Drewe et al. SpringerPlus (2015) 4:65
DOI 10.1186/s40064-015-0808-y

SpringerPlus
a SpringerOpen Journal

REVIEW Open Access

A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients

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Abstract

The cardinal climacteric symptoms of hot flushes and night sweats affect 24-93% of all women during the physiological transition from reproductive to post-reproductive life. Though efficacious, hormonal therapy and partial oestrogenic compounds are linked to a significant increase in breast cancer. Non-hormonal treatments are thus greatly appreciated. This systematic review of published hormonal and non-hormonal treatments for climacteric, and breast and prostate cancer-associated hot flushes, examines clinical efficacy and therapy-related cancer risk modulation.

A PubMed search included literature up to June 19, 2014 without limits for initial dates or language, with the search terms, (*hot flush** OR *hot flash**) AND (*clinical trial** OR *clinical stud**) AND (*randomi** OR *observational*) NOT *review*). Retrieved references identified further papers. The focus was on hot flushes; other symptoms (night sweats, irritability, etc.) were not specifically screened. Included were some 610 clinical studies where a measured effect of the intervention, intensity and severity were documented, and where patients received treatment of pharmaceutical quality. Only 147 of these references described studies with alternative non-hormonal treatments in post-menopausal women and in breast and prostate cancer survivors; these results are presented in Additional file 1.

The most effective hot flush treatment is oestrogenic hormones, or a combination of oestrogen and progestins, though benefits are partially outweighed by a significantly increased risk for breast cancer development.

This review illustrates that certain non-hormonal treatments, including selective serotonin reuptake inhibitors, gabapentin/pregabalin, and *Cimicifuga racemosa* extracts, show a positive risk-benefit ratio.

Key points

- Several non-hormonal alternatives to hormonal therapy have been established and registered for the treatment of vasomotor climacteric symptoms in peri- and post-menopausal women.
- There are indications that non-hormonal treatments are useful alternatives in patients with a history of breast and prostate cancer. However, confirmation by larger clinical trials is required.

Keywords: Climacteric symptoms; Vasomotor symptoms; Menopause; Non-hormonal treatments; Systematic review

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Introduction

Well-characterised primary symptoms associated with the climacterium include hot flushes (HF), sweating, insomnia, nervousness and irritability, palpitations, changes in libido, dyspareunia, depression, musculoskeletal pain, vaginal pruritus and dryness, pain and/or inflammation, and increased bone turnover (Burger et al. 2002; Crandall et al. 2011). These symptoms vary in frequency and severity, and are presumed to be evoked by the physiological decrease in ovarian function as women transition from reproductive to post-reproductive life (Kronenberg 1990; Nakano et al. 2012; Crandall et al. 2011; Hunter et al. 2012). In other patients, the same symptoms may be caused by chemotherapy or surgery relating to breast cancer or other malignancies. The prevalence of the cardinal vasomotor symptoms, HF and night sweating, varies between 24 and 93% in peri- and post-menopausal women (Kronenberg 1990; Nakano et al. 2012; Crandall et al. 2011; Hunter et al. 2012), and is observed in more than 65% of breast cancer patients (Adelson et al. 2005). Patients with chemotherapy-induced ovarian insufficiency experience even more severe symptoms than patients undergoing normal ageing (Adelson et al. 2005; Carpenter et al. 1998), and the effect on the quality of life varies greatly among those affected.

Even men experience HF during normal ageing, evoked by gradually decreasing testosterone levels. One Swedish survey found that 31% of non-castrated ageing men reported HF and, of these, the quality of life was affected in 50% (Spetz et al. 2003). Aggravated symptoms are observed when testosterone concentrations decrease rapidly, such as during anti-androgen treatment or after orchiectomy for prostate cancer (Adelson et al. 2005). About 63%-80% of post-orchiectomy prostate cancer patients complained of long-lasting HF (Charig & Rundle 1989; Karling et al. 1994; Schow et al. 1998). More than 48% of these patients complained of sustained flushes 5 years after onset, and more than 40% experienced flushes even 8 years after castration (Karling et al. 1994).

Aetiology

Though not fully understood, several authors propose that the aetiology of HF is due to a changed thermoregulation set point of the hypothalamus evoked by the abruptly-lowered oestrogen levels during menopause (Adelson et al. 2005; Kronenberg 1994). Other neuroendocrine hormones (e.g., α-adrenergic mechanisms (Berendsen 2000; Rosenberg & Larsen 1991)) may be involved in this disturbance of temperature regulation. Oestrogen interacts with neurotransmitters, such as norepinephrine and endogenous opioids (Casper & Yen 1985; Rebar & Spitzer 1987), as well as serotonin (Berendsen 2000), and thereby alters the temperature regulation set point in the hypothalamus.

Post-menopausal women show a diminished serotonergic activity compared to pre-menopausal controls. After oestrogen hormone replacement therapy, serotonin activity becomes partly normalised (Blum et al. 1996; Gonzales & Carrillo 1993; Halbreich et al. 1995). Serotonin 5-HT_{2A} receptors play a key role in the development of HF in the hypothalamus. These receptors are up-regulated during oestrogen withdrawal (Biegon 1990). Blockage of 5-HT_{2A} receptors by the 5-$HT_{2,3}$ receptor blocker, mirtazapine, in post-menopausal women reduced the frequency and intensity of HF (Waldinger et al. 2000). On the other hand, activation of 5-HT_2 receptors with *m*-chlorophenylpiperazine, a 5-$HT_{2A:2C}$ receptor agonist, induced post-menopausal symptoms, such as sweating and hot and cold flushes and palpitations (Berendsen 2000) (and references cited therein). The frequency and severity of HF secondary to medical castration for advanced prostate cancer are reduced with sertraline (Roth & Scher 1998). It has also been shown that 5-HT_{1A}, 5-HT_{1D} and 5-HT_7 receptors are also involved in hypothalamic thermoregulation (Hedlund et al. 2003; Naumenko et al. 2011). *Cimicifuga racemosa* extracts (CRE) bind to the serotonin receptors 5-HT_{1A}, 5-HT_{1D} and 5-HT_7 (Burdette et al. 2003; Powell et al. 2008), and a part of its effect on HF may be mediated by these receptors. In addition, oestrogen increases the density of 5-HT_{2A} receptors in the *nucleus accumbens*, suggesting an effect of oestrogen withdrawal on mood and may explain the onset of depressive symptoms in menopause (Fink & Sumner 1996; Fink et al. 1996).

Treatment of climacteric symptoms with hormone therapy

Different treatments have been established for climacteric symptoms. For many years, hormone therapy (HT) using oestrogen or a combination of oestrogen and progestins was the gold standard. Much evidence exists that HT effectively reduces climacteric symptoms in women (as indicated by a Cochrane meta-analysis of 24 randomised, placebo-controlled trials (MacLennan et al. 2009)).

HT of climacteric symptoms and risk of breast cancer

As early as 1997, initial epidemiologic evidence showed that HT may increase the risk of breast cancer. One meta-analysis (Collaborative Group on Hormonal Factors in Breast Cancer 1997) of 51 epidemiologic studies comparing data from 52,705 women with breast cancer, and including 108,411 women without breast cancer, revealed that the prevalence of breast cancer was significantly increased in women using HT, and rose with duration of use. Several subsequent studies have confirmed these data.

The large prospective Women's Health Initiative (WHI) trial that included 16,608 post-menopausal women was prematurely terminated due to a significantly increased risk of breast cancer development (nominal hazard ratios (HR) 1.26 (95% confidence interval (95% CI) 1.00-1.59), coronary heart disease (HR 1.29 (95% CI 1.02-1.63)), stroke (HR 1.41 (95% CI 1.07-1.85)) and venous thromboembolic disease (HR 2.11 (95% CI 1.58-2.82)) in the hormone-treated arm (Rossouw et al. 2002).

Several other prospective und epidemiological studies (Chlebowski et al. 2009; Collaborative Group on Hormonal Factors in Breast Cancer 1997; Beral & Million Women Study Collaborators 2003; Porch et al. 2002; Weiss et al. 2002; Beral et al. 2002) confirmed these findings; for a review, cf. (Collins et al. 2005).

In one large study combining data from a randomised trial (n = 16,608) and an observational study (n = 41,449) in the WHI population, temporal trends of breast cancer diagnosis were analysed in groups who received daily oestrogen plus medroxyprogesterone acetate or placebo (Chlebowski et al. 2003). This study revealed that the breast cancer risk increased steadily throughout the mean follow-up of 5.6 years of the intervention period in both study groups. However, at the end of the intervention phase, hazard-ratio increased significantly for total breast cancer (HR 1.24 (95% CI 1.02-1.50); $p < 0.001$)) and for invasive breast cancer (HR 1.24 (95% CI 1.01-1.50); $p = 0.003$) in the oestrogen plus medroxyprogesterone acetate group compared with placebo. Interestingly, the elevated risk in the hormone-treated group decreased rapidly after stopping HT treatment, however, a small and not significantly increased risk (HR 1.15 (95% CI 0.98-1.37)) was still present after 11 years of follow up (Stevenson et al. 2011). The decrease was unrelated to mammography frequency, since this was unchanged in the two groups. These results also concurred with anecdotal evidence that withdrawal of HT alone led to breast cancer regression (Powles & Hickish 1995). A subgroup analysis showed that the breast cancer risk of combined treatment with oestrogen and progestin increased only in the subgroup of patients who received a hormonal treatment prior to the study (adjusted HR 1.96 (95% CI 1.17-3.27), N = 4311) and not among the patients who never used hormonal treatment before (HR 1.02 (95% CI 0.77-1.36); N = 12297) (Anderson et al. 2006).

In the *Million Women Study* (n = 1,084,110), current HT users demonstrated a significantly increased relative risk (RR): 1.66 (95% CI 1.58-1.75) for developing breast cancer, whereas past users had no increased risk (RR 1.01 (95% CI 0.94-1.09)). The breast cancer risk increased with duration of HT treatment and was more pronounced with oestrogen-progestagen combinations and, with respect to receptor status, were mixed and did not show a significant increase in oestrogen receptor-positive cancers (Chlebowski et al. 2003). However, dose or HT preparation (oral vs. transdermal vs. implant) did not affect overall results (Beral & Million Women Study Collaborators 2003). Other studies have shown diverging results: a trend ($p = 0.09$) towards a lower risk (Prentice et al. 2008) for breast cancer development and significantly lower risk using monotherapy with conjugated equine oestrogen alone compared to combination HT (Ross et al. 2000; Saxena et al. 2010; Beral et al. 2011).

After publication of the WHI studies and the Million Women Study, HT use decreased drastically worldwide (Hersh et al. 2004; Canfell et al. 2008; Antoine et al. 2011). Notably, the lowered use was accompanied by a significant decrease in breast cancer incidence in many countries (Canfell et al. 2008; Ravdin et al. 2007; Canfell et al. 2009) that was more evident in oestrogen-receptor positive than in oestrogen-receptor negative cancers, and in women older than 50 years of age (Ravdin et al. 2007). It was most prominent in countries with a high absolute prevalence of HT use and could not be explained by changes in the mammography rate; cf. review by Zbuk and Anand (Zbuk & Anand 2012). Using epidemiologic data between the years 2000 (118,724 patients) to 2007 (154,447) from Israel, Silverman *et al.* (Silverman et al. 2011) could clearly discriminate between the effect of HT and mammography rate for the risk of breast cancer development and confirmed that the drop in HT frequency caused a parallel drop in the breast cancer rate. After cessation of HT, the increased risk of breast cancer disappeared within 2 years (Narod 2011; Chlebowski et al. 2009; Beral et al. 2011).

Risk assessment of HT treatment in breast cancer patients

There is a need for medical management of climacteric symptoms in cancer patients. In one survey, only 20.5% of women being treated for breast cancer and suffering from moderate to severe HF actually received any treatment for their symptoms (Gupta et al. 2006). In an earlier study in 190 women with breast cancer, the prevalence of post-menopausal symptoms, such as HF, was 65%; half of the women felt that they needed treatment of these symptoms (Couzi et al. 1995).

The safety of HT in breast cancer patients was reviewed in 20 studies by Antoine *et al.* (Antoine et al. 2007). Citing 10 prospective and two randomised studies that were heterogeneous with respect to tumour characteristics, prognostic factors and therapies, the authors conclude that there are no reassuring data indicating that HT is not without risks. Antoine also cited two studies that showed decreased recurrence rates and two others with lowered breast cancer mortality under HT treatment (Antoine et al. 2007). Nevertheless, one randomised study (HABITS trial, n = 434) showed that HT increased the recurrence of breast cancer significantly

(relative HR 3.3; 95% CI 1.5-7.4; p = 0.02) (Holmberg & Anderson 2004), and was therefore prematurely terminated. The other randomised study (von Schoultz & Rutqvist 2005) (Stockholm trial, n = 378) did not show any difference in the cancer recurrence rate between HT and the control group (relative HR 0.82; 95% CI 0.35-1.9). Since the overall analysis of both studies revealed a significantly greater risk of cancer recurrence in the HT group (relative HR 1.8; 95% CI 1.03-3.1), the Stockholm trial was likewise discontinued. The authors therefore concluded that guidelines should advise against using HT in patients with a history of breast cancer (Antoine et al. 2007).

Progestogens are effective in treating post-menopausal symptoms: In one open (Erlik et al. 1981) and one prospective randomised trial (Loprinzi et al. 1994a), more than 80% of patients showed symptom improvement after receiving megestrol acetate. The latter study also included 66 men with prostate cancer who complained of HF after androgen deprivation therapy. The degree of symptom relief was similar in women and men. However, the safety of progestagens has not been established.

Treatment with synthetic compounds with partial estrogenic activity

The minimum requirements for the clinical evaluation of new products in the treatment of vasomotor symptoms have been defined by the Food and Drug Administration (FDA) (FDA. U.S. Department of Health and Human Services Food and Drug Administration 2003) and the European Medicines Agency (EMA) (EMEA. Committee for Medicinal products for human use (CHMP) 2005). Besides the definition of outcome parameters and the methods of their evaluation, these guidelines set standards requiring at least 12 weeks of treatment for a randomised controlled clinical trial. This considers the need for chronic treatment in this indication. Many of the academia-driven studies have been performed with shorter treatment durations, and could therefore be considered as providing merely supportive evidence.

Tibolone

Tibolone is a synthetic steroid gonadomimetic with weak oestrogenic, androgenic and progestogenic properties (Baber et al. 2005). Its action has been described as a **s**elective **t**issue o**e**strogenic **a**ctivity **r**egulator (STEAR) (Kloosterboer 2004), meaning that the amount of tissue enzymes (sulfatase, sulfotransferase, and 17β-hydroxysteroid dehydrogenase) control the sum of active ligands for steroid receptors, and may be responsible for tissue-specific effects. This concept may also explain certain discrepancies from *in vitro* investigations: *In vitro,* tibolone exerts a proliferative effect on an oestrogen–receptor-positive breast cancer cell line (MCF-7), indicating a potential tumour promoting effect (Lippert et al. 2002; Mueck et al. 2003). *In vivo*, the proliferative effects of tibolone were investigated in a randomised controlled trial by measuring the content of the nuclear antigen Ki-67 (a proliferation marker) in breast tissue biopsies after treatment with tibolone, oestradiol/norethisterone acetate or placebo. No increase in proliferation was seen in the tibolone or placebo group, whereas a significant increase was observed in the oestradiol/norethisterone acetate group (Conner et al. 2004). This was further investigated in a randomised, placebo-controlled study in patients with oestrogen receptor-positive primary breast cancer (Kubista et al. 2007). However, the treatment duration was only 14 days and only a trend of a beneficial effect on proliferation was observed.

Several studies have investigated tibolone as a potential alternative to classical HT to reduce climacteric symptoms (Landgren et al. 2002; Hammar et al. 1998). One international study conducted at 38 sites throughout Europe, South Africa and Mexico with 485 women compared tibolone (2.5 mg/d) to desvenlafaxine (100 mg/d) and placebo, examining reduction in the number of HF. No difference was noted between desvenlafaxine and placebo, but tibolone significantly reduced the number of HF when compared to placebo ($p < 0.001$), though there was a significant increase in the number of tibolone subjects who experienced bleeding ($p < 0.024$) (Bouchard et al. 2012).

In a large randomised study in 4,538 post-menopausal women (Cummings et al. 2008), the effect of tibolone was compared to placebo over 34 months with regard to bone fracture, breast cancer development and cardiovascular diseases. Compared to placebo, patients in the tibolone group had a decreased risk of vertebral fractures ($p < 0.001$), a decreased risk of non-vertebral fractures ($p < 0.01$), and a decreased risk of developing invasive breast ($p = 0.02$) and colon cancer ($p = 0.04$). On the other hand, patients had an increased risk of stroke ($p = 0.02$), for which the study was prematurely terminated.

Tibolone's symptom-alleviating effects have also been demonstrated in breast cancer survivors in several clinical studies (Baber et al. 2005; Kroiss et al. 2005). In one prospective study, 103 post-menopausal women received either tibolone, oestrogen plus medroxyprogesterone acetate (i.e., HT) or placebo for one year (Marchesoni et al. 2006). An increase in mammographic breast density (as a surrogate marker for the development of breast cancer) was observed in 45% after HT, but only in 2.3% after tibolone treatment, and none in the placebo group (Marchesoni et al. 2006; Greendale et al. 1999). However, a later study did not confirm these results (Kutlu et al. 2004).

The safety and efficacy of tibolone have been studied in great depth in the large LIBERATE (Livial Intervention

following Breast Cancer; Efficacy, Recurrence And Tolerability) trial (Kenemans et al. 2009) in 3,148 women with breast cancer and severe climacteric symptoms due to treatment with tamoxifen, aromatase inhibitors, gonadotropin-releasing hormone analogues or chemotherapy. Patients were randomised to receive either 2.5 mg/d tibolone or placebo. The primary endpoint was the rate of breast cancer recurrence. After a median follow-up of 3.1 years, patients in the tibolone group had a significantly higher recurrence rate ($p = 0.001$, HR 1.40 (95% CI 1.14-1.70)) than after placebo treatment. Vasomotor symptoms and bone-mineral density improved significantly with tibolone compared to placebo. From the finding that breast cancer recurrence was more evident in patients with oestrogen-receptor positive tumours, the authors concluded that tibolone exerted an oestrogenic effect, and that its use in patients "with a known, past or suspected breast cancer will remain contraindicated". The LIBERATE trial bone sub-study recruiting 763 women confirmed these results with the clarification that the increase in breast cancer recurrence and tibolone use was higher in women having normal bone mineral density than in those with lower bone density (Bundred et al. 2012).

