et al., 2010	Study comparing acupuncture and venlafaxine for 12 weeks with health measurements for one year	<p><b>Sample:</b> N = 50 (25 in each arm)</p> <p><b>Inclusion criteria:</b> (1) stage 0–III pre- or postmenopausal patients with breast cancer on hormone therapy with tamoxifen or arimidex; (2) 14 hot flashes per week; (3) 18 years of age; (4) may have been treated locally with surgery or radiation and must have completed chemotherapy; (5) may be receiving radiation therapy but otherwise must be within five years after treatment; (6) must be on a stable dose of hormone therapy for four weeks or more without plans to discontinue therapy for the duration of the study; (7) Karnofsky performance status; (8) life expectancy of at least six months.</p> <p><b>Design:</b> Randomized controlled trial</p>	<p>Hot Flash Diary (number and severity of hot flashes;</p> <p>Menopause- Specific Quality of Life Questionnaire (MenQOL)</p>	<p>Both groups exhibited significant decreases in hot flashes, depressive symptoms, and other QOL symptoms. Acupuncture was as effective as venlafaxine. By two weeks after treatment, the venlafaxine group experienced significant increases in hot flashes, whereas hot flashes in the acupuncture group remained at low levels. The venlafaxine group experienced 18 incidences of adverse effects (e.g., nausea, dry mouth, dizziness, anxiety), whereas the acupuncture group experienced no negative adverse effects. Acupuncture had the additional benefit of increased sex drive in some women, and most reported an improvement in their energy, clarity of thought, and sense of well-being.</p>	<p>Small sample size</p> <p>Long-term follow-up was one year</p>
<b>Black Cohosh: PEP Weight of Evidence Category: Effectiveness Not Established</b>					
Hernández Muñoz & Pluchino, 2003	To examine the effect of <i>Cimicifuga racemosa</i> (CR BNO 1055) on hot flashes caused by tamoxifen adjuvant therapy in	<p><b>Sample Size:</b> 136 breast cancer survivors aged 35–52 years who completed treatment with segmental or total mastectomy, radiation therapy and adjuvant chemotherapy.</p> <p><b>Study Design:</b> Two-armed,</p>	<p>Control visits occurred every two months at which time the supply of CR BNO 1055 was replaced and clinical assessments made.</p> <p>Hot flashes were considered</p>	<p>The patterns were significantly different between the two groups on testing the differences between proportions with Fisher's exact test (<math>p &lt; 0.01</math>).</p>	<p>Methodologic problems included an open label trial (participants aware of their intervention) and arms were unequal in size (twice as many participants in the Black Cohosh group as in the usual</p>

Hot Flashes

Evidence Table

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
	<p>young premenopausal breast cancer survivors. This treatment presents an off-label use of CR BNO 1055 (also known as black cohosh).</p> <p>Participants took one tablet twice daily with meals for 60 days. Duration of treatment was five years for tamoxifen, and 12 months for CR BNO 1055. Participants were instructed not to initiate new therapies for hot flashes, while participating in the study.</p>	<p>randomized and open-label. Participants were randomly assigned (1-2) to receive tamoxifen 20 mg per day orally (usual-care group; n = 46; mean age = 47 years) or tamoxifen plus CR BNO 1055 corresponding to 20 mg of herbal drug (intervention group n=90; mean age = 46 years.). The primary endpoint was to assess the effect of CR BNO 1055 on the frequency and intensity of hot flashes.</p> <p><b>Inclusion Criteria:</b> Premenopausal status with regular menstruation and normal duration of cycle, and breast cancer diagnosis with estrogen receptor-positive tumor.</p> <p><b>Exclusion criteria:</b> Refusal to consider a study treatment for relief of symptoms, history of other cancers, and serious chronic medical conditions.</p>	<p>severe when five or more heat episodes occurred during the day and were accompanied by sweating, sleep disturbances, feeling of irritation, and anxiety. A few episodes of heat with discrete sweating were classified as moderate hot flashes. Participants completed hot flash diaries at baseline, at every control visit, and at the end of the study at 12 months.</p>	<p>Among the 46 study participants included into the usual-care group, 73.9% experienced severe hot flashes and 26.1% moderate symptoms. Among the 90 study participants in the intervention group, at the end of the study, 46.7% were free of hot flashes, and 24.4% reported severe symptoms.</p> <p><b>Conclusion:</b> In the intervention group, the administration of CR BNO 1055 in combination with tamoxifen for a 12-month period significantly reduced the vasomotor episodes induced by tamoxifen, in breast cancer survivors.</p>	<p>care group).</p>
<p>Jacobson et al., 2001</p>	<p>Randomized clinical trial of black cohosh for treatment of hot flashes among women with a history of breast cancer. The black cohosh and placebo were supplied by the manufacturer. Each participant received 130 tablets</p>	<p><b>Sample:</b> 85 participants (59 on tamoxifen, 26 not on tamoxifen); 42 participants were assigned to treatment; 43 were assigned to placebo; 69 completed all three hot flash diaries</p> <p><b>Study design:</b> Two-arm randomization, double-blind, placebo-controlled study to assess the effect of black cohosh on the frequency and intensity of hot flashes. Participants stratified based on if they used tamoxifen.</p>	<p>Participants were asked to record in a hot flash diary the number of hot flashes and the intensity of each. Participants scored severity as 1 = mild, 2 = moderate, and 3 = severe, for three days before starting to take any study pills, then again on days 27 to 30, and on days 57 to 60. FSH and LH levels were measured in a</p>	<p>Sample size was chosen for 90% power to detect a 30% difference between groups in mean numbers of hot flashes, with a SD of 4.0. All analyses were stratified by tamoxifen use. The primary efficacy end point was mean numbers of hot flashes at 57 to 60 days. The safety end points were changes in mean levels of</p>	<p>A limitation of this study is that participation lasted only two months.</p>

