

# Non-hormonal interventions for hot flushes in women with a history of breast cancer (Review)

Rada G, Capurro D, Pantoja T, Corbalán J, Moreno G, Letelier LM, Vera C



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[Intervention Review]

# Non-hormonal interventions for hot flushes in women with a history of breast cancer

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## ABSTRACT

### Background

Hot flushes are common in women with a history of breast cancer. Hormonal therapies are known to reduce these symptoms but are not recommended in women with a history of breast cancer due to their potential adverse effects. The efficacy of non-hormonal therapies is still uncertain.

### Objectives

To assess the efficacy of non-hormonal therapies in reducing hot flushes in women with a history of breast cancer.

### Search strategy

We searched the Cochrane Breast Cancer Group Specialised Register, CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE, LILACS, CINAHL, PsycINFO (August 2008) and WHO ICTRP Search Portal. We handsearched reference lists of reviews and included articles, reviewed conference proceedings and contacted experts.

### Selection criteria

Randomized controlled trials (RCTs) comparing non-hormonal therapies with placebo or no therapy for reducing hot flushes in women with a history of breast cancer.

### Data collection and analysis

Two authors independently selected potentially relevant studies, decided upon their inclusion and extracted data on participant characteristics, interventions, outcomes and the risk of bias of included studies.

## **Main results**

Sixteen RCTs met our inclusion criteria. We included six studies on selective serotonin (SSRI) and serotonin-norepinephrine (SNRI) reuptake inhibitors, two on clonidine, one on gabapentin, two each on relaxation therapy and homeopathy, and one each on vitamin E, magnetic devices and acupuncture. The risk of bias of most studies was rated as low or moderate. Data on continuous outcomes were presented inconsistently among studies, which precluded the possibility of pooling the results. Three pharmacological treatments (SSRIs and SNRIs, clonidine and gabapentin) reduced the number and severity of hot flushes. One study assessing vitamin E did not show any beneficial effect. One of two studies on relaxation therapy showed a significant benefit. None of the other non-pharmacological therapies had a significant benefit. Side-effects were inconsistently reported.

## **Authors' conclusions**

Clonidine, SSRIs and SNRIs, gabapentin and relaxation therapy showed a mild to moderate effect on reducing hot flushes in women with a history of breast cancer.

## **PLAIN LANGUAGE SUMMARY**

### **Non-hormonal interventions for reducing hot flushes in women with a history of breast cancer**

Breast cancer is one of the most frequent cancers worldwide and its treatment can produce disturbing symptoms including hot flushes, the sudden feeling of heat in the face, neck and chest. Hormonal treatments are used to control such symptoms in postmenopausal women but for women with a history of breast cancer these are not recommended as they can induce cancer growth. The aim of this review is to evaluate the efficacy of non-hormonal interventions in treating hot flushes in such women.

We found 10 randomised controlled studies assessing pharmacological therapies and six assessing non-pharmacological treatments (complementary or alternative therapies). The 10 studies on pharmacological therapies included two on clonidine (an antihypertensive that stimulates a norepinephrine receptor implicated in the initiation of flushes), one on gabapentin (an anticonvulsant that diminishes hot flushes through an unknown mechanism), six on selective serotonin or serotonin-norepinephrine reuptake inhibitors (antidepressants that increase the levels of serotonin and norepinephrine, both implicated in the generation of hot flushes) particularly venlafaxine, paroxetine, sertraline and fluoxetine, and one on vitamin E (mechanism unknown).

Clonidine, antidepressants and gabapentin reduced the number and severity of hot flushes. Vitamin E did not reduce the number or severity of hot flushes.

Of the six studies evaluating non-pharmacological therapies, two were on homeopathy (one evaluated a single homeopathic remedy in a group and the Hyland's menopause formula in a second group; and the other study evaluated homeopathic medicines in tablet, granule or liquid form, prepared by a single pharmacy), two on relaxation therapy (occupational therapist-guided relaxation consisting in stress management, written information about stress, deep breathing techniques, muscle relaxation and guided imagery), one on acupuncture (eight treatment sessions, 19 acupuncture points) and one on magnetic therapy (magnetic devices attached to participants' skin, placed over acupuncture or acupressure sites).

In the studies on non-pharmacological therapies, relaxation therapy was the only one that probably reduced the frequency and severity of hot flushes. Homeopathy, acupuncture and magnetic therapy may not lead to any differences in the number and severity of hot flushes.

One limitation of our review is that it is not possible to say if some treatments are better than others. Another limitation is that adverse effects were not clearly reported in all studies.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Vitamin E compared to Placebo for hot flushes in women with a history of breast cancer						
<b>Patient or population:</b> patients with hot flushes in women with a history of breast cancer <b>Settings:</b> <b>Intervention:</b> Vitamin E <b>Comparison:</b> Placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Vitamin E				
<b>Frequency of hot flushes</b> Number of hot flushes per day (follow-up: 4 weeks)	The mean frequency of hot flushes in the control groups was <b>6.6 HF per day</b>	The mean Frequency of hot flushes in the intervention groups was <b>0.15 lower</b> (2.45 lower to 2.16 higher)		104 (1)	⊕⊕⊕⊕ <b>high</b>	
<b>Hot flushes score</b> Number of HF x severity (from 1 to 4) (follow-up: 4 weeks)	The mean hot flushes score in the control groups was <b>14.4 points</b>	The mean Hot flushes score in the intervention groups was <b>0.82 lower</b> (4.68 lower to 3.05 higher)		104 (1)	⊕⊕⊕⊕ <b>high</b>	

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

## BACKGROUND

### Description of the condition

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related mortality in women, worldwide. Annually, more than a million women are diagnosed with this condition and over 411,000 die (Ferlay 2004). Over 4.4 million women diagnosed with breast cancer in the last five years are currently alive, making breast cancer the most prevalent cancer (Parkin 2005).

Women with breast cancer can experience climacteric symptoms, because of natural menopause but also as a consequence of the treatment they receive. Some breast cancer treatments target estrogen production which is known to impact on the growth of breast cancer (e.g. the endocrine therapies tamoxifen and aromatase inhibitors) and others impact on the natural function of the ovaries (chemotherapy) and cause premature menopause. One of the most common treatment-related symptoms is hot flushes (i.e. the sudden feeling of heat in the face, neck and chest) (WHO 1996), which occur more frequently and with more intensity in breast cancer treated women than in postmenopausal women (Gupta 2006; McPhail 2000). Hot flushes may interfere with normal habits, disrupt sleep and compromise quality of life (Carpenter 1998; Gupta 2006; Stein 2000). Additionally, they may decrease long-term compliance with breast cancer therapy (Cella 2008).

The pathophysiology of hot flushes is still uncertain but is probably caused by an exaggerated response of the thermoregulatory centre in the hypothalamus that is induced by decreased estrogen and progesterone levels (Freedman 2005). Another possible mechanism is sympathetic activation of central  $\alpha 2$ -adrenergic receptors, which modulate the core temperature threshold needed for widespread cutaneous vasodilation and profuse upper body sweating.

### Description of the intervention

For women without a history of breast cancer, hormone therapy with estrogen or combined estrogen and progestogen is highly effective for the treatment of hot flushes (MacLennan 2004), but their long term use increases the risk of various conditions, such as venous thromboembolism, cardiovascular diseases, dementia, gallbladder disease and breast cancer (Farquhar 2005). The trade-off between the potential benefit of alleviating symptoms with hormones and the increased risk of these conditions is still a matter of debate, but there is consensus that their use should be limited to the shortest possible period (Beral 2003; Chlebowski 2003; Rossouw 2002).

Hormonal therapy is usually contraindicated in women with a history of breast cancer. Estrogen and progesterone promote epithelial growth and differentiation of breast cancer cells. Cellular concentrations of estrogen receptor or progesterone receptor are demonstrated in approximately 60% of breast cancer tumors

and these are therefore considered to be hormonally responsive (Allegra 1980). Confirming the latter, a recent randomized trial showed that treatment with a estrogen and progestogen combination more than doubled the risk of breast cancer recurrence after a median follow up of four years (Holmberg 2008). Additionally, women with breast cancer have an increased risk of thrombosis as a consequence of the disease itself or from treatments employed for long-term secondary prevention (for example tamoxifen). This, added to the well demonstrated risk of thrombosis associated with hormonal therapies, constitutes another reason to avoid hormonal therapies in this group of patients (Deitcher 2004; Rossouw 2002). Progestational agents alone are effective in relieving hot flushes (Goodwin 2008) but theoretical concerns and in vitro data suggest they may unfavourably affect prognosis (Hofseth 1999). Observations from the Women's Health Initiative trial (WHI) also cast doubts on the long-term effects of progestational agents since an increase in breast cancer risk was observed in women enrolled in the estrogen-progestin arm of the study but not in the estrogen alone arm (Anderson 2004; Rossouw 2002).

Other commonly employed options for hormone therapy are black cohosh, phytoestrogens and tibolone. All of these demonstrate possible estrogenic action, so their use in women with breast cancer is generally not recommended (Grady 2006; Sturdee 2008).

All these reasons have prompted the search for safer alternatives to treat hot flushes in women with a history of breast cancer. The concept of non-hormonal therapy has emerged and includes any treatment which is known not to have proven or supposed hormonal activity (to be estrogen-like).

### How the intervention might work

Anecdotal reports initially drew attention to the use of new generation antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), as a method of treating hot flushes (Loprinzi 2009). Even though their mechanism of action is not widely understood, serotonin and noradrenaline (norepinephrine) act at various levels in the regulation of body temperature and the initiation of hot flushes (Sturdee 2008). A systematic review evaluating the effects of non-hormonal therapies in both postmenopausal and breast cancer related hot flushes identified six studies of SSRIs and SNRIs. This review concluded that there was some evidence for efficacy, but most studies had methodological deficiencies (Nelson 2006).

Given the role of norepinephrine in the initiation of hot flushes, the  $\alpha 2$ -adrenergic agonists clonidine and methyl dopa have also been evaluated. The review by Nelson (Nelson 2006) identified 10 and three studies respectively, and concluded that there was some benefit for clonidine in relieving hot flushes but adverse effects were frequent, whereas methyl dopa was probably not effective.

Other options assessed for treating hot flushes include the anticonvulsant gabapentin and vitamin E (Barton 1998; Pandya 2005). Their mechanisms of action are unknown.

Psychological factors may contribute to hot flushes. Some situations such as those causing embarrassment and stress can trigger hot flushes, probably through sympathetic activation. Interventions aimed at managing these aspects (Freedman 2005) such as relaxation-based procedures, exercise and other non-pharmacological therapies have been investigated in postmenopausal women but with inconclusive results (Daley 2007; Loprinzi 2008; Sturdee 2008).

### Why it is important to do this review

Current evidence does not support the safety of any hormonal therapy for women with a history of breast cancer. Therefore, a rigorous evaluation of non-hormonal alternatives is highly relevant.

The review by Nelson (Nelson 2006) did not find clear evidence of a different effect of therapies between postmenopausal women and women receiving tamoxifen. However, this conclusion was based on few studies with important methodological limitations. Considering the different physiology underlying hot flushes in women with breast cancer, it is important to evaluate this group separately. Based on the current available information it is premature to assume that effective therapies in postmenopausal women will have the same effect in women with a history of breast cancer.

## OBJECTIVES

The aim of this review was to assess the efficacy of non-hormonal interventions for the treatment of hot flushes in women with a history of breast cancer.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled clinical trials.

#### Types of participants

Women of any age experiencing any of the following.

1. Hot flushes due to endocrine therapy for breast cancer treatment. Endocrine therapy includes:

- surgical removal of the ovaries;
- hormonal manipulation leading to symptoms of estrogen deficiency (such as with tamoxifen, fulvestrant or aromatase inhibitors).

2. Hot flushes due to menopause secondary to treatment for breast cancer (chemotherapy or radiation therapy) and with or without concomitant endocrine therapy.

3. Hot flushes due to menopause in women with a history of breast cancer.

We included studies that evaluated a combination of women with a history of breast cancer and perimenopausal women if data from the breast cancer patients were presented separately or > 80% of participants had the above-mentioned criteria.

### Types of interventions

Any trial assessing a non-hormonal therapy compared to placebo or a non-treated control group.

Non-hormonal therapy was defined as any treatment which is known not to have proven or supposed hormonal activity (not estrogen-like).

We included the following.

- Pharmacological agents such as: vitamin E, clonidine, ergotamine-phenobarbital-belladonna, gabapentin, veralipride, SSRIs and SNRIs (venlafaxine, paroxetine, sertraline, fluoxetine, mirtazapine, trazodone).

- Non-pharmacological therapies such as: meditation, yoga, ayurveda, aromatherapy, acupuncture, magnetic therapy, applied relaxation, biofeedback, hypnosis, behavioural treatments (breathing exercises like paced respiration, aerobic exercise).

We excluded studies evaluating the following compounds because they have proven or possible estrogen-like mechanisms:

- plant phytoestrogens (i.e. isoflavones that are derived from soy or red clover);
- black cohosh, or *Cimicifuga racemosa* (Fitzpatrick 2003);
- tibolone.

### Types of outcome measures

Hot flushes were defined as a sudden sensation of heat or sweat centered on the face and upper chest.

#### Primary outcomes

- Frequency of hot flushes.
- Severity of hot flushes as reported through validated instruments such as patient diaries or other well-validated methods.
- Hot flushes scores were considered if they included frequency and severity of hot flushes.

#### Secondary outcomes

- Recurrence of breast cancer or survival, or both.
- Any side-effects of non-hormonal therapies or any effect not listed as an outcome and reported as a side-effect by the authors.



- Health-related quality of life as measured by any validated generic or condition-specific instrument.

## Search methods for identification of studies

### Electronic searches

1) The following electronic databases were searched with no language or publication restrictions.

(a) Cochrane Breast Cancer Group Specialised Register (22 August 2008). Details of the search strategy used by the Group for the identification of studies for the Register, and the procedure used to code references, are outlined in the Group's module ([www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html](http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html)). Studies with any of the keywords 'hot flush', 'hot flushes', 'hot flash', 'hot flashes', 'vasomotor symptoms', 'non-hormonal therapy', 'non hormonal therapy', 'selective serotonin reuptake inhibitors' or 'SSRI' were extracted for consideration.

(b) Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 3), [Appendix 1](#).

(c) CINAHL (1982 to August 2008), [Appendix 2](#).

(d) PsycINFO (1887 to August 2008), [Appendix 3](#).

(e) LILACS (1986 to August 2008), [Appendix 4](#).

(f) Considering that CENTRAL includes MEDLINE and EMBASE, we only made supplementary searches in these databases as old articles may not be well indexed (MEDLINE: January 1966 to December 2005, [Appendix 5](#); EMBASE: 1974 to April 2005, [Appendix 6](#)).

(g) WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (performed search 21 May 2010) (<http://apps.who.int/trialsearch/>), [Appendix 7](#).

### Searching other resources

2) Grey literature.

In order to identify articles potentially missed through the electronic searches, grey literature and unpublished studies, an expanded search was performed that included the following strategies:

(a) handsearching of reference lists of all retrieved articles, texts and other reviews on the topic;

(b) handsearching of conference proceedings of the ASCO Annual Meeting (2000 to 2004); and

(c) contacting experts for further information: the Cochrane Breast Cancer Review Group and key authors of publications included in this review.

## Data collection and analysis

We performed the analysis in accordance with the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 ([Cochrane Handbook](#)).

### Selection of studies

Titles and abstracts identified through the search strategy were scanned independently by two authors (GM and JC). If no abstract was available the full-text paper was obtained for detailed evaluation. Two authors (DC and GR) then independently assessed the full text of all potentially eligible trials against the above mentioned criteria for inclusion in the review.

### Data extraction and management

Two authors (DC and GR) independently extracted data using forms designed for this review. Extracted data included: number of participants allocated to each group, losses to follow up, exclusions and the reasons, number of participant centres, study setting, baseline characteristics of patients (i.e. age, breast cancer status, tamoxifen use), intervention characteristics (i.e. dose and duration), frequency of hot flushes, severity, score, quality of life and adverse effects.