Non-hormonal alternatives to HT in the treatment of climacteric symptoms

Some of the non-hormonal treatments (e.g., isoflavones and vitamins) are marketed as food supplements in different countries (Europe, USA and Canada). Cimicifuga racemosa is currently registered as a herbal medicinal drug for the treatment of climacteric complaints in several European countries (among them, Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Hungary, Sweden, Switzerland, and UK) and Australia, South Korea, South Africa. In some countries (such as USA) Cimicifuga racemosa is used as a food supplement. Paroxetine is registered in the USA for treatment of climacteric complaints. Registration of desvenlafaxine was rejected in the USA, and a New Drug Application (NDA) was withdrawn by the manufacturer in Europe. So far as we know, none of the other mentioned compounds are registered for the treatment of menopausal symptoms.

Literature search methodology

The search was carried out using the PubMed database and included all literature up to June 19, 2014. No limits were set for language. References cited in the papers retrieved were used to locate further papers. The following search terms were used: (hot flush* OR hot flash*) AND (clinical trial* OR clinical stud*) AND (randomi* OR observational) NOT review). This search revealed 609 clinical studies. Only 147 of these references described studies with alternative, non-hormonal treatments for HF in post-menopausal women and in breast cancer survivors, and these are presented in Additional file 1. All effort was made to include statistical relevance (p values, confidence intervals) whenever possible. It was noted that, in many of the earlier studies (prior to 2000), this informative criterion was less rigorously provided.

Dopamine agonists

As mentioned above (Berendsen 2000; Rosenberg & Larsen 1991), it is thought that α-adrenergic mechanisms participate in the pathophysiology of HF. And as is often the case in medicine, anecdotal reports pique interest in the testing of a specific drug for a new indication. In this instance, hypertensive women being treated with methyldopa, an α-adrenergic, centrally-active sympatholytic, reported improvement in HF symptoms. In two randomised, placebo-controlled trials each lasting 4 weeks and involving 40 post-menopausal women each, respectively (Nesheim & Saetre 1981; Andersen et al. 1986), significant improvement in HF symptoms was reported. Another study expounded on this and compared the following: bromocriptine (dopaminergic), liposom (indirect dopaminergic), veralipride (antidopaminergic), domperidone (a peripheral antidopaminergic) and placebo for treating vasomotor symptoms of menopause (Zichella et al. 1986). As all active treatments proved effective, different pathways were postulated: A direct action would be expected from dopamine, and direct and indirect dopaminergic agents, while the antidopaminergic drugs are thought to evoke a secondary dopamine-like activity via the short-loop feedback exerted by hyperprolactinaemia on tuberoinfundibular dopamine neurons, or perhaps stimulation of the opioid system (Zichella et al. 1986). Though improvement in HF was seen, concerns about side effects (depression, anxiety, decreased alertness, lethargy, dizziness, headaches, myalgia, etc.) led to other avenues being pursued.

Adrenergic agonists

Clonidine, as a centrally-active antihypertensive and α_2-adrenoceptor agonist, seemed promising for the treatment of HF.

Effects of oral clonidine were tested against no treatment in 30 women where significant improvement in HF frequency, severity and duration were noted (Chow et al. 1993).

In a small randomised prospective double-blind study ($n = 29$), *transdermal* therapy with clonidine (corresponding to 0.1 mg/d) over 8 weeks significantly reduced the number (80%, $p < 0.04$), severity (73%, $p < 0.04$) and duration (67%, $p < 0.03$) of HF, compared to 36%, 29% and 21% for placebo, respectively (Nagamani et al. 1987).

In two larger randomised, double-blind, placebo-controlled cross-over trials in post-menopausal patients, significant improvements in the number, severity and duration of HF were observed: In the first study (n = 100), patients received *oral* clonidine in doses ranging from 0.025 to 0.075 mg b.i.d. for 4 weeks; effects were then compared to placebo (Clayden et al. 1974). In the second study (n = 66), patients received a fixed oral dose of 0.050 mg clonidine or placebo twice daily for 4 weeks (Edington et al. 1980), here however, more adverse events (AEs) were observed in the clonidine vs. placebo groups (dry mouth: 11 vs. 4, insomnia: 8 vs. 4). Since the reduction in HF frequency was small although statistically significant, the authors concluded that clonidine was a medication "that makes flushing more tolerable".

The effect of low-dose oral clonidine therapy (up to 0.4 mg/day) for up to 4 weeks was further investigated in several other small studies (n = 10-30); results showed either a significant reduction in the number and severity of HF (Laufer et al. 1982; Chow et al. 1993) or no effect (Wren & Brown 1986), but again, in very small patient numbers and thus of limited value.

Positive effects were confirmed in a larger randomised double-blind cross-over study in 110 female *breast cancer survivors* receiving concomitant tamoxifen treatment (Goldberg et al. 1994), where transdermal clonidine (equivalent to a daily oral dose of 0.1 mg) or placebo was given for 4 weeks. Clonidine therapy reduced HF frequency (20% lower than baseline values, $p < 0.0001$) and severity (10% lower than baseline values, $p = 0.02$), but accompanied by more AEs (dry mouth, $p < 0.001$; constipation, $p < 0.02$; itchiness under the patch, $p < 0.01$ and drowsiness, $p < 0.05$). Transdermal clonidine (corresponding to 0.1 mg/d) was also studied in 70 male *prostate cancer survivors* where no significant decrease in HF was noted ($p = 0.57$) (Loprinzi et al. 1994b).

In a larger trial, the effects of oral clonidine were assessed in 194 post-menopausal women with breast cancer who were receiving tamoxifen treatment (Pandya et al. 2000). After 8 weeks of treatment, frequency of HF decreased by 38% in the clonidine group compared to 24% in the placebo group ($p = 0.006$); however, patients receiving clonidine reported more sleep disturbances (41% vs. 21%; $p = 0.02$).

In another double-blind, randomised phase III study that compared clonidine and venlafaxine in 80 breast cancer survivors, most still receiving endocrine treatment, the primary end-point was defined as the frequency of hot flushes after 4 weeks of treatment using HF and other symptom questionnaires. HF frequency was −7.6 HF for venlafaxine and −4.85 for clonidine ($p = 0.025$). Four clonidine and six venlafaxine patients discontinued due to side effects (Loibl et al. 2007). And in another venlafaxine vs. clondine double-blind, cross-over study in 60 breast cancer survivors, clonidine showed fewer side effects and a higher reduction in HF (55%) when compared with venlafaxine (49%), though statistical significance was not reached. Discontinuation due to side effects was observed in 5/53 for clonidine, and in 14/59 for venlafaxine ($p = 0.038$) (Buijs et al. 2009).

In a recent double-blind, placebo-controlled trial, 102 patients with a history of breast cancer were randomly assigned (2:2:1) to oral daily doses of either venlafaxine 75 mg, clonidine 0.1 mg, or placebo for 12 weeks (Boekhout et al. 2011). Results from the average daily HF scores were assessed both at the week 12 time point, and over the entire 12 weeks. During week 12, hot flush scores were significantly lower in the clonidine group versus placebo ($p = 0.03$), but not significant between venlafaxine and placebo ($p = 0.07$), though the median HF scores were identical in the clonidine and venlafaxine groups at this point. However, over the course of the 12-week trial, there were significant differences between both treatments and placebo ($p < 0.001$ for venlafaxine vs. placebo; $p = 0.045$ for clonidine vs. placebo). Frequencies of nausea ($p = 0.02$), constipation ($p = 0.04$), and severe appetite loss were higher in the venlafaxine group.

Depending on the study, clonidine is either superior or inferior to venlafaxine as an effective treatment in the management of HF in patients with breast cancer, though not without AEs, such as insomnia, constipation or dry mouth. Other studies are discussed under venlafaxine.

No information is yet available as to whether clonidine treatment can modulate the risk of breast cancer recurrence. On one hand, *in vitro* studies from a group in Argentina have demonstrated a proliferative effect (increase in thymidine incorporation) of clonidine in MCF-7 breast cancer cells (Vázquez et al. 1999), in the mouse mammary tumour cell line MC4-L5 (Bruzzone et al. 2008) and in stromal fibroblasts (Bruzzone et al. 2011). In a case-controlled study using data from 2,079 patients who received clonidine treatment (Friedman et al. 2011), a slight but not significant increase in breast cancer development was observed (odds ratio (OR) 1.08 (95% CI 0.98–1.20)). Based on the widespread use of clonidine, the lack of significant epidemiological data suggests that these results are most likely without clinical relevance.

Gabapentin/pregabalin

The first evidence that gabapentin/pregabalin exerted a beneficial effect on HF was reported in 2000 by Guttuso (Guttuso 2000), based on results from six patients. Hypothesised mechanisms of action in HF amelioration are modulation of calcium currents and mitigation of hypothalamic tachykinin activity (Baber et al. 2005).

In a further uncontrolled pilot study (Loprinzi et al. 2002a) in 24 post-menopausal women of whom 20 were

evaluable, gabapentin was given in doses of 300 to 900 mg/day. With four drop-outs due to AEs (e.g. lightheadedness and dizziness), the 16 remaining subjects reported a mean reduction in HF frequency and score of 66% and 70%, respectively.

In a randomised, double-blind, placebo-controlled trial in 59 post-menopausal women with seven or more HF per day, the effects of 900 mg oral gabapentin on HF frequency were assessed after 12 weeks of treatment. Gabapentin evoked a 45% reduction in HF frequency and a 54% reduction in the HF composite score compared to the placebo response (29% ($p = 0.02$) and 31% ($p = 0.01$), respectively). In an extension phase, patients were studied in an *open-label trial* where the dose of gabapentin could be increased up to 2700 mg/day, as needed. Treatment with the higher dose showed a further reduction of 54% and 67%, respectively. Common AEs in the gabapentin group were somnolence ($n = 6$), dizziness ($n = 4$) and rash with and without peripheral oedema ($n = 2$), which were not observed in the placebo group. Four patients in the gabapentin group withdrew their consent and terminated participation because of dizziness, rash, heart palpitations and peripheral oedema, respectively. Two patients temporarily reduced the gabapentin dose due to dizziness and sleepiness. In the extension phase, two patients previously in the placebo arm withdrew from the study due to dizziness and peripheral oedema (Guttuso et al. 2003).

In another randomised, double-blind, placebo-controlled, parallel group trial including 60 women with postmenopausal symptoms, the effect of gabapentin (titrated to 2400 mg/day) was compared to conjugated oestrogens (0.625 mg/day) and placebo for the treatment of moderate-to-severe HF (Reddy et al. 2006) with 20 women per arm. Both active treatments showed a significant and comparable reduction in mean HF composite score vs. placebo after 12 weeks of treatment: oestrogen (72%, $p = 0.016$) and gabapentin (71%, $p = 0.004$). In the placebo group, the mean HF composite score decreased by 54%. In the gabapentin group, slightly more AEs of headache, dizziness and disorientation were observed.

In one randomised trial (Loprinzi et al. 2007) including 118 patients having HF symptoms that were insufficiently-controlled with antidepressant therapy alone (primarily venlafaxine or paroxetine), adding up to 900 mg/d gabapentin resulted in a 54% (95% CI, 34% to 70%) and 56% (95% CI, 26% to 71%) median reduction in HF frequency and score, which was not statistically better than gabapentin treatment alone, 49% (95% CI 26% to 58%) and 60% (95% CI, 33% to 73%), respectively.

In a randomised, double-blind, placebo-controlled trial in 200 menopausal women, the effect of 3×300 mg gabapentin on vasomotoric symptoms was studied over 4 weeks (Butt et al. 2008). Significant decreases for gabapentin over placebo were noted in both the HF score (51.0% vs. 26.5%, $p < 0.001$) and frequency (45.7% vs. 24.7%, $p < 0.001$) for the gabapentin vs. placebo groups, respectively. However, gabapentin treatment was accompanied by a significantly higher rate of AEs than placebo in the first treatment week, but these later abated (dizziness: 18% vs. 1%; unsteadiness: 14% vs. 1%, and drowsiness: 12% vs. 1%).

In two recent randomised placebo-controlled trial in 60 and 50 menopausal women, the effect of gabapentin on vasomotoric symptoms were further confirmed: In the first study (Saadati et al. 2013), when given over 12 weeks, 900 mg gabapentin significantly decreased both HF frequency and severity (both $p < 0.001$). In the second study (Agarwal et al. 2014), the results were confirmed in 50 post-menopausal women after 12 weeks treatment, which was then extended to 24 weeks. Impressive reductions in HF frequency (59.1% and 60.6%) compared to placebo were noted at 12 ($p = 0.008$) and 24 weeks ($p = 0.005$), and the composite score decreased by about 80% already at 12 weeks, which continued until the end of the study (both $p = 0.001$).

A different, gastrorententive galenic formulation of gabapentin was studied in a large randomised, placebo-controlled study in 600 menopausal patients (Pinkerton et al. 2014), providing a continuous drug release in the upper small intestine for 8 to 9 hours. Gabapentin was given asymmetrically (600 mg in the morning and 1200 mg in the evening) over 12 weeks, after which the HF frequency ($p = 0.0007$) and severity ($p = 0.012$) decreased modestly, but significantly compared to placebo. These effects were maintained up to 24 weeks ($p = 0.0174$ and $p = 0.0457$, respectively). Slightly more (5%) women under gabapentin than placebo withdrew because of AEs (16.7% and 11.5%, respectively). Most common in the start phase were dizziness (12.7% and 3.4%), headache (9.3% and 8.1%) and somnolence (6.0% and 2.7%), which levelled off to comparable values over the study period.

Another double-blind RCT (Loprinzi et al. 2010) was performed using pregabalin to treat HF in 207 post-menopausal women. Two doses (2×75 mg/d and 2×150 mg/d) of pregabalin were compared to placebo for a treatment period of 6 weeks. The HF score decreased significantly by 50%, 65% ($p = 0.009$) and 71% ($p = 0.007$) for the placebo, 75 mg b.i.d. and 150 mg b.i.d. group, respectively.

Breast cancer

In a pilot study involving 22 breast cancer survivors receiving tamoxifen therapy, HF were treated with 3×300 mg daily gabapentin for 4 weeks. HF duration decreased by 73.6% ($p = 0.027$) frequency by 44.2% ($p < 0.001$), and severity by 52.6% ($p < 0.001$). Four women dropped out due to AEs (nausea, rash, somnolence), while 8/16

women who finished the study showed a complete response (Pandya et al. 2004).

A large study (Pandya et al. 2005) in 420 breast cancer survivors (300 mg/d or 900 mg/d GP vs. placebo over 8 weeks) also confirmed the effect in this patient population: After 8 weeks of treatment, only the 900 mg dose showed a significant reduction in HF frequency (44%, $p < 0.0001$) and severity (46%; $p < 0.0001$) versus 15% and 15% in the placebo group. However, the study duration was too short to assess whether the treatment modulated the risk of tumour recurrence.

In a smaller cross-over RCT (N = 66) Bordeleau *et al.* (Bordeleau et al. 2010) showed that gabapentin (up to 900 mg/d) and venlafaxine (up to 75 mg/d) demonstrated a similar 66% reduction in HF score in breast cancer survivors ($p < 0.001$); 32% of patients preferred gabapentin, while 68% venlafaxine. The latter showed more nausea, appetite loss, constipation, and reduced negative mood changes than gabapentin, whereas gabapentin demonstrated more dizziness and increased appetite compared with venlafaxine (all $p < 0.05$).

Prostate cancer

Two studies investigated the effect of gabapentin in prostate cancer survivors undergoing androgen deprivation therapy: In a double-blind, placebo controlled trial (Loprinzi et al. 2009) in 223 men, slight to moderate and dose-dependent effects on HF frequency and severity could be demonstrated in a short-term study over 4 weeks. Compared to baseline, HF frequency and score decreased by 21.5 (95% CI: 11.3-30.9%) and 27.0% (95% CI: 12.1-36.1%) after placebo and by 45.5% (95% CI: 31.1-50.6%) and 44.4% (95% CI: 35.2-56.3%) after administration of 900 mg/d, respectively. Only in the highest dose could a significantly greater reduction in HF frequency ($p = 0.02$) compared to placebo be demonstrated. In an extension of the above-cited study (Moraska et al. 2010), 147 patients were either switched from placebo to gabapentin or continued gabapentin treatment for eight additional weeks with doses of gabapentin titrated up to 900 mg/d. The treatment was well tolerated. Effects of previous high dose treatments were maintained and those of low dose and placebo treatments were improved. The majority of the patients opted to take a dose of 600 mg/d. However, no data were obtained regarding the question of whether gabapentin was able to modulate prostate cancer disease.

In summary, results from several randomised controlled trials (RCTs) in post-menopausal women without cancer (Loprinzi et al. 2002a; Guttuso et al. 2003; Reddy et al. 2006; Loprinzi et al. 2007; Butt et al. 2008; Saadati et al. 2013; Agarwal et al. 2014; Pinkerton et al. 2014; Loprinzi et al. 2010) and in breast and prostate cancer survivors (Pandya et al. 2004; Pandya et al. 2005; Bordeleau et al. 2010; Loprinzi et al. 2009; Moraska et al. 2010), gabapentin showed no or a slight effect at lower doses (<900 mg/d GP) or moderate effects at higher doses, ranging from 44% (Pandya et al. 2005) to 71% (Loprinzi et al. 2010; Reddy et al. 2006). The study durations were, in general, short (4–8 weeks) except in three studies (Guttuso et al. 2003; Reddy et al. 2006; Saadati et al. 2013) that continued for 12 weeks and two studies for 24 weeks (Agarwal et al. 2014; Pinkerton et al. 2014).

Antidepressant drugs

Various antidepressant drugs (e.g., selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)) have been studied to treat post-menopausal symptoms. The rationale of using antidepressant drugs is two-fold: Firstly, many patients with climacteric symptoms suffer from depressive symptoms and secondly, antidepressant drugs acting on synaptic serotonin concentrations may beneficially interfere with the pathophysiology of HF (Burdette et al. 2003; Hedlund et al. 2003; Naumenko et al. 2011).

Selective serotonin reuptake inhibitors (SSRI)

Paroxetine

In 2003, Stearns and colleagues performed a large randomised, double-blind, placebo-controlled, parallel group study in 165 post-menopausal women administering placebo or 12.5 mg/d or controlled-release 25.0 mg/d for 6 weeks (Stearns et al. 2003). The mean HF frequency (and median composite score) decreased by 37.8% (1.8), 62.2% (3.3) and 64.6% (3.2) in the placebo, 12.5 mg/d and 25 mg/d paroxetine groups, respectively. Although not statistically significant, AEs (mainly headache, dizziness, nausea, and insomnia) were predominantly observed with the higher paroxetine dose. This same group confirmed these results in 2005 in a double-blind, cross-over, placebo-controlled study involving 151 post-menopausal women. Women received first paroxetine (10 or 20 mg/d) or placebo for 4 weeks, and then the other treatment option (Stearns et al. 2005). The 10 mg dose reduced the hot flush frequency and composite score by 40.6% and 45.6% vs. 13.7% and 13.7% for placebo, respectively ($p = 0.0006$ and $p = 0.0008$) and 20 mg paroxetine by 51.7% and 56.1% vs. 26.6% and 28.8% for placebo ($p = 0.002$ and $p = 0.004$, respectively). While efficacy was similar with the two paroxetine doses, women were less likely to discontinue the low dose paroxetine, which was also associated with a significant improvement in sleep compared to placebo ($p = 0.01$).