Hot Flashes

Evidence Table

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
	and took one tablet twice daily with meals for 60 days.	<p><b>Inclusion criteria:</b> Participants had to have completed primary therapy, including chemotherapy and radiation therapy, at least two months before entering the trial.</p> <p><b>Exclusion criteria:</b> Use of hormonal replacement therapy for hot flashes, pregnancy, major psychiatric illness, or recurrent or metastatic breast cancer.</p>	subset of participants at the first and final visit.	<p>FSH and LH at the start and end of study participation associated with treatment. In hot flash intensity, both groups experienced a decline during the first month of study participation. The differences between groups in intensity at the end of the study were not significant. For the overall hot flash activity score the differences between the treatment and placebo groups adjusted for tamoxifen were not statistically significant. Changes in FSH and LH levels of also did not differ between the two groups.</p> <p><b>Conclusion:</b> Data provide little evidence of either harm or benefit from using black cohosh to control hot flashes</p>	
Pockaj et al., 2006	Double-blind, randomized, cross-over clinical trial with two, four-week periods was used to study the efficacy of black cohosh (one capsule, <i>Cimicifuga racemosa</i> 20 mg twice daily) for the treatment of hot flashes in women with	<p><b>Sample:</b> 132 participants were randomized. 107 participants (81%) completed the first five weeks of hot flash diaries; 99 participants (75%) completed the entire nine weeks of therapy.</p> <p>Mean Age: 56 years</p> <p><b>Study design:</b> Double-blind, randomized, cross-over clinical trial with two four-week periods.</p> <p><b>Inclusion criteria:</b> History of breast</p>	Participants completed a prospective, daily hot flash diary for the nine weeks of the study: during the baseline week and then during the two four-week crossover treatment periods. Hot flash scores were measured by assigning points to each hot flash based on severity (1 for mild to 4 for very severe) and	The primary end point was the average inpatient hot flash score (which is a construct of average daily hot flash severity and frequency) difference between the baseline week and the last study week of the first treatment period. Hot flash activity was analyzed in a number of ways, including the difference between treatment	A subset of participants did not have a diagnosis of breast cancer but met the eligibility criteria of a perceived increased risk of breast cancer, or did not want to take estrogen because of the increased risk of breast cancer. Numbers of participants with and without a breast cancer diagnosis were not specified.

**Hot Flashes  
Evidence Table**

**(Literature search completed through February 2010)**

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
	<p>and without a history of breast cancer.</p> <p>Participants received four weeks of therapy with black cohosh or an identical appearing placebo. The black cohosh or placebo was given as one tablet twice per day. After completing the first four weeks, participants were crossed over to the alternative treatment arm.</p>	<p>cancer, a perceived increased risk of breast cancer, or did not want to take estrogen due to the increased risk of breast cancer. Participants experienced bothersome hot flashes (14 or more per week) for at least one month. Concomitant therapy with tamoxifen, raloxifene, or an aromatase inhibitor was allowed as long as patient had been on the therapy for one month. Use of vitamin E and/or soy was allowed if the patient had been on a stable dose for one month or more and planned to continue the same dose during the entire study period.</p> <p><b>Exclusion criteria:</b> Receiving concomitant chemotherapy, androgens, or estrogens. Any prior use of black cohosh; use of antidepressants within the prior two weeks (or planned use during the next nine weeks); or current or planned use of other agents for treating hot flashes (e.g., clonidine, belladonna alkaloids, dehydroepiandrosterone). Other oral herbal therapies, therapeutic herbal teas, or tinctures during the study period were not allowed because of potential interactions with black cohosh.</p>	<p>then adding the points for a given time period.</p>	<p>week 4 (study week 5) and baseline activity (study week 1) in terms of hot flash score was compared between placebo and black cohosh arms by standard two-sided Wilcoxon procedures. Confidence intervals were constructed for median reductions in hot flash frequency and score. Patients receiving black cohosh reported a mean decrease in hot flash score of 20% (comparing the fourth treatment week to the baseline week) compared with a 27% decrease for patients on placebo (p = .53). Mean hot flash frequency was reduced 17% on black cohosh and 26% on placebo (p = .36). Patient treatment preferences were measured after completion of both treatment periods. Thirty-four percent of patients preferred the black cohosh treatment, 38% preferred the placebo, and 28% did not prefer either treatment. Toxicity was minimal across both groups.</p> <p><b>Conclusion:</b> This trial failed to</p>	