### Assessment of risk of bias in included studies

The risk of bias of the included studies was assessed by two authors (DC and GR) using the criteria established in the Cochrane Handbook for Systematic Reviews of Interventions ([Cochrane Handbook](#)). A third author (TP) resolved any discrepancies.

### Measures of treatment effect

Most outcomes were presented as continuous data. For the majority of studies it was not possible to directly obtain the standard deviations of the outcomes from the study reports, since there was great inconsistency in the way data were presented. We tried to calculate standard deviations from standard errors, confidence intervals or P values. When it was not possible, we contacted authors in order to obtain suitable data for meta-analysis.

### Unit of analysis issues

We included both parallel and cross-over randomized controlled trials. In cross-over studies we included data from both the first period and the cross-over period since a carry-over effect was not demonstrated in any of the studies.

### Dealing with missing data

We analysed only the available data and addressed the potential impact of missing data on the findings of the review in the [Discussion](#) section. We did not conduct other approaches in order to handle missing data.

### Assessment of heterogeneity

We planned to qualitatively examine heterogeneity between studies for the treatment effect of each intervention by inspecting the distribution of point estimates for the effect measure and the overlap in their confidence intervals on a forest plot. Quantitatively, we considered that a Chi<sup>2</sup> statistic (Q statistic) with  $P < 0.10$  or the inconsistency between studies (I<sup>2</sup> statistic) greater than 40% as evidence of relevant heterogeneity.

### Assessment of reporting biases

Due to the small number of studies included in each category, funnel plots or other ways of investigating publication bias were not performed. Considering that all the studies reported the main outcomes there was little reason to suspect selective reporting.

### Data synthesis

When applicable, we carried out meta-analysis of outcome measurements made on the same scale and considered the measure as a mean difference (MD) with 95% confidence interval (CI). We used the fixed-effect inverse variance model to estimate the pooled measure of treatment effect.

### Subgroup analysis and investigation of heterogeneity

Since we were unable to pool the results, we could not perform subgroup analyses.

### Sensitivity analysis

We did not perform sensitivity analyses due to the small number of studies included in each group and the impossibility of pooling results.

## RESULTS

### Description of studies

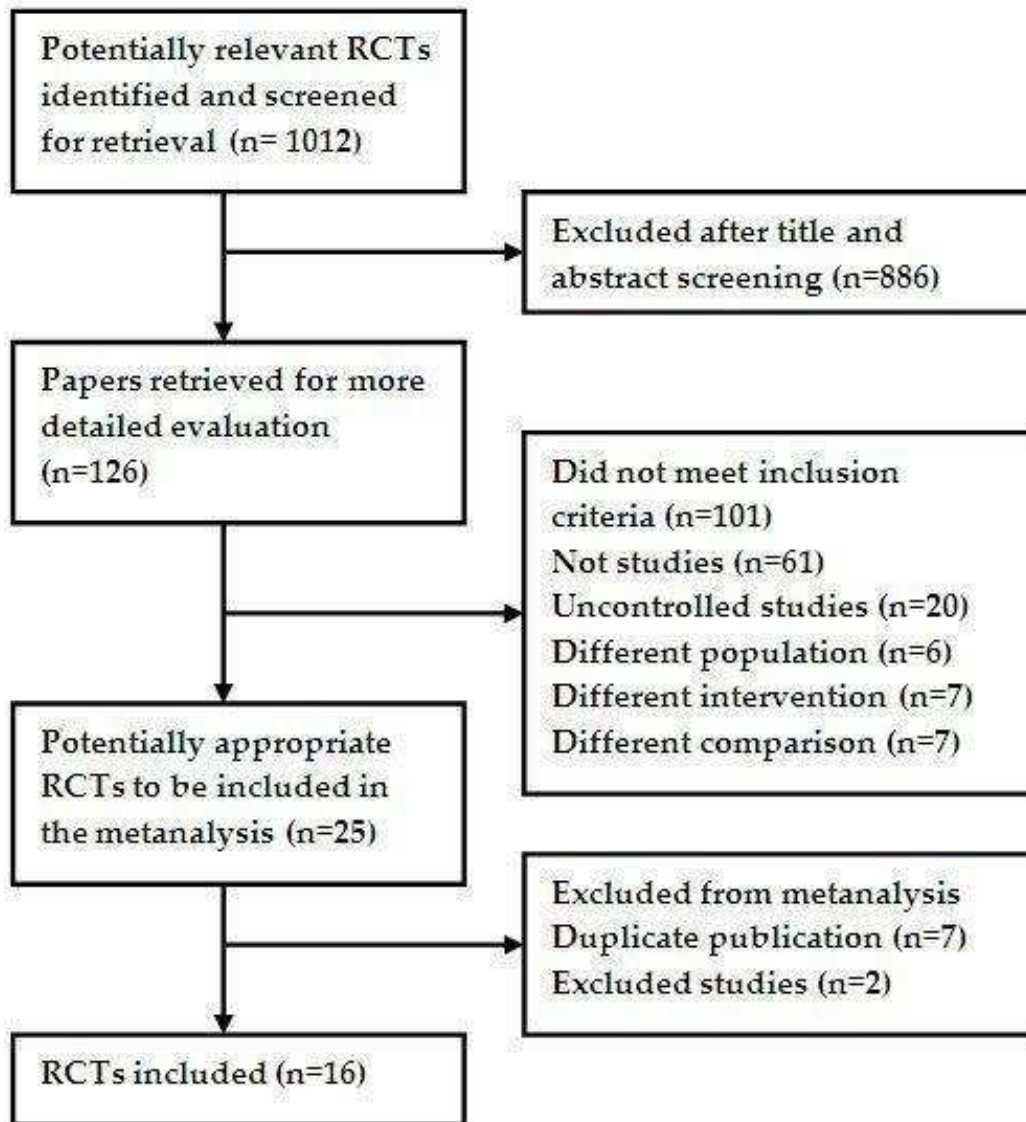
See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#).

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#)

### Results of the search

The comprehensive literature search retrieved 1012 references that were subsequently screened. Of these, 126 were potentially eligible and the full-text reports were evaluated. We excluded 101 papers that did not meet our inclusion criteria for reasons detailed in [Figure 1](#) and considered for inclusion a total of 25 references reporting on trials. Seven references corresponded to preliminary results of included studies or duplicate publications. We excluded two trials that initially met our criteria, for reasons detailed in the table of [Excluded studies](#). Therefore, the review included 16 studies reported in 15 references. For a detailed description of the search process see the QUORUM flow diagram ([Figure 1](#)).

Figure 1. Quorum flow diagram



## Included studies

Two studies did not address the proportion of women with a history of breast cancer, so it was not possible to be certain if our criterion of at least 80% of participants having breast cancer history was met (Loprinzi 2000; Loprinzi 2002). The author of both studies was contacted and confirmed that breast cancer status was not assessed, however a substantial proportion of patients received tamoxifen (54% and 69%). Therefore, it was likely that women with a history of breast cancer constituted the majority of the included participants. Since our criterion was an arbitrary limit we decided to include both studies, as opposed to the guidelines provided by the recent version of the Cochrane Handbook (Cochrane Handbook 5.0.2).

Of the included studies, six evaluated the SSRI and SNRI antidepressants fluoxetine (Loprinzi 2002), paroxetine (Stearns 2005), sertraline (Kimmick 2006) and venlafaxine (Carpenter 2007a; Carpenter 2007b; Loprinzi 2000); two studies evaluated clonidine, one using a transdermal patch (Goldberg 1994) and the other an oral formulation (Pandya 2000); one study evaluated gabapentin (Pandya 2005); and one vitamin E tablets (Barton 1998). Six studies tested non-pharmacological interventions: one study evaluated magnetic therapy (six magnetic devices attached to participant's skin, placed over acupuncture or acupressure sites) (Carpenter 2002); two assessed relaxation therapies (occupational therapist-guided relaxation consisting of stress management, written information about stress, deep breathing techniques, muscle relaxation and guided imagery) (Fenlon 1999; Fenlon 2008); one acupuncture (eight treatment sessions, 19 acupuncture points) (Deng 2007); and two homeopathy (one study evaluated a single homeopathic remedy in one group and Hyland's menopause formula in a second group, and the other study evaluated homeopathic medicines in tablet, granule or liquid form, prepared by a single pharmacy) (Jacobs 2005; Thompson 2005).

Four studies included more than one active treatment arm (Jacobs 2005; Loprinzi 2000; Pandya 2005; Stearns 2005). Nine studies had a cross-over design (Barton 1998; Carpenter 2002; Carpenter 2007a; Carpenter 2007b; Deng 2007; Goldberg 1994; Kimmick 2006; Loprinzi 2002; Stearns 2005).

The number of participants per study ranged from a minimum of 15 to a maximum of 420, with a median of 85. Thirteen studies included exclusively women with a history of breast cancer (Barton 1998; Carpenter 2002; Carpenter 2007a; Carpenter 2007b; Deng 2007; Fenlon 1999; Fenlon 2008; Goldberg 1994; Jacobs 2005; Kimmick 2006; Pandya 2000; Pandya 2005; Thompson 2005) and three included both women with a history of breast cancer, women at high risk of breast cancer or had concerns about breast cancer (Loprinzi 2000; Loprinzi 2002; Stearns 2005). Three studies included only women using tamoxifen (Goldberg 1994;

Kimmick 2006; Pandya 2000). In the remaining studies, tamoxifen use ranged from 51% to 80% of women. Aromatase inhibitors use was reported in only two studies, where it ranged from 6% to 23% (Deng 2007; Stearns 2005). In seven studies the setting was not clearly reported (Barton 1998; Carpenter 2002; Goldberg 1994; Jacobs 2005; Kimmick 2006; Loprinzi 2000; Loprinzi 2002). The rest of the studies were performed mainly in oncology or breast cancer referral clinics. One study was conducted in the outpatient department of an homeopathic hospital (Jacobs 2005). The duration of the studies ranged from three days to one year.

All studies reported on frequency (mostly number of hot flushes per day) and some numeric measure of severity of hot flushes with the exception of one study that reported on frequency only (Deng 2007). The same hot flush severity score (number of hot flushes per day x severity on a scale of 1 to 4, with 4 the maximum severity) was used in eight studies (Barton 1998; Fenlon 2008; Goldberg 1994; Jacobs 2005; Kimmick 2006; Loprinzi 2000; Pandya 2000; Stearns 2005). Quality of life was measured on different scales and was inconsistently reported. The majority of trials did not report on adverse effects in detail.

## Excluded studies

See: the table [Characteristics of excluded studies](#)

One study was of a program that included some drugs with possible hormonal action was excluded because data did not allow us to discriminate which participants received the different drugs (Ganz 2000).

One trial in which women were randomised to Shugan-liangxue compound was excluded because there was too little information on the compound to be sure of its non-hormonal mechanism, and we did not find published literature to support the safety of this compound in women with breast cancer (Li 2006).

## Risk of bias in included studies

The 'Risk of bias' tables for each study are given in the table [Characteristics of included studies](#).

## Allocation

All studies were randomized but in four the method was not described (Carpenter 2002; Fenlon 1999; Goldberg 1994; Kimmick 2006).

Concealment was rated as adequate in nine (Carpenter 2007a; Carpenter 2007b; Deng 2007; Fenlon 1999; Fenlon 2008; Jacobs 2005; Pandya 2000; Stearns 2005; Thompson 2005) and unclear in the other seven studies.

## Blinding

Participants were blinded to the intervention in all but the two studies of relaxation therapy (Fenlon 1999; Fenlon 2008). In the study of acupuncture (Deng 2007) the acupuncturist was not blinded but the other care givers were. Blinding status of other participants was described in six studies (Barton 1998; Carpenter 2007a; Carpenter 2007b; Deng 2007; Loprinzi 2000; Thompson 2005). Given that the majority of outcomes were self assessed, we generally considered participants and providers for blinding (instead of recollectors or assessors) in order to develop the judgment on quality in the 'Risk of bias' tables.

## Incomplete outcome data

All studies based their analyses on the patients with complete data by the end of the study. Completeness of follow up ranged from 60% to 97%. Only two studies evaluated the effects of missing data on results (Loprinzi 2000; Pandya 2000).

## Selective reporting

All studies reported the outcomes that we considered most important. There was no reason to suspect selective reporting of outcomes.

## Other potential sources of bias

We did not identify any additional sources of bias.

## Effects of interventions

See: [Summary of findings for the main comparison](#) SoF vitamin E versus placebo; [Summary of findings 2](#) SoF gabapentin versus placebo

There was great inconsistency in the way of reporting continuous outcomes. We could not obtain suitable data for meta-analysis from authors so we presented measures of treatment effect using data as reported in the study reports.

## Effects on hot flushes frequency and severity score

### Clonidine

We found two studies (252 assessable participants) evaluating a transdermal and an oral formulation of clonidine.

One study (Goldberg 1994), including 89 assessable patients, tested a transdermal patch. At week four, the hot flush frequency in the intervention arm, as a median, had a reduction from baseline of 44% compared to the reduction in the placebo arm of 27% ( $P = 0.04$ ). The median combined severity score decreased 56% from baseline with the intervention and 30% with placebo ( $P = 0.04$ ). For the effect after cross-over, the difference at week eight

was reported as significant for both frequency ( $P < 0.0001$ ) and the combined severity score ( $P = 0.0006$ ).

A second study (Pandya 2000) that evaluated an oral formulation included 163 assessable patients. At week eight, the hot flush frequency had a mean reduction from baseline of 38% in the treatment arm compared to 24% with placebo (difference in percentage reduction of means of 14%; 95% CI 3% to 27%;  $P = 0.006$ ). The severity score was reduced by 45% with clonidine and 26% with placebo ( $P = 0.006$ ).

### Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)

Six studies (Carpenter 2007a; Carpenter 2007b; Kimmick 2006; Loprinzi 2000; Loprinzi 2002; Stearns 2005) including 451 assessable women evaluated the effects of different SSRIs and SNRIs (venlafaxine, paroxetine, fluoxetine and sertraline).

Even though all studies measured the same outcomes, the way of reporting them precluded any possibility of pooling (reasons detailed in [Measures of treatment effect](#)), and each study was reported separately.

Venlafaxine (extended release formulation) was evaluated in three different doses in three studies.

Loprinzi 2000 included 191 assessable participants who received three different doses (37.5, 75 and 150 mg) of venlafaxine. The placebo group had a median decrease from baseline of 19% in the frequency of hot flushes at week four (95% CI 14 to 28). The three active arms had greater reductions: 30% for the low dose (95% CI 22 to 53;  $P < 0.001$ ), 46% for the intermediate dose (95% CI 36 to 63;  $P < 0.001$ ), and 58% for the highest dose of venlafaxine (95% CI 42 to 67;  $P < 0.001$ ).

The severity score reduction was also superior in the active arms. The median decrease from baseline was 27% in the placebo group (95% CI 11 to 34), 37% in the low-dose arm (95% CI 26 to 54;  $P < 0.001$ ), 61% in the intermediate dose arm (95% CI 50 to 68;  $P < 0.001$ ) and 61% in the high-dose arm (95% CI 48 to 75;  $P < 0.001$ ) versus placebo.

Another two studies on venlafaxine, reported together in a single paper, evaluated two doses (37.5 and 75 mg) for 12 weeks.

The low-dose study (Carpenter 2007a) included 31 assessable patients. In the treatment group, the mean daily frequency measured by skin conductance monitoring decreased by 1.7 hot flushes per day (22%) compared with baseline whereas in the placebo group no change from baseline was observed (adjusted mean difference  $P < 0.001$ ). Similar reductions were observed in the frequency measured by written diary entries (mean decrease from baseline 42% with the low dose versus 18% with placebo;  $P < 0.001$ ) and electronic event markers (mean decrease from baseline 41% with the low dose versus 22% with placebo;  $P < 0.001$ ). The mean severity decreased 7% from baseline in the treatment group and increased 6% with placebo ( $P < 0.001$ ).