Simon *et al.* reported the results of two large RCTs in a total of 1184 menopausal women (Simon et al. 2013). Both studies evaluated the effect of 7.5 mg daily paroxetine or placebo, one study (N = 614) over 12, the other (N = 570) over 24 weeks. In the 12-week study, HF frequency decreased significantly more from baseline (−33% vs. -23.5%;

$p < 0.0001$) at week 4, and week 12 (−43.5% vs. -37.3%; $p = 0.009$). However, HF severity score decreased significantly only at week 4 (-0.09 vs. -0.05; $p = 0.0048$) but not at week 12 (−0.10 vs. -0.09; $p = 0.2893$). In the 24-week study, HF frequency decreased significantly more from baseline (−28.9% vs. -19.0%; $p < 0.0001$) at week 4, and at week 12 (−37.2% vs. -27.6%; $p = 0.0001$. The severity score decreased significantly at week 4 (−0.09 vs. -0.06; $p = 0.0452$) and week 12 (−0.12 vs. -0.07; $p = 0.0114$). Final results for HF frequency and severity at week 24 were not provided.

In 2013, Huang *et al.* (Huang et al. 2013) compared paroxetine alone to paroxetine plus isopropanolic *Cimicifuga racemosa* extract. Results from the Kupperman (HF frequency and severity) and Hamilton depression scales (HAMD) for the combined treatment were superior with the combined treatment vs. paroxetine alone ($p < 0.01$ and $p < 0.05$, respectively).

Breast cancer In 2000, Stearns and colleagues investigated the effect of paroxetine in an observational pilot study in 30 women with prior breast cancer over a treatment period of 5 weeks at a dose of 10 mg/day for one week, followed by 20 mg daily (Stearns et al. 2000). The HF frequency was reduced by 67% and severity by 75% (95% CI: 56%-79% and 66%-85%, respectively). Though somnolence was observed in four patients leading to drug discontinuation in two patients and likewise dose reduction in two, there was a statistically significant improvement in depression, sleep disturbances, anxiety, and quality of life scores.

Sertraline

In a double-blind, placebo-controlled, crossover trail in 102 menopausal women, sertraline 50 mg/d or placebo was given over 4 weeks (Gordon et al. 2006). The number of hot flushes was significantly lower during sertraline treatment than placebo ($p = 0.002$): mean reduction for the difference of 2.8 (95% CI 0.8-4.9; $p = 0.007$ during daytime and 2.3 (95% CI 0.3-4.2; $p = 0.03$) during nighttime. The severity of hot flushes was not significantly different between the treatments, but there was a significant improvement in HF score ($p = 0.001$) on sertraline. However, although significant, the overall benefit was comparatively small.

No significant effect in alleviating HF frequency and intensity better than placebo was found in a blinded, placebo-controlled RCT involving 99 menopausal women taking 50 or 100 mg sertraline daily for 6 weeks (Grady et al. 2007). Inconclusive results were observed in a further placebo-controlled RCT in 102 women where HF symptoms and severity score improved over nine weeks in one-third of the women, one-third showed no change, and one-third worsened (Kerwin et al. 2007). In another placebo-controlled RCT in 44 menopausal women (Aedo et al. 2011), a higher percentage of patients ($p = 0.01$) showed a symptomatic improvement of climacteric symptoms (e.g., 35.3% placebo and 81.3% sertraline).

Breast cancer Two studies investigated sertraline in women at high risk of, or having, breast cancer and on adjuvant tamoxifen therapy. Kimmick studied 62 women who received either 50 mg sertraline/day or placebo for 6 weeks in a randomised, double-blind, cross-over design. Treatment effects were only small: a 50% decrease in HF frequency was observed in 36% of the sertraline patients versus 27% receiving placebo ($p = 0.7$); (Kimmick et al. 2006). Wu (Wu et al. 2009) compared 25–100 mg/d vs. placebo in 65 women who had either had, or were at high risk for, breast cancer in a 6-week study (4-week treatment phase). No significant differences were noted in either the HF frequency or severity score between the groups.

In five case reports, Roth *et al*. (Roth & Scher 1998) showed sertraline improved HF symptoms in **prostate cancer survivors** who were also treated for concomitant depression.

Fluoxetine

In a placebo-controlled, double-blind study with a follow-up period of 36 weeks, 150 healthy women with menopausal symptoms were randomised into three groups receiving placebo, fluoxetine, or citalopram (Suvanto-Luukkonen et al. 2005). The initial 10 mg SSRI doses (for fluoxetine and citalopram) increased to 20 mg after 4 weeks and to 30 mg after 24 weeks. The main outcome measures were HF frequency and Kupperman index. No significant differences were observed in the number of HF or severity index between placebo and both SSRIs. The authors concluded that citalopram and fluoxetine cannot be recommended for treating menopausal complaints when vasomotor symptoms are the primary problem.

In 2007, Oktem and colleagues compared 20 mg fluoxetine with 40 mg *Cimcifuga racemosa* extract (CRE) in 120 menopausal women. After 24 weeks, the HF symptom score were significantly reduced in the CRE group (85% vs. 62%), and night sweats were likewise fewer with CRE (both $p < 0.01$).

Breast cancer A modest treatment effect was obtained in 81 female **breast cancer survivors**. Patients were treated with fluoxetine, 20 mg daily, or placebo over 4 weeks in a randomised, double-blind. cross-over design (Loprinzi et al. 2002b) and demonstrated a 50% decrease in HF score in the fluoxetine versus 36% in the placebo arm ($p = 0.02$).

Citalopram

In a placebo-controlled, double-blind study (cf, Section Fluoxetine, (Suvanto-Luukkonen et al. 2005)), no significant differences were observed in the number of HF or severity index among citalopram, fluoxetine and placebo.

More positive, dose-independent results were obtained in another placebo-controlled trial involving 254 post-menopausal women and 10, 20, or 30 mg/d citalopram (the same dose range as in the study above (Suvanto-Luukkonen et al. 2005)) given for 6 weeks and compared to placebo (Barton et al. 2010). From baseline, reductions in HF frequency (46%, 43% and 50%, $p \leq 0.001$) and mean HF scores (49%, 50%, 55%, $p \leq 0.002$) for the respective increasing citalopram were superior to placebo (20% and 23%, respectively). Citalopram was well-tolerated without any significant AEs.

Breast cancer In a four-week study, citalopram was investigated in 26 breast cancer survivors at doses of 10 mg during week 1, and 20 mg for weeks 2–4. A 58% reduction in HF frequency and a 64% reduction in HF score from baseline were reported (Barton et al. 2003).

Escitalopram

In a small, uncontrolled pilot study in 25 menopausal women, the effect of escitalopram was assessed at doses of 10–20 mg/d (flexibly dosed for 8 weeks) in treating HF. Women reported a significant decrease in HF frequency (52.2%) and severity (53.8%) from baseline (both $p = 0.0001$). With a responder being defined by at least a 50% decrease in HF frequency (Defronzo Dobkin et al. 2009), 16 patients were treatment responders, with an average decrease of 55%.

These results were partly contradicted in two small ($N = 16$ and $N = 26$) double blind, placebo-controlled pilot studies (Freedman et al. 2011). Escitalopram was given at a dose of 10 mg/d (study 1) or 20 mg/d (study 2) over 8 weeks. Escitalopram at 10 mg or 20 mg/day was not effective in treating menopausal HF.

Expanded results from one randomised, double-blind, placebo-controlled, parallel arm trial for 8 weeks in 205 women with menopausal symptoms reported the efficacy and tolerability of 10–20 mg/day escitalopram on HF frequency, severity and bother (Freeman et al. 2011; Carpenter et al. 2012; Ensrud et al. 2012). At baseline, HF frequency was 9.78/day (SD 5.60) and, at week 8, was significantly less in the escitalopram group versus placebo (−4.60 vs. −3.20; $p = 0.004$). In the escitalopram group, 55% (versus 36% in the placebo group) reported ≥50% decreases in HF frequency ($p = 0.009$), and significant decreases in HF severity were likewise noted ($p = 0.003$). New complaints reported by >10% in the escitalopram group included dizziness/lightheadedness (14%), vivid dreams (13%), nausea (11%) and hyperhydrosis (11%). Some 4% (7 escitalopram, 2 placebo) discontinued the study due to side effects.

Venlafaxine

After the exploitation of the SSRIs (e.g., paroxetine, sertraline, fluoxetine, citalopram and escitalopram) in treating vasomotor symptoms, the SNRIs (e.g., venlafaxine, desvenlafaxine) were put to the test. One study reported on 80 post-menopausal patients who were randomised to receive either placebo or 37.5 mg extended-release daily venlafaxine for one week, followed by 11 weeks of 75 mg venlafaxine. Although there was a trend toward lower HF severity scores in the treatment group, the difference between treatments did not reach significance ($p = 0.25$). Three AEs, dry mouth, sleeplessness, and decreased appetite, were significantly more frequent in the venlafaxine group (Evans et al. 2005).

Loprinzi *et al.* compared two doses of oral venlafaxine (37.5 mg/d and 75 mg/d) to i.m. medroxyprogesterone acetate (MPA) in 218 post-menopausal women. MPA was superior in all aspects, including lower toxicity: A 50% decrease in HF frequency was achieved by 46% in the VEN group, and 74% in the MPA group; furthermore, a 55% decrease in the HF score was noted for VEN, while this result was 79% for MPA (all $p < 0.0001$) (Loprinzi et al. 2006).

Breast and prostate cancer In spite of genetic variations among patients, it has been shown that venlafaxine is a weaker inhibitor of cytochrome P450 2D6 (CYP2D6) than paroxetine, and thus only slightly reduces plasma concentrations of endoxifen, the potent tamoxifen metabolite (Pritchard 2010) (This is discussed in further detail under 4.2, Safety of Antidepressants in Patients with a History of Breast Cancer, and 4.2.3, Interactions with Tamoxifen). Extrapolating, venlafaxine could thus potentially be preferable to SSRIs in the treatment of cancer survivors suffering from HF.

Loprinzi tested this hypothesis using velafaxine in breast (82%) and prostate cancer survivors (18%). After 4 weeks of treatment, 12.5 mg b.i.d. venlafaxine was shown to be effective in reducing - by at least half - the frequency of vasomotor symptoms in 54% of patients; and 58% reported a median 55% reduction in the HF score (95% CI 22-71%). Three patients terminated participation – two due to AEs (decreased concentration, depression, nausea, dry mouth, fatigue, and sleepiness) and 1 switched treatment to megestrol acetate (Loprinzi et al. 1998).

Carpenter tested venlafaxine in breast cancer survivors in two sequential, double-blind, placebo-controlled cross-over trials using low, 37.5 mg/d ($n = 57$) and high doses, 75 mg/d ($n = 20$) (Carpenter et al. 2007).

Compared to placebo, both doses significantly reduced HF frequency (42% and 25% (both $p = 0.001$), respectively) and severity (7% and 27% (both $p < 0.001$), respectively). This study further observed that, when at least a 50% relief in physiological hot flashes was achieved, an improvement in secondary outcomes, such as quality of life parameters, including sleep, decreased fatigue, etc. was correspondingly noted. The authors proposed using this 50% threshold as a standard for evaluating other pharmacological and/or behavioural therapies.

Similar to the study of Loprinzi cited above (Loprinzi et al. 1998), positive results (38% reported at least a 50% decrease in HF frequency, and 63% reported a median decrease of 54% in the HF score) were noted in another uncontrolled pilot study among 23 androgen-deprived prostate cancer survivors using 12.5 mg venlafaxine b.i.d. (Quella et al. 1999).

Loprinzi's group confirmed these findings in a larger double-blind, placebo-controlled study in 229 breast cancer survivors by investigating the dose-dependence of venlafaxine's therapeutic effects (Loprinzi et al. 2000). After a baseline assessment week, venlafaxine treatments started at 37.5 mg daily and gradually increased to 75 mg or 150 mg daily for four weeks. Median HF frequencies and scores were reduced from baseline by 19 and 27% (placebo); 30 and 37% (37.5 mg); 46 and 61% (75 mg); and 58 and 61% (150 mg) (all $p < 0.001$). Adverse effects (dry mouth, decreased appetite, nausea, and constipation) were significantly higher compared to placebo in the 75 and 150 mg venlafaxine groups.

Three double-blind studies (Loibl et al. 2007; Buijs et al. 2009; Boekhout et al. 2011), previously cited in the clonidine section, compared various doses of venlafaxine and clonidine in breast cancer survivors; results from these studies were inconclusive viz. efficacy, but venlafaxine tended to have more AEs. And in another study that compared venlafaxine to gabapentin in 66 breast cancer survivors, venlafaxine showed similar efficacy but again more AEs (Bordeleau et al. 2010).

Contrasting results were found in one double-blind, placebo-controlled RCT in 120 prostate cancer survivors. Venlafaxine, at a dose of 75 mg/d, given either together with milk protein or with 160 mg/d soy isoflavones showed no significant effect of HF frequency or severity when compared to placebo plus milk protein or 160 mg/d soy isoflavones (Vitolins et al. 2013).

In conclusion, though some studies dispute venlafaxine's efficacy (Evans et al. 2005; Vitolins et al. 2013) several other studies suggest a beneficial effect of venlafaxine in the treatment of post-menopausal vasomotor symptoms, also for breast and prostate cancer survivors, either alone (Loprinzi et al. 1998; Carpenter et al. 2007; Quella et al. 1999), or against placebo (Loprinzi et al. 2000), or compared to another active compound (Loprinzi et al. 2006; Loibl et al. 2007; Buijs et al. 2009; Boekhout et al. 2011; Bordeleau et al. 2010). However, the treatment duration of each of these studies was too short to investigate a potential increase in breast cancer recurrence. In addition to the AEs cited in these studies that have led to certain patients discontinuing the trial associated with venlafaxine (e.g., hypertension, decreased appetite, nausea/vomiting and constipation, sleeping problems, and sexual disturbances), breast enlargement is also a concern with this drug (Amsterdam et al. 1997) and is discussed below under *Safety of Antidepressants in Patients with a History of Breast Cancer*.

Desvenlafaxine

Desvenlafaxine (*O*-desmethylvenlafaxine) is the active metabolite of venlafaxine, and was studied in five large randomised, placebo-controlled trials (Speroff et al. 2008; Archer et al. 2009a; Archer et al. 2009b; Bouchard et al. 2012; Pinkerton et al. 2013) involving 2,582 post-menopausal patients for at least 12 weeks. All but one (Bouchard et al. 2012) of these studies showed a significant beneficial effect in treating vasomotor symptoms. However, none of these studies were performed in breast cancer survivors. Although the drug was approved as an antidepressant in the USA and Canada, the EMA did not approve desvenlafaxine for the treatment of major depression or menopausal complaints and the manufacturer therefore withdrew the European applications for both indications (EMEA 2014).

Mirtazapine, moclobemide and bupropion

Mirtazapine treatment (15–30 mg/d) for HF was serendipitously discovered in two depressed patients with post-menopausal complaints (Waldinger et al. 2000). Since HF and perspiration completely disappeared after one week of treatment, medication use was extended to two more patients without clinical signs of depression but with the same climacteric symptoms. The authors postulated that the 5-HT_{2A} blocking properties may account for the effect on HF. In a single-arm pilot study in 22 women (Perez et al. 2004), 59% with breast cancer of whom 9% and 45% were on raloxifene or tamoxifen treatments, respectively, patients received incremental doses of mirtazapine (7.5 (wash-in phase), 15 or 30 mg/day). At the end of the 4-week treatment, the median frequency and severity of HF decreased substantially by 52.5% and 59.5%, respectively. Similar results were obtained in another uncontrolled trial in 40 breast cancer survivors receiving 30 mg/d mirtazapine over 12 weeks (Biglia et al. 2007). A 55.6% reduction in HF frequency ($p < 0.05$) and 61.9% reduction in HF score relative to baseline ($p < 0.05$) were observed. Seven patients discontinued the study due to side effects, mostly somnolence. However, to date, no randomised clinical trials have been

published and the benefit of this treatment cannot be adequately assessed.

There are also individual studies investigating two other anti-depressants, bupropion and moclobemide, in treating vasomotor symptoms. There have been anecdotal observations that bupropion, used for nicotine dependence and depression, can relieve HF symptoms. A pilot study lasting 4 treatment weeks was carried out in 21 patients, including breast and prostate cancer survivors, who built up to a 300 mg bupropion daily dose. Results showed that there was no significant reduction noted over that which would be expected from placebo (Perez et al. 2006).

Two different doses of moclobemide, 150 mg or 300 mg/d, were tested against placebo for 5 weeks in 30 postmenopausal women. The lower dose of this reversible, selective inhibitor of monoamine oxidase-A reduced the HF severity score by 69.8%, compared to 35.0% in the higher dose and 24.4% with placebo (Tarim et al. 2002).

Safety of antidepressants in patients with a history of breast cancer

Prolactin and carcinogenesis

Certain antidepressant drugs modulate prolactin levels. Serum prolactin levels were investigated in 70 psychiatric patients where it was noted that patients on imipramine or amitriptyline treatment showed consistently higher prolactin levels compared to untreated controls (Turkington 1972). Prolactin is mitogenic, stimulates proliferation and suppresses apoptosis in breast and prostate cancer cells (Harvey et al. 2006) and is therefore important in the development of treatment-resistance in breast cancer cells (Carver et al. 2009).

Evidence from preclinical and clinical data show that elevated prolactin levels cause proliferation of breast tissue and result in breast enlargement, which may be markers for an increased risk of breast cancer development and important factors in the carcinogenicity of mammary tissue (Ingram et al. 1990; Arendt et al. 2011; Harvey et al. 2006; Clevenger et al. 2009; Carver et al. 2009). Breast enlargement was investigated and found in 39% of 59 women who received chronic SSRI or venlafaxine treatment for more than 8 weeks for depression (Amsterdam et al. 1997). Mammoplasia was reported in 64% of paroxetine-, 25% fluoxetine-, 25% sertraline- and 11% venlafaxine-treated patients. In the paroxetine group, a significant ($p < 0.01$) increase in prolactin serum concentrations was observed compared to pre-treatment values. Post-menopausal women with elevated plasma prolactin levels have a significantly higher risk of breast cancer (Hankinson et al. 1999). Several other reports on prolactin-related gynaecomastia, galactorrhoea, mastalgia or breast enlargement after tricyclic antidepressants, SSRIs and venlafaxine (Kropp et al. 2004; González et al. 2000; Bronzo & Stahl 1993; Bonin et al. 1994; Scurlock & Meehan 1996; Bonin et al. 1997), have confirmed these findings.