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
				provide any evidence that black cohosh reduced hot flashes more than the placebo.	
<b>Hypnosis: PEP Weight of Evidence Category: Effectiveness Not Established</b>					
Elkins et al., 2004	Hypnosis was used to deliver suggestions of coolness, to manage anxiety and stress, and reduce insomnia.	Two cases of women with hot flashes	Women recorded the number and severity of hot flashes on a daily basis before and during a hypnosis intervention.	Both women had a decrease in the number and severity of hot flashes.	Case study with an N = 2. Descriptive statistics only.
Elkins et al., 2007	Pilot study of the use of hypnosis to reduce hot flashes. Each participant received four weekly sessions of hypnosis using a standardized transcript and was instructed in self-hypnosis.	<b>Sample:</b> 16 breast cancer survivors <b>Design:</b> Pilot study	Daily diaries of the frequency and severity of their hot flashes. Baseline and post-treatment ratings of the degree to which hot flashes interfered with daily activities and QOL using the Hot Flash-Related Daily Interference Scale	Results indicated a 59% decrease in total daily hot flashes and a 70% decrease in weekly hot flash scores from their baselines. Participants experienced a significant decrease in the degree to which hot flashes interfered with daily activities for all measures including work, social activities, leisure activities, sleep, mood, concentration, relations with others, sexuality, enjoyment of life, and overall QOL.	Small sample size and limitations inherent in single group pre-post study design. All of the participants expressed interest in hypnosis, which may indicate some selection bias. Because no comparable control group was used, identifying the exact efficacy of hypnosis as a treatment for hot flashes is not possible.
Elkins et al., 2008	Compare a hypnosis intervention (five weekly sessions) or no treatment	<b>Sample:</b> Sixty female breast cancer survivors with hot flashes <b>Design:</b> Randomly assigned to treatment with hypnosis or no treatment <b>Inclusion criteria:</b> Eligible patients had to have a history of primary breast cancer without evidence of detectable disease and 14 or more weekly hot flashes for at least one month.	Hot Flash Related Daily Interference Scale	Fifty-one randomly assigned women completed the study. By the end of the treatment period, hot flash scores (frequency and average severity) decreased 68% from baseline to end point in the hypnosis arm ( $p \leq 001$ ). Significant improvements in	Study lasted five weeks. No physiologic monitoring of hot flashes. No long-term follow-up

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
				self-reported anxiety, depression, interference of hot flashes on daily activities, and sleep were observed for patients who received the hypnosis intervention ( $p \leq .005$ ) in comparison to the no treatment control group.	
Younus et al., 2003	Observe the effect of hypnosis on hot flashes and overall QOL in symptomatic patients. A secondary objective was to observe the effect of hypnosis on fatigue.	Ten healthy volunteers and four patients with breast cancer (total 14 patients) with hot flashes	Each participant had four, one hour per week sessions of hypnosis. The same physician, with the help of a nurse, conducted every session. All participants recorded frequency, duration, and severity of hot flashes in a hot flash diary.	The frequency ( $p < 0.0001$ ), duration ( $p < 0.0001$ ), and severity ( $p < 0.0001$ ) of hot flashes were significantly reduced. The overall QOL was also improved ( $p < 0.05$ ). The participants enjoyed better sleep and had less insomnia ( $p < 0.012$ ). There was a significant improvement on current fatigue level ( $p = 0.017$ ), reduction in the total fatigue level was not statistically significant.	Pilot study with a very small sample size mixed with healthy participants and people with breast cancer
<b>Peer Counseling: PEP Weight of Evidence Category: Effectiveness Not Established</b>					
Schover et al., 2006	Evaluate a peer counseling program to improve sexual function, increase knowledge about reproductive health, and decrease menopausal symptoms and infertility-related	<b>Sample:</b> 60 African American women. Convenience sample from MD Anderson <b>Design:</b> Random assignment to immediate counseling or a three-month waitlist. Three peer counselors conducted a three-session intervention using a detailed workbook.	Breast Cancer Prevention Trial Menopause Symptom Checklist	Women had fewer problems with hot flashes. Knowledge of reproductive issues improved significantly from baseline to three-month follow-up ( $p < .0001$ ), as did emotional distress ( $p < .0047$ ) and menopause symptoms ( $p < .0128$ ). Sexually dysfunctional women became less	Small convenience sample Short follow-up time (3 months) Hot flashes were not the primary focus of the study

**Hot Flashes**

**Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
	distress for African American breast cancer survivors.			distressed (p < .0167).	
<b>Relaxation Therapy: PEP Weight of Evidence Category: Effectiveness Not Established</b>					
Fenlon et al., 2008	Assess the efficacy of relaxation training in reducing the incidence of hot flashes in women with primary breast cancer. The intervention group received a single relaxation training session and was instructed to use practice tapes on a daily basis at home for one month; the control group received no intervention.	<b>Sample:</b> 150 women from three breast cancer centers in England <b>Design:</b> Randomized controlled trial <b>Inclusion criteria:</b> Postmenopausal women diagnosed with primary breast cancer and suffering from menopausal hot flashes. Any level of severity was accepted for inclusion in the trial as long as the women found the flashes to be troublesome. Postmenopausal was defined as six months without menstruation.	The incidence of flashes was measured using a diary, kept by the women, of every flash as it occurred over the period of one week. The women also gave a measure of the severity of each flash using four predefined categories of flashes: (a) length of flash, (b) physical manifestation, (c) emotional response, and (d) behavioral response. For each of these domains, four levels of severity (graded 1–4) using the Hunter Menopause Scale.	Of 150 women recruited to the trial, 104 women completed the trial to the primary endpoint at one month and 97 completed all three months. The incidence and severity of hot flashes, as recorded by diaries, each significantly declined over one month (p < 0.001 and p < 0.01, respectively), compared with the control group. Distress caused by flashes also significantly declined in the treatment group over one month (p < 0.01), compared with the control. No significant differences between the treatment group and the control group at three months and no changes in anxiety or QOL were reported.	A large amount of attrition.
<b>Vitamin E: PEP Weight of Evidence Category: Effectiveness Not Established</b>					
Barton et al., 1998	Placebo controlled, randomized, crossover trial of vitamin E in breast cancer survivors. Participants received an eight-	<b>Sample size:</b> 125 women were randomized; 5 participants on the placebo-arm withdrew before starting study medication, which resulted in 120 patients assessable for toxicity. 105 participants completed five weeks of	Baseline hot-flash counts for each woman were obtained for the first seven days. Starting the second week and for the remaining seven weeks, study medication was	Treatment efficacy was measured using three variables: mean daily hot-flash frequency, mean daily hot-flash severity (grades 1 to 4 to represent mild, moderate,	No significant limitations