The 75 mg venlafaxine study (Carpenter 2007b) included 15 assessable patients. Compared with baseline, the mean daily frequency measured by skin conductance monitoring decreased by

one hot flush per day (14%) in the treatment group and increased by 1.4 hot flushes per day (13%) in the placebo group ( $P = 0.013$ ). Frequency measured from written diary entries (mean decrease from baseline 25% versus 4%;  $P = 0.001$ ) and electronic event markers (mean change from baseline 4% decrease versus 22% increase;  $P < 0.001$ ) were also lower in the treatment group. The mean severity decreased by 27% from baseline in the treatment group and 5% in the placebo group ( $P < 0.001$ ).

One study evaluating fluoxetine at a dose of 20 mg versus placebo (Loprinzi 2002) included 68 assessable patients in a cross-over trial with two periods of four weeks each. After eight weeks, the active period was superior to the placebo period with a median decrease from baseline of 1.5 hot flushes per day (19%;  $P = 0.01$ ) and 3.1 score units per day (24%;  $P = 0.02$ ) compared with placebo.

Stearns 2005 evaluated two different doses of paroxetine for eight weeks compared to placebo in 107 assessable participants in a cross-over trial. In the paroxetine periods hot flushes were reduced from baseline more than in the placebo periods regardless of the dose. In the 10 mg arms, the mean percentage reduction in hot flush frequency was 40.6% in the active period compared with 13.7% in the placebo period (mean difference 27.0%;  $P = 0.0006$ ). The mean percentage reduction in severity score was 45.6% in the active period compared to 13.7% in the placebo period ( $P = 0.0008$ ).

For patients in the 20 mg arm, the mean percentage reduction of hot flush frequency was 51.7% in the active period compared with 26.6% reduction in the placebo period (mean difference 25.2%;  $P = 0.002$ ). The mean percentage reduction in severity score was 56.1% in the active period compared with 28.5% in the placebo period ( $P < 0.001$ ).

One study used sertraline 50 mg versus placebo in 39 assessable participants (Kimmick 2006). The study was powered to evaluate complete resolution of hot flushes at six weeks of treatment. Because there were no cases of complete hot flush resolution the study was underpowered. A second period of six weeks was added to test the cross-over effect, however the dropout rate was high. In the primary analysis at week six, there was no difference in reduction from baseline for sertraline compared to placebo with a mean reduction from baseline of 1.6 daily hot flushes in the sertraline group and 1.5 in the placebo group ( $P = 0.9$ ). At week 12, no significant differences were found on hot flush frequency or score reductions from baseline. The group that switched to sertraline had a reduction, compared to week six, of 0.9 daily hot flushes; and the arm that switched to placebo had an increase of 1.5 daily hot flushes ( $P = 0.03$ ). The score was reduced by 3.2 points at week six in the sertraline group and 4.6 points in the placebo group ( $P = 0.7$ ). At week 12, the group that changed to sertraline had a reduction, compared with week six, of 1.7 points; and the arm that changed to placebo had an increase of 3.4 points ( $P = 0.03$ ). A mixed model analysis found no carry-over effects for the hot flush frequency ( $P = 0.25$ ) or score ( $P = 0.13$ ) and did not find any treatment effects for hot flush frequency ( $P = 0.73$ ) or hot flush

score ( $P = 0.68$ ).

### Vitamin E

One study including 105 assessable participants evaluated vitamin E 800 IU (Barton 1998). After four weeks of therapy there was no significant effect on the frequency of hot flushes (mean difference -0.15; 95% CI -2.45 to 2.16;  $P = 0.90$ ) nor on the severity score (mean difference -0.82; 95% CI -4.68 to 3.05;  $P = 0.68$ ).

### Gabapentin

One study including 347 assessable women evaluated two different doses of gabapentin (Pandya 2005). The frequency of hot flushes was reduced with the 900 mg/day dose of gabapentin (mean change -2.1; 95% CI -2.95 to -1.23). A lower dose (300 mg/day) did not achieve a significant effect (mean change -0.8; 95% CI -1.7 to 0.1). The same effects were observed on severity scores (low dose mean change -1.79; 95% CI -4.38 to 0.80 and high dose mean change -4.88; 95% CI -7.23 to -2.53).

### Non-pharmacological therapies

We identified six studies evaluating the effects of non-pharmacological therapies. Homeopathy and relaxation therapy were each evaluated in two studies, and a magnetic device and acupuncture in single studies.

The first study on homeopathy (Thompson 2005) included 45 assessable women who received a tailored homeopathic prescription or placebo. There were no significant effects observed in a four-item profile score that included two self-rated symptom items, an activity of daily living item and a general feeling of well-being item (mean difference -0.10; 95% CI -4.86 to 4.66).

The second study on homeopathy (Jacobs 2005) compared two forms of homeopathy (single or combination therapy) with placebo in 79 assessable participants. There were no statistical differences among comparisons for the frequency or severity score of hot flushes.

The first study on relaxation therapy (Fenlon 1999) included 16 women and found no significant differences in the effects of this treatment on the number of hot flushes per day (mean difference 0.50; 95% CI -1.23 to 2.23) nor the severity score (mean difference 0.64; 95% CI -2.10 to 3.38). A larger study by the same author (Fenlon 2008) included 150 women. The number of hot flushes decreased at one month (median difference 7 hot flushes per week; 95% CI 4 to 7;  $P < 0.001$ ) but the effect was not significant at three months (median difference 5 hot flushes per week; 95% CI 0 to 10;  $P < 0.06$ ). Severity of hot flushes was also lower at one month (median difference 0.54; 95% CI 0.11 to 1.01;  $P = 0.01$ ) but the difference became non-significant at three months (median difference 0.56; 0.02 to 1.18;  $P = 0.05$ ).

A study including 11 women (Carpenter 2002) evaluated a magnetic device compared to a placebo device. There was no difference between the arms in terms of number of hot flushes (mean difference 1.63; 95% CI -5.69 to 8.95).

One study with 67 assessable women (Deng 2007) evaluated real

versus sham acupuncture. There was no difference between the arms in the frequency of hot flushes per day (mean difference - 0.10; 95% CI -3.63 to 3.43).

### **Effects on quality of life**

Twelve of 16 included studies measured quality of life but the quality of reporting was very poor. We were not able to pool these results because the studies used different scales (Hot Flash-related Daily Interference Scale: [Carpenter 2002](#); General Health Questionnaire of 60 questions: [Fenlon 1999](#); SF 36 Quality of Life Score: [Jacobs 2005](#); two single-item global quality-of-life questions: [Loprinzi 2000](#); Uniscale global quality-of-life instrument: [Loprinzi 2002](#); Single question rating overall QOL from 1 to 10: [Pandya 2000](#); The Center for Epidemiologic Studies Depression Scale, seven anxiety items of the Hospital Anxiety and Depression Scale, the Medical Outcomes Study Sleep Problems Index, MOS Sexual Problems Index and a self-rating questionnaire of overall health-related QOL standardized in the EuroQOL Linear Rating Scale: [Stearns 2005](#); 36-item Medical Outcomes Survey with its eight subscales: [Carpenter 2007a](#); [Carpenter 2007b](#); European Organization for Research and Treatment of Cancer Quality of Life Questionnaire: [Thompson 2005](#); Functional Assessment of Cancer Therapy-Breast: [Kimmick 2006](#); Functional Assessment of Cancer Therapy-Endocrine subscale: [Fenlon 2008](#)).

Among the studies that used clonidine, one did not report on quality of life ([Goldberg 1994](#)) and the other found no differences compared with the control group ([Pandya 2000](#)). In the six studies using SSRIs and SNRIs, no significant differences in quality of life measures were found except in the study using venlafaxine ([Loprinzi 2000](#)), where an improvement in quality of life scores was seen among the participants taking the drug; this was independent of the dose. In the two studies evaluating the role of homeopathy, one did not find any differences ([Thompson 2005](#)) and the other found an improvement in quality of life scores in women using single or combination homeopathy ([Jacobs 2005](#)). The other non-pharmacological intervention trials ([Carpenter 2002](#); [Fenlon 1999](#); [Fenlon 2008](#)) did not find differences between the treatment and control groups. The gabapentin ([Pandya 2005](#)), vitamin E ([Barton 1998](#)) and acupuncture ([Deng 2007](#)) trials did not report on quality of life outcomes.

### **Effects on patient preferences**

Five of nine studies with a cross-over design measured patient preference for one or other of the treatments after both periods had

been completed ([Barton 1998](#); [Goldberg 1994](#); [Kimmick 2006](#); [Loprinzi 2002](#); [Stearns 2005](#)).

The preference for vitamin E or placebo was 32% or 29%, and 38% did not have a preference ([Barton 1998](#)). Preference for clonidine, placebo or no preference was expressed by 48%, 25% and 27% of women ( $P = 0.02$ ) in one study ([Goldberg 1994](#)). Sertraline or placebo was preferred by 49% or 11% ( $P = 0.006$ ); 41% had no preference ([Kimmick 2006](#)). In the case of fluoxetine or placebo or none, the preferences were 47%, 22% or 31% ( $P = 0.14$ ) ([Loprinzi 2002](#)). In a study with two doses of paroxetine, 60% of patients wished to continue on the 10 mg per day dose and 46% on the 20 mg per day dose ([Stearns 2005](#)).

### **Adverse effects**

Thirteen of 16 included studies mentioned adverse effects. No major adverse effects were reported. Overall the quality of the adverse effect reporting was low and it was not possible to calculate risk estimates.

The clonidine dermal patch was associated with an increased frequency of dry mouth, constipation, dizziness and itching under the patch ([Goldberg 1994](#)). Clonidine significantly increased sleep disorders ([Pandya 2000](#)). Women in the studies evaluating venlafaxine ([Carpenter 2007a](#); [Carpenter 2007b](#); [Loprinzi 2000](#)), paroxetine ([Stearns 2005](#)) and sertraline ([Kimmick 2006](#)) reported an increased incidence of nausea. Venlafaxine also increased the risk of decreased appetite, mouth dryness and constipation, with a higher incidence in women taking the higher doses. Sertraline was associated with a slight increase in fatigue and malaise, diarrhoea, and anxiety or nervousness. The study that used fluoxetine ([Loprinzi 2002](#)) did not find differences between groups in the incidence of adverse effects.

The vitamin E study ([Barton 1998](#)) did not find any differences in adverse effects. Gabapentin caused an increase in sleeping disorders but the study obtained data on adverse effects only if these were the reason for withdrawing, so they are likely to be underestimated ([Pandya 2005](#)).

No differences between the different study groups were found for the studies with homeopathy ([Jacobs 2005](#); [Thompson 2005](#)). Acupuncture was associated with minor adverse effects such as slight bleeding or bruising at the needle site ([Deng 2007](#)).

Three studies of non-pharmacological interventions ([Carpenter 2002](#); [Fenlon 1999](#); [Fenlon 2008](#)) did not report on the occurrence of adverse effects.

## ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Gabapentin compared to Placebo for hot flushes in women with a history of breast cancer						
<b>Patient or population:</b> patients with hot flushes in women with a history of breast cancer						
<b>Settings:</b> Ambulatory clinic						
<b>Intervention:</b> Gabapentin						
<b>Comparison:</b> Placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Gabapentin				
<b>Frequency of hot flushes</b> Number of hot flushes per day (follow-up: 8 weeks)	The mean frequency of hot flushes in the control groups was <b>8.8 HF per day</b>	The mean Frequency of hot flushes in the intervention groups was <b>4.21 lower</b> (5 to 3.42 lower) <sup>1</sup>		233 (1)	⊕⊕⊕⊕ <b>high</b> <sup>2,3</sup>	
<b>Hot flushes score</b> Number of HF x severity (from 1 to 4) (follow-up: 8 weeks)	The mean hot flushes score in the control groups was <b>19.9 points</b>	The mean Hot flushes score in the intervention groups was <b>9.94 lower</b> (12.02 to 7.86 lower)		233 (1)	⊕⊕⊕⊕ <b>high</b> <sup>2,3</sup>	

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.



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<sup>1</sup> Effect estimates correspond to data for 900 mg dose

<sup>2</sup> Allocation concealment unclear. A large proportion of patients were not assessable at the end of the study.

<sup>3</sup> 900 mg dose achieved a larger effect than 300 mg dose.

## DISCUSSION

### Summary of main results

This review shows that some non-hormonal therapies have a mild to moderate effect in reducing the frequency and intensity of hot flushes in women with a history of breast cancer. The 16 included studies assessed eight different interventions (four pharmacological and four non-pharmacological).

Due to the inconsistency in the way data were presented, we were not able to calculate a pooled estimate of the effects of the different interventions and so we do not know the relative magnitude of the benefit for each treatment.

The evidence on clonidine shows a statistically significant reduction in hot flushes in both studies. Clonidine however also produces frequent adverse effects that may outweigh any benefit.

All the studies on SSRIs and SNRIs had a statistically significant effect favoring the intervention. Even though this response was far from complete, these drugs have only minor adverse effects and their safety profile has been well established from research in other clinical settings (Gartlehner 2008). Added to their low cost and widespread access, this makes them an attractive alternative for women with a history of breast cancer. It should be noted, however, that paroxetine may interfere with the metabolism of tamoxifen and is not recommended in women taking this drug for their breast cancer (Jin 2005).

We found one small study of vitamin E that showed no significant effect of this treatment.

The only study of gabapentin evaluated two different doses, with a significant response for the 900 mg/day dose but not for a lower dose. The 900 mg/day dose reduced hot flushes by 2.1 per day. This effect constitutes a greater reduction than the reductions achieved by the other interventions included in this review but no direct comparisons are available.

From the non-pharmacological therapies, two studies on homeopathy, one on magnetic devices and one on acupuncture showed no significant benefit. Two studies evaluating a very similar form of relaxation therapy had different results. One of them, with a small sample size, showed no benefit. The other trial with a bigger sample size demonstrated a reduction of one hot flush per day at one month, but this benefit became non-significant by the third month.

### Overall completeness and applicability of evidence

It is important to note that our review is not designed to compare the effects of different therapies. Our goal was to determine whether any of these non-hormonal interventions were effective and therefore we did not include studies that directly compared

active interventions. Therefore, indirect comparisons from this review must be interpreted with caution.

We found very limited evidence supporting non-pharmacological alternatives such as homeopathy, magnetic devices and acupuncture for the treatment of hot flushes. Even though all of these studies had limited power to show an effect, it is important to note that none of the studies showed a significant benefit.

The applicability of the results of this review is limited in several ways. First, the review did not include direct comparisons between treatments and, as discussed, it is not possible to draw conclusion on which intervention is best or which is the optimum dose for a particular drug. Second, all studies provided information for short periods of follow up (maximum 12 weeks). Therefore, inferences about chronic use of the interventions should be made carefully. Third, the paucity of data on adverse effects makes it difficult to perform an adequate assessment of benefit to risk.

### Quality of the evidence

The main limitation in the quality of the evidence from this review relates to the loss of follow up, which ranged from 3% to 40% in the included studies. The loss of this data could potentially result in an overestimation of the true effect, by not considering participants who possibly had less benefit or no benefit at all. Furthermore, losses to follow up were pronounced in those studies evaluating the interventions that appeared to be more effective. For instance, 17% of the participants in the study of gabapentin were not assessable at the end of the study. On the other hand, one point of reassurance is the dose response gradient between low and higher doses, even though more women could not be assessed in the low-dose group. An important number of participants in the SSRI/SNRI studies were also not assessable (range 8% to 40%). The fact that the larger study is the one with better follow up (Loprinzi 2000) makes the estimate less prone to bias.

An important limitation of the studies on relaxation therapy is the lack of blinding. The effect of relaxation therapy was mild to moderate and was not maintained at three months. It is very difficult to be certain if the benefit obtained in one of these studies is real or could be explained by its quality limitations, particularly a placebo effect.