A mechanistic explanation of the prolactin increase after treatment with tricyclic antidepressants and SSRIs was provided by the finding that 5-HT neurons are believed to maintain a tonic inhibitory influence on dopamine function (Bonin et al. 1997). In addition to this indirect effect, tricyclic antidepressants and fluoxetine bind directly to intracellular, growth regulatory histamine receptors that are associated with anti-oestrogen binding sites. With this background in mind, the effects of amitriptyline and fluoxetine on tumour growth were investigated in rodents (Brandes et al. 1992), at concentrations corresponding to the treatment of human depression. Tumour latency decreased by 30-40% and frequency increased 2-fold in the DMBA (7,12-dimethylbenz[a]anthraene) model for chemically-induced breast cancer.

In contrast to this evidence, the carcinogenic risk of fluoxetine was evaluated in three carcinogenicity studies in rats and mice performed by the manufacturer (Eli Lilly & Co.). In these studies, fluoxetine was given over a period of 24 months in doses up to 10 mg/kg (Bendele et al. 1992), without any signs of treatment-related neoplasm development. However, in a different study in male rats, administration of 10 mg/kg i.p. fluoxetine did not affect resting serum prolactin levels but strongly potentiated stress-induced prolactin release (Krulich 1975).

Epidemiological evidence

To date, the clinical relevance of these effects in the safety assessment of antidepressant drugs has not been completely elucidated with regard to the risk of breast cancer development or recurrence. There is epidemiologic evidence that long-term use of the modern antidepressant drugs may be associated with a higher risk for developing breast cancer: In a case–control study using data from the Ontario Cancer Registry and controls, the risk for cancer development for long-term use of antidepressant drugs was investigated (Cotterchio et al. 2000). Compared with controls, use of tricyclic antidepressants for longer periods (>2 years) was associated with an elevated risk of breast cancer development (adjusted OR = 2.1, 95% CI 0.9-5.0), however, this increase in risk lacked statistical significance. Of the six most commonly reported antidepressant medications, only paroxetine use was associated with an increase in breast cancer risk (adjusted OR = 7.2, 95% Cl 0.9-58.3).

The Women's Health Study (Kato et al. 2000) was performed in 15,270 women who participated in a mammographic screening programme. During an average of 7.3 years of follow-up, 566 incident cases of breast cancer were detected. The use of any type of psychotropic

treatment at baseline was associated with a significantly increased relative risk of 1.39 (95% CI 1.11-1.74).

A follow-up case–control study using a larger sample from the same registry was performed by Steingart *et al*. (Steingart et al. 2003). In this study of 3,077 breast cancer patients, 441 used antidepressants; controls included 2,994 patients without breast cancer diagnosis, including 372 with antidepressant treatment. The analysis showed a significantly increased unadjusted risk for breast cancer for patient with 'ever' use of antidepressants (OR 1.17, 95% CI 1.01 – 1.36), especially for SSRI use (OR 1.33 (95% CI 1.07-1.66). Among the SSRIs, sertraline showed a significantly increased risk (OR 1.58 (95% CI 1.03-2.41) and paroxetine a borderline increased risk (OR 1.55, 95% CI 1.00-2.40). However, when risk was adjusted for other confounding factors associated with breast cancer risk, significance was lost, although the point estimates remained more or less the same.

In a large retrospective cohort study of 109,004 female health plan members who used various antidepressants between 1995 and 2000, paroxetine use was evaluated against breast cancer risk (Haque et al. 2005), where it was shown that the age-adjusted relative risk (RR) comparing "ever" users of paroxetine with other antidepressants was 1.12 (95% CI 0.96–1.31). Women who used paroxetine for 2 or more years did not show an increased risk of breast cancer compared to women who used it for a shorter period. Furthermore, use of SSRIs in general did not result in a statistically increased risk (RR 1.14 (95% CI 0.87-1.49)).

Results from another hospital-based case–control study (Kelly et al. 1999) in 5,814 women with breast cancer, 5,095 patients with other malignancies and 5,814 women without malignancies, researchers investigated the relative risk for developing breast cancer with regular use of antidepressants and structurally similar drugs. Though no significant increases in risk for any category of regular use were noted, the relative risk estimate for regular SSRI use in the previous year, 1.8, was of borderline statistical significance (95% confidence interval: 1.0, 3.3).

In a third case–control study, use of antidepressant drugs was investigated in patients with invasive breast cancer (n = 938) and controls (n = 771) (Moorman et al. 2003). Overall, women with invasive breast cancer did not report antidepressant use more frequently than controls (OR 1.0; 95% CI: 0.7-1.2). However, there was a trend that SSRI use for 36 months or longer was more prevalent in breast cancer patients than in controls (OR 2.2, 95% CI 0.8-6.3). Interestingly, carcinoma *in situ* cases reported antidepressant use significantly less frequently than controls (OR 0.6; 95% CI 0.4–0.8).

Another population-based case–control study included 975 elderly breast cancer cases and 1,007 age- and residence-matched controls conducted in Washington State (Chien et al. 2006). Antidepressant use information was obtained by structured in-person interviews. Overall, no association between ever use of antidepressants and breast cancer risk was noted (OR 1.2, 95% CI 0.9–1.6). However, compared to never users, ever SSRI users had significantly elevated risks of progesterone receptor (PR) negative and oestrogen receptor (ER) positive/PR-negative breast cancers (OR 1.8, 95% CI 1.1–3.6 and OR 2.0, 95% CI 1.1–3.8, respectively), but not of tumours with other hormone receptor profiles.

Contradicting results were obtained in a recent population-based study in 2,908 incident breast cancer cases and 2,927 control women (Wernli et al. 2009). There was no increased breast cancer risk in patients who received antidepressant drugs (OR 0.89, 95% CI 0.78-1.01).

In a large, retrospective cohort study based on prescription fillings by breast-cancer free women, (Wang et al. 2001), 38,273 females taking any antidepressant drug were compared to 32,949 women who took any other medication between 1989–1991. Use of antidepressant drugs was unrelated to the development of breast cancer (HR 1.04, 95% CI 0.87-1.25).

Coogan *et al*. (Coogan et al. 2008) used data from 820 invasive breast cancer cases in a case–control study and compared it to 2,852 hospitalised controls. The OR for all breast cancer cases was not elevated among regular users of SSRIs (OR 0.89, 95% CI 0.62-1.29). The results of this study were confirmed in 2,138 patients with invasive breast cancer and 2,858 controls (Coogan et al. 2005). The OR was 1.1 (95% CI 0.8-1.7) for regular use of SSRIs and 0.7 (95% CI 0.4-1.5) for use of 4 or more years. No ORs were elevated for any specifically-investigated SSRI.

Finally, this finding was again confirmed by a recent population-based case–control study in 2,129 women with primary invasive breast cancer and 21,297 randomly-selected control women (Ashbury et al. 2012). In this large study, no conclusive evidence of an increased breast cancer risk associated with the use of SSRIs was found, independent of the degree of serotonin reuptake inhibition or duration of use.

Discussion and Conclusion: Epidemiological studies, especially register-based ones, do rarely control for all of the possible confounding factors. Therefore, they do not prove a potential causal relationship. However, they may raise attention for possible associations and may motivate to perform a prospective study. Therefore, prospective long-term studies are needed to finally judge the risk of antidepressant treatment and breast cancer development.

Interaction with tamoxifen

Fluoxetine and paroxetine, and to a much lesser extent, possibly sertraline, citalopram and escitalopram, are inhibitors of the cytochrome P450 isoform CYP2D6

(Preskorn et al. 2007; Lam et al. 2002; Desmarais & Looper 2009; Desmarais & Looper 2010) that is important for metabolising tamoxifen, the therapy of choice in the adjuvant hormonal treatment of patients with oestrogen receptor-positive breast cancer. As a pro-drug, its active metabolite, endoxifen, is formed by a CYP2D6-mediated reaction (Pritchard 2010). SSRIs and, in particular, fluoxetine and paroxetine as the strongest CYP2D6 inhibitors, may therefore prevent the formation of the active metabolite from inactive tamoxifen (Crewe et al. 1997; Desta et al. 2004) and put breast cancer patients under anti-oestrogenic treatment at an increased risk of breast cancer recurrence (Singh et al. 2011). This was suggested by a population based cohort study in 2,430 women (Kelly et al. 2010), where the importance of CYP2D6 inhibition by SSRI could clearly be demonstrated. For paroxetine, the risk of death from breast cancer increased significantly with the proportion of time that tamoxifen was given concomitantly with paroxetine.

No increase in recurrence risk (OR 1.1, 95% CI 1.1-1.7) was demonstrated by a recent case–control study for citalopram and its S-isomer in 732 Danish patients who received tamoxifen for at least one year (Lash et al. 2011a; Lash et al. 2011b). This result may reflect the low inhibitory potency of citalopram and escitalopram. On the other hand, the lack of effect of citalopram or other SSRIs may be also due to the small number of patients who were studied in each of the subgroups.

In a recent matched case–control study in 3,901 breast cancer survivors (Goetz et al. 2013), patients were treated over 5 years either with tamoxifen alone, or after initial treatment with tamoxifen for 2 years, were switched to anastrozole, an aromatase inhibitor, which is neither a pro-drug nor metabolised by cytochrome CYP2D6. Homozygote-poor metabolisers for CYP2D6 tended to have a higher rate of breast cancer recurrence with continued tamoxifen use (OR 2.40; 95% CI 0.86-6.66, $p = 0.09$).

In a recent meta-analysis (Zeng et al. 2013), 20 clinical trials (11,701 breast cancer patients) were included where the impact of CYP2D6 polymorphisms on tamoxifen efficacy was assessed. Extensive metabolisers were associated with significantly improved disease-free survival (HR 1.37; 95% CI 1.12-1.69; $p = 0.002$) and overall survival (HR 1.25; 95% CI 1.03-1.50; $p = 0.021$).

On the basis of the available data, there is some evidence that co-administration of SSRIs (at least of fluoxetine and paroxetine) with tamoxifen may result in an increase in breast cancer recurrence in patients with anti-oestrogen therapy. Since alternative drugs are available that do not interact with CYP2D6, such combinations should be avoided (Binkhorst et al. 2013). In addition, pheno- or genotyping of patients for CYP2D6 poor metaboliser status may be warranted.

Natural remedies and complementary medicine

In 2004, Fugate and Church assessed the efficacy and safety of non-hormonal, non-oestrogen treatments of menopause-associated vasomotor symptoms in a systematic review (Fugate & Church 2004). This review included non-prescriptional (dietary isoflavones, vitamin E, black cohosh, dong quai, evening primrose oil, physical activity, phytoestrogens, and red clover) as well as prescriptional treatments (clonidine hydrochloride, gabapentin, methyldopa, mirtazapine, propranolol hydrochloride, selective serotonin-reuptake inhibitors (SSRIs), and venlafaxine. However, in contrast to the present review, studies in cancer patients were explicitly excluded.

Vitamin E

The efficacy of vitamin E in treating climacteric symptoms was investigated by Ziaei and colleagues using 400 IU/d softgel vitamin E tablets. They reported significantly reduced HF frequency (5.00 ± 3.34 vs. 3.19 ± 2.74) and severity scores (2.37 ± 0.74, 1.80 ± 0.87) when compared to placebo ($p < 0.0001$) (Ziaei et al. 2007).

The effects of vitamin E (800 IU daily) and placebo were studied over 4 weeks by Barton in a randomised, placebo-controlled, cross-over design in 120 breast cancer survivors. Although vitamin E preparations reduced the frequency of HF significantly compared to placebo in patients with a history of breast cancer and mild symptoms, the magnitude of the effect was small (one HF less per day), and therefore not clinically relevant (Barton et al. 1998).

Phyto-oestrogens and vasomotor symptoms

The effects of phyto-oestrogens, plant-based compounds that exert oestrogen-like effects, on vasomotor menopausal symptoms were assessed in two Cochrane reviews in 2007 and 2013 (Lethaby et al. 2007; Lethaby et al. 2013). The more recent meta-analysis comprised 43 randomised controlled trials with a total of 4364 participants, however trials with breast cancer survivor had been excluded. Thirty-three of them have also been included in our review. Ten studies were excluded since they did not contain detailed information on HF frequency and/or severity or dealt with (mixed) dietary rather than pharmacological interventions. Certain trials found that some phyto-oestrogen treatments in peri- and post-menopausal women evoked a slight improvement in the frequency and severity of HF and night sweats when compared to placebo (Albertazzi et al. 1998; Scambia et al. 2000; Han et al. 2002; van de Weijer & Barentsen 2002; Jeri 2002; Sammartino et al. 2003; Nahas et al. 2004; Nahas et al. 2007; Khaodhiar et al. 2008; Cheng et al. 2007; Radhakrishnan et al. 2009; Ye et al. 2012; Aso et al. 2012; Mainini et al. 2013; D'Anna et al. 2007; D'Anna et al. 2009; Ferrari 2009; Evans et al.

2011) or with other compounds (Murkies et al. 1995; Crisafulli et al. 2004; Labos et al. 2013). However, many trials were small and confounded by a high risk of bias and unusually high placebo effect. Also, other investigations showed either no or an inconclusive benefit from soy isoflavone administration (Baber et al. 1999; Knight et al. 1999; Upmalis et al. 2000; St Germain et al. 2001; Burke et al. 2003; Faure et al. 2002; Campagnoli et al. 2005; Tice et al. 2003; Penotti et al. 2003; Secreto et al. 2004; Lewis et al. 2006). It is worth mentioning that the study that used the highest dose of isoflavones (200 mg/d) showed an exacerbation of HF symptoms (Levis et al. 2011). Those studies that compared phyto-oestrogens in breast and prostate cancer survivors likewise showed no conclusive evidence that phytooestrogen supplements effectively reduce HF (Quella et al. 2000; Van Patten et al. 2002; Nikander et al. 2003; MacGregor et al. 2005; Sharma et al. 2009). Under the heading, Phyto-oestrogens – Isoflavones (ISOF), Additional file 1 summarises the findings from the latest Cochrane review on this topic.

Isoflavones and breast/prostate cancer recurrence

With regard to preventing recurrence in breast cancer survivors, the data on beneficial effects of phyto-oestrogens are conflicting here as well. The inhibitory effect of enterolactone, a metabolite and marker of dietary lignans, on human aromatase by mammalian lignans and isoflavonoid phyto-oestrogens has been shown *in vitro* (Adlercreutz et al. 1993; Adlercreutz 1995), though the protective effects against breast cancer are only slight. It is not yet known whether this is due to a healthy diet or indeed evoked by the presence of dietary phyto-oestrogens (Adlercreutz 2002a; Adlercreutz 2002b). The effect of dietary phyto-oestrogen ingestion on the survival of breast cancer patients was investigated in 1,140 patients (Buck et al. 2011) by determining enterolactone for a median follow-up of 6.1 years. Enterolactone levels correlated positively with patient survival. The highest quartile of serum enterolactones was associated with a significantly reduced risk of death, but only in oestrogen receptor-negative tumours (HR 0.27 (95% CI 0.08-0.87)). It has been suggested that the high concentration of lignans in vegetarians, by inhibiting aromatase (=oestrogen synthetase) in peripheral and/or cancer cells and lowering oestrogen levels, may play a protective role as antipromotional compounds during growth of oestrogen-dependent cancers (Adlercreutz et al. 1993).

However, it is noteworthy that genistein, the most prevalent isoflavone in soy, can stimulate breast cancer growth and may interfere with the anti-tumour activity of tamoxifen (Duffy & Cyr 2003). Likewise, the isoflavone, biochanin A, may attenuate the effects of tamoxifen and the aromatase inhibitor, letrozole (Du et al. 2012; Singh et al. 2012; Ju et al. 2008).

Melatonin

Chen *et al.* (Chen et al. 2014) studied the effect of melatonin at a dose of 3 mg/d over 16 weeks on HF frequency and severity in 95 breast cancer survivors in a double-blind placebo-controlled RCT. There was, compared to placebo, a significant improvement in subjects' sleep quality, but no significant decrease in HF frequency or severity between treatments.

Herbal supplements and vasomotor symptoms

Herbal supplements are widely used for vasomotor symptoms, with varying degrees of efficacy. Among the more frequently studied are hops (Heyerick et al. 2006; Erkkola et al. 2010), red clover (Hidalgo et al. 2005; Geller et al. 2009; Lipovac et al. 2012), flaxseed (Lewis et al. 2006; Colli et al. 2012; Pruthi et al. 2012), St. John's Wort (*Hypericum perforatum*) (Al-Akoum et al. 2009; Abdali et al. 2010; Uebelhack et al. 2006; Briese et al. 2007), evening primrose (*Oenothera biennis*) (Farzaneh et al. 2013), French maritime pine bark (Pycngenol) (Yang et al. 2007; Kohama & Negami 2013); Sibiric Rhubarb (*Rheum rhaponticum*) (Heger et al. 2006; Kaszkin-Bettag et al. 2007; Kaszkin-Bettag et al. 2009; Hasper et al. 2009), valerian root (*Valeriana officinalis*) (Mirabi & Mojab 2013), Guaraná *(Paullinia cupana*) (Oliveira et al. 2013), and magnesium (Park et al. 2011). Summaries of these studies can be found in Additional file 1.

Black cohosh (*Cimicifuga racemosa*)

One of the most widely studied and efficacious phytopharmaceuticals, CR (*Cimicifuga racemosa* L. *Actaea racemosa* L., black cohosh), is a perennial medicinal plant native to North America where it has been used for centuries in indigenous medicine for the treatment of many varied conditions. However, today's sole accepted indications are menopause-related neurovegetative and emotional symptoms. Black cohosh or *Cimicifuga racemosa* extracts (CRE) are described in a 2003 monograph of the European Scientific Cooperative on Phytotherapy (ESCOP) as a pharmacologically-active treatment for climacteric symptoms (ESCOP Monographs 2003). Furthermore, in the 2010 community herbal monograph of the Committee on Herbal Medicinal Products (HMPC) of the EMA (EMEA 2010), a well-established use status was granted. CREs are registered as treatment for menopausal symptoms in many European countries (among them, Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Hungary, Sweden, Switzerland, and UK) and Australia, South Korea, South Africa. In some countries (such as USA) CRE are used as a food supplement.