Hot Flashes

Evidence Table

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
	<p>week supply of study medication (400 IU of vitamin E succinate or placebo twice daily) labeled with the days and weeks</p>	<p>study; 104 finished all nine weeks.  <b>Age range:</b> 33–67  <b>Study design:</b> Women were stratified by age (18 to 49 years and 50 years and older), current tamoxifen use (yes or no), duration of hot flashes (less than 9 months versus 9 months or more), average frequency of flushes (2–3 per day, 4–9 per day, or 10 or more per day), and current multivitamin use (yes or no).  <b>Inclusion criteria:</b> Older than age 18 with a history of breast cancer. Must have had hot flashes for at least one month with a frequency of at least 14 times per week. Life expectancy of six months or more and an ECOG performance status of 0 or 1. Tamoxifen use was allowed  <b>Exclusion criteria:</b> Current or planned therapy with chemotherapy, androgens, estrogens, progestational agents, corticosteroids, or other agents used for treating hot flashes was not allowed. Women who took more than two multivitamin tablets per day or more than 60 IU of vitamin E daily were excluded, as were pregnant or lactating women, those with a history of bleeding, immune deficiencies, or thrombophlebitis.</p>	<p>taken and the women continued to keep a daily diary of hot flash severity and frequency.</p>	<p>severe, and very severe), and mean daily hot flash score (frequency times average severity). All factors were measured during the last week of each treatment and compared with baseline week. The 105 participants who finished the first treatment period showed a similar reduction in hot flash frequencies for the two study arms. (25% versus 22%; <math>p = .90</math>). This effect represents an average decrease of roughly 1.6 hot flashes per day to a level of 4.7 hot flashes per day. The hot flash score decreased by 28% with vitamin E and 20% with placebo (<math>p = .68</math>). A crossover analysis, however, showed that vitamin E was associated with a minimal decrease in hot flashes (one less hot flash per day than was seen with a placebo) (<math>p \leq .05</math>). At the study end, participants did not prefer vitamin E over the placebo. No toxicity was demonstrated.  <b>Conclusion:</b> Although this trial</p>	

Hot Flashes

Evidence Table

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
				was able to show a statistically significant hot flash reduction with vitamin E compared to a placebo, the clinical magnitude of this reduction was marginal.	
Biglia et al., 2009 (See also Gabapentin)	<p>To assess the efficacy and the tolerability of gabapentin 900 mg/day compared to vitamin E for the control of vasomotor symptoms in women with breast cancer.</p> <p>Vitamin E was chosen as a placebo-equivalent on the basis of previous experience (Barton, 1998) showing only minimal effect on hot flushes in breast cancer participants, and no toxicity or side-effects. Participants were randomly allocated to one of two treatment groups: vitamin E 800 IU/day or gabapentin 900 mg/day by oral route (Neurontin 300 mg capsules) for a period of 12 weeks.</p>	<p><b>Sample size:</b> 115 postmenopausal women. Among the women allocated to vitamin E, 16.36% never started therapy and 34.78% dropped out because of inefficacy.</p> <p><b>Median age:</b> 50 years</p> <p><b>Study design:</b> Randomized non-placebo-controlled, nonblinded study.</p> <p><b>Inclusion criteria:</b> Breast cancer surgically treated at least one year prior; no evidence of systemic disease; eight or more hot flushes per day. Postmenopausal status (amenorrhea for more than 12 months or amenorrhea for 6–12 months with a serum FSH level greater than 40 mIU/ml and estradiol less than 20 pg/ml or bilateral oophorectomy or ovarian suppression by GnRH analogs).</p> <p>Adjuvant therapy with tamoxifen, aromatase inhibitors or GnRH analogs, provided that it was started at least two months before.</p> <p><b>Exclusion criteria:</b> Use of any antidepressant treatment, progestagens or any other medication to treat hot flushes within the previous three months. Concomitant chemotherapy.</p>	Each participant filled a one-week self-report diary on hot flushes at study entry and daily during the 12 weeks of study. In order to assess the duration of treatment efficacy, participants filled out the hot flush diary for three months after treatment discontinuation.	Treatment efficacy was assessed by two measures: frequency (total number of hot flushes) and severity score, calculated by assigning scores of 1, 2, 3 and 4, respectively, to mild, moderate, severe and very severe hot flushes. This hot flush diary had previously been validated (Sloan et al., 2001). Each value was obtained by averaging of data collected over 1 week. Differences and percentage changes from baseline to weeks 4, 8, and 12 were calculated. Among the women allocated to vitamin E, 16.36% never started therapy and 34.78% dropped out because of inefficacy. Hot flush frequency and score decreased by 57.05% and 66.87%, respectively ( $p = 50.05$ ) in the gabapentin group. The effect of vitamin E was fairly small: hot flush frequency and severity score	Small sample size; high dropout rate