### Agreements and disagreements with other studies or reviews

We have no knowledge of other systematic reviews evaluating non-hormonal therapies alone in women with a history of breast cancer. Four previous systematic reviews looked at the effects of non-hormonal therapies on hot flushes and included a combination of postmenopausal women and women with a history of breast cancer (Bordeleau 2007; Cheema 2007; Nedrow 2006; Nelson 2006). These reviews included some therapies that we consider to be hor-

monal (for example phytoestrogens, black cohosh, tibolone). The conclusions yielded from these reviews, with a broader question, were similar to those that we obtained, that is a mild to moderate benefit from some pharmacological treatments but little or no effect from non-pharmacological options.

Although the conclusions from the reviews with a broader question and our review are similar, we think it is premature to assume that hot flushes can be managed in the same way in postmenopausal women and women with a history of breast cancer. Aside from the biological and psychological differences between these two populations, the studies on the latter represent a small proportion of the total and the amount of evidence on each group of interventions is very limited.

## AUTHORS' CONCLUSIONS

### Implications for practice

Based on a limited number of studies, it appears that clonidine has some benefit in relieving hot flushes in women with a history of breast cancer but with side-effects. The epidermal patch, in particular, was associated with dry mouth, constipation, dizziness and itching. Any recommendation for its use would need to consider the impact of hot flushes on quality of life against the potential side-effects for an individual.

The benefits shown with SSRIs and SNRIs are promising, particularly due to their good safety profile. However, since the absolute benefit is rather small, the costs and each woman's preference should guide recommendations.

Based on a single study, gabapentin also shows benefit in high doses, but not with lower doses. There is a trade-off between this potentially greater benefit, cost considerations and the need for more frequent administration (three times a day).

Vitamin E was not effective. Considering there is no plausible mechanism for an effect of this treatment on hot flushes, it should not be considered as an alternative therapy for this condition.

There is little evidence on non-pharmacological therapies and the majority of studies did not show any benefit. The only exception is relaxation therapy, which showed a mild effect in the short term. This benefit was not sustained at three months. The risk of bias of

the study showing benefit was high so it is difficult to be certain if there is a real effect.

In summary, the evidence supports three pharmacological and probably one non-pharmacological intervention to reduce the frequency and intensity of hot flushes in women with a history of breast cancer.

### Implications for research

In women with breast cancer and hot flushes there are some questions that still remain regarding which class of drugs, and which drug within a class (that is SSRIs and SNRIs) or which dose is more effective.

The effect of combined therapies is also an important factor which should be considered in future research, particularly as none of the evaluated treatments fully resolved symptoms.

Research on other pharmacological and non-pharmacological treatments is clearly needed.

Research on some complementary therapies is also needed. Even though there is some evidence on the potential hormonal mechanism of some agents (e.g. black cohosh, soy products) there is still no consensus regarding their clinical relevance. These agents are widely used in clinical practice.

The following should be included and reported on in future trials.

- Validated scores of severity of hot flushes, like the one employed in the majority of trials of pharmacological therapies. Outcomes should be measured in the long term, ideally longer than three months.
- Numbers of participants developing individually identified adverse effects.
- Efforts should be made to obtain complete follow-up data. If this is not achieved, losses must be taken into account in the analyses.
- The method of reporting continuous outcomes is critical for systematic reviews. A consensus in the way of reporting hot flushes is required.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Barton 1998

Methods	Cross-over design. Randomization with method of dynamic allocation. Stratified by age, current tamoxifen use, duration of hot flushes, average frequency of flushes, and current multivitamin use. Described as double-blind.	
Participants	Country: United States Setting: not described. Inclusion criteria: Over 18 years with a history of breast cancer. At least 14 episodes of hot flushes per week, for at least one month. Life expectancy of six months. Performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale. Exclusion criteria: Current or planned therapy with chemotherapy, androgens, estrogens, progestational agents, corticosteroids, or other agents used for treating hot flushes. Use of multivitamin tablets over two times per day or over 60 IU of vitamin E. Pregnant or lactating women. History of bleeding tendencies, immune deficiencies, or thrombophlebitis. Characteristics of participants: Age range or mean not described: 66% were older than 50 years. Mean daily hot-flush frequency: 6.5 times per day. 60% on tamoxifen. Number of participants/assessable participants: 120/105 for first period. Numbers of assessable participants in treatment first/control first arms at the end of the study (not reported for the first period): 54/50	
Interventions	Arm 1: Vitamin E succinate 800 IU daily Arm 2: Identical-appearing placebo  Study duration: Four weeks for each period. No washout between cross-over periods.	
Outcomes	Hot-flush frequency. Hot-flush severity. Hot-flush score (number of hot flushes per day x severity in a scale of 1 to 4, being 4 the maximum severity). Patient preference during each period of the cross over.	
Notes	5 of 125 participants were excluded after randomization, and before starting study medication. Only the first period of the cross-over study analysed.	
<i>Risk of bias</i>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>

**Barton 1998** (Continued)

Adequate sequence generation?	Yes	Stratified randomization with method of dynamic allocation.
Allocation concealment?	Unclear	B - Unclear.
Blinding? All outcomes	Yes	Described as double-blind, but not clear if assessors or researchers are blinded.
Incomplete outcome data addressed? All outcomes	Unclear	15 of 120 (12.5%) of women did not provide data for the first period. The analyses followed the intention-to-treat principle, except for five patients on the placebo arm who withdrew before starting study medication, and were excluded from analysis.
Free of selective reporting?	Yes	Main outcomes are reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Carpenter 2002**

Methods	Cross-over design. Method of randomization not described. Patients blinded. Other participants not clear.
Participants	Country: United States Setting: Cancer center. Inclusion criteria: Over 18 years of age with a first-time diagnosis of breast cancer experiencing daily hot flushes. No history of other types of cancer. Free of cancer or currently completing treatment for breast cancer. Postmenopausal. Exclusion criteria: Contraindications for magnets (including presence of implanted devices). Use of other hot flushes treatments. Characteristics of participants: Mean age 57 years. Baseline hot flush frequency: mean 10 hot flushes per day. 55% on tamoxifen.  Number of participants/assessable participants: 15/11. Numbers of assessable participants in treatment first/control first arms: 6/5.



**Carpenter 2002** (Continued)

Interventions	<p>Arm 1: Six magnetic devices attached to participants skin placed over acupuncture/acupressure sites used to balance yin energy (female, calming) and treat hot flushes. Acupuncturists located the sites and a nurse installed the devices. Magnetic devices consisted of four separate magnets of alternating polarity.</p> <p>Arm 2: Identical placebo devices.</p> <p>Study duration: 72 hours for each period. Ten days washout between cross-over periods.</p>
Outcomes	<p>Frequency of hot flushes measured by sternal skin conductance.</p> <p>Frequency, severity (from 0 to 10) and bothering (from 0 to 10) of hot flushes measured by hot flushes diary.</p> <p>Hot Flush-related Daily Interference Scale (HFRDIS).</p> <p>Acceptability of the device.</p>
Notes	Only the first period of the cross-over study analysed.

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method not described.
Allocation concealment?	Unclear	B - Unclear.
Blinding? All outcomes	Unclear	Participants blinded. Other participants not clear.
Incomplete outcome data addressed? All outcomes	Unclear	4 of 15 (27%) of women did not provide data. The analyses followed the intention-to-treat principle.
Free of selective reporting?	Unclear	Main outcomes are reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Carpenter 2007a**

Methods	<p>Cross-over design.</p> <p>Computer-generated randomization sequence (without blocking or stratification).</p> <p>Participants, providers and investigators blinded.</p>
Participants	<p>Country: United States</p> <p>Setting: Cancer center clinics</p> <p>Inclusion criteria:</p> <p>Adult women with a history of breast cancer, experiencing daily hot flushes (1 per day), disease-free and functioning, postmenopausal or using a method of birth control, nondepressed.</p>

**Carpenter 2007a** (Continued)

	<p>Exclusion criteria: History of other cancer, tamoxifen or aromatase inhibitor use, antidepressants use, hot flush treatment within the past four weeks, pregnant or lactating.</p> <p>Characteristics of participants: mean age 50.5 years 51% taking endocrine therapy. Baseline frequency of hot flushes: between 6 (written diary) and 7.7 (event marker associated with skin conductance monitor) per day.</p> <p>Number of participants/assessable participants: 52/31. Numbers of assessable women in treatment first/placebo first arms:16/15.</p>
Interventions	<p>Arm 1: Venlafaxine 37.5 mg daily (extended release formulations). Arm 2: Identical-appearing placebo. Study duration: Six weeks for each period. No washout between cross-over periods.</p>
Outcomes	<p>Frequency of hot flushes (24-hour ambulatory sternal skin conductance monitoring and written diaries once a week to tabulate electronic events). Severity of hot flushes, rated from 0 (not at all) to 10 (extremely severe). Bother of hot flushes, rated from 0 (not at all) to 10 (extremely bothersome). Hot flush interference with daily activities, and quality of life (Hot Flash-Related Daily Interference Scale). Depressive symptoms were evaluated through a Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders at week 6, and the 17-item Hamilton Rating Scale-Depression (Ham-D) at week 2, 4 and 6. Negative affect index (combination of four questionnaires to measure anxiety, depression and other negative mood states). Fatigue (Profile of Mood States Short Form fatigue subscale). Sleep quality (The Pittsburgh Sleep Quality Index). Quality of life (36-item Medical Outcomes Survey with its eight subscales). Blood pressure and other side-effects.</p>
Notes	Two studies described in the same article (Carpenter 2007a; Carpenter 2007b).

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated sequence.
Allocation concealment?	Yes	A - Clear.
Blinding? All outcomes	Yes	Participants, providers and investigators blinded. Verification of blinding at the end of the study.
Incomplete outcome data addressed? All outcomes	No	21 of 52 (40%) women did not provide data. The analyses followed the intention-to-treat principle.

**Carpenter 2007a** (Continued)

Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Unclear	Yes

**Carpenter 2007b**

Methods	Cross-over design. Computer-generated randomization sequence (without blocking or stratification). Participants and providers blinded.
Participants	Country: United States Setting: Cancer center clinics. Inclusion criteria: Adult women with a history of breast cancer, experiencing daily hot flushes (1 per day), disease-free and functioning, postmenopausal or using a method of birth control, nondepressed. Exclusion criteria: History of other cancer, tamoxifen or aromatase inhibitor use, antidepressants use, hot flush treatment within the past four weeks, pregnant or lactating. Characteristics of participants: mean age 53 years 63% taking endocrine therapy. Baseline frequency of hot flushes: between 6 (written diary) and 7.7 (Event marker associated with skin conductance monitor) per day  Number of patients/assessable women: 18/15 Numbers of assessable women in treatment first/placebo first arms: 7/8
Interventions	Arm 1: venlafaxine 37.5 mg daily for one week, then venlafaxine 75 mg daily for four weeks, then venlafaxine 37.5 mg daily for one week (extended release formulations) Arm 2: Identical-appearing placebo Study duration: six weeks for each period. No washout between cross-over periods.
Outcomes	Frequency of hot flushes (24-hour ambulatory sternal skin conductance monitoring and written diaries once a week to tabulate electronic events). Severity of hot flushes, rated from 0 (not at all) to 10 (extremely severe). Bother of hot flushes, rated from 0 (not at all) to 10 (extremely bothersome). Hot flush interference with daily activities, and quality of life (Hot Flash-Related Daily Interference Scale). Depressive symptoms were evaluated through a Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders at week 6, and the 17-item Hamilton Rating Scale-Depression (Ham-D) at week 2, 4 and 6. Negative affect index (combination of four questionnaires to measure anxiety, depression and other negative mood states). Fatigue (Profile of Mood States Short Form fatigue subscale). Sleep quality (The Pittsburgh Sleep Quality Index). Quality of life (36-item Medical Outcomes Survey with its eight subscales). Blood pressure and other side-effects.

**Carpenter 2007b** (Continued)

Notes	Two studies described in the same article (Carpenter 2007a; Carpenter 2007b)	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Computer generated sequence
Allocation concealment?	Yes	A- Clear
Blinding? All outcomes	Yes	Participants, providers and investigators blinded. Verification of blinding at the end of the study.
Incomplete outcome data addressed? All outcomes	Unclear	3 of 18 (16%) women did not provide data. The analyses followed the intention-to-treat principle.
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Unclear	Yes

**Deng 2007**

Methods	Cross-over design. Randomization sequence generated by computer. Stratified by concurrent treatment, concurrent use of hot flush medication, baseline hot flushes, and menopausal status. Participants, researchers and others involved in patient care were blinded. Acupuncturists and research assistant not blinded.
Participants	Country: United States Setting: Cancer Center. Inclusion criteria: Women undergoing treatment for breast cancer with three or more hot flushes per day. Karnofsky performance score over 60 Exclusion criteria: Planned surgery, chemotherapy, radiotherapy or immunotherapy. Initiation or cessation of hormonal therapy during the trial or within three weeks before the trial. Pharmacologic treatment of hot flushes or any use of SSRIs. Skin infection. Acupuncture treatment in the six weeks prior to study. Acupuncture treatment for hot flushes in the previous six months. Characteristics of participants (Real/Sham): Median age 55 years Mean baseline hot flush frequency: 8.7/10

Deng 2007 (Continued)

	<p>93% postmenopausal.            Tamoxifen (48/33%), aromatase Inhibitors (19/30%), SSRIs (38/30%).            Number of participants/assessable participants: 72/67.            Numbers of assessable participants in treatment first/control first arms: 39/28.</p>	
Interventions	<p>Arm 1: Real acupuncture.            Arm 2: Sham acupuncture.</p> <p>Both treatments were administered twice-weekly (eight treatment sessions in weeks 1 through 4) in 19 points, for four weeks.            Sham and true acupuncture treatments were delivered by several licensed acupuncturists (not always by the same acupuncturist) with at least three years of formal postgraduate training, and 3 to 25 years of continuous practice.            Different needles in both group in order to provide real or sham acupuncture. No electrical stimulation or other interventions were applied.            The frequency and duration of the sham acupuncture intervention were identical to those of true acupuncture. External conditions were also identical (relaxation period before acupuncture, music and eye pillow).            Study duration: six weeks of treatment (only first period included in analysis).</p>	
Outcomes	<p>Hot flush frequency (diary).</p>	
Notes	<p>Only the participants in the sham acupuncture group were crossed over to the true acupuncture group at week seven. Only the first period of the cross-over study analysed.</p>	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Computer-generated sequence.
Allocation concealment?	Yes	A - Clear.
Blinding? All outcomes	Yes	Acupuncturist and research assistant not blinded. All other participants blinded.
Incomplete outcome data addressed? All outcomes	Unclear	5 of 72 (7%) did not provide data, withdrew or were excluded. Two participants in the real acupuncture group were not treated according to allocated and were excluded.
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	No	Baseline differences in baseline symptoms, and use of tamoxifen, aromatase Inhibitors and SSRIs.