A recent Cochrane meta-analysis (Leach & Moore 2012), comprising 16 RCTs and recruiting a total of 2027 women with climacteric complaints, investigated CR for treating vasomotor symptoms. The authors point

out that, due to the large degree of heterogeneity among the studies, pooling of the results was not possible. They state there is adequate justification for conducting more studies on this topic, but summarise that there was insufficient evidence to support the use of CR for menopausal symptoms. The conclusions of the authors, however, have been recently questioned by Beer *et al.* (Beer et al. 2013) who criticised that the selection of clinical studies in the Cochrane meta-analysis was biased. Not even half of the selected 16 studies were conducted within the indication using authorised products and several positive clinical studies were excluded or not identified (Osmers et al. 2005; Stoll 1987; Wuttke et al. 2003; Schellenberg et al. 2012). Using a re-analysis of all appropriate placebo-controlled clinical studies, they obtained a standardised mean difference of 0.385 in favour of CR ($p < 0.0001$).

Randomised, controlled trials that have shown a pharmacological effect and meeting the strict requirements of the FDA and EMA (FDA. U.S. Department of Health and Human Services Food and Drug Administration 2003; EMEA. Committee for Medicinal products for human use (CHMP) 2005), including at least 12 weeks duration, have been undertaken with CRE in 19 clinical studies among healthy menopausal women (Drewe et al. 2013; Lopatka et al. 2007; Vermes et al. 2005; Liske et al. 2002; Frei-Kleiner et al. 2005; Schellenberg et al. 2012; Osmers et al. 2005; Ross 2012; Newton et al. 2006; Geller et al. 2009; Stoll 1987; Wuttke et al. 2003; Nappi et al. 2005; Bai et al. 2007; Uebelhack et al. 2006; Briese et al. 2007; Oktem et al. 2007) and in breast cancer survivors (Hernández Munoz & Pluchino 2003; Rostock et al. 2011). Four other studies (Huang et al. 2013; Pockaj et al. 2004; Jacobson et al. 2001; Pockaj et al. 2006) did not meet the 12-week criterion, and can thus just be considered as supportive research, though for thoroughness, they are also cited in Additional file 1.

Various doses of ethanolic and isopropanolic formulations of CRE have been investigated in menopausal women (Drewe et al. 2013; Lopatka et al. 2007; Vermes et al. 2005; Liske et al. 2002) and results showed a significant decrease in HF symptoms and scores. When compared to placebo (Frei-Kleiner et al. 2005; Schellenberg et al. 2012; Osmers et al. 2005; Ross 2012), similarly positive results were observed. When combined or compared with other actives (Newton et al. 2006; Geller et al. 2009; Stoll 1987; Wuttke et al. 2003; Nappi et al. 2005; Bai et al. 2007; Uebelhack et al. 2006; Briese et al. 2007; Oktem et al. 2007; Huang et al. 2013), CRE was at least as efficacious as the other compound(s), except in (Newton et al. 2006) where herbal regimens did not reduce vasomotor symptoms.

Studies have also been conducted in breast cancer survivors using CRE alone (Pockaj et al. 2004), where HF were reduced by half; CRE vs. placebo (Jacobson et al. 2001; Pockaj et al. 2006) where no significant difference was achieved, and CRE with tamoxifen (Hernández Munoz & Pluchino 2003; Rostock et al. 2011), where again, significant improvements were noted.

Mechanism of action of CR

CR's mechanism of action on climacteric symptoms is not yet clear. Selective modulation of oestrogen receptors, serotonergic, antioxidant and anti-inflammatory effects have been proposed (Ruhlen et al. 2008). CR binds to the serotonin receptors, 5-HT_{1A}, 5-HT_{1D} and 5-HT_7 (Burdette et al. 2003; Powell et al. 2008). From these, 5-HT_{1A} and 5-HT_7 are also expressed in the hypothalamus and are involved in thermoregulation (Burdette et al. 2003; Hedlund et al. 2003; Naumenko et al. 2011).

There are conflicting data as to whether CREs act as phyto-oestrogens. Early studies in uterine and pituitary cells of ovariectomised rats showed that a chloroform fraction from a methanolic CRE did bind to oestrogen receptors (ER) (Jarry et al. 1985). Another study showed some evidence for an oestrogenic effect of CR in mice and oestrogen-dependent human breast cancer MCF-7 cells (Liu et al. 2001a). Partly contradicting these findings, the same group showed that CRE did not alter expression of different oestrogen-inducible genes (e.g., presenelin-2, progesterone receptor) (Liu et al. 2001b).

Later studies showed that a CRE did not bind to the oestrogen receptors Erα and ERβ (Jarry et al. 2003). Gene expression analysis showed that treatment with CREs down-regulates the expression of Erα (Gaube et al. 2007). The lack of an oestrogenic effect of CREs may be partly explained by an inhibition of the local oestrogen synthesis in breast tissue (Stute et al. 2007) or inhibition of the conversion of oestrone sulphate to active oestradiol in MCF-7 and MDA-123 breast cancer and human granulosa lutein cells (Rice et al. 2007). Furthermore, in MCF-7 cells, repetitive administration of CRE lead-induced gene expression opposite to 17β-oestradiol and more similar to tamoxifen (Gaube et al. 2007).

Two studies from the same group showed weak oestrogenic effects (e.g., lowering of LH secretion, bone remodelling, vaginal mucosa) in menopausal women and ovarectomised rats (Düker et al. 1991; Wuttke et al. 2006). However, most recent studies confirm the absence of any oestrogenic effect: In an oestrogen-sensitive fish (Japanese medaka), Zang *et al.* (Zhang et al. 2003) showed that, in contrast to the phyto-oestrogen genistein and oestradiol, CRE and some of its constituents (e.g., cimiracemoside A, 25-*O*-methyl-cimigenoside, actein, 26-deoxy-actein) did not change oestrogenic activity. In transcriptional-activation assays in yeast in oestrogen-dependent *S. cerevisiae* strain PL3, an isopropanolic extract (40%) did not show any oestrogenic activity (Pockaj et al. 2004).

Different herbal treatments, hormone therapy (HT) or placebo were administered to 351 patients in a 1-year, double-blind, placebo-controlled RCT (HALT-Study, Herbal Alternatives for Menopause (Reed et al. 2008)) study. After 12 and 52 weeks treatment, the HT group had a lower percentage of parabasal cells and vaginal dryness than did the placebo group ($p < 0.05$). Abnormal bleeding was reported in 16.9% of women. When used alone or as part of a multi-botanical product with or without soy dietary changes, CR exerted no effects on vaginal epithelium, endometrium, or reproductive hormones, indicating no local or systemic oestrogenic effects in patients.

CR's lack of clinically-significant oestrogenic effects was further concluded by a lack of change in vaginal cytology and corresponding sexual hormones during 24-weeks of treatment in 152 peri- and post-menopausal women (Liske et al. 2002) where CRE treatment significantly reduced the frequency and severity of HF. These finding were corroborated by several other clinical studies, where the absence of systemic oestrogenic effects of CREs on sexual hormones and/or vaginal or endometrial thickness have been described (Nappi et al. 2005; Liske et al. 2002; Düker et al. 1991; Wuttke et al. 2006; Ruhlen et al. 2007; Rauš et al. 2006; Reed et al. 2008).

In vitro effects of CREs on cell proliferation in oestrogen-dependent breast cancer cells

The effect of CREs on human oestrogen receptor-positive and –negative breast cancer cell lines has been tested in different *in vitro* experiments where the results are often contradictory. The majority of published studies were able to show an inhibition of proliferation, or no effect, of CREs on cell proliferation.

The growth of oestrogen-dependent human breast cancer MCF-7 cells was not stimulated after a 48-hour treatment with an alcoholic CRE (Amato et al. 2002). An inhibitory effect on cell proliferation of oestrogen receptor-positive human mammary carcinoma cell lines was shown for the mammary carcinoma cell line 435 (Neßelhut et al. 1993), the human breast adenocarcinoma MCF-7 cells (Bodinet & Freudenstein 2002; Bodinet & Freudenstein 2004; Zierau et al. 2002; Garita-Hernandez et al. 2006; Al-Akoum et al. 2007; Rice et al. 2007; Gaube et al. 2007), T47D cells (Zava et al. 1998; Dixon-Shanies & Shaikh 1999), the ER^{-}Her2 over-expressing breast cancer cell line MDA-MB-453 (Einbond et al. 2004; Einbond et al. 2006), EMT6 mouse mammary tumour cells (Rockwell et al. 2005) and MDA-MB-231 cells, which are associated with a highly-invasive potential (Al-Akoum et al. 2007; Hostanska et al. 2007; Rice et al. 2007).

CREs, or partly-isolated triterpene constituents of CREs, inhibited oestrogen-stimulated proliferation (Bodinet & Freudenstein 2004; Zierau et al. 2002; Al-Akoum et al. 2007) and enhanced the effects of tamoxifen (Bodinet & Freudenstein 2004; Al-Akoum et al. 2007), 5-fluorouracil, paclitaxel, doxorubicine and docetaxel (Rockwell et al. 2005; Einbond et al. 2006) in breast cancer cells.

This anti-cancer effect has been confirmed for some of the constituents of CR (Einbond et al. 2008). Among them, actein (β-D-xylopyranoside) showed an IC_{50} of 8.4 μM for the inhibition of growth of Her2 overexpressing MDA-MB-453 cells and of 32.5 μM for Her2 transfected and 45.8 μM for parenteral cells. Actein treatment altered the actin filament distribution of, and induced apoptosis in, these cells.

The mechanisms of the anti-proliferating effects have not yet been identified. However, modulation of cyclin D1 promoter activity and transcription activity of the p21 gene promoter may be involved (Garita-Hernandez et al. 2006). Changes in the gene expression pattern during chronic treatment with CRE have been investigated in MCF-7 cells in comparison with oestradiol and tamoxifen (Gaube et al. 2007). The pattern of gene induction was opposite to oestradiol and more similar to tamoxifen. Induced genes exhibited an antiproliferative and apoptosis-sensitising manner, as well as an increase in mRNAs coding for gene products involved in several stress response pathways.

Beyond those effects related to acute or sub-chronic administration, CRE may exert a chemopreventive effect. Treatment of rats starting from 56 weeks of age for 40 weeks resulted in a dose-dependent reduction of mammary adenocarcinomas (Einbond et al. 2012). This effect may be related to the observed reduced Ki-67 and cyclin D1 protein expression in fibroadenomas.

CR and tumour cell growth

It has been reported that inhibition of proliferation and induction of apoptosis are due to the action of triterpene glycosides and the cinnamic acid esters contained in CREs (Hostanska et al. 2004a; Hostanska et al. 2004b). In a further *in vitro* test for invasive potential of highly-invasive oestrogen receptor-negative MDA-MB 231 human breast cancer cells, 5 μg/ml doses of triterpene glycosides and the cinnamic acid esters reduced cell invasion by 34% and 25.5%, respectively (Hostanska et al. 2007). Similar results were obtained by Lupu *et al.* (Lupu et al. 2003). For various CREs (hexane, ethyl acetate and water), no oestrogenic activity (growth induction, regulation of oestrogen-dependent gene expression) has been demonstrated. In addition, anchorage-independent growth was investigated in oestrogen receptor positive MCF7 and T47D cells; thereby indicating possible progression of early stage breast cancer to a more aggressive state and the potential to build metastases (Mori et al. 2009). CR did not stimulate anchorage-dependent growth of breast cancer cells (Lupu et al. 2003).

The cytotoxic effects of powder from CR roots were shown in oestrogen-sensitive MCF-7 cells. Tamoxifen stimulated the growth of MCF-7 cells at high concentrations; on the other hand, when given alone, inhibited oestrogen-induced cell growth in a dose-dependent manner. Contrasting to these results, CR did not stimulate MCF-7 cell growth when given alone and blocked oestrogen-induced cell growth dose-dependently. The combination of tamoxifen with CR showed an enhanced (synergistic) cytotoxic effect of CR. It also inhibited growth of oestrogen-independent MDA-MB-231 breast cancer cells and this effect was synergistically enhanced by tamoxifen in a dose-dependent manner (Al-Akoum et al. 2007).

After acute administration of a CRE (at a dose of 6, 60, or 600 mg/kg) to mice, no signs of an oestrogenic effect could be detected (Einer-Jensen et al. 1996). Due to different oestrogenic effects of an isopropanolic CRE in various organs in ovariectomised rats, a selective oestrogen receptor modulator (SERM) activity has been postulated (Seidlová-Wuttke et al. 2003).

Stimulatory effects on tumour proliferation were studied in an *in vivo* oestrogen-receptor positive breast cancer model (Freudenstein et al. 2002), where mammary tumours were induced by 7,12-dimethylbenz[a]anthracene administration in female rats. After ovariectomy, growth of hormone-dependent mammary tumours was not stimulated by an isopropanolic CRE or placebo given over 6 weeks in contrast to animals treated with 450 μg/kg/day of the oestrogen, mestranol. Furthermore, there was neither a direct effect on uterine tissue proliferation nor an indirect effect on pituitary-secreted, oestrogen-regulated hormones exerted by the CRE.

The effect of CRE on *in vivo* tumour growth was further investigated in RUCA-I rats, an endometrial adenocarcinoma model. In contrast to tamoxifen, there was no stimulation of ectopic growth or an increase in the metastasising potential of the primary tumour noted with CR (Nisslein & Freudenstein 2004).

However, in contrast to the above investigations, one study using transgenic mice expressing c-erbB2 (MMTV-neu mouse model), showed that CRE significantly increased the incidence of lung metastases in tumour-positive animals when compared to mice fed a control diet free of isoflavones. Interestingly, no effect of CR on mammary tumour development was observed. This shows that CRE did not influence breast cancer risk if given prior to tumour formation (Davis et al. 2008). However, the literature indicates that these results have not been either confirmed nor refuted by other groups nor is supporting evidence available from clinical studies in patients with breast cancer.

CR and cytochrome P450 interaction

In vitro experiments using human liver microsomes suggested that methanolic extracts of CR significantly inhibit several cytochrome isoforms (IC_{50}: CYP2B6: 49.2 μg/ml, CYP2C19: 23.9-36.3 μg/ml, and CYP2E1: 11.5 μg/ml) (Sevior et al. 2010). In a human interaction study, CR (80 mg) was given over 14 days to 19 healthy subjects. No clinically relevant interaction with CYP3A4 could be demonstrated using midazolam as the test drug (Gurley et al. 2006a). In MDA-MB-453 and MCF-7 human breast cancer cells, CYP1A1, CYP1B1 (Einbond et al. 2007; Gaube et al. 2007) and ABCC3 (MRP3) (Einbond et al. 2007) were up-regulated. One *in vitro* study showed that a CRE inhibited the formation of tamoxifen metabolites by CYP3A4 and CYP2D6, with IC_{50} values of 16.5 and 50.1 μg/mL, respectively. Eight triterpene glycosides were also identified as competitive CYP3A4 inhibitors, with IC_{50} values ranging from 2.3-5.1 μM, and protopine and allocryptopine alkaloids were shown to be competitive CYP2D6 inhibitors, with K_i values 78 and 122 nM, respectively (Li et al. 2011).

In 12 healthy volunteers, only a low, but clinically not relevant, interaction potential was shown for CYP2D6 when CR was given over 28 days (Gurley et al. 2005). The lack of an interaction of CR with CYP3A4, CYP2D6 and ABCB1 (P-glycoprotein) was confirmed in four separate human studies in healthy volunteers (Gurley et al. 2005; Gurley et al. 2006a; Gurley et al. 2008; Gurley et al. 2006b).

Although there is evidence for an interaction potential of CR and its constituents with tamoxifen metabolism, the clinical data nevertheless indicate that there is no relevant inhibition of CYP2A4 or CYP2D6. Therefore, a clinically relevant interaction of CR with tamoxifen is most unlikely.

Clinical effects of CR with regard to tumour development

Three notable studies assess breast density measurements as a biomarker for the risk of breast cancer development.

In a large prospective, open study in 400 post-menopausal women, the endometrial safety and breast density were studied before and after a 52-week CRE treatment (Rauš et al. 2006). No case of hyperplasia occurred and no serious adverse endometrial outcomes were found, indicating endometrial safety. Endometrial thickness, measured by endovaginal ultrasonography, did not increase during treatment. An increase in breast density was found in only one woman who was diagnosed with invasive breast cancer which, based on history, was unrelated to the CR.

In the second trial, the influence of CR on mammary breast density was investigated in a prospective, open, uncontrolled safety study in 74 post-menopausal women (Hirschberg et al. 2007). Breast density was assessed by

mammography and proliferation of breast tissue by fine needle aspiration histology using Ki-67/MIB-1 monoclonal antibody. Assessment performed at baseline and after 24 weeks showed no increase in mammographic breast density or breast cell proliferation.

Lundström confirmed these results by comparing two studies (Lundström et al. 2011): The first, a prospective, open, uncontrolled drug safety study in 65 post-menopausal women who were treated with 20 mg CR twice daily and the second, a randomised, placebo-controlled clinical study in 154 post-menopausal women who were treated with either oestradiol 2 mg/norethisterone acetate 1 mg (E2/NETA), tibolone 2.5 mg or placebo. Mammograms were performed at baseline and showed comparable breast density for each treatment. Renewed mammograms after 24 weeks of treatment showed that both E2/NETA and tibolone significantly increased breast density (14.3%, and 2.3%, respectively, both $p < 0.001$) while CR and placebo had no effect on breast density. These differences were highly significant ($p < 0.0001$) (Lundström et al. 2011).

In a study evaluating 149 patients, two doses (39 and 127.3 mg/d) of an isopropanolic CRE were studied in a double-blind RCT for the treatment of climacteric symptoms over a 24-week period (Liske et al. 2002). Compared to baseline, both treatments significantly decreased climacteric symptoms, but no oestrogen-induced change in vaginal mucosal thickness or sex hormones were observed, indicating a lack of local and overall oestrogenic effects.

In a retrospective case–control study (Rebbeck et al. 2007), use of CRE was associated with a significantly lower risk of developing breast cancer (adjusted OR 0.39; 95% CI 0.22-0.70), however, the sub-sample of patients treated with CR was rather small. Similar results were found in a large German case–control study in 10,121 post-menopausal women (Obi et al. 2009), where 3,464 incident breast cancer cases were compared to 6,657 controls. Ever use of isopropanolic CRE was associated with a borderline reduced risk for the development of breast cancer (OR 0.80; 95% CI 0.63-1.00). No protective effect of CR (HR 1.17; 95% CI 0.75-1.82) was seen in a large case–control study (Brasky et al. 2010) in 35,016 post-menopausal women, however, the number of incident breast-cancer cases in the CR subpopulation was too small ($n = 21$) to allow a meaningful conclusion.