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
		<p>Uncontrolled hypertension. Impaired renal or hepatic function, diabetes.</p>		<p>were reduced by 10.02% and 7.28%, respectively (<math>p &gt; 0.05</math>). <b>Conclusion:</b> Gabapentin 900 mg/day is effective for relieving hot flushes in participants previously treated for breast cancer. Vitamin E has only marginal effect on vasomotor symptoms.</p>	
<p><b>Yoga: PEP Weight of Evidence Category: Effectiveness Not Established</b></p>					
<p>Carson et al., 2009</p>	<p>Evaluate the effects of a yoga intervention on menopausal symptoms in a sample of survivors of early-stage breast cancer</p>	<p><b>Sample:</b> N = 37 <b>Design:</b> randomized controlled to either eight-week yoga awareness program (gentle yoga poses, meditation, and breathing exercises) or to control group. <b>Inclusion criteria:</b> experiencing at least one hot flash per day on four or more days per week; no signs of active breast cancer; no current cytotoxic chemotherapy; diagnosed with breast cancer at stages IA–IIB two or more years ago; no hormone replacement therapy currently or within prior three months; stabilized on a constant regimen of menopausal symptom medications and supplements for at least three weeks; if taking antidepressants, stabilized at a fixed dose for at least three months. <b>Exclusion:</b> Residing more than 70 miles from the research site, currently engaged in intensive yoga practice (more than three days/week), had</p>	<p>Daily reports of hot flashes collected at baseline, after treatment program, and three months after treatment via an interactive telephone system.</p>	<p>After treatment, women who received the yoga program showed significantly greater improvements relative to the control condition in hot-flash frequency, severity, and total scores and in levels of joint pain, fatigue, sleep disturbance, symptom-related bother, and vigor. At three months follow-up, patients maintained their treatment gains in hot flashes.</p>	<p>Very small sample size Only three months follow-up Heterogeneous sample Not clear what menopausal symptom medications included and if they confounded results 182 women screened; 37 enrolled; overall completion 81%</p>

**Hot Flashes  
Evidence Table**

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
		received treatment for serious psychiatric disorders in the previous six months, or does not speak English.			
<b>Homeopathy: PEP Weight of Evidence Category: Effectiveness Unlikely</b>					
Clover & Ratsey, 2002	<p>Uncontrolled, pilot outcome study of homeopathic treatment of hot flashes</p> <p>Six homeopathic medications were mentioned as “most prescribed”: <i>Amyl nitrosum</i>, <i>Calc carb</i>, <i>Lachesis</i>, <i>Natrum mur</i>, <i>Pulsitilla</i>, and <i>Sepia</i>.</p>	<p><b>Sample size:</b> 31 participants completed the initial consultation and one follow-up visit. Three groups of subjects were included: 1. Menopausal symptoms/no cancer history (n = 11) 2. Menopausal symptoms/breast cancer/no recent tamoxifen (n = 7) 3. Menopausal symptoms/breast cancer/taking tamoxifen (n = 13)</p> <p><b>Study design:</b> Uncontrolled, pilot outcome study of homeopathic treatment of hot flashes. Stratified for breast cancer (yes versus no) and tamoxifen use (yes versus no).</p> <p><b>Inclusion criteria:</b> All women seen in an outpatient homeopathic clinic in Glasgow, Scotland.</p> <p><b>Exclusion criteria:</b> None</p>	<p>Questionnaires assessing frequency and severity of hot flushes and changes in conventional medications that might influence hot flushes were completed at initial consultation and at follow-up visits.</p>	<p>The number of participants that reported improvement in hot flush frequency and severity were as follows. Group 1: 8 (73%), 8 (73%) Group 2: 6 (86%), 6 (86%) Group 3: 10 (77%), 10 (77%)</p> <p>There was a “clinical impression of useful benefit.”</p>	<p>Small sample size (31 participants) Age of participants and cause of menopausal symptoms not described Questionnaire not validated Follow-up inconsistent Homeopathic medications not described in text or table.</p>

Hot Flashes

Evidence Table

(Literature search completed through February 2010)

Authors and Year	Characteristics of the Intervention	Sample and Setting Characteristics, Study Design, Conceptual Model	Measures	Results and Conclusions	Limitations, Major and Minor Flaws, Cautions, Contraindications, Special Training Needs, and Costs
Jacobs et al., 2005	A preliminary trial evaluating effectiveness of two types of homeopathy for treatment of menopausal symptoms in breast cancer survivors. At the initial visit, a homeopathic practitioner conducted a homeopathic evaluation of each participant and prescribed an individualized homeopathic medication that best matched the symptom profile for that participant. A homeopathic pharmacist randomized the participants to one of three treatment groups: (1) a placebo combination medicine and a verum single remedy; (2) a verum combination medicine and a placebo single remedy; or (3) two	<p><b>Sample size:</b> 83 participants completed the initial homeopathic visit and were randomized into one of the three treatment groups (see as follows). Of this total, 28 patients (33.7%) withdrew, including 11 who reported no relief from hot flashes, 7 who had a cancer recurrence or withdrew because of other illness, 5 who said the study was inconvenient, and 4 who were lost to follow up. 66 participants completed at least six months of the study (80.5%).</p> <p><b>Study design:</b> Randomized, double-blinded, placebo-controlled. Participants stratified by age (younger or older than 50 years), breast cancer staging, and use of tamoxifen. Participants received controlled individualized homeopathic single remedy, homeopathic combination medicine, or a placebo.</p> <p><b>Inclusion criteria:</b> Women with a history of breast cancer who had completed all surgery, chemotherapy, and radiation treatment. Tamoxifen use was allowed. Participants had a history of hot flashes for at least one month, with an average of at least three hot flashes per day in the week prior to beginning treatment.</p> <p><b>Exclusion criteria:</b> Other medications for the treatment of hot flashes, including specific vitamin regimens, herbs, estrogen or progestational</p>	Homeopathic providers saw or called participants every two months for one year. Participants were mailed a one-week daily hot flush diary to complete during the week prior to call.	<p>No significant difference was reported for the primary outcome measure, the hot flash severity score, or in the total hot flashes among the three groups in the univariate model adjusted for baseline, time, and tamoxifen use over the period of 1 year.</p> <p>The single remedy group had a lower severity score and fewer hot flashes as a whole, which was most marked during the first three months of the study, with a positive trend (<math>p = 0.1</math>) at three months compared to placebo. However, in the combination homeopathy group not receiving tamoxifen there was a statistically significant <i>increase</i> in the hot flash severity score compared to placebo (<math>p = 0.01</math>) and a highly significant difference when compared to single homeopathic remedy (<math>p = 0.001</math>). Similarly, there was a highly significant <i>increase</i> in the total number of hot flashes in the combination group compared to placebo (<math>p =</math></p>	<p>Small sample size precludes definitive answers.</p> <p>Difficulty in retaining participants for one year was a major problem.</p> <p>Use of three arms made treatment decisions difficult although the average number of remedy changes found over the one-year study period is not unusual in homeopathic practice.</p> <p>Use of the homeopathic combination medicine in an ongoing daily regimen, rather than as it is used in current over-the-counter treatment, was a major flaw in this study.</p>