**Fenlon 1999**

Methods	Parallel-group design. Method of randomization not described. Participants and providers not blinded.
Participants	Country: United Kingdom Setting: Breast cancer follow-up clinic in a cancer hospital. Inclusion criteria: Women with a history of treated non metastatic breast cancer with hot flushes. Exclusion criteria: None described. Characteristics of participants: Mean age 49 (range 29 to 74). Median daily hot flush frequency: 4 per day in treatment group and 5 in control. 79% on tamoxifen. Number of participants/assessable participants: 24/16. Numbers of assessable participants in treatment/control arms: 8/8.
Interventions	Arm 1: Occupational therapist-guided relaxation (deep breathing and guided imagery) . Arm 2: No treatment. Study duration: one month of treatment.
Outcomes	Hot flush frequency. General Health Questionnaire. Distress (0-10 visual analogue scale). Problem factor (0-10 visual analogue scale). Interference (0-10 visual analogue scale).
Notes	

***Risk of bias***

<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Unclear	Method not described.
Allocation concealment?	Yes	A - Adequate.
Blinding? All outcomes	No	Participants and providers not blinded.
Incomplete outcome data addressed? All outcomes	Unclear	8 of 24 (33%) of women did not provide complete data. The analyses followed the intention-to-treat principle.
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Fenlon 2008**

Methods	Parallel-group design. Computer-generated randomization list. Stratified according to clinic site and age. Participants and providers not blinded.	
Participants	Country: United Kingdom Study setting: Three breast cancer follow-up clinics in England.  Inclusion criteria: Women with a history primary breast cancer with hot flushes described as troublesome by the patient. Exclusion criteria: Use of estrogen therapy, aromatase inhibitors, or any other hormone therapies except tamoxifen. Use of remedies or prescription medicines likely to have an impact on hot flushes, such as acupuncture, venlafaxine, progesterones, or clonidine. Characteristics of participants: Mean age 55, range from 36 to 77 years. Baseline hot-flush frequency: Mean 4.5 per day for treatment and 5.3 for control group. 55% on tamoxifen. Number of participants/assessable participants: 150/104. Numbers of assessable participants in treatment/control arms: 50/54.	
Interventions	Arm 1: Relaxation therapy. Arm 2: Control group. Relaxation therapy consisted of: One-hour session of occupational therapist-guided relaxation (stress management; written information about stress; and a session of relaxation using deep breathing techniques, muscle relaxation and guided imagery). Audiotape to use at home for 20 minutes once per day for at least one month. Control: One session with a specialist nurse to discuss hot flushes and menopause management. Study duration: One month of treatment. Two months of additional follow up.	
Outcomes	Hot flushes frequency and severity through self-administered diary. Hot flushes score (number of hot flushes per day x severity in a scale of 1 to 4, being 4 the maximum severity). Hunter menopause scale (distress caused by flushes). Quality of life, using Functional Assessment of Cancer Therapy with the endocrine subscale (FACT-ES). Anxiety, using the Spielberger State/Trait Anxiety Index (STAI). All outcomes evaluated at months one and three.	
Notes		
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Computer-generated sequence.

**Fenlon 2008** (Continued)

Allocation concealment?	Yes	A - Adequate.
Blinding? All outcomes	No	Participants and providers not blinded.
Incomplete outcome data addressed? All outcomes	Unclear	46 of 150 (31%) of women did not complete the study or provide complete data at one month. The analyses followed the intention-to-treat principle.
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Goldberg 1994**

Methods	Cross-over design. Method of randomization not described. Stratified by age, duration of tamoxifen use, duration of hot-flush symptoms, and the average frequency and severity of hot flushes. Described as double blind.
Participants	Country: United States Setting: not described. Inclusion criteria: Adult women receiving tamoxifen for breast cancer. At least seven episodes of hot flushes per week, for at least one month. Life expectancy of six months. Performance status of 0 or 1 on the Eastern Cooperative Oncology Group. Exclusion criteria: Use of chemotherapy, androgens, estrogens, progestational agents, corticosteroids, monoamine oxidase inhibitors, levodopa, piribedil, tricyclic antidepressants, or sedatives such as benzodiazepines or barbiturates. Poorly controlled hypertension, coronary insufficiency, history of myocardial infarction, symptomatic coronary artery disease, peripheral or cerebral vascular disease, syncope, symptomatic hypotension, significant hepatic or renal dysfunction, a history of significant mental depression. Widespread skin disease, or a history of allergic or adverse reactions to clonidine. Pregnant or nursing patients. Characteristics of participants: Median age 54 years. Baseline hot flushes: Median frequency (hot flush per day) 6.1 in clonidine first arm and 7.0 in placebo first arm. Number of participants/assessable participants: 110/89 (86 for severity of hot flushes). Numbers of assessable participants in treatment first/control first arms: 42/47.



**Goldberg 1994** (Continued)

Interventions	<p>Arm 1: Transdermal clonidine patch (equivalent to a daily oral dose of 0.1 mg). Patches changed weekly.</p> <p>Arm 2: Identical-appearing placebo patches.</p> <p>Study duration: four weeks for each period. No washout between cross-over periods.</p>
Outcomes	<p>- Average daily number of hot flushes and average daily score (number of hot flushes per day x severity in a scale of 1 to 4, being 4 the maximum severity). Severity was graded as mild, moderate, severe and very severe. A self-administered questionnaire was used to collect the information about hot flushes through a daily diary hot-flush questionnaire.</p> <p>- Side-effects.</p>
Notes	

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method not described.
Allocation concealment?	Unclear	B - Unclear.
Blinding? All outcomes	Yes	Described as double blind.
Incomplete outcome data addressed? All outcomes	Unclear	21/110 (19%) and 24/110 (22% ) of women did not provide complete data for hot flushes frequency and hot flushes severity, respectively. Losses unequally balanced between groups. The analyses followed the intention-to-treat principle.
Free of selective reporting?	Unclear	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Unclear	Yes

**Jacobs 2005**

Methods	<p>Parallel-group design.</p> <p>Computer-generated randomization. Stratified by age, breast cancer staging and use of tamoxifen.</p> <p>Participants and providers blinded.</p>
Participants	<p>Country: United States</p> <p>Setting: Not described.</p> <p>Inclusion criteria:</p> <p>Women with a history of breast cancer (carcinoma in situ and stages I to III).</p>

Jacobs 2005 (Continued)

	<p>At least three episodes of hot flushes per day for at least one month.          Exclusion criteria:          Use of other hot flushes treatments, including vitamin regimens, herbs, estrogen or progestational agents, antidepressants, or sleep medications.          Chronic health problems such as rheumatoid arthritis, asthma, heart disease and inflammatory bowel disease necessitating treatment with corticosteroids.          Chemotherapy or radiation therapy expected to be received in the next year.          Pregnant or planned to become pregnant in the next year.          Characteristics of participants:          Mean age 55.5 years.          Mean daily hot-flush frequency not mentioned.          58% on tamoxifen. Tamoxifen use was allowed, other drugs not mentioned but 65% were taking unspecified hormones.          Number of participants/assessable participants: 83/79.          Numbers of assessable participants in Arm 1/Arm 2/control arm: 24/29/26.</p>	
Interventions	<p>Arm 1: Single homeopathic remedy.          Arm 2: Combination homeopathic remedy (Hyland's menopause).          Arm 3: Identical-appearing placebo.          Study duration: One year.</p>	
Outcomes	<p>Total number of hot flushes.          Hot flush score (number of hot flushes per day x severity in a scale of 1 to 4, being 4 the maximum severity).          Kupperman Menopausal Index.          SF-36 Quality of Life Score.</p>	
Notes	<p>28 withdrawals. Not clear if considered for calculations.</p>	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Computer-generated.
Allocation concealment?	Yes	A - Adequate.
Blinding? All outcomes	Yes	Participants and providers blinded.
Incomplete outcome data addressed? All outcomes	Yes	Only 4 of 83 women lost to follow up (5%) . Intention-to-treat analyses.
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Kimnick 2006**

Methods	<p>Cross-over design.  Method of randomization not described. Stratified by menopausal status and average number of hot flushes per day.  Described as double blind.</p>	
Participants	<p>Country: United States  Setting: Not described.  Inclusion criteria:  Women over 18 years with localized breast cancer (including stages 0-IIIb; American Joint Committee on Cancer, version 5), receiving adjuvant tamoxifen therapy.  At least one hot flush per day (or more than seven hot flushes per week).  Exclusion criteria:  Pregnant or breastfeeding.  History of seizure disorder or hepatic or renal insufficiency.  Use of estrogen, progestational agents, corticosteroids, androgens, or other antidepressants.  Characteristics of participants:  Mean age 54 (range 36 to 77 years).  Baseline hot flush frequency was 5.8 and score 11.5.  Number of participants/assessable participants: 62/39.  Numbers of assessable participants in treatment first/control first arms: 20/19.</p>	
Interventions	<p>Arm 1: Sertraline 50 mg daily.  Arm 2: Placebo.  Study duration: six weeks for each period. No washout between cross-over periods.</p>	
Outcomes	<ul style="list-style-type: none"> <li>- Hot flush self-assessment diary, frequency and intensity, score (number of hot flushes per day x severity in a scale of 1 to 4, being 4 the maximum severity).</li> <li>- Questionnaires for mood status, the Center for Epidemiologic Studies depression (CES-D).</li> <li>- Functional Assessment of Cancer Therapy-Breast (FACT-B) for quality of life in cancer patients.</li> </ul>	
Notes		
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Unclear	Method not described.
Allocation concealment?	Unclear	B - Unclear.
Blinding? All outcomes	Yes	Described as double blind.
Incomplete outcome data addressed? All outcomes	Unclear	23 of 62 (37%) of the originally randomized women did not provide baseline data or withdrew. Potential bias introduced for

**Kimmick 2006** (Continued)

		substantial number of incomplete data was not assessed. Intention-to-treat analysis.
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Loprinzi 2000**

Methods	Parallel-group design. Randomization with method of dynamic allocation. Stratified according to age, current tamoxifen use, duration of symptoms, and average frequency of hot flushes per day. Participants and providers blinded. Statisticians not blinded to treatment assignment.
Participants	Country: United States Setting: Not described. Inclusion criteria: Women with a history of breast cancer or concerned about taking estrogens for fear of breast cancer. Troublesome hot flushes, at least 14 times per week for at least a month. Life expectancy at least six months; performance status of 0-1 on the Eastern Cooperative Oncology Group scale. Exclusion criteria: use of venlafaxine in the past; use of antidepressants within preceding two years; pregnancy; breastfeeding; use of hot flushes treatment within two weeks; uncontrolled hypertension. Characteristics of participants: Mean age not reported. Tamoxifen use 69%. Baseline hot flushes: Mean frequency 8.0, mean score 13.3. Number of participants/assessable participants: 221/191. Numbers of assessable participants in arm 1/arm 2/arm 3/arm 4 (placebo): 49/43/49/50.
Interventions	Venlafaxine (extended release) vs placebo (identical appearance): Arm 1: 37.5 mg daily for 28 days; Arm 2: 37.5 mg daily for 7 days, then 75 mg daily for 21 days; Arm 3: 37.5 mg daily for 7 days, 75 mg daily for 7 days, then 150 mg daily for 14 days. Arm 4: Placebo for 28 days. Study duration: four weeks of treatment. Additional follow up for six months.
Outcomes	- Average daily number of hot flushes and average daily score (number of hot flushes per day x severity in a scale of 1 to 4, being 4 the maximum severity). Severity was graded as mild, moderate, severe and very severe. A previously validated questionnaire was used to collect the information about hot flushes through a daily diary hot-flush questionnaire. - Two single-item global quality-of-life questions. - Beck depression inventory. - Blood pressure and other side-effects.

**Loprinzi 2000** (Continued)

Notes	8/229 participants were excluded after randomization, and before starting study medication. Effect of missing data was analysed. Results were consistent.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Stratified randomization by a method of dynamic allocation.
Allocation concealment?	Unclear	B - Unclear.
Blinding? All outcomes	Yes	Participants and physicians blinded. Blinding of other participants not explicit but likely, except for statisticians.
Incomplete outcome data addressed? All outcomes	Unclear	30 of 221 (14%) were not assessable at the end of the study. Analyses following the intention-to-treat principle (with the exception of 8 participants excluded after randomization).
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Loprinzi 2002**

Methods	Cross-over design. Randomization with method of dynamic allocation. Stratified randomisation by age, tamoxifen use, duration and frequency of hot flushes. Reported as double blind.
Participants	Country: United States Setting: Not described. Inclusion criteria: Women with history of breast cancer or at increased risk. At least 14 hot flushes per week for at least one month. No evidence of malignant disease. Exclusion criteria: Use of antineoplastic chemotherapy, androgens, estrogens, progestational drugs, coumadin or substances for the treatment of hot flushes. Previous use of fluoxetine or any other antidepressant for two years before study entry. Characteristics of participants: Mean age not described. 74% of participants over 50 years.

**Loprinzi 2002** (Continued)

	Tamoxifen use: 55%. Baseline hot flushes: Mean frequency 7.9, mean score 13.4. Number of participants/assessable participants: 81/68 for first period. Numbers of assessable participants in treatment first/control first arms: 33/35.
Interventions	Arm 1: Fluoxetine 20 mg/day. Arm 2: Identical-appearing placebo. Study duration: four weeks for each period. No washout between cross-over periods.
Outcomes	- Average daily number of hot flushes and average daily score (number of hot flushes per day x severity in a scale of 1 to 4, being 4 the maximum severity). Severity was graded as mild, moderate, severe and very severe. A previously validated questionnaire was used to collect the information about hot flushes through a daily diary hot-flush questionnaire. - Depression (Beck depression inventory). - Quality of life (uniscale global QOL instrument). - Side-effects.
Notes	6/87 participants were excluded after randomization, and before starting study medication.

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Stratified randomisation by a method of dynamic allocation.
Allocation concealment?	Unclear	B - Unclear.
Blinding? All outcomes	Yes	Reported as double blind.
Incomplete outcome data addressed? All outcomes	No	13 of 81 (19%) of the originally randomized women did not take the drug or provide data for analyses. Potential bias introduced for substantial number of incomplete data was not assessed. Analyses following the intention-to-treat principle (with the exception of six participants excluded after randomization).
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Pandya 2000**

Methods	Parallel-group design. Randomization by using a computer program via centralised office. Stratified by time since menopause, duration of tamoxifen therapy and baseline frequency of hot flushes. Described as double-blind
Participants	Country: United States Setting: Clinical practice of medical oncologists. Inclusion criteria: Women receiving tamoxifen for breast cancer. At least 1 hot flush per day for one month. Exclusion criteria: Premenopausal. Use of chemotherapy or endocrine therapy for breast cancer. Use of antihypertensive agents, monoamine oxidase inhibitors, L-dopa, piribedil, tricyclic antidepressants or sedatives. Coronary insufficiency, recent history of myocardial infarction, symptomatic cardiac disease, peripheral or cerebrovascular disease, syncope or symptomatic hypotension. Allergy or adverse reaction to clonidine. Abnormal hepatic or renal function. Characteristics of participants: Mean age 54 (range 35 to 75 years). Baseline hot flushes: Mean frequency 7.7, mean severity 2.2. Number of participants/assessable participants: 198/149. Numbers of assessable participants at week 8 in treatment/control arms: 84/79.
Interventions	Arm 1: Oral clonidine 0.1 mg at bedtime. Arm 2: Placebo. Study duration: eight weeks of treatment. Four weeks of additional follow up.
Outcomes	- Hot flushes frequency and severity score (number of hot flushes per day x severity in a scale of 1 to 4, being 4 the maximum severity). A self-report questionnaire was used to collect the information through a daily diary. - Quality of life (1-10 scale). - Side-effects.
Notes	Effect of missing data was analysed. Results were consistent.

***Risk of bias***

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated sequence.
Allocation concealment?	Yes	A - Adequate.
Blinding? All outcomes	Yes	Described as double-blind.