The risk of breast cancer recurrence where the primary outcome was disease-free survival was investigated in 18,861 patients having a previous breast cancer diagnosis (Heinecke-von Zepelin et al. 2007), among whom 1,102 patients received isopropanolic CRE for a mean overall observation period of 3.6 years. Controlling for age, tamoxifen use and other confounders, the Cox regression model demonstrated a statistically significant protective effect of isopropanolic CR on recurrence rate (HR 0.83, 95% CI 0.69-0.99).

Males

Several studies have shown that those anti-androgen treated, or surgically castrated, men who develop severe HF symptoms respond well to treatments that are effective against menopausal symptoms in women, in particular, oestrogens, though often accompanied with breast tenderness, gynaecomastia and an increased risk of cardiovascular and thrombembolic events (Adelson et al. 2005).

Alternatively, *in vitro* experiments indicate that treatment with CREs may benefit prostate cancer patients. Anti-proliferative effects of CR for several prostate cancer cell lines and *in vivo* tumours have been observed. Most studies describe induction of apoptotic cellular response and subsequent reduction in proliferation and partly prostate-specific antigen secretion in androgen dependent tumour cells (LNCaP) (Hostanska et al. 2005; Jarry et al. 2007; Jarry et al. 2005). In addition, 5α-reductase (the key enzyme for dihydro-testosterone synthesis) was inhibited by CR in the rat prostate (Seidlová-Wuttke et al. 2006), possibly indicating its suitability in preventing and treating prostate cancer and benign prostate hyperplasia.

Further, one study showed *in vivo* anti-proliferative and growth inhibitory effects for implanted prostate cancer in immunodeficient (nu/nu) athymic nude mice (Seidlova-Wuttke et al. 2006). However, a controlled clinical trial is yet to be performed.

Discussion

The most effective treatment of climacteric symptoms is HT with oestrogen or a combination of oestrogen and progestins (MacLennan et al. 2009). However, the benefits are partly outweighed by a significantly increased risk for the development of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 1997; Porch et al. 2002; Rossouw et al. 2002; Weiss et al. 2002; Beral et al. 2002; Beral & Million Women Study Collaborators 2003; Chlebowski et al. 2009). After publication of the WHI studies (Rossouw et al. 2002) and the Million Women Study (Beral & Million Women Study Collaborators 2003), HT use decreased drastically worldwide (Hersh et al. 2004; Canfell et al. 2008; Antoine et al. 2011), accompanied by a significant decrease in breast cancer incidence (Canfell et al. 2008; Ravdin et al. 2007; Canfell et al. 2009).

Recently, the risk-benefit ratio of HT was reassessed for various ages and time intervals since menopause onset. The North American Menopause Society (NAMS) (NAMS 2012) proposed that duration of treatment should be limited to younger women up to the age of 50 to 59 years; beyond which, HT is associated with

increased risks. Similar recommendations were issued by the International Menopause Society (IMS) in 2011 (Sturdee et al. 2011), which considered HT as a first-line therapy choice for climacteric symptoms. Finally, a global consensus on the use of HT was obtained by The American Society for Reproductive Medicine, The Asia Pacific Menopause Federation, The Endocrine Society, The European Menopause and Andropause Society, The International Menopause Society, The International Osteoporosis Foundation and The North American Menopause Society (de Villiers et al. 2013). They stated that HT "is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause". Although some HT restrictions have been withdrawn, there is still a considerable need for non-hormonal treatment alternatives, especially for elderly post-menopausal women or cancer patients of both genders. Therefore, this present work aimed to assess the risk-benefit ratio of various non-hormonal treatment options. Among them, four non-hormonal treatments appear to have significant evidence for a beneficial effect in treating vasomotor climacteric or androgen-ablation symptoms, although some studied the effects over a period shorter than 12 weeks: gabapentin/pregabalin (Loprinzi et al. 2002a; Guttuso et al. 2003; Reddy et al. 2006; Loprinzi et al. 2007; Butt et al. 2008; Saadati et al. 2013; Agarwal et al. 2014; Pinkerton et al. 2014; Loprinzi et al. 2010; Pandya et al. 2004; Pandya et al. 2005; Bordeleau et al. 2010; Loprinzi et al. 2009; Moraska et al. 2010), SSRIs (Stearns et al. 2003; Stearns et al. 2005; Simon et al. 2013; Huang et al. 2013; Stearns et al. 2000; Gordon et al. 2006; Grady et al. 2007; Kerwin et al. 2007; Aedo et al. 2011; Kimmick et al. 2006; Wu et al. 2009; Suvanto-Luukkonen et al. 2005; Oktem et al. 2007; Loprinzi et al. 2002b; Barton et al. 2010; Barton et al. 2003; Defronzo Dobkin et al. 2009; Freedman et al. 2011; Freeman et al. 2011; Carpenter et al. 2012; Ensrud et al. 2012), venlafaxine/desvenlafaxine (Evans et al. 2005; Loprinzi et al. 2006; Loprinzi et al. 1998; Carpenter et al. 2007; Quella et al. 1999; Loprinzi et al. 2000; Loibl et al. 2007; Buijs et al. 2009; Boekhout et al. 2011; Bordeleau et al. 2010; Vitolins et al. 2013; Speroff et al. 2008; Archer et al. 2009a; Archer et al. 2009b; Cheng et al. 2013; Bouchard et al. 2012; Pinkerton et al. 2013), and CREs (Drewe et al. 2013; Lopatka et al. 2007; Vermes et al. 2005; Liske et al. 2002; Frei-Kleiner et al. 2005; Schellenberg et al. 2012; Osmers et al. 2005; Ross 2012; Newton et al. 2006; Geller et al. 2009; Stoll 1987; Wuttke et al. 2003; Nappi et al. 2005; Bai et al. 2007; Uebelhack et al. 2006; Briese et al. 2007; Oktem et al. 2007; Huang et al. 2013; Pockaj et al. 2004; Jacobson et al. 2001; Pockaj et al. 2006; Hernández Munoz & Pluchino 2003; Rostock et al. 2011).

Randomised, controlled trials that have shown a pharmacological effect and are at least 12 weeks duration, as required by FDA and EMA (FDA. U.S. Department of Health and Human Services Food and Drug Administration 2003; EMEA. Committee for Medicinal products for human use (CHMP) 2005) have only been undertaken for gabapentin (Guttuso et al. 2003; Reddy et al. 2006); (Saadati et al. 2013) #3447 (Agarwal et al. 2014; Pinkerton et al. 2014); SSRIs: (Simon et al. 2013; Aedo et al. 2011; Suvanto-Luukkonen et al. 2005; Oktem et al. 2007), venlafaxine (Evans et al. 2005; Boekhout et al. 2011; Vitolins et al. 2013), desvenlafaxine (Speroff et al. 2008; Archer et al. 2009a; Archer et al. 2009b; Cheng et al. 2013; Bouchard et al. 2012; Pinkerton et al. 2013), isoflavones (Albertazzi et al. 1998; Han et al. 2002; van de Weijer & Barentsen 2002; Jeri 2002; Sammartino et al. 2003; Nahas et al. 2004; Nahas et al. 2007; Khaodhiar et al. 2008; Cheng et al. 2007; Radhakrishnan et al. 2009; Ye et al. 2012; Aso et al. 2012; Mainini et al. 2013; D'Anna et al. 2007; D'Anna et al. 2009; Ferrari 2009; Evans et al. 2011; Murkies et al. 1995; Crisafulli et al. 2004; Labos et al. 2013; Upmalis et al. 2000; Faure et al. 2002); hops (Heyerick et al. 2006); red clover (Hidalgo et al. 2005; Lipovac et al. 2012), flaxseed (Colli et al. 2012), St. John's wort (Uebelhack et al. 2006; Briese et al. 2007), French maritime pine bark (Yang et al. 2007; Kohama & Negami 2013), Sibiric Rhubarb (Heger et al. 2006; Kaszkin-Bettag et al. 2007; Kaszkin-Bettag et al. 2009; Hasper et al. 2009), and CREs (Drewe et al. 2013; Lopatka et al. 2007; Vermes et al. 2005; Liske et al. 2002; Frei-Kleiner et al. 2005; Schellenberg et al. 2012; Osmers et al. 2005; Ross 2012; Newton et al. 2006; Geller et al. 2009; Stoll 1987; Wuttke et al. 2003; Nappi et al. 2005; Bai et al. 2007; Uebelhack et al. 2006; Briese et al. 2007; Oktem et al. 2007; Hernández Munoz & Pluchino 2003; Rostock et al. 2011).

Conclusion

Several non-hormonal alternatives to hormonal therapy have been established and confirmed for the treatment of vasomotor climacteric symptoms in peri- and post-menopausal women. Although there are indications that these treatments are useful in patients with a history of breast cancer, this still requires confirmation by larger clinical trials.

This systematic analysis did not carry out any of its own clinical research involving patients and the statements relating to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments thus do not apply.

Additional file

Additional file 1: Clinical effect of non-hormonal treatments in menopausal and cancer patients.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors (JD, KAB and CZ) have made substantive intellectual contributions to this study according to ICMJE guidelines. All of them have been qualified as authors. All authors read and approved the final manuscript.

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Received: 11 August 2014 Accepted: 9 January 2015
Published online: 10 February 2015

References
Abdali K, Khajehei M, Tabatabaee HR (2010) Effect of St John's wort on severity, frequency, and duration of hot flashes in premenopausal, perimenopausal and postmenopausal women: a randomized, double-blind, placebo-controlled study. Menopause 17(2):326–331, doi:10.1097/gme.0b013e3181b8e02d

Adelson KB, Loprinzi CL, Hershman DL (2005) Treatment of hot flushes in breast and prostate cancer. Expert Opin Pharmacother 6(7):1095–1106

Adlercreutz H (1995) Phytoestrogens: epidemiology and a possible role in cancer protection. Environ Health Perspect 103(Suppl 7):103–112

Adlercreutz H (2002a) Phyto-oestrogens and cancer. Lancet Oncol 3(6):364–373

Adlercreutz H (2002b) Phytoestrogens and breast cancer. J Steroid Biochem Mol Biol 83(1–5):113–118

Adlercreutz H, Bannwart C, Wahala K, Makela T, Brunow G, Hase T, Arosemena PJ, Kellis JT Jr, Vickery LE (1993) Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. J Steroid Biochem Mol Biol 44(2):147–153

Aedo S, Cavada G, Campodonico I, Porcile A, Irribarra C (2011) Sertraline improves the somatic and psychological symptoms of the climacteric syndrome. Climacteric 14(5):590–595, doi:10.3109/13697137.2011.568645

Agarwal N, Singh S, Kriplani A, Bhatla N, Singh N (2014) Evaluation of gabapentin in management of hot flushes in postmenopausal women. Post Reprod Health 20(1):36–38, doi:10.1177/1754045313518527

Al-Akoum M, Dodin S, Akoum A (2007) Synergistic cytotoxic effects of tamoxifen and black cohosh on MCF-7 and MDA-MB-231 human breast cancer cells: an *in vitro* study. Can J Physiol Pharmacol 85(11):1153–1159

Al-Akoum M, Maunsell E, Verreault R, Provencher L, Otis H, Dodin S (2009) Effects of Hypericum perforatum (St. John's wort) on hot flashes and quality of life in perimenopausal women: a randomized pilot trial. Menopause 16(2):307–314, doi:10.1097/gme.0b013e31818572a0

Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E, De Aloysio D (1998) The effect of dietary soy supplementation on hot flushes. Obstet Gynecol 91(1):6–11, doi:S0029784497005978

Amato P, Christophe S, Mellon PL (2002) Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. Menopause 9(2):145–150

Amsterdam JD, Garcia-Espana F, Goodman D, Hooper M, Hornig-Rohan M (1997) Breast enlargement during chronic antidepressant therapy. J Affect Disord 46(2):151–156, doi:S0165-0327(97)00086-4

Andersen O, Engebretsen T, Solberg VM, Orbo A (1986) α-Methyldopa for climacteric hot flushes. A double-blind, randomized, cross-over study. Acta Obstet Gynecol Scand 65(5):405–409

Anderson GL, Chlebowski RT, Rossouw JE, Rodabough RJ, McTiernan A, Margolis KL, Aggerwal A, David Curb J, Hendrix SL, Allan Hubbell F, Khandekar J, Lane DS, Lasser N, Lopez AM, Potter J, Ritenbaugh C (2006) Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. Maturitas 55(2):103–115, doi:10.1016/j.maturitas.2006.05.004

Antoine C, Liebens F, Carly B, Pastijn A, Neusy S, Rozenberg S (2007) Safety of hormone therapy after breast cancer: a qualitative systematic review. Hum Reprod 22(2):616–622

Antoine C, Ameye L, Moreau M, Paesmans M, Rozenberg S (2011) Evolution of breast cancer incidence in relation to hormone replacement therapy use in Belgium. Climacteric 14(4):464–471

Archer DF, Dupont CM, Constantine GD, Pickar JH, Olivier S (2009a) Desvenlafaxine for the treatment of vasomotor symptoms associated with menopause: a double-blind, randomized, placebo-controlled trial of efficacy and safety. Am J Obstet Gynecol 200(3):238e1–238e10, doi:10.1016/j.ajog.2008.10.057

Archer DF, Seidman L, Constantine GD, Pickar JH, Olivier S (2009b) A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause. Am J Obstet Gynecol 200(2):172e1–172e10, doi:10.1016/j.ajog.2008.09.877

Arendt LM, Rugowski DE, Grafwallner-Huseth TA, Garcia-Barchino MJ, Rui H, Schuler LA (2011) Prolactin-induced mouse mammary carcinomas model estrogen resistant luminal breast cancer. Breast Cancer Res 13(1):R11, doi:10.1186/bcr2819

Ashbury JE, Levesque LE, Beck PA, Aronson KJ (2012) Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants. Prolactin Breast Cancer Frontiers Oncol 2:177, doi:10.3389/fonc.2012.00177

Aso T, Uchiyama S, Matsumura Y, Taguchi M, Nozaki M, Takamatsu K, Ishizuka B, Kubota T, Mizunuma H, Ohta H (2012) A natural S-equol supplement alleviates hot flushes and other menopausal symptoms in equol nonproducing postmenopausal Japanese women. J Womens Health (Larchmt) 21(1):92–100, doi:10.1089/jwh.2011.2753c

Baber RJ, Templeman C, Morton T, Kelly GE, West L (1999) Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. Climacteric 2(2):85–92, doi:10.3109/13697139909025571

Baber R, Hickey M, Kwik M (2005) Therapy for menopausal symptoms during and after treatment for breast cancer: safety considerations. Drug Saf 28(12):1085–1100

Bai W, Henneicke-von Zepelin H-H, Wang S, Zheng S, Liu J, Zhang Z, Geng L, Hu L, Jiao C, Liske E (2007) Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. Maturitas 58(1):31–41, doi:10.1016/j.maturitas.2007.04.009

Barton DL, Loprinzi CL, Quella SK, Sloan JA, Veeder MH, Egner JR, Fidler P, Stella PJ, Swan DK, Vaught NL, Novotny P (1998) Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. J Clin Oncol 16:495–500

Barton DL, Loprinzi CL, Novotny P, Shanafelt T, Sloan J, Wahner-Roedler D, Rummans TA, Christensen B, Dakhill SR, Martin LS (2003) Pilot evaluation of citalopram for the relief of hot flashes. J Support Oncol 1(1):47–51

Barton DL, LaVasseur BI, Sloan JA, Stawis AN, Flynn KA, Dyar M, Johnson DB, Atherton PJ, Diekmann B, Loprinzi CL (2010) Phase III, placebo-controlled trial of three doses of citalopram for the treatment of hot flashes: NCCTG trial N05C9. J Clin Oncol 28(20):3278–3283

Beer AM, Osmers R, Schnitker J, Bai W, Mueck AO, Meden H (2013) Efficacy of black cohosh (Cimicifuga racemosa) medicines for treatment of menopausal symptoms - comments on major statements of the Cochrane Collaboration report 2012 "black cohosh (Cimicifuga spp.) for menopausal symptoms (review)". Gynecol Endocrinol 29(12):1022–1025, doi:10.3109/09513590.2013.831836

Bendele RA, Adams ER, Hoffman WP, Gries CL, Morton DM (1992) Carcinogenicity studies of fluoxetine hydrochloride in rats and mice. Cancer Res 52(24):6931–6935

Beral V, Million Women Study Collaborators (2003) Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 362(9382):419–427

Beral V, Banks E, Reeves G (2002) Evidence from randomised trials on the long-term effects of hormone replacement therapy. Lancet 360(9337):942–944

Beral V, Reeves G, Bull D, Green J (2011) Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J Natl Cancer Inst 103(4):296–305

Berendsen HH (2000) The role of serotonin in hot flushes. Maturitas 36(3):155–164

Biegon A (1990) Effects of steroid hormones on the serotonergic system. Ann N Y Acad Sci 600:427–432, discussion 32–4

Biglia N, Kubatzki F, Sgandurra P, Ponzone R, Marenco D, Peano E, Sismondi P (2007) Mirtazapine for the treatment of hot flushes in breast cancer survivors: a prospective pilot trial. Breast J 13(5):490–495

Binkhorst L, Mathijssen RH, van Herk-Sukel MP, Bannink M, Jager A, Wiemer EA, van Gelder T (2013) Unjustified prescribing of CYP2D6 inhibiting SSRIs in women treated with tamoxifen. Breast Cancer Res Treat 139(3):923–929, doi:10.1007/s10549-013-2585-z

Blum I, Vered Y, Lifshitz A, Harel D, Blum M, Nordenberg Y, Harsat A, Sulkes J, Gabbay U, Graff E (1996) The effect of estrogen replacement therapy on plasma serotonin and catecholamines of postmenopausal women. Isr J Med Sci 32(12):1158–1162

Bodinet C, Freudenstein J (2002) Influence of *Cimicifuga racemosa* on the proliferation of estrogen receptor-positive human breast cancer cells. Breast Cancer Res Treat 76(1):1–10

Bodinet C, Freudenstein J (2004) Influence of marketed herbal menopause preparations on MCF-7 cell proliferation. Menopause 11(3):281–289

Boekhout AH, Vincent AD, Dalesio OB, van den Bosch J, Foekema-Tons JH, Adriaansz S, Sprangers S, Nuijen B, Beijnen JH, Schellens JH (2011) Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. J Clin Oncol 29(29):3862–3868, doi:10.1200/JCO.2010.33.1298

Bonin B, Vandel P, Vandel S (1994) Fluvoxamine and galactorrhea. A case report. Therapie 49(2):149–151