**Hot Flashes  
Evidence Table**

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	<p>placebo medications. All study medications were donated by the Standard Homeopathic Company. The treatments were identical in taste, appearance, and odor and were dispensed in identical containers. The combination medicine was <i>Hyland's Menopause</i>, which is sold over-the-counter in the United States. It contained three homeopathic medicines: <i>Amyl nitrate</i>, <i>Sanguinaria canadensis</i>, and <i>Lachesis</i>.</p>	<p>agents, antidepressants, or sleep medications. Concurrent chronic health problems such as rheumatoid arthritis, asthma, heart disease, and inflammatory bowel disease and corticosteroid use. Those expected to receive additional chemotherapy or radiation treatment within the next year were not allowed to participate. Women who were pregnant or planned to become pregnant in the next year were also excluded.</p>		<p>0.006) and compared to single remedy (<math>p=0.002</math>) in the group not receiving tamoxifen. There was also a Statistically significant increase in headaches in the group receiving the homeopathic combination at 6 months (<math>p = 0.04</math>) and 12 months (<math>p = 0.03</math>).</p> <p>In the multivariate analysis, which included baseline values, time, age, last month in the study, and treatment group, the same statistically significant relationships between treatment group and tamoxifen/no tamoxifen were found for both severity score and total number of hot flashes.</p>	
<p>Thompson &amp; Reilly, 2003</p>	<p>Prospective observational study of homeopathic approach to treatment of estrogen-withdrawal symptoms in women with breast cancer. Active intervention was homeopathic approach, which includes a 60-minute</p>	<p><b>Sample Size:</b> 45 participants; 40 women completed the study. <b>Age Range:</b> 34–71; just over half were aged 50–59 years. <b>Inclusion criteria:</b> 45 consecutive patients seen at the outpatient clinic at Glasgow Homeopathic Hospital with breast cancer and estrogen withdrawal symptoms. 32 participants were taking tamoxifen; 21 had undergone adjuvant chemotherapy; 20 were taking</p>	<p>A numerical self-rating scale, where 0 = no problem, and 10 = tremendous problem, was used to identify patient symptoms. Hot flashes were rated as the most common symptom (<math>n = 38</math>).</p>	<p>Table shows significant improvement in hot flashes between baseline and last visit (<math>p &lt; 0.001</math>).</p>	<p>Small sample size. Study used a convenience sample of consecutive patients, some of who were taking antidepressants (not specified) and clonidine, which may both be used to manage hot flashes. Length of study and schedule of follow up visits not apparent.</p>

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	consultation and the prescription of an individualized homeopathic remedy. A total of 25 remedies were used for the first prescription. <i>Pulsatilla</i> , <i>Sepia</i> , and sulfur were each used on more than three occasions for the first prescription.	medications such as antidepressants and clonidine; 3 had metastatic disease at study entry. <b>Exclusion criteria:</b> None			Assessment of hot flash frequency and severity was not the primary outcome measure of the study, just one of several symptoms assessed. Primary endpoint was the “effect on daily living” scores. Homeopathy regimens were not defined, which could pose a problem for study replication. Exact reduction in hot flashes is difficult to determine.
<b>Soy: PEP Weight of Evidence Category: Effectiveness Unlikely</b>					
MacGregor et al., 2005	A randomized double-blind controlled trial of soy supplements versus placebo for treatment of menopausal symptoms in participants with early breast cancer and hot flashes <b>Methods:</b> Participants were randomized to receive either two soy capsules or two identical placebo capsules twice daily for 12 weeks in a double-blind fashion. The soy capsules each	<b>Sample Size:</b> 72 participants with early breast cancer and hot flashes were randomized to 12 weeks of treatment with soy capsules or with placebo. To be considered a worthwhile treatment strategy, soy extract would need to benefit around half of the participants treated. Thus, 32 evaluable participants per arm were needed. <b>Study design:</b> Study was stratified for initial sweating/flushing score (< 2, p = 2); age at randomization (younger than 50 years, older than 50 years); currently having adjuvant tamoxifen or after ovarian suppression (yes or no). <b>Median age:</b> 51 years <b>Inclusion criteria:</b> Any concomitant medications for preexisting disease were allowed.	QOL and menopausal symptoms scores assessed at baseline, and weeks 4, 8, and 12. A four-question menopausal scale was developed for the study to assess control of menopausal symptoms measured by combined estimates of severity of sweats (day or night) and flushes.	<b>Results:</b> There was no significant difference in menopausal symptoms between the placebo and soy capsule arms of the study.  Toxicity was mild and primarily gastrointestinal. There was no significant difference in toxicity between the 2 arms.	No significant limitations