**Pandya 2000** (Continued)

Incomplete outcome data addressed? All outcomes	Unclear	49 of 198 (25%) did not provide data at the end of the study. Potential bias introduced for substantial number of incomplete data was assessed.
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Pandya 2005**

Methods	Parallel-group design. Computer-generated sequence. Stratified by site and duration of hot flushes. Participants and providers blinded.
Participants	Country: United States Setting: Oncology clinic. Inclusion criteria: Adult women with a history of breast cancer, experiencing two or more hot flushes per day. Exclusion criteria: Use of chemotherapy, steroidal contraception, venlafaxine, clonidine or anticonvulsants. Pregnancy or breastfeeding. Coronary insufficiency, recent history of myocardial infarction, symptomatic cardiac disease, peripheral or cerebrovascular disease, stroke, syncope, or symptomatic hypotension. Hepatic or renal dysfunction. Allergy to gabapentin. Characteristics of participants: Mean age 55 years. Baseline hot flush frequency: Mean 8.6 (range 2 to 54). 71% on tamoxifen. Number of participants/assessable participants: 420/347. Numbers of assessable participants in 300 mg arm/ 900 mg arm/placebo: 114/120/113.
Interventions	Arm 1: Gabapentin 300mg/day (orally, three times a day). Arm 2: Gabapentin 900mg/day (orally, three times a day). Arm 3: Identical-appearing placebo. Study duration: eight weeks of treatment.
Outcomes	- Hot flushes frequency and severity score (number of hot flushes per day x severity in a scale of 1 to 4, being 4 the maximum severity). A self-report questionnaire was used to collect the information through a daily diary. - Patient-reported symptoms inventory (11 point scale on fatigue, pain, nausea, sleep disturbance, shortness of breath, memory, appetite, drowsiness, vomiting and distress).
Notes	



**Pandya 2005** (Continued)

<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Computer-generated sequence.
Allocation concealment?	Unclear	B - Unclear.
Blinding? All outcomes	Yes	Participants and providers blinded.
Incomplete outcome data addressed? All outcomes	No	73 of 420 (17%) were not evaluable by the end of the follow up. Potential bias introduced for substantial number of incomplete data was not assessed.
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Stearns 2005**

Methods	Cross-over design. Computer-generated sequence. Stratified by age and anti-estrogen use. Participants were blinded, not known if providers, assessors or analysts were blinded.
Participants	Country: United States Setting: Six cancer clinics. Inclusion criteria: Over 18 years with or without a history of breast cancer. At least 14 episodes of hot flushes per week, for at least one month. Life expectancy of 6 months. Performance status of 0 or 2 on the Eastern Cooperative Oncology Group scale. Creatinine and bilirubin less than two times normal level. Exclusion criteria: Use of other treatments for hot flushes. Use of chemotherapy, radiation therapy, HT (estrogen and/or progestin), antidepressants, and monoamine oxidase inhibitors. Characteristics of participants: 81% with a history of breast cancer. Age range 27 to 76 years. Mean daily hot-flush frequency: 7.9 times per day. 64% on anti-estrogen therapy. Number of participants/assessable participants: 151/107. Numbers of assessable participants in arm 1/arm 2/placebo arm: 28/23/56.

**Stearns 2005** (Continued)

Interventions	Arm 1: Paroxetine 10mg/day. Arm 2: Paroxetine 20mg/day. Arm 3: Identical-appearing placebo. Study duration: four weeks for each period. No washout between cross-over periods.	
Outcomes	<ul style="list-style-type: none"> <li>- Average daily number of hot flushes and average daily score (number of hot flushes per day x severity in a scale of 1 to 4, being 4 the maximum severity). Severity was graded as mild, moderate, severe and very severe. A previously validated questionnaire was used to collect the information about hot flushes through a daily diary hot-flush questionnaire.</li> <li>- Kupperman Menopausal Index.</li> <li>- Patient preference during each period of the cross-over.</li> <li>- Center for Epidemiologic Studies Depression Scale.</li> <li>- Hospital Anxiety and Depression Scale.</li> <li>- Medical Outcomes Study Sleep Problem Index.</li> <li>- Medical Outcomes Study Sexual Problem Index.</li> <li>- EuroQOL Linear Rating Scale.</li> </ul>	
Notes		
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Computer-generated sequence.
Allocation concealment?	Yes	A - Adequate (consecutively numbered sealed envelopes).
Blinding? All outcomes	Yes	Participants were blinded. Not clear if providers were blinded.
Incomplete outcome data addressed? All outcomes	No	44 of 151 (29%) were not included in analyses. Potential bias introduced for substantial number of incomplete data was not assessed.
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

## Thompson 2005

Methods	Parallel-group design. Randomization through random numbers table kept by the pharmacy. All participants blinded.	
Participants	Country: United Kingdom Setting: Outpatient department of a homeopathic hospital. Recruited from oncology center, surgical breast units, and community (through poster advertising). Inclusion criteria: Women with breast cancer with more than 3 hot flushes per day. Exclusion criteria: Metastatic disease. Use of other treatments for hot flushes. Severe concurrent illness. Undergoing or about to receive adjuvant chemotherapy. Characteristics of participants: Mean age 52 years. 80% on tamoxifen. Baseline hot flush frequency: 7.5 per day. Number of participants/assessable participants: 53/45. Numbers of assessable participants in treatment/control arms: 23/22.	
Interventions	Arm 1: Homeopathic medicines (in tablet, granule or liquid form). Arm 2: Identical placebo preparation. All prescriptions made by the same doctor. Homeopathy and placebo prepared by a single pharmacy. Study duration: 16 weeks.	
Outcomes	Activity score. Profile score (MYMOP) that includes symptom scores, daily living disruption and general well-being. Frequency and severity of hot flushes. Quality of life (EORTC QLC-C30). Hospital anxiety and depression scale. Overall satisfaction with homeopathy. Impact on daily living. Side-effects.	
Notes	Eight withdrawals. Not clear if considered for calculations.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Randomization through random numbers table.
Allocation concealment?	Yes	A - Adequate.

**Thompson 2005** (Continued)

Blinding? All outcomes	Yes	All participants blinded.
Incomplete outcome data addressed? All outcomes	Unclear	8 of 53 (15%) were lost to follow up. All randomized women were analysed, but not clear if withdrawals considered for calculations.
Free of selective reporting?	Yes	Main outcomes reported. There is no reason to suspect selective reporting.
Free of other bias?	Yes	Yes

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
Ganz 2000	Intervention consists of a program that may include some drugs with possible hormonal action. Data do not allow to discriminate which participants received different drugs.
Li 2006	Even though the abstract reports that Shugan-liangxue compound contains no phytoestrogen, there is too little information to be sure of its non-hormonal mechanism. We didn't find published literature to support the inclusion of this compound.

**Characteristics of studies awaiting assessment** [ordered by study ID]

**Dyer 2008**

Methods	Randomised controlled cross-over trial Participants blinded
Participants	Country: United Kingdom Setting: Out-patient clinics at both sites of the hospital Inclusion criteria: Women suffering from hot flushes as a result of treatment for breast cancer Exclusion criteria: Any woman suffering from adverse reactions to cosmetics, perfumes or menthol, already currently using a cooling spray for hot flushes or unable to attend hospital to collect spray bottles and diaries Characteristics of participants: Median age: water = 52 years (33-69); hydrolats = 52 years (35-70)
Interventions	Arm 1: Spray A (peppermint and neroli) for month 1, then Spray B (water) for month 2, then choose Spray A or B Arm 2: Spray B (water) for month 1, then Spray A (peppermint and neroli) for month 2, then choose Spray A or B

**Dyer 2008** (Continued)

Outcomes	Number of women choosing hydrolat spray in preference to water spray to palliate hot flushes Level of hot flush annoyance for each woman (descriptive purposes) Visual Analogue Scale (VAS)
Notes	4/44 dropped out

**Elkins 2008**

Methods	Randomized controlled trial All participants unblinded
Participants	Country: United States Setting: Unknown recruitment setting. Hypnosis undertaken by clinician with 40 hours training Inclusion criteria: Women > 18 years old with a history of breast cancer and more than 14 hot flashes per week Exclusion criteria: Use of other treatments (i.e. chemotherapy, androgens, estrogens, progestational drugs) or any treatment for hot flashes Use of antihormonal agents for breast cancer at variable dose No participation in other mind-body therapy (i.e. relaxation therapy, biofeedback, yoga) Characteristics of participants: Mean age: control = 58 years ± 2 months; hypnosis = 55 years ± 10 months Baseline hot flush frequency: control = 7.52; hypnosis = 7.77 Numbers of assessable participants in control/hypnosis arms: 24/27
Interventions	Arm 1: hypnosis intervention (5 weekly session each lasting approximately 50 minutes with a trained clinician and participants were given instructions in self hypnosis for at-home practice) Arm 2: no treatment Study duration: five weeks of treatment or remained on a no-treatment waiting list for 5 weeks
Outcomes	-Daily number of hot flashes (frequency) -Hot flash severity score (1 point equalled mild hot flash, two points equalled moderate hot flash, three points equalled severe hot flash and four points equalled very severe hot flash). Hot flash score equalled severity average for one week x hot flash frequency for that one week -HFRDIS (Hot Flash Related Daily Interference Scale) -Centre for Epidemiologic Studies Depression Scale (CEDSD) -Hospital Anxiety and Depression Scale - Anxiety Subscale (HADS-A) -Medical Outcomes Study Sleep Scale (MOS-Sleep Scale)
Notes	9/60 participants were lost to follow up or withdrew post-randomisation Effect of missing data was analysed. Results were consistent

**ISRCTN33947463**

Methods	Randomized controlled trial (with waiting list control)
Participants	<p>Country: United Kingdom</p> <p>Setting: Unknown recruitment setting</p> <p>Inclusion criteria:</p> <p>Women who have had stage I/II breast cancer with no clinical evidence of recurrence</p> <p>Have been amenorrhoeic for 36 months irrespective of menopausal status at time of diagnosis or have had a surgical bilateral oophorectomy</p> <p>Are experiencing vasomotor symptoms (i.e. hot flushes or night sweats) with or without vaginal dryness</p> <p>Exclusion criteria:</p> <p>Currently taking HRT or have received oral or transdermal HRT within the last 3 months or have received HRT implant within the last 5 years</p> <p>Receiving chemotherapy</p> <p>Receiving gonadotrophin-releasing hormone e.g. Zoladex</p> <p>Are pregnant</p> <p>Characteristics of participants:</p> <p>Unknown</p> <p>Number of participants/assessable participants: Unknown</p>
Interventions	<p>Arm 1: 3 sessions of hypnosis over 3 weeks</p> <p>Arm 2: control arm, similar treatment but delayed for 3 weeks</p> <p>Study duration: both groups to keep diaries of vasomotor events and complete Quality of Life questionnaires at strategic points through a 16 week period</p>
Outcomes	<p>-Reduction in frequency or intensity of flushing compared with waiting list control</p> <p>-Treatment effects and improvements maintained for over 3 months</p> <p>-Sustained effect passed 4 months</p>
Notes	

**Loprinzi 2010**

Methods	<p>Placebo-controlled, randomized trial design</p> <p>Participants stratified by age (&gt; or &lt; 50 years), use of tamoxifen, raloxifene or aromatase inhibitor (yes versus no), duration of hot flashes (&gt; or &lt; 9 months) and estimated daily frequency of hot flashes (4 to 9 versus &gt;9)</p> <p>Randomization through a dynamic allocation procedure (by the North Central Cancer Treatment Group (NCCTG))</p> <p>All participants blinded until study completion</p>
Participants	<p>Country: United States</p> <p>Setting: Unknown recruitment setting</p> <p>Inclusion criteria:</p> <p>Women with more than 28 hot flashes per week. Hot flashes must be present for at least one month prior to study entry</p> <p>Participants able to complete questionnaires by themselves or with assistance</p> <p>Exclusion criteria:</p> <p>Receiving antineoplastic chemotherapy, androgens, progestogen agents, estrogens</p> <p>Use of gabapentin or pregabalin in the past</p> <p>Current or planned use of other agents for hot flashes (exception being stable doses of vitamin E, soy products and/</p>

**Loprinzi 2010** (Continued)

	<p>or antidepressants)</p> <p>Concurrent history of renal insufficiency or child bearing potential</p> <p>Characteristics of participants:</p> <p>Percentage 18 - 49 years of age: 21%; &gt; 50 years of age: 79%</p> <p>Breast cancer history: 40%</p> <p>Baseline hot flush frequency: 4 - 9 hot flashes = 57%; 10+ = 43%</p> <p>Concurrent aromatase inhibitor = 21%, raloxifene = 2%, tamoxifen = 11%</p> <p>Number of participants/assessable participants:191/163</p> <p>Numbers of assessable participants in placebo/pregabalin 75 mg BD arm/pregabalin 150 mg BD arm: 51/56/56</p>
Interventions	<p>Pregabalin versus placebo (identical appearance):</p> <p>Arm 1: Placebo for 6 weeks;</p> <p>Arm 2: 50 mg for 1st week, 50 mg BD for 2nd week, 75 mg BD for 4 additional weeks;</p> <p>Arm 3: 50 mg for 1st week, 50 mg BD for 2nd week, 75 mg BD for 3rd week, 150 mg BD for 3 additional weeks</p> <p>Study duration: six weeks of treatment.</p>
Outcomes	<p>-Change-from-baseline hot flash score during treatment week 6 between pregabalin 150 mg BD and placebo. Hot flash score was calculated by combining severity (i.e. mild, moderate, severe and very severe) and frequency of hot flash from average across each study week</p> <p>-Change-from-baseline hot flash score during treatment week 6 between pregabalin 75 mg BD and placebo</p> <p>-Change-from-baseline hot flash score during treatment week 6 between pregabalin 150 mg BD and pregabalin 75 mg BD versus placebo</p> <p>-Toxicity profiles</p> <p>-Moods (from POMS)</p> <p>-HFRDIS scores between either treatment arms and placebo</p>
Notes	<p>44/207 participants were excluded after randomisation, due to cancelling, drop-out for toxicities and failing to complete or return study diary forms</p> <p>No mention of missing data</p>

**NCT00425776**

Methods	Randomized controlled double-blinded trial
Participants	<p>Country: Denmark</p> <p>Setting: Unknown recruitment setting</p> <p>Inclusion criteria:</p> <p>Women &gt; 35 years old treated for breast cancer, have hot flushes and sleeping disturbances</p> <p>Exclusion criteria:</p> <p>Any use of estrogen as tablets or plaster</p> <p>Characteristics of participants:</p> <p>Unknown</p> <p>Number of participants/assessable participants:</p> <p>Unknown</p>
Interventions	<p>Arm 1: Active comparator (real acupuncture)</p> <p>Arm 2: Sham comparator (sham acupuncture)</p> <p>Arm 3: No intervention (no kind of acupuncture)</p>

NCT00425776 (Continued)

	Acupuncture occurs once a week for 5 weeks
Outcomes	-Hot flushes rating scale -Sleep disturbances (yes or no) -Measure of se-estrogen and se-endorphin before and after acupuncture
Notes	

### Characteristics of ongoing studies [ordered by study ID]

#### ISRCTN13771934

Trial name or title	A trial of a non-medical treatment for menopausal symptoms in women with breast cancer
Methods	Randomised controlled trial
Participants	-Aged 18 and older and have had early stage breast cancer -Have completed radiotherapy and chemotherapy -No evidence of distant metastatic disease -May have had ductal carcinoma in situ -Experience hot flushes/night sweats for at least 2 months -Completed active treatment and in remission -Prior medical treatment for hot flushes/night sweats will be recorded
Interventions	Arm 1: Cognitive behavioural therapy (61.5 hour sessions for 6 weeks). Arm 2: Usual care  Duration: 3 months assessment and treatment, and 6 months follow-up post-randomisation
Outcomes	Problem rating of hot flushes and night sweats (measured at 12 weeks post-randomisation) Frequency of hot flushes and night sweats (physiologically measured and self reported) Mood, sleep and quality of life Treatment cost-effectiveness
Starting date	September 2009
Contact information	Myra Hunter (myra.hunter@kcl.ac.uk)
Notes	Anticipated end date: December 2011



**NCT00363909**

Trial name or title	Citalopram in treating postmenopausal women with hot flashes
Methods	Randomised, placebo-controlled, double-blind
Participants	Postmenopausal women with a history of breast cancer (no current malignant disease) or no history of breast cancer and refused estrogen replacement therapy due to perceived increased risk of breast cancer
Interventions	Arm 1: 3 different doses (i.e. low, medium or high) of citalopram hydrobromide Arm 2: placebo
Outcomes	Different in average hot flash score from baseline until week 7 of treatment Toxicity Mood and hot flash related daily interference with activities
Starting date	November 2006
Contact information	Debra Barton (Mayo Clinic), Beth La Vasseur (Saint Joseph Mercy Cancer Center), Charles L Loprinzi (Mayo Clinic)
Notes	