Bonin B, Vandel P, Sechter D, Bizouard P (1997) Paroxetine and galactorrhea. Pharmacopsychiatry 30(4):133–134, doi: 10.1055/s-2007-979499

Bordeleau L, Pritchard KI, Loprinzi CL, Ennis M, Jugovic O, Warr D, Haq R, Goodwin PJ (2010) Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol 28(35):5147–5152

Bouchard P, Panay N, de Villiers TJ, Vincendon P, Bao W, Cheng RJ, Constantine G (2012) Randomized placebo- and active-controlled study of desvenlafaxine for menopausal vasomotor symptoms. Climacteric 15(1):12–20, doi:10.3109/13697137.2011.586445

Brandes LJ, Arron RJ, Bogdanovic RP, Tong J, Zaborniak CL, Hogg GR, Warrington RC, Fang W, LaBella FS (1992) Stimulation of malignant growth in rodents by antidepressant drugs at clinically relevant doses. Cancer Res 52(13):3796–3800

Brasky TM, Lampe JW, Potter JD, Patterson RE, White E (2010) Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort. Cancer Epidemiol Biomarkers Prev 19(7):1696–1708, doi:10.1158/1055-9965.EPI-10-0318

Briese V, Stammwitz U, Friede M, Henneicke-von Zepelin HH (2007) Black cohosh with or without St. John's wort for symptom-specific climacteric treatment–results of a large-scale, controlled, observational study. Maturitas 57(4):405–414

Bronzo MR, Stahl SM (1993) Galactorrhea induced by sertraline. Am J Psychiatry 150(8):1269–1270

Bruzzone A, Pinero CP, Castillo LF, Sarappa MG, Rojas P, Lanari C, Luthy IA (2008) Alpha2-adrenoceptor action on cell proliferation and mammary tumour growth in mice. Br J Pharmacol 155(4):494–504, doi:10.1038/bjp.2008.278

Bruzzone A, Pinero CP, Rojas P, Romanato M, Gass H, Lanari C, Luthy IA (2011) Alpha(2)-Adrenoceptors enhance cell proliferation and mammary tumor growth acting through both the stroma and the tumor cells. Curr Cancer Drug Targets 11(6):763–774

Buck K, Vrieling A, Zaineddin AK, Becker S, Husing A, Kaaks R, Linseisen J, Flesch-Janys D, Chang-Claude J (2011) Serum enterolactone and prognosis of postmenopausal breast cancer. J Clin Oncol 29(28):3730–3738, doi:10.1200/JCO.2011.34.6478

Buijs C, Mom CH, Willemse PH, Marike Boezen H, Maurer JM, Wymenga AN, de Jong RS, Nieboer P, de Vries EG, Mourits MJ (2009) Venlafaxine versus clonidine for the treatment of hot flashes in breast cancer patients: a double-blind, randomized cross-over study. Breast Cancer Res Treat 115(3):573–580, doi:10.1007/s10549-008-0138-7

Bundred NJ, Kenemans P, Yip CH, Beckmann MW, Foidart JM, Sismondi P, Schoultz B, Vassilopoulou-Sellin R, Galta RE, Lieshout EV, Mol-Arts M, Planellas J, Kubista E (2012) Tibolone increases bone mineral density but also relapse in breast cancer survivors: LIBERATE trial bone substudy. Breast Cancer Res 14(1):R13

Burdette JE, Liu J, Chen SN, Fabricant DS, Piersen CE, Barker EL, Pezzuto JM, Mesecar A, Van Breemen RB, Farnsworth NR, Bolton JL (2003) Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. J Agric Food Chem 51(19):5661–5670

Burger HG, Dudley EC, Robertson DM, Dennerstein L (2002) Hormonal changes in the menopause transition. Recent Prog Horm Res 57:257–275

Burke GL, Legault C, Anthony M, Bland DR, Morgan TM, Naughton MJ, Leggett K, Washburn SA, Vitolins MZ (2003) Soy protein and isoflavone effects on vasomotor symptoms in peri- and postmenopausal women: the Soy Estrogen Alternative Study. Menopause 10(2):147–153

Butt DA, Lock M, Lewis JE, Ross S, Moineddin R (2008) Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. Menopause 15(2):310–318, doi:10.1097/gme.0b013e3180dca175

Campagnoli C, Abba C, Ambroggio S, Peris C, Perona M, Sanseverino P (2005) Polyunsaturated fatty acids (PUFAs) might reduce hot flushes: an indication from two controlled trials on soy isoflavones alone and with a PUFA supplement. Maturitas 51(2):127–134, doi:10.1016/j.maturitas.2004.11.002

Canfell K, Banks E, Moa AM, Beral V (2008) Decrease in breast cancer incidence following a rapid fall in use of hormone replacement therapy in Australia. Med J Aust 188(11):641–644

Canfell K, Banks E, Clements M, Kang YJ, Moa A, Armstrong B, Beral V (2009) Sustained lower rates of HRT prescribing and breast cancer incidence in Australia since 2003. Breast Cancer Res Treat 117(3):671–673

Carpenter JS, Andrykowski MA, Cordova M, Cunningham L, Studts J, McGrath P, Kenady D, Sloan D, Munn R (1998) Hot flashes in postmenopausal women treated for breast carcinoma: prevalence, severity, correlates, management, and relation to quality of life. Cancer 82(9):1682–1691

Carpenter JS, Storniolo AM, Johns S, Monahan PO, Azzouz F, Elam JL, Johnson CS, Shelton RC (2007) Randomized, double-blind, placebo-controlled crossover trials of venlafaxine for hot flashes after breast cancer. Oncologist 12(1):124–135, doi:10.1634/theoncologist.12-1-124

Carpenter JS, Guthrie KA, Larson JC, Freeman EW, Joffe H, Reed SD, Ensrud KE, LaCroix AZ (2012) Effect of escitalopram on hot flash interference: a randomized, controlled trial. Fertil Steril 97(6):1399–1404, doi:10.1016/j.fertnstert.2012.03.001

Carver KC, Arendt LM, Schuler LA (2009) Complex prolactin crosstalk in breast cancer: new therapeutic implications. Mol Cell Endocrinol 307(1–2):1–7, doi:10.1016/j.mce.2009.03.014

Casper RF, Yen SS (1985) Neuroendocrinology of menopausal flushes: an hypothesis of flush mechanism. Clin Endocrinol (Oxf) 22(3):293–312

Charig CR, Rundle JS (1989) Flushing. Long-term side effect of orchiectomy in treatment of prostatic carcinoma. Urology 33(3):175–178

Chen WY, Giobbie-Hurder A, Gantman K, Savoie J, Scheib R, Parker LM, Schernhammer ES (2014) A randomized, placebo-controlled trial of melatonin on breast cancer survivors: impact on sleep, mood, and hot flashes. Breast Cancer Res Treat 145(2):381–388, doi:10.1007/s10549-014-2944-4

Cheng G, Wilczek B, Warner M, Gustafsson JA, Landgren BM (2007) Isoflavone treatment for acute menopausal symptoms. Menopause 14(3 Pt 1):468–473, doi:10.1097/GME.0b013e31802cc7d0

Cheng RJ, Dupont C, Archer DF, Bao W, Racketa J, Constantine G, Pickar JH (2013) Effect of desvenlafaxine on mood and climacteric symptoms in menopausal women with moderate to severe vasomotor symptoms. Climacteric 16(1):17–27, doi:10.3109/13697137.2012.672495

Chien C, Li CI, Heckbert SR, Malone KE, Boudreau DM, Daling JR (2006) Antidepressant use and breast cancer risk. Breast Cancer Res Treat 95(2):131–140, doi:10.1007/s10549-005-9056-0

Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, Rodabough RJ, Gilligan MA, Cyr MG, Thomson CA, Khandekar J, Petrovitch H, McTiernan A (2003) Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 289(24):3243–3253, doi:10.1001/jama.289.24.3243C

Chlebowski RT, Kuller LH, Prentice RL, Stefanick ML, Manson JE, Gass M, Aragaki AK, Ockene JK, Lane DS, Sarto GE, Rajkovic A, Schenken R, Hendrix SL, Ravdin PM, Rohan TE, Yasmeen S, Anderson G (2009) Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 360(6):573–587, doi: 10.1056/NEJMoa0807684

Chow S-N, Lin Y-H, Chen R-J, Huang S-C, Chen C-K (1993) Treatment of menopausal flushes with oral clonidine. Curr Ther Res 54(5):476–481

Clayden JR, Bell JW, Pollard P (1974) Menopausal flushing: double-blind trial of a non-hormonal medication. Br Med J 1(5905):409–412

Clevenger CV, Gadd SL, Zheng J (2009) New mechanisms for PRLr action in breast cancer. Trends Endocrinol Metab 20(5):223–229, doi:10.1016/j.tem.2009.03.001

Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 350(9084):1047–1059, doi:S0140673697082330 [pii]

Colli MC, Bracht A, Soares AA, de Oliveira AL, Boer CG, de Souza CG, Peralta RM (2012) Evaluation of the efficacy of flaxseed meal and flaxseed extract in reducing menopausal symptoms. J Med Food 15(9):840–845, doi:10.1089/jmf.2011.0228

Collins JA, Blake JM, Crosignani PG (2005) Breast cancer risk with postmenopausal hormonal treatment. Hum Reprod Update 11(6):545–560

Conner P, Christow A, Kersemaekers W, Soderqvist G, Skoog L, Carlstrom K, Tani E, Mol-Arts M, von Schoultz B (2004) A comparative study of breast cell proliferation during hormone replacement therapy: effects of tibolon and continuous combined estrogen-progestogen treatment. Climacteric 7(1):50–58

Coogan PF, Palmer JR, Strom BL, Rosenberg L (2005) Use of selective serotonin reuptake inhibitors and the risk of breast cancer. Am J Epidemiol 162(9):835–838, doi:10.1093/aje/kwi301

Coogan PF, Strom BL, Rosenberg L (2008) SSRI use and breast cancer risk by hormone receptor status. Breast Cancer Res Treat 109(3):527–531, doi:10.1007/s10549-007-9664-y

Cotterchio M, Kreiger N, Darlington G, Steingart A (2000) Antidepressant medication use and breast cancer risk. Am J Epidemiol 151(10):951–957

Couzi RJ, Helzlsouer KJ, Fetting JH (1995) Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. J Clin Oncol 13(11):2737–2744

Crandall CJ, Tseng CH, Crawford SL, Thurston RC, Gold EB, Johnston JM, Greendale GA (2011) Association of menopausal vasomotor symptoms with increased bone turnover during the menopausal transition. J Bone Miner Res 26(4):840–849, doi:10.1002/jbmr.259

Crewe HK, Ellis SW, Lennard MS, Tucker GT (1997) Variable contribution of cytochromes P450 2D6, 2C9 and 3A4 to the 4-hydroxylation of tamoxifen by human liver microsomes. Biochem Pharmacol 53(2):171–178

Crisafulli A, Marini H, Bitto A, Altavilla D, Squadrito G, Romeo A, Adamo EB, Marini R, D'Anna R, Corrado F, Bartolone S, Frisina N, Squadrito F (2004) Effects of genistein on hot flushes in early postmenopausal women: a randomized, double-blind EPT- and placebo-controlled study. Menopause 11(4):400–404

Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, Mol-Arts M, Kloosterboer L, Mosca L, Christiansen C, Bilezikian J, Kerzberg EM, Johnson S, Zanchetta J, Grobbee DE, Seifert W, Eastell R (2008) The effects of tibolone in older postmenopausal women. N Engl J Med 359(7):697–708

D'Anna R, Cannata ML, Atteritano M, Cancellieri F, Corrado F, Baviera G, Triolo O, Antico F, Gaudio A, Frisina N, Bitto A, Polito F, Minutoli L, Altavilla D, Marini H, Squadrito F (2007) Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 1-year randomized, double-blind, placebo-controlled study. Menopause 14(4):648–655, doi:10.1097/01.gme.0000248708.60698.98

D'Anna R, Cannata ML, Marini H, Atteritano M, Cancellieri F, Corrado F, Triolo O, Rizzo P, Russo S, Gaudio A, Frisina N, Bitto A, Polito F, Minutoli L, Altavilla D, Adamo EB, Squadrito F (2009) Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 2-year randomized, double-blind, placebo-controlled study. Menopause 16(2):301–306, doi:10.1097/gme.0b013e318186d7e2

Davis VL, Jayo MJ, Ho A, Kotlarczyk MP, Hardy ML, Foster WG, Hughes CL (2008) Black cohosh increases metastatic mammary cancer in transgenic mice expressing c-erbB2. Cancer Res 68(20):8377–8383

de Villiers TJ, Gass ML, Haines CJ, Hall JE, Lobo RA, Pierroz DD, Rees M (2013) Global consensus statement on menopausal hormone therapy. Climacteric 16(2):203–204, doi:10.3109/13697137.2013.771520

Defronzo Dobkin R, Menza M, Allen LA, Marin H, Bienfait KL, Tiu J, Howarth J (2009) Escitalopram reduces hot flashes in nondepressed menopausal women: A pilot study. Ann Clin Psychiatry 21(2):70–76, doi:acp_2102a

Desmarais JE, Looper KJ (2009) Interactions between tamoxifen and antidepressants via cytochrome P450 2D6. J Clin Psychiatry 70(12):1688–1697, doi:10.4088/JCP.08r04856blu

Desmarais JE, Looper KJ (2010) Managing menopausal symptoms and depression in tamoxifen users: implications of drug and medicinal interactions. Maturitas 67(4):296–308, doi:10.1016/j.maturitas.2010.08.005

Desta Z, Ward BA, Soukhova NV, Flockhart DA (2004) Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. J Pharmacol Exp Ther 310(3):1062–1075

Dixon-Shanies D, Shaikh N (1999) Growth inhibition of human breast cancer cells by herbs and phytoestrogens. Oncol Rep 6(6):1383–1387

Drewe J, Zimmermann C, Zahner C (2013) The effect of a *Cimicifuga racemosa* extracts Ze 450 in the treatment of climacteric complaints - an observational study. Phytomedicine 20(8–9):659–666, doi: 10.1016/j.phymed.2013.02.012

Du M, Yang X, Hartman JA, Cooke PS, Doerge DR, Ju YH, Helferich WG (2012) Low-dose dietary genistein negates the therapeutic effect of tamoxifen in athymic nude mice. Carcinogenesis 33(4):895–901, doi:10.1093/carcin/bgs017

Duffy C, Cyr M (2003) Phytoestrogens: potential benefits and implications for breast cancer survivors. J Womens Health (Larchmt) 12(7):617–631

Düker EM, Kopanski L, Jarry H, Wuttke W (1991) Effects of extracts from Cimicifuga racemosa on gonadotropin release in menopausal women and ovariectomized rats. Planta Med 57(5):420–424

Edington RF, Chagnon JP, Steinberg WM (1980) Clonidine (Dixarit) for menopausal flushing. Can Med Assoc J 123(1):23–26

Einbond LS, Shimizu M, Xiao D, Nuntanakorn P, Lim JT, Suzui M, Seter C, Pertel T, Kennelly EJ, Kronenberg F, Weinstein IB (2004) Growth inhibitory activity of extracts and purified components of black cohosh on human breast cancer cells. Breast Cancer Res Treat 83(3):221–231

Einbond LS, Shimizu M, Xiao D, Nuntanakorn P, Lim JT, Suzui M, Seter C, Cheng R, Jiang B, Pertel T, Kennelly EJ, Kronenberg F, Weinstein IB (2006) Actein and a fraction of black cohosh potentiate antiproliferative effects of chemotherapy agents on human breast cancer cells. Planta Med 72(13):1200–1206

Einbond LS, Su T, Wu HA, Friedman R, Wang X, Jiang B, Hagan T, Kennelly EJ, Kronenberg F, Weinstein IB (2007) Gene expression analysis of the mechanisms whereby black cohosh inhibits human breast cancer cell growth. Anticancer Res 27(2):697–712

Einbond LS, Wen-Cai Y, He K, Wu HA, Cruz E, Roller M, Kronenberg F (2008) Growth inhibitory activity of extracts and compounds from Cimicifuga species on human breast cancer cells. Phytomedicine 15(6–7):504–511

Einbond LS, Soffritti M, Degli Esposti D, Tibaldi E, Lauriola M, Bua L, He K, Genovese G, Su T, Huggins L, Wang X, Roller M, Wu HA (2012) Chemopreventive potential of black cohosh on breast cancer in Sprague–Dawley rats. Anticancer Res 32(1):21–30

Einer-Jensen N, Zhao J, Andersen KP, Kristoffersen K (1996) Cimicifuga and Melbrosia lack oestrogenic effects in mice and rats. Maturitas 25(2):149–153

EMEA (2010) Community herbal monograph on *Cimicifuga racemosa* (L.) Nutt., rhizoma. EMA/HMPC/600717/2007 Corr. Eur Med Agency. 1–6. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2011/01/WC500100981.pdf

EMEA (2014) Questions and answers on the withdrawal of the marketing application for Pristiqs In: EMEA/CHMP/125421/2008. 2008. http://www.emea.europa.eu/docs/en_GB/document_library/Medicine_QA/2010/01/WC500066945.pdf. Last Access: June

EMEA. Committee for Medicinal products for human use (CHMP) (2005) Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (CPMP/EWP/021/97)

Ensrud KE, Joffe H, Guthrie KA, Larson JC, Reed SD, Newton KM, Sternfeld B, Lacroix AZ, Landis CA, Woods NF, Freeman EW (2012) Effect of escitalopram on insomnia symptoms and subjective sleep quality in healthy perimenopausal and postmenopausal women with hot flashes: a randomized controlled trial. Menopause 19(8):848–855, doi:10.1097/gme.0b013e3182476099

Erkkola R, Vervarcke S, Vansteelandt S, Rompotti P, De Keukeleire D, Heyerick A (2010) A randomized, double-blind, placebo-controlled, cross-over pilot study on the use of a standardized hop extract to alleviate menopausal discomforts. Phytomedicine 17(6):389–396

Erlik Y, Meldrum DR, Lagasse LD, Judd HL (1981) Effect of megestrol acetate on flushing and bone metabolism in post-menopausal women. Maturitas 3(2):167–172

ESCOP Monographs (2003) The Scientific Foundation for Herbal Medicinal Products. *Cimicifugae rhizoma*. Black cohosh, 2nd edn. Georg Thieme-Verlag, Stuttgart, New York, pp 79–91

Evans ML, Pritts E, Vittinghoff E, McClish K, Morgan KS, Jaffe RB (2005) Management of postmenopausal hot flushes with venlafaxine hydrochloride: a randomized, controlled trial. Obstet Gynecol 105(1):161–166

Evans M, Elliott JG, Sharma P, Berman R, Guthrie N (2011) The effect of synthetic genistein on menopause symptom management in healthy postmenopausal women: a multi-center, randomized, placebo-controlled study. Maturitas 68(2):189–196, doi:10.1016/j.maturitas.2010.11.012