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	contained 235 mg of soy extract with 17.5 mg of isoflavones. Total dose of isoflavones was 70 mg/day. Placebo capsules were identical to soy capsules.				
Quella et al., 2000	Evaluation of Soy Phytoestrogens for the Treatment of hot flashes in Breast Cancer Survivors: A North Central Cancer Treatment Group Trial	<p><b>Sample size:</b> 177 participants with a history of breast cancer. 149 participants (84%) provided useable efficacy data for the entire nine weeks of the study.</p> <p><b>Study design:</b> All participants were randomized in a double-blind crossover design to one of two groups (soy or placebo) and crossed-over after four weeks. Participants were stratified according to age, duration of hot flashes, and the average daily hot flash frequency using a dynamic allocation procedure that balances marginal distributions. Also stratified by current tamoxifen or raloxifene use (yes or no).</p>	After a baseline documentation week, women received four weeks of either soy tablets or placebo. Then crossed-over to the opposite for the last four weeks. Daily questionnaires documenting hot flashes frequency, intensity, and perceived side effects. The soy product was formulated in 600 mg tablets. Participants took one tablet three times per day (150 mg of isoflavones day), an amount similar to that consumed with three glasses soy milk.	The soy product did not alleviate hot flashes in breast cancer survivors. No toxicity was observed. These data failed to suggest any patient preference for the soy compound over the placebo preparation.	<p>Optimal daily dose of soy required to recognize a clinical response may be questioned.</p> <p>Data related to estimated intake of 150–200 mg daily in the Asian diet endorsed the choice of 150 mg/day.</p> <p>Experience from conventional HRT suggests that length of time on the soy isoflavones (four weeks) may be too short to elicit a clinical response. Study durations of less than three months have been excluded from overviews of the effects of HRT.</p>
Van Patten, 2002	Effect of Soy Phytoestrogens on Hot Flashes in Postmenopausal Women With Breast Cancer: A	<p><b>Sample size:</b> 157 participants who had been previously treated for breast cancer were randomized from August 1998 to February 2000. Nine women (6%) became ineligible after randomization, and 25 (16%) dropped</p>	Women recorded the number/severity of hot flashes with a daily diary for 4 weeks at baseline, then for 12 weeks while consuming 500 ml of a soy or placebo	<b>Conclusion:</b> This trial does not support the use of a soy beverage containing phytoestrogens as a treatment for hot flashes in breast cancer survivors. The soy beverage	No significant limitations

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	<p>Randomized, Controlled Clinical Trial</p>	<p>out because of time commitment (n = 9), intolerance of the study beverage (n = 10, 7 in the soy group, 3 in the placebo group), or other reasons (n = 6). The remaining 123 women completed the study by June 2000.  <b>Mean age:</b> 55 years  <b>Study design:</b> Randomized, placebo-controlled, double-blind clinical trial. Participants were stratified for tamoxifen use and randomized to a soy beverage (n = 59) containing 90 mg of isoflavones or to a placebo rice beverage (n= 64).  <b>Inclusion criteria:</b> Women had completed treatment for breast cancer more than four months prior to enrollment (tamoxifen use was allowed), were menopausal (12 or more months of amenorrhea), and had not used HRT for 4 or more months, were experiencing troubling hot flashes, defined as a score (frequency × intensity) of 10 or more per week. Women using complementary therapies and prescription medications, including tamoxifen, were eligible if no change in therapy for four months or longer. All participants were instructed to avoid soy-based foods and soy supplements during the study.  <b>Exclusion Criteria:</b>                      Based primarily on factors that modify</p>	<p>beverage.                      The primary outcome variable was the mean 24-hour hot flash score, created by summing the hot flash score (frequency × intensity) during the day and night. The main analysis, with Student's t test, was a comparison between groups in the change in the mean 24-hour hot flash score during the 4 weeks of baseline compared with the last 4 weeks of treatment. This analysis was also conducted for the hot flash number and score during the day and night and the hot flash number per 24 hours. Secondary analyses included a comparison between groups of: (1) consumption and acceptability ratings for each beverage, (2) frequency of side effects, (3) responses to the study exit questionnaire, and (4) serum isoflavone concentrations. The average serum isoflavone concentration of the soy beverage was also calculated. All statistical tests were two tailed and used a</p>	<p>did not alleviate hot flashes in women with breast cancer any more than did a placebo. Mild gastrointestinal side effects were experienced by both groups but occurred with greater frequency and severity with soy.</p>	