**NCT00582244**

Trial name or title	Cognitive behavioral therapy (CBT) and physical exercise for climacteric symptoms in breast cancer patients experiencing treatment-induced menopause: a multicenter randomised trial (EVA project)
Methods	Randomized controlled trial Intervention model: factorial assignment Open label
Participants	-Women 30 - 50 years old with histologically confirmed primary breast cancer -All women will have been premenopausal at the time of diagnosis, have completed adjuvant chemotherapy (with the exception of trastuzumab (Herceptin)) a minimum of 4 months and a maximum of 5 years prior to study entry -Women may currently be receiving adjuvant hormonal therapy
Interventions	Arm 1: Experimental CBT and relaxation Arm 2: Experimental physical activity Arm 3: Experimental CBT and physical activity Arm 4: No intervention control group
Outcomes	Menopausal symptoms Vasomotor symptoms, urinary symptoms, sexuality, body- and self image, psychological distress, quality of life
Starting date	January 2008
Contact information	Saskia Duijts (s.duijts@nki.nl)

**NCT00582244** (Continued)

Notes	Anticipated end date: December 2010
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**NCT00641303**

Trial name or title	Acupuncture in reducing muscle and bone symptoms in women receiving letrozole, exemestane, or anastrozole for stage 0, stage 1, stage 11, or stage III breast cancer
Methods	Randomized controlled double-blind trial Stratified according to participation in the aromatase inhibitor trial “A multicenter randomised clinical trial correlating the effects of 24 months of exemestane or letrozole on surrogate markers of response with aromatase polymorphism”
Participants	-Women >18 years old with histologically confirmed invasive carcinoma of the breast (stage 0-III disease) -Estrogen receptor and/or progesterone receptor positive immunohistochemical staining -Must be receiving a standard dose of aromatase inhibitor therapy -No known metastatic (stage IV) breast cancer -No prior acupuncture for any reason -No other concurrent systemic therapy (i.e. chemotherapy, biologic therapy or radiotherapy)
Interventions	Arm 1: Control (sham comparator) - patients receive 8 weekly sessions of acupuncture treatment Arm 2: Treatment (experimental) - patients receive 8 weekly sessions of acupuncture treatment  Patients followed for 24 weeks. Patients in Arm 1 may receive 4 free acupuncture sessions (not sham) after the 24 week follow-up visit
Outcomes	Health Assessment Questionnaire Disability Index (HAQ-DI) score Pain scores on visual analog scale (VAS) Change in amount and/or frequency of oral analgesic use Number of patients who discontinue aromatase inhibitor therapy Change in menopausal symptoms (NSABP revised), hot flash frequency (HFRDIS), sleep quality (PSQI), depression score (CESD), and overall quality of life (EuroQOL) in patients at weeks 4, 8, and 24 vs week 0 of acupuncture treatment Change in plasma estrogen concentrations, beta endorphin concentration and cytokine profile from week 0 to week 8
Starting date	May 2008
Contact information	Vered Stearns (Sidney Kimmel Comprehensive Cancer Centre)
Notes	Anticipated end date: April 2010

**NCT00956813**

Trial name or title	Flaxseed in treating postmenopausal women with hot flashes who have a history of breast cancer or other cancer or who do not wish to take estrogen therapy
Methods	Randomised, placebo-controlled, double-blind Stratified according to: -age (18-49 years versus >50 years) -treatment with tamoxifen citrate, selective estrogen receptor modulators or aromatase inhibitors (yes versus no) -duration of hot flashes (<9 months versus >9 months) -daily frequency of hot flashes (4-9 versus >10)
Participants	-Women >18 years old with a history of breast cancer or other cancer (without malignant disease) or no history of breast cancer and wishes to avoid estrogen due to perceived increase breast cancer risk
Interventions	Arm 1: Oral flaxseed in the form of a bar similar to a granola bar once daily Arm 2: Oral placebo bar once daily Treatment continues for 6 - 12 weeks; patients in Arm 2 may cross-over to receive treatment as in Arm 1 after 6 weeks
Outcomes	Hot flash score at week 7 Toxicity as measured by CTCAE v3.0 Mood General menopausal symptoms Hot flash-related daily interference on activities
Starting date	October 2009
Contact information	Debra Barton (Mayo Clinic)
Notes	Anticipated end date: October 2010

## DATA AND ANALYSES

This review has no analyses.

## APPENDICES

### Appendix I. CENTRAL search strategy

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Host: Wiley

Date of search: 19 July 2008

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1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomised controlled trials/
4. random allocation/
5. double-blind method/
6. single-blind method/
7. or/1-6
8. clinical trial.pt.
9. exp clinical trials
10. (clin\$ adj25 trial\$).tw.
11. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj25 (blind\$ or mask\$)).tw.
12. placebos/
13. placebo\$.tw.
14. random\$.tw.
15. research design/
16. or/8-15
17. animal/ not (human/ and animal/)
18. 7 or 16
19. 18 not 17
20. exp breast neoplasms/
21. exp "neoplasms, ductal, lobular, and medullary"/
22. exp fibrocystic disease of breast/
23. or/20-22
24. exp breast/
25. breast.tw.
26. 24 or 25
27. (breast adj milk).mp.
28. (breast adj tender\$).mp.
29. or/27-28
30. 26 not 29
31. exp neoplasms/
32. 30 and 31
33. exp lymphedema/
34. 33 and 30
35. (breast adj25 neoplasm\$).mp.

(Continued)

36. (breast adj25 cancer\$).mp.
37. (breast adj25 tumour\$).mp.
38. (breast adj25 tumor\$).mp.
39. (breast adj25 carcinoma\$).mp.
40. (breast adj25 adenocarcinoma\$).mp.
41. (breast adj25 sarcoma\$).mp.
42. (breast adj50 dcis).mp.
43. (breast adj25 ductal).mp.
44. (breast adj25 infiltrating).mp.
45. (breast adj25 intraductal).mp.
46. (breast adj25 lobular).mp.
47. (breast adj25 medullary).mp.
48. or/35-47
49. 23 or 32 or 34 or 48
50. exp mastectomy/
51. 49 or 50
52. exp "Analytical, Diagnostic and Therapeutic Techniques and Equipment (Non MeSH)"/
53. 52 and 30
54. 53 or 51
55. exp mammary neoplasms/
56. (mammary adj25 neoplasm\$).mp.
57. (mammary adj25 cancer\$).mp.
58. (mammary adj25 tumour\$).mp.
59. (mammary adj25 tumor\$).mp.
60. (mammary adj25 carcinoma\$).mp.
61. (mammary adj25 adenocarcinoma\$).mp.
62. (mammary adj25 sarcoma\$).mp.
63. (mammary adj50 dcis).mp.
64. (mammary adj25 ductal).mp.
65. (mammary adj25 infiltrating).mp.
66. (mammary adj25 intraductal).mp.
67. (mammary adj25 lobular).mp.
68. (mammary adj25 medullary).mp.
69. or/55-68
70. 54 or 69
71. exp breast self-examination/
72. (breast adj25 self\$).mp.
73. (breast adj25 screen\$).mp.
74. exp mammography/
75. or/70-74
76. mammograph\$.tw.
77. 76 and 30
78. 75 or 77
79. Flushing/
80. flush\$.mp.
81. flash\$.mp.
82. Vasomotor.mp.
83. Vasomotor\$.mp.
84. or/79-83

(Continued)

85. non hormonal therapy.mp.
86. "not hormonal therapy".mp.
87. "therapy not hormonal".mp.
88. serotonin uptake inhibitors.mp.
89. (Serotonin and norepinephrine reuptake inhibitors).mp.
90. fluoxetine.mp.
91. sertraline.mp.
92. paroxetine.mp.
93. citalopram.mp.
94. serotonin antagonists.mp.
95. Venlafaxine.mp.
96. Mirtazapine.mp.
97. trazodone.mp.
98. Gabapentin.mp.
99. clonidine.mp.
100. Veralipride.mp.
101. methyldopa.mp.
102. vitamin E.mp.
103. Bellerгал.mp.
104. (ergotamine and phenobarbital and belladonna).mp.
105. exp Acupuncture/
106. Acupuncture.mp.
107. exp Complementary therapies/
108. thinking/
109. odors/
110. oils, volatile/
111. Magnetic therapy.mp.
112. Exercise/
113. Physical fitness/
114. or/85-113
115. 19 and 78 and 84 and 114

## Appendix 2. CINAHL search strategy

**Host: EBSCO**  
**1981 to August 2008**

1. MH "Random Assignment"
2. MH "Random Sample+"
3. MH "Crossover Design"
4. MH "Clinical Trials+"
5. MH "Comparative Studies"
6. MH "Control (Research)+"
7. MH "Control Group"
8. MH "Factorial Design"
9. MH "Quasi-Experimental Studies+"

(Continued)

10. MH "Placebos"
11. MH "Meta Analysis"
12. MH "Sample Size"
13. MH "Research, Nursing"
14. MH "Research Question"
15. MH "Research Methodology+"
16. MH "Evaluation Research+"
17. MH "Concurrent Prospective Studies"
18. MH "Prospective Studies"
19. MH "Nursing Practice, Research-Based"
20. MH "Solomon Four-Group Design"
21. MH "One-Shot Case Study"
22. MH "Pretest-Posttest Design+"
23. MH "Static Group Comparison"
24. MH "Study Design"
25. MH "Clinical Research+"
26. clinical nursing research or random\* or cross?over or placebo\* or control\* or factorial or sham\* or meta?analy\* or systematic review\* or blind\* or mask\* or trial\*
27. or/1-26
28. MH "Breast Neoplasms"
29. MH "Fibrocystic Disease of Breast"
30. MH "Breast"
31. TX breast
32. or/28-31
33. TI breast N6 milk or AB breast N6milk or MW breast N6 milk
34. TI breast N6 tender\* or AB breast N6 tender\* or MW breast N6 tender\*
35. or/32-33
36. 32 not 35
37. MH "Neoplasms+"
38. 36 and 37
39. MH "Lymphedema+"
40. 39 and 36
41. TI breast N25 neoplasm\* or AB breast N25 neoplasm\* or MW breast N25 neoplasm
42. TI breast N25 cancer\* or AB breast N25 cancer\* or MW breast N25 cancer\*
43. TI breast N25 tumour\* or AB breast N25 tumour\* or MW breast N25 tumour\*
44. TI breast N25 tumor\* or AB breast N25 tumor\* or MW breast N25 tumor\*
45. TI breast N25 carcinoma\* or AB breast N25 carcinoma\* or MW breast N25 carcinoma\*
46. TI breast N25 adenocarcinoma\* or AB breast N25 adenocarcinoma\* or MW breast N25 adenocarcinoma\*
47. TI breast N25 sarcoma\* or AB breast N25 sarcoma\* or MW breast N25 sarcoma\*
48. TI breast N50 dcis or AB breast N50 dcis or MW breast N50 dcis
49. TI breast N25 ductal or AB breast N25 ductal or MW breast N25 ductal
50. TI breast N25 infiltrating or AB breast N25 infiltrating or MW breast N25 infiltrating
51. TI breast N25 intraductal or AB breast N25 intraductal or MW breast N25 intraductal
52. TI breast N25 lobular or AB breast N25 lobular or MW breast N25 lobular
53. TI breast N25 medullary or AB breast N25 medullary or MW breast N25 medullary
54. or/41-53
55. 38 or 40 or 54
56. MH "Mastectomy+"
57. 55 or 56

(Continued)

58. TI mammary N25 neoplasm\* or AB mammary N25 neoplasm\* or MW mammary N25 neoplasm\*
59. TI mammary N25 cancer\* or AB mammary N25 cancer\* or MW mammary N25 cancer\*
60. TI mammary N25 tumour\* or AB mammary N25 tumour\* or MW mammary N25 tumour\*
61. TI mammary N25 tumor\* or AB mammary N25 tumor\* or MW mammary N25 tumor\*
62. TI mammary N25 carcinoma\* or AB mammary N25 carcinoma\* or MW mammary N25 carcinoma\*
63. TI mammary N25 adenocarcinoma\* or AB mammary N25 adenocarcinoma\* or MW mammary N25 adenocarcinoma\*
64. TI mammary N25 sarcoma\* or AB mammary N25 sarcoma\* or MW mammary N25 sarcoma\*
65. TI mammary N50 dcis or AB mammary N50 dcis or MW mammary N50 dcis
66. TI mammary N25 ductal or AB mammary N25 ductal or MW mammary N25 ductal
67. TI mammary N25 infiltrating or AB mammary N25 infiltrating or MW mammary N25 infiltrating
68. TI mammary N25 intraductal or AB mammary N25 intraductal or MW mammary N25 intraductal
69. TI mammary N25 lobular or AB mammary N25 lobular or MW mammary N25 lobular
70. TI mammary N25 medullary or AB mammary N25 medullary or MW mammary N25 medullary
71. or/58-70
72. 57 or 71
73. MH "Breast Self-Examination"
74. TI breast N25 self\* or AB breast N25 self\* or MW breast N25 self\*
75. TI breast N25 screen\* or AB breast N25 screen\* or MW breast N25 screen\*
76. MH "Mammography"
77. or/72-76
78. TX mammograph\*
79. 78 and 36
80. 77 or 79
81. TI flush\* or AB flush\* or MW flush\*
82. TI flash\* or AB flash\* or MW flash\*
83. TI vasomotor\* or AB vasomotor\* or MW vasomotor\*
84. or/81-83
85. 27 and 80 and 84

### Appendix 3. PsycINFO search strategy

**Host: EBSCO**  
**1887 to August 2008**

1. MH "Random Assignment"
2. MH "Random Sample+"
3. MH "Crossover Design"
4. MH "Clinical Trials+"
5. MH "Comparative Studies"
6. MH "Control (Research)+"
7. MH "Control Group"
8. MH "Factorial Design"
9. MH "Quasi-Experimental Studies+"
10. MH "Placebos"
11. MH "Meta Analysis"
12. MH "Sample Size"



(Continued)

13. MH "Research, Nursing"
14. MH "Research Question"
15. MH "Research Methodology+"
16. MH "Evaluation Research+"
17. MH "Concurrent Prospective Studies"
18. MH "Prospective Studies"
19. MH "Nursing Practice, Research-Based"
20. MH "Solomon Four-Group Design"
21. MH "One-Shot Case Study"
22. MH "Pretest-Posttest Design+"
23. MH "Static Group Comparison"
24. MH "Study Design"
25. MH "Clinical Research+"
26. clinical nursing research or random\* or cross?over or placebo\* or control\* or factorial or sham\* or meta?analy\* or systematic review\* or blind\* or mask\* or trial\*
27. or/1-26
28. MH "Breast Neoplasms"
29. MH "Fibrocystic Disease of Breast"
30. MH "Breast"
31. TX breast
32. or/28-31
33. TI breast N6 milk or AB breast N6milk or MW breast N6 milk
34. TI breast N6 tender\* or AB breast N6 tender\* or MW breast N6 tender\*
35. or/32-33
36. 32 not 35
37. MH "Neoplasms+"
38. 36 and 37
39. MH "Lymphedema+"
40. 39 and 36
41. TI breast N25 neoplasm\* or AB breast N25 neoplasm\* or MW breast N25 neoplasm
42. TI breast N25 cancer\* or AB breast N25 cancer\* or MW breast N25 cancer\*
43. TI breast N25 tumour\* or AB breast N25 tumour\* or MW breast N25 tumour\*
44. TI breast N25 tumor\* or AB breast N25 tumor\* or MW breast N25 tumor\*
45. TI breast N25 carcinoma\* or AB breast N25 carcinoma\* or MW breast N25 carcinoma\*
46. TI breast N25 adenocarcinoma\* or AB breast N25 adenocarcinoma\* or MW breast N25 adenocarcinoma\*
47. TI breast N25 sarcoma\* or AB breast N25 sarcoma\* or MW breast N25 sarcoma\*
48. TI breast N50 dcis or AB breast N50 dcis or MW breast N50 dcis
49. TI breast N25 ductal or AB breast N25 ductal or MW breast N25 ductal
50. TI breast N25 infiltrating or AB breast N25 infiltrating or MW breast N25 infiltrating
51. TI breast N25 intraductal or AB breast N25 intraductal or MW breast N25 intraductal
52. TI breast N25 lobular or AB breast N25 lobular or MW breast N25 lobular
53. TI breast N25 medullary or AB breast N25 medullary or MW breast N25 medullary
54. or/41-53
55. 38 or 40 or 54
56. MH "Mastectomy+"
57. 55 or 56
58. TI mammary N25 neoplasm\* or AB mammary N25 neoplasm\* or MW mammary N25 neoplasm\*
59. TI mammary N25 cancer\* or AB mammary N25 cancer\* or MW mammary N25 cancer\*
60. TI mammary N25 tumour\* or AB mammary N25 tumour\* or MW mammary N25 tumour\*