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		<p>estrogen or phytoestrogen metabolism or that had the potential to require medical intervention: smokers, using antibiotics, inflammatory bowel disease, liver impairment (gamma-glutamyl transferase and alkaline phosphatase of <math>\geq 1.5</math> times normal), or recurrent breast cancer. Also, soy allergy or regular consumption of soy foods.</p>	<p>significance level of alpha = 0.05.</p>		
<p>Nikander et al., 2004</p>	<p>Effects of daily use of isoflavonoids on climacteric symptoms and QOL in postmenopausal women who had been treated for breast cancer</p>	<p><b>Sample size:</b> Sixty-two postmenopausal symptomatic women were randomized to use either phytoestrogen (tablets containing 114 mg of isoflavonoids) or a placebo for three months; the treatment regimens were reversed after a 2-month washout period. Six women discontinued the trial for various reasons during the first phase. Thus, fifty-six women completed the study.  <b>Mean age:</b> 54 (<math>\pm 6</math> years)  <b>Study design:</b> A randomized placebo-controlled crossover trial of phytoestrogens in treatment of menopause in breast cancer participants  <b>Inclusion criteria:</b> breast cancer survivors (none using tamoxifen) who reported incapacitating hot flashes and other climacteric symptoms after the onset of spontaneous menopause, as seen from their high circulating levels of</p>	<p><b>Methods:</b> Phytoestrogen tablets and similar-looking placebo tablets (six tablets per day) were taken every 12 hours with a glass of water. The participants were seen at the research center before and after each treatment period. At each visit the participants were interviewed about hot flashes and other typical climacteric symptoms using the Kupperman index and Menopausal Visual Analogue scale. Blood levels were followed of phytoestrogens, FSH, LH, estradiol, and sex hormone-binding globulin, liver enzymes, and creatinine levels. Compliance with treatment was confirmed by diary records and by</p>	<p><b>Results:</b> The use of phytoestrogens led to significant rises in the levels of phytoestrogens, whereas the placebo regimen had no effect. Kupperman indexes at the end of treatment with phytoestrogen or placebo did not differ. Hot flashes and the other components of the Kupperman index were not relieved by the phytoestrogen regimen when evaluated separately.  <b>Conclusion:</b> Pure isoflavonoids at a dose of 114 mg for three months did not relieve hot flashes or other menopausal symptoms in participants with breast cancer.</p>	<p>Author responses regarding potential limitations:            1. Study period was of short duration (three months). This is an unlikely issue because the levels of phytoestrogens were constantly elevated beginning 6 to 8 hours after the start of the trial, in contrast to HRT which alleviates hot flashes within the first few days of initiation.            2. Possibility that phytoestrogens may trigger changes in target organs in processes requiring more than three months. It would be valuable to have long-term data on the effects of phytoestrogens.            3. Were doses physiologically suitable? Doses appeared sufficiently large, given the elevations in phytoestrogen levels in participants.</p>

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		<p>FSH and LH.  <b>Exclusion criteria:</b> Use of sex steroids (including tamoxifen); use of natural products with possible estrogenic activity; use of drugs possibly affecting climacteric symptoms, metabolism, or absorption of phytoestrogens (e.g., antibiotics during the previous three months); and history of any thromboembolic or hepatic event.</p>	<p>measurement of serum phytoestrogen levels.</p>		
<p>Sharma et al., 2009</p>	<p>Study to evaluate the effects of high dose isoflavones, equivalent to that consumed by Asian populations, on the consequences of androgen deprivation therapy (ADT) for prostate cancer, such as sexual dysfunction, poor QOL, vasomotor symptoms and altered cognition.</p>	<p><b>Sample size:</b> 39 men undergoing ADT for prostate cancer were enrolled; 33 completed the study.  <b>Study design:</b> Randomized, double-blind, placebo controlled, 12-week pilot trial of high-dose isoflavones ingested by men with prostate cancer undergoing ADT. Participants were randomly assigned to receive 20 gm soy protein containing 160 mg total isoflavones (17) versus taste-matched placebo (20 gm whole milk protein).  <b>Inclusion criteria:</b> Men 21 years old or older undergoing medical or surgical ADT for at least three months.  <b>Exclusion criteria:</b> Hepatic, renal, thyroid or neurologic disease, active psychiatric disorder, current chemotherapy or glucocorticoids, appetite or weight promoting agents, substance abuse, triglycerides greater</p>	<p><b>Methods:</b> The intervention contained 20 gm Revival® (Physicians Laboratories) soy protein consisting of 160 mg total isoflavones as powder to be mixed with beverages. Placebo contained 20 gm whole milk protein and similar nutrients as the intervention except for isoflavones. Active and placebo powders appeared and tasted similar. Supplements were ingested once daily for 12 weeks, and dispensed at the baseline and 6-week visits. Data were gathered at study baseline, and weeks 6 and 12. Men tolerated the compound well with only one withdrawing from study because he</p>	<p><b>Results:</b> Men were not well matched for hot flashes, with the isoflavones group reporting higher scores (increased distress) than men on placebo at baseline and at study end. However, within group analysis showed no significant changes in the vasomotor distress score in either group. Using the Kupperman scale, men on isoflavones did not show any significant improvement in hot flashes compared to those on placebo. At 12 weeks, there were no significant differences between the two groups in any outcome measure. No safety issues were found during the study.  <b>Conclusions:</b> This pilot study</p>	<p><b>Limitations:</b> This pilot study had a small sample size and short treatment duration. Future studies should use variable doses of isoflavones for a longer period before ruling out beneficial isoflavone effects in this population.</p>

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		<p>than 500 mg/dl, or allergy to soy protein or cow milk. Men already on soy supplements were washed out for at least three months before entry. After enrollment, men were instructed to refrain from ingesting any kind of soy product during the 12-week study period.</p>	<p>disliked its taste. Overall compliance was high at approximately 80%. Compliance was based on the number of sachets returned by each patient at treatment weeks 6 and 12.</p>	<p>of high-dose isoflavones in androgen deprived men showed no significant improvement in cognition, vasomotor symptoms or any other aspect of QOL measures compared to placebo.</p>	