(Continued)

61. TI mammary N25 tumor\* or AB mammary N25 tumor\* or MW mammary N25 tumor\*
62. TI mammary N25 carcinoma\* or AB mammary N25 carcinoma\* or MW mammary N25 carcinoma\*
63. TI mammary N25 adenocarcinoma\* or AB mammary N25 adenocarcinoma\* or MW mammary N25 adenocarcinoma\*
64. TI mammary N25 sarcoma\* or AB mammary N25 sarcoma\* or MW mammary N25 sarcoma\*
65. TI mammary N50 dcis or AB mammary N50 dcis or MW mammary N50 dcis
66. TI mammary N25 ductal or AB mammary N25 ductal or MW mammary N25 ductal
67. TI mammary N25 infiltrating or AB mammary N25 infiltrating or MW mammary N25 infiltrating
68. TI mammary N25 intraductal or AB mammary N25 intraductal or MW mammary N25 intraductal
69. TI mammary N25 lobular or AB mammary N25 lobular or MW mammary N25 lobular
70. TI mammary N25 medullary or AB mammary N25 medullary or MW mammary N25 medullary
71. or/58-70
72. 57 or 71
73. MH "Breast Self-Examination"
74. TI breast N25 self\* or AB breast N25 self\* or MW breast N25 self\*
75. TI breast N25 screen\* or AB breast N25 screen\* or MW breast N25 screen\*
76. MH "Mammography"
77. or/72-76
78. TX mammograph\*
79. 78 and 36
80. 77 or 79
81. TI flush\* or AB flush\* or MW flush\*
82. TI flash\* or AB flash\* or MW flash\*
83. TI vasomotor\* or AB vasomotor\* or MW vasomotor\*
84. or/81-83
85. 27 and 80 and 84

#### Appendix 4. LILACS search strategy

Host: BIREME ([www.bireme.br/bvs/I/ibd.htm](http://www.bireme.br/bvs/I/ibd.htm))  
1986 to August 2008

1. sofoco\$
2. hot flush\$
3. hot flash\$
4. Bochorn\$
5. Vasomoto\$
6. flash\$
7. flush\$
8. fogacho\$
9. OR/1-8

## Appendix 5. MEDLINE search strategy

Host: Ovid

January 1966 to December 2005

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomised controlled trials/
4. random allocation/
5. double-blind method/
6. single-blind method/
7. or/1-6
8. ANIMALS.sh. not HUMAN.sh.
9. 7 not 8
10. clinical trial.pt.
11. exp clinical trials/
12. (clin\$ adj25 trial\$).tw.
13. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj25 (blind\$ or mask\$)).tw.
14. placebos.sh
15. placebo\$.ti,ab.
16. random\$.ti,ab.
17. RESEARCH DESIGN.sh.
18. or/10 17
19. 18 not 8
20. 19 not 9
21. 9 or 20
22. exp breast neoplasms/
23. exp "neoplasms, ductal, lobular, and medullary"/
24. exp fibrocystic disease of breast/
25. or/22-24
26. exp breast/
27. breast.tw.
28. 26 or 27
29. (breast adj milk).ti,ab,sh.
30. (breast adj tender\$).ti,ab,sh.
31. or/29-30
32. 28 not 31
33. exp neoplasms/
34. 32 and 33
35. exp lymphedema/
36. 35 and 32
37. (breast adj25 neoplasm\$).ti,ab,sh.
38. (breast adj25 cancer\$).ti,ab,sh.
39. (breast adj25 tumour\$).ti,ab,sh.
40. (breast adj25 tumor\$).ti,ab,sh.
41. (breast adj25 carcinoma\$).ti,ab,sh.
42. (breast adj25 adenocarcinoma\$).ti,ab,sh.
43. (breast adj25 sarcoma\$).ti,ab,sh.
44. (breast adj50 dcis).ti,ab,sh.
45. (breast adj25 ductal).ti,ab,sh.

(Continued)

46. (breast adj25 infiltrating).ti,ab,sh.
47. (breast adj25 intraductal).ti,ab,sh.
48. (breast adj25 lobular).ti,ab,sh.
49. (breast adj25 medullary).ti,ab,sh.
50. or/37-49
51. 25 or 34 or 36 or 50
52. exp mastectomy/
53. 51 or 52
54. exp "Analytical, Diagnostic and Therapeutic Techniques and Equipment"/
55. 54 and 32
56. 55 or 53
57. exp mammary neoplasms/
58. (mammary adj25 neoplasm\$).ti,ab,sh.
59. (mammary adj25 cancer\$).ti,ab,sh.
60. (mammary adj25 tumour\$).ti,ab,sh.
61. (mammary adj25 tumor\$).ti,ab,sh.
62. (mammary adj25 carcinoma\$).ti,ab,sh.
63. (mammary adj25 adenocarcinoma\$).ti,ab,sh.
64. (mammary adj25 sarcoma\$).ti,ab,sh.
65. (mammary adj50 dcis).ti,ab,sh.
66. (mammary adj25 ductal).ti,ab,sh.
67. (mammary adj25 infiltrating).ti,ab,sh.
68. (mammary adj25 intraductal).ti,ab,sh.
69. (mammary adj25 lobular).ti,ab,sh.
70. (mammary adj25 medullary).ti,ab,sh.
71. or/57-70
72. 56 or 71
73. exp breast self-examination/
74. (breast adj25 self\$).ti,ab,sh.
75. (breast adj25 screen\$).ti,ab,sh.
76. exp mammography/
77. or/72-76
78. mammograph\$.tw.
79. 78 and 32
80. 77 or 79
81. Flushing/
82. flush\$.ti,ab,sh.
83. flash\$.ti,ab,sh.
84. Vasomotor.mp.
85. Vasomotor\$.ti,ab,sh.
86. or/81-85
87. non hormonal therapy.mp.
88. "not hormonal therapy".mp.
89. (therapy not hormonal).mp.
90. "therapy not hormonal".mp.
91. serotonin uptake inhibitors/
92. (Serotonin and norepinephrine reuptake inhibitors).mp.
93. fluoxetine/
94. Phenyl Ethers.mp.

(Continued)

95. limit 94 to yr=1974-1978
96. propylamines/
97. limit 96 to yr=1966-1978
98. sertraline/
99. sertraline.mp.
100. limit 99 to yr=1983-1998
101. 11-Naphthylamine.mp.
102. limit 101 to yr=1983-1998
103. paroxetine/
104. Paroxetine.mp.
105. limit 104 to yr=1980-1992
106. Dioxolanes/
107. limit 106 to yr=1978-1982
108. Piperidines/
109. limit 108 to yr=1982-1992
110. citalopram/
111. antidepressive agents/
112. limit 111 to yr=1977-1988
113. propylamines/
114. limit 113 to yr=1977-1988
115. serotonin antagonists/
116. limit 115 to yr=1978-1988
117. Venlafaxine.mp.
118. Mirtazapine.mp.
119. trazodone/
120. piperazines/
121. limit 120 to yr=1971-1974
122. pyridines/
123. limit 122 to yr=1971-1974
124. Triazoles/
125. limit 124 to yr=1971-1974
126. Gabapentin.mp.
127. clonidine/
128. Antihypertensive agents/
129. limit 128 to yr=1966-1971
130. Imidazoles/
131. limit 130 to yr=1966-1971
132. Veralipride.mp.
133. methyldopa/
134. vitamin E/
135. Bellergal.mp.
136. ergotamine-phenobarbital-belladonna.mp.
137. exp Acupuncture/
138. exp Complementary therapies/
139. thinking/
140. limit 139 to yr=1970-1974
141. odors/
142. limit 141 to yr=1986-1995
143. oils, volatile/

(Continued)

144. limit 143 to yr=1986-1996
145. Magnetic therapy/
146. Exercise/
147. exertion/
148. limit 147 to yr=1966-1988
149. Physical fitness/
150. limit 149 to yr=1966-1988
151. or/87-150
152. 21 and 80 and 86 and 151

## Appendix 6. EMBASE search strategy

**Host: OVID**  
**1974 to April 2005**

1. exp breast cancer/
2. exp neoplasms/ and medullary.mp.
3. exp fibrocystic disease of breast/
4. or/1-3
5. exp breast/
6. breast.tw.
7. 5 or 6
8. (breast adj milk).ti,ab,sh.
9. (breast adj tender\$).ti,ab,sh.
10. or/8-9
11. 7 not 10
12. exp neoplasms/
13. 11 and 12
14. exp lymphedema/
15. 14 and 11
16. (breast adj25 neoplasm\$).ti,ab,sh.
17. (breast adj25 cancer\$).ti,ab,sh.
18. (breast adj25 tumour\$).ti,ab,sh.
19. (breast adj25 tumor\$).ti,ab,sh.
20. (breast adj25 carcinoma\$).ti,ab,sh.
21. (breast adj25 adenocarcinoma\$).ti,ab,sh.
22. (breast adj25 sarcoma\$).ti,ab,sh.
23. (breast adj25 dcis).ti,ab,sh.
24. (breast adj25 ductal).ti,ab,sh.
25. (breast adj25 infiltrating).ti,ab,sh.
26. (breast adj25 intraductal).ti,ab,sh.
27. (breast adj25 lobular).ti,ab,sh.
28. (breast adj25 medullary).ti,ab,sh.
29. or/16-28
30. 4 or 13 or 15 or 29
31. exp mastectomy/

(Continued)

32. 30 or 31
33. exp mammary neoplasms/
34. (mammary adj25 neoplasm\$).ti,ab,sh.
35. (mammary adj25 cancer\$).ti,ab,sh.
36. (mammary adj25 tumour\$).ti,ab,sh.
37. (mammary adj25 tumor\$).ti,ab,sh.
38. (mammary adj25 carcinoma\$).ti,ab,sh.
39. (mammary adj25 adenocarcinoma\$).ti,ab,sh.
40. (mammary adj25 sarcoma\$).ti,ab,sh.
41. (mammary adj25 dcis).ti,ab,sh.
42. (mammary adj25 ductal).ti,ab,sh.
43. (mammary adj25 infiltrating).ti,ab,sh.
44. (mammary adj25 intraductal).ti,ab,sh.
45. (mammary adj25 lobular).ti,ab,sh.
46. (mammary adj25 medullary).ti,ab,sh.
47. or/33-46
48. 32 or 47
49. exp breast self-examination/
50. (breast adj25 self\$).ti,ab,sh.
51. (breast adj25 screen\$).ti,ab,sh.
52. exp mammography/
53. or/48-52
54. mammograph\$.tw.
55. 54 and 11
56. 53 or 55
57. exp clinical trial/
58. comparative study/
59. drug comparison/
60. major clinical study/
61. randomization/
62. crossover procedure/
63. double blind procedure/
64. single blind procedure/
65. placebo/
66. prospective study/
67. ((clinical or controlled or comparative or placebo or prospective or randomi#ed) adj3 (trial or study)).ti,ab.
68. (random\$ adj7 (allocat\$ or allot\$ or assign\$ or basis\$ or divid\$ or order\$)).ti,ab.
69. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj7 (blind\$ or mask\$)).ti,ab.
70. (cross?over\$ or (cross adj1 over\$)).ti,ab.
71. or/57-70
72. 56 and 71
73. limit 72 to human
74. flushing/
75. hot flush/
76. flush\$.ti,ab,sh.
77. flash\$.ti,ab,sh.
78. vasomotor.mp.
79. vasomotor\$.ti,ab,sh.
80. or/74-79

(Continued)

81. non hormonal therapy.mp.
82. (therapy not hormonal).mp.
83. exp serotonin uptake inhibitors/
84. serotonin reuptake inhibitors.mp.
85. norepinephrine reuptake inhibitors.mp.
86. fluoxetine/
87. sertraline/
88. paroxetine/
89. citalopram/
90. venlafaxine/
91. mirtazapine/
92. trazodone/
93. gabapentin/
94. clonidine/
95. veralipride/
96. methyl dopa/
97. alpha tocopherol/
98. bellergal/
99. ergotamine-phenobarbital-belladonna.mp.
100. alternative medicine/
101. meditation/
102. yoga/
103. ayurvedic drug/
104. ayurvedic.mp.
105. acupuncture/
106. magnetic therapy.mp.
107. leisure/
108. relaxation.mp.
109. feedback system/
110. hypnosis/
111. behaviour therapy/
112. exp exercise/
113. or/81-112
114. 73 and 80 and 113

## Appendix 7. WHO ICTRP Search Portal

Host: <http://apps.who.int/trialsearch/>

21 May 2010

Advanced search (with Recruitment set at ALL):

Search 1.

Condition field: breast cancer AND flush

Intervention field: hormone

Search 2.

Condition field: flush

Intervention field: hormone

Search 3.

Condition field: hot

Intervention field: hormone



Search 4.

Intervention field: breast cancer AND hot flash

## **HISTORY**

Protocol first published: Issue 3, 2004

Review first published: Issue 9, 2010

## **CONTRIBUTIONS OF AUTHORS**

Gabriel Rada: background, criteria for considering studies. Data extraction and quality assessment of included studies. Statistical analyses. Manuscript redaction.

Luz María Letelier: review methods. Discrepancies resolution. Manuscript redaction.

Javiera Corbalán: screening of studies.

Tomás Pantoja: criteria for considering studies, statistical analyses.

Daniel Capurro: criteria for considering studies, review methods. Data extraction and quality assessment of included studies. Manuscript redaction.

Gladys Moreno: screening of studies.

Claudio Vera: statistical analyses. Manuscript redaction.

## **DECLARATIONS OF INTEREST**

None

## **SOURCES OF SUPPORT**

### **Internal sources**

- Pontificia Universidad Católica de Chile, Chile.

The University did not provide a specific support for the development of the review, but all the authors receive a fixed salary from the institution.

### **External sources**

- None, Not specified.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

*On types of interventions (under 'Criteria for considering studies for this review')*

We decided to include any study independent of the time of follow up, even though we had established that we were going to include “any non-hormonal therapy administered for at least one month”. This decision was made before screening for articles so should not have introduced selection bias.

*On Search methods for identification of studies*

We did not perform handsearching as we did not identify any relevant journal that was not already included in the Cochrane Breast Cancer Group Specialized Register.

*On Assessment of Methodological Quality (under 'Methods of the Review')*

The quality assessment followed the same principles to that stated in the protocol. In order to facilitate the presentation and understanding, they are shown in 'Risk of bias' tables and 'Summary of findings' tables.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Acupuncture Therapy; Amines [therapeutic use]; Breast Neoplasms [complications; \*drug therapy]; Clonidine [therapeutic use]; Cyclohexanecarboxylic Acids [therapeutic use]; Excitatory Amino Acid Antagonists [therapeutic use]; Homeopathy [methods]; Hot Flashes [etiology; \*therapy]; Magnetic Field Therapy; Norepinephrine [antagonists & inhibitors]; Randomized Controlled Trials as Topic; Relaxation Therapy; Serotonin Antagonists [therapeutic use]; Vitamin E [therapeutic use]; Vitamins [therapeutic use]; gamma-Aminobutyric Acid [therapeutic use]

### MeSH check words

Female; Humans