Farzaneh F, Fatehi S, Sohrabi MR, Alizadeh K (2013) The effect of oral evening primrose oil on menopausal hot flashes: a randomized clinical trial. Arch Gynecol Obstet 288(5):1075–1079, doi:10.1007/s00404-013-2852-6

Faure ED, Chantre P, Mares P (2002) Effects of a standardized soy extract on hot flushes: a multicenter, double-blind, randomized, placebo-controlled study. Menopause 9(5):329–334

FDA. U.S. Department of Health and Human Services Food and Drug Administration (2003) Center for Drug Evaluation and Research (CDER). Guidance for industry. Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms — Recommendations for clinical evaluation. Rockville, MD

Ferrari A (2009) Soy extract phytoestrogens with high dose of isoflavones for menopausal symptoms. J Obstet Gynaecol Res 35(6):1083–1090, doi:10.1111/j.1447-0756.2009.01058.x

Fink G, Sumner BE (1996) Oestrogen and mental state. Nature 383(6598):306
Fink G, Sumner BE, Rosie R, Grace O, Quinn JP (1996) Estrogen control of central neurotransmission: effect on mood, mental state, and memory. Cell Mol Neurobiol 16(3):325–344
Freedman RR, Kruger ML, Tancer ME (2011) Escitalopram treatment of menopausal hot flashes. Menopause 18(8):893–896, doi:10.1097/gme.0b013e31820ccae9
Freeman EW, Guthrie KA, Caan B, Sternfeld B, Cohen LS, Joffe H, Carpenter JS, Anderson GL, Larson JC, Ensrud KE, Reed SD, Newton KM, Sherman S, Sammel MD, LaCroix AZ (2011) Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. JAMA 305(3):267–274, doi:10.1001/jama.2010.2016
Frei-Kleiner S, Schaffner W, Rahlfs VW, Bodmer C, Birkhauser M (2005) Cimicifuga racemosa dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. Maturitas 51(4):397–404
Freudenstein J, Dasenbrock C, Nisslein T (2002) Lack of promotion of estrogen-dependent mammary gland tumors *in vivo* by an isopropanolic *Cimicifuga racemosa* extract. Cancer Res 62(12):3448–3452
Friedman GD, Udaltsova N, Habel LA (2011) Norepinephrine antagonists and cancer risk. Int J Cancer 128(3):737–738, doi:10.1002/ijc.25351
Fugate SE, Church CO (2004) Nonestrogen treatment modalities for vasomotor symptoms associated with menopause. Ann Pharmacother 38(9):1482–1499, doi:10.1345/aph.1D610
Garita-Hernandez M, Calzado MA, Caballero FJ, Macho A, Munoz E, Meier B, Brattstrom A, Fiebich BL, Appel K (2006) The growth inhibitory activity of the *Cimicifuga racemosa* extract Ze 450 is mediated through estrogen and progesterone receptors-independent pathways. Planta Med 72(4):317–323
Gaube F, Wolfl S, Pusch L, Kroll TC, Hamburger M (2007) Gene expression profiling reveals effects of Cimicifuga racemosa (L.) NUTT. (black cohosh) on the estrogen receptor positive human breast cancer cell line MCF-7. BMC Pharmacol 7:11
Geller SE, Shulman LP, van Breemen RB, Banuvar S, Zhou Y, Epstein G, Hedayat S, Nikolic D, Krause EC, Piersen CE, Bolton JL, Pauli GF, Farnsworth NR (2009) Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. Menopause 16(6):1156–1166
Goetz MP, Suman VJ, Hoskin TL, Gnant M, Filipits M, Safgren SL, Kuffel M, Jakesz R, Rudas M, Greil R, Dietze O, Lang A, Offner F, Reynolds CA, Weinshilboum RM, Ames MM, Ingle JN (2013) CYP2D6 metabolism and patient outcome in the Austrian Breast and Colorectal Cancer Study Group trial (ABCSG) 8. Clin Cancer Res 19(2):500–507, doi:10.1158/1078-0432.CCR-12-2153
Goldberg RM, Loprinzi CL, O'Fallon JR, Veeder MH, Miser AW, Mailliard JA, Michalak JC, Dose AM, Rowland KM Jr, Burnham NL (1994) Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. J Clin Oncol 12(1):155–158
Gonzales GF, Carrillo C (1993) Blood serotonin levels in postmenopausal women: effects of age and serum oestradiol levels. Maturitas 17(1):23–29
González E, Minguez L, Sanguino RM (2000) Galactorrhea after paroxetine treatment. Pharmacopsychiatry 33(3):118
Gordon PR, Kerwin JP, Boesen KG, Senf J (2006) Sertraline to treat hot flashes: a randomized controlled, double-blind, crossover trial in a general population. Menopause 13(4):568–575, doi:10.1097/01.gme.0000196595.82452.ca
Grady D, Cohen B, Tice J, Kristof M, Olyaie A, Sawaya GF (2007) Ineffectiveness of sertraline for treatment of menopausal hot flushes: a randomized controlled trial. Obstet Gynecol 109(4):823–830
Greendale GA, Reboussin BA, Sie A, Singh HR, Olson LK, Gatewood O, Bassett LW, Wasilauskas C, Bush T, Barrett-Connor E (1999) Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. Ann Intern Med 130(4 Pt 1):262–269
Gupta P, Sturdee DW, Palin SL, Majumder K, Fear R, Marshall T, Paterson I (2006) Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life. Climacteric 9(1):49–58
Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Khan IA, Shah A (2005) In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. Clin Pharmacol Ther 77(5):415–426
Gurley B, Hubbard MA, Williams DK, Thaden J, Tong Y, Gentry WB, Breen P, Carrier DJ, Cheboyina S (2006a) Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin. J Clin Pharmacol 46(2):201–213
Gurley BJ, Barone GW, Williams DK, Carrier J, Breen P, Yates CR, Song PF, Hubbard MA, Tong Y, Cheboyina S (2006b) Effect of milk thistle (Silybum marianum) and black cohosh (Cimicifuga racemosa) supplementation on digoxin pharmacokinetics in humans. Drug Metab Dispos 34(1):69–74
Gurley BJ, Swain A, Hubbard MA, Williams DK, Barone G, Hartsfield F, Tong Y, Carrier DJ, Cheboyina S, Battu SK (2008) Clinical assessment of CYP2D6-mediated herb-drug interactions in humans: effects of milk thistle, black cohosh, goldenseal, kava kava, St. John's wort, and Echinacea. Mol Nutr Food Res 52(7):755–63
Guttuso TJ Jr (2000) Gabapentin's effects on hot flashes and hypothermia. Neurology 54(11):2161–2163
Guttuso T Jr, Kurlan R, McDermott MP, Kieburtz K (2003) Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. Obstet Gynecol 101(2):337–345, doi:S0029784402027126 [pii]
Halbreich U, Rojansky N, Palter S, Tworek H, Hissin P, Wang K (1995) Estrogen augments serotonergic activity in postmenopausal women. Biol Psychiatry 37(7):434–441
Hammar M, Christau S, Nathorst-Boos J, Rud T, Garre K (1998) A double-blind, randomised trial comparing the effects of tibolone and continuous combined hormone replacement therapy in postmenopausal women with menopausal symptoms. Br J Obstet Gynaecol 105(8):904–911
Han KK, Soares JM Jr, Haidar MA, de Lima GR, Baracat EC (2002) Benefits of soy isoflavone therapeutic regimen on menopausal symptoms. Obstet Gynecol 99(3):389–394
Hankinson SE, Willett WC, Michaud DS, Manson JE, Colditz GA, Longcope C, Rosner B, Speizer FE (1999) Plasma prolactin levels and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst 91(7):629–634
Haque R, Enger SM, Chen W, Petitti DB (2005) Breast cancer risk in a large cohort of female antidepressant medication users. Cancer Lett 221(1):61–65, doi:10.1016/j.canlet.2004.11.003
Harvey PW, Everett DJ, Springall CJ (2006) Hyperprolactinaemia as an adverse effect in regulatory and clinical toxicology: role in breast and prostate cancer. Hum Exp Toxicol 25(7):395–404
Hasper I, Ventskovskiy BM, Rettenberger R, Heger PW, Riley DS, Kaszkin-Bettag M (2009) Long-term efficacy and safety of the special extract ERr 731 of Rheum rhaponticum in perimenopausal women with menopausal symptoms. Menopause 16(1):117–131, doi:10.1097/GME.0b013e3181806446
Hedlund PB, Danielson PE, Thomas EA, Slanina K, Carson MJ, Sutcliffe JG (2003) No hypothermic response to serotonin in 5-HT7 receptor knockout mice. Proc Natl Acad Sci U S A 100(3):1375–80, doi:10.1073/pnas.0337340100
Heger M, Ventskovskiy BM, Borzenko I, Kneis KC, Rettenberger R, Kaszkin-Bettag M, Heger PW (2006) Efficacy and safety of a special extract of Rheum rhaponticum (ERr 731) in perimenopausal women with climacteric complaints: a 12-week randomized, double-blind, placebo-controlled trial. Menopause 13(5):744–759, doi:10.1097/01.gme.0000240632.08182.e4
Heinecke-von Zepelin H-H, Meden H, Kostev K, Schröder-Bernhard D, Stammwitz U, Becher H (2007) Isopropanolic black cohosh extract and recurrence-free survival after breast cancer. Int J Clin Pharmacol Ther 45(3):143–154
Hernández Munoz G, Pluchino S (2003) Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer. Maturitas 44(Suppl 1):S59–S65
Hersh AL, Stefanick ML, Stafford RS (2004) National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA 291(1):47–53, doi:10.1001/jama.291.1.47
Heyerick A, Vervarcke S, Depypere H, Bracke M, De Keukeleire D (2006) A first prospective, randomized, double-blind, placebo-controlled study on the use of a standardized hop extract to alleviate menopausal discomforts. Maturitas 54(2):164–175, doi:10.1016/j.maturitas.2005.10.005
Hidalgo LA, Chedraui PA, Morocho N, Ross S, San MG (2005) The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: a randomized, double-blind, placebo-controlled study. Gynecol Endocrinol 21(5):257–264, doi:10.1080/09513590500361192
Hirschberg AL, Edlund M, Svane G, Azavedo E, Skoog L, von Schoultz B (2007) An isopropanolic extract of black cohosh does not increase mammographic breast density or breast cell proliferation in postmenopausal women. Menopause 14(1):89–96
Holmberg L, Anderson H (2004) HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer-is it safe?), a randomised comparison: trial stopped. Lancet 363:453–455
Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R (2004a) Evaluation of cell death caused by triterpene glycosides and phenolic substances from

Cimicifuga racemosa extract in human MCF-7 breast cancer cells. Biol Pharm Bull 27(12):1970–1975

Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R (2004b) *Cimicifuga racemosa* extract inhibits proliferation of estrogen receptor-positive and negative human breast carcinoma cell lines by induction of apoptosis. Breast Cancer Res Treat 84(2):151–160

Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R (2005) Apoptosis of human prostate androgen-dependent and -independent carcinoma cells induced by an isopropanolic extract of black cohosh involves degradation of cytokeratin (CK) 18. Anticancer Res 25(1A):139–147

Hostanska K, Nisslein T, Freudenstein J, Reichling J, Saller R (2007) Inhibitory effect of an isopropanolic extract of black cohosh on the invasiveness of MDA-mB 231 human breast cancer cells. In vivo (Athens, Greece) 21(2):349–55

Huang YX, Song L, Zhang X, Lun WW, Pan C, Huang YS (2013) Clinical study of combined treatment of remifemin and paroxetine for perimenopausal depression. Zhonghua yi xue za zhi 93(8):600–602

Hunter MS, Gentry-Maharaj A, Ryan A, Burnell M, Lanceley A, Fraser L, Jacobs I, Menon U (2012) Prevalence, frequency and problem rating of hot flushes persist in older postmenopausal women: impact of age, body mass index, hysterectomy, hormone therapy use, lifestyle and mood in a cross-sectional cohort study of 10,418 British women aged 54–65. BJOG 119(1):40–50, doi:10.1111/j.1471-0528.2011.03166.x

Ingram DM, Nottage EM, Roberts AN (1990) Prolactin and breast cancer risk. Med J Aust 153(8):469–473

Jacobson JS, Troxel AB, Evans J, Klaus L, Vahdat L, Kinne D, Lo KM, Moore A, Rosenman PJ, Kaufman EL, Neugut AI, Grann VR (2001) Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 19(10):2739–2745

Jarry H, Harnischfeger G, Düker E (1985) Studies on the endocrine efficacy of the constituents of Cimicifuga racemosa: 2. in vitro binding of constituents to estrogen receptors. Planta Med 4:316–319

Jarry H, Metten M, Spengler B, Christoffel V, Wuttke W (2003) In vitro effects of the Cimicifuga racemosa extract BNO 1055. Maturitas 44(1):S31–S38

Jarry H, Thelen P, Christoffel V, Spengler B, Wuttke W (2005) Cimicifuga racemosa extract BNO 1055 inhibits proliferation of the human prostate cancer cell line LNCaP. Phytomedicine 12(3):178–182

Jarry H, Stromeier S, Wuttke W, Nahrstedt A (2007) Petasiphenone, a phenol isolated from Cimicifuga racemosa, *in vitro* inhibits proliferation of the human prostate cancer cell line LNCaP. Planta Med 73(2):184–187

Jeri A (2002) The use of an isoflavone supplement to relieve hot flushes. Female Pat 27:47–49

Ju YH, Doerge DR, Woodling KA, Hartman JA, Kwak J, Helferich WG (2008) Dietary genistein negates the inhibitory effect of letrozole on the growth of aromatase-expressing estrogen-dependent human breast cancer cells (MCF-7Ca) in vivo. Carcinogenesis 29(11):2162–2168, doi:10.1093/carcin/bgn161

Karling P, Hammar M, Varenhorst E (1994) Prevalence and duration of hot flushes after surgical or medical castration in men with prostatic carcinoma. J Urol 152(4):1170–1173

Kaszkin-Bettag M, Ventskovskiy BM, Kravchenko A, Rettenberger R, Richardson A, Heger PW, Heger M (2007) The special extract ERr 731 of the roots of Rheum rhaponticum decreases anxiety and improves health state and general well-being in perimenopausal women. Menopause 14(2):270–283, doi:10.1097/01.gme.0000251932.48426.35

Kaszkin-Bettag M, Ventskovskiy BM, Solskyy S, Beck S, Hasper I, Kravchenko A, Rettenberger R, Richardson A, Heger PW (2009) Confirmation of the efficacy of ERr 731 in perimenopausal women with menopausal symptoms. Altern Ther Health Med 15(1):24–34

Kato I, Zeleniuch-Jacquotte A, Toniolo PG, Akhmedkhanov A, Koenig K, Shore RE (2000) Psychotropic medication use and risk of hormone-related cancers: the New York University Women's Health Study. J Public Health Med 22(2):155–160

Kelly JP, Rosenberg L, Palmer JR, Rao RS, Strom BL, Stolley PD, Zauber AG, Shapiro S (1999) Risk of breast cancer according to use of antidepressants, phenothiazines, and antihistamines. Am J Epidemiol 150(8):861–868

Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, Austin PC, Paszat LF (2010) Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. Br Med J 340:c693, doi:10.1136/bmj.c693

Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, Vassilopoulou-Sellin R, Yip CH, Egberts J, Mol-Arts M, Mulder R, van Os S, Beckmann MW (2009) Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol 10(2):135–146

Kerwin JP, Gordon PR, Senf JH (2007) The variable response of women with menopausal hot flashes when treated with sertraline. Menopause 14(5):841–845

Khaodhiar L, Ricciotti HA, Li L, Pan W, Schickel M, Zhou J, Blackburn GL (2008) Daidzein-rich isoflavone aglycones are potentially effective in reducing hot flashes in menopausal women. Menopause 15(1):125–132

Kimmick GG, Lovato J, McQuellon R, Robinson E, Muss HB (2006) Randomized, double-blind, placebo-controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. Breast J 12(2):114–122, doi:10.1111/j.1075-122X.2006.00218.x

Kloosterboer HJ (2004) Tissue-selectivity: the mechanism of action of tibolone. Maturitas 48(Suppl 1):S30–S40

Knight DC, Howes JB, Eden JA (1999) The effect of Promensil, an isoflavone extract, on menopausal symptoms. Climacteric 2(2):79–84, doi:10.3109/13697139909025570

Kohama T, Negami M (2013) Effect of low-dose French maritime pine bark extract on climacteric syndrome in 170 perimenopausal women: a randomized, double-blind, placebo-controlled trial. J Reprod Med 58(1–2):39–46

Kroiss R, Fentiman IS, Helmond FA, Rymer J, Foidart JM, Bundred N, Mol-Arts M, Kubista E (2005) The effect of tibolone in postmenopausal women receiving tamoxifen after surgery for breast cancer: a randomised, double-blind, placebo-controlled trial. BJOG 112(2):228–233

Kronenberg F (1990) Hot flashes: epidemiology and physiology. Ann N Y Acad Sci 592:52–86, discussion 123–33

Kronenberg F (1994) Hot flashes: phenomenology, quality of life, and search for treatment options. Exp Gerontol 29(3–4):319–336

Kropp S, Ziegenbein M, Grohmann R, Engel RR, Degner D (2004) Galactorrhea due to psychotropic drugs. Pharmacopsychiatry 37(Suppl 1):S84–S88, doi:10.1055/s-2004-815515

Krulich L (1975) The effect of a serotonin uptake inhibitor (Lilly 110140) on the sercretion of prolactin in the rat. Life Sci 17(7):1141–1144

Kubista E, Planellas Gomez JV, Dowsett M, Foidart JM, Pohlodek K, Serreyn R, Nechushkin M, Manikhas AG, Semiglazov VF, Hageluken CC, Singer CF (2007) Effect of tibolone on breast cancer cell proliferation in postmenopausal ER+ patients: results from STEM trial. Clin Cancer Res 13(14):4185–4190

Kutlu T, Ficicioglu C, Basaran T, Basaran E, Topaloglu T (2004) Mammographic breast density changes after 1 year of tibolone use. Maturitas 48(2):133–136

Labos G, Trakakis E, Pliatsika P, Augoulea A, Vaggopoulos V, Basios G, Simeonidis G, Creatsa M, Alexandrou A, Iliodromiti Z, Kassanos D, Lambrinoudaki I (2013) Efficacy and safety of DT56a compared to hormone therapy in Greek post-menopausal women. J Endocrinol Invest 36(7):521–526, doi:10.3275/8926

Lam YW, Gaedigk A, Ereshefsky L, Alfaro CL, Simpson J (2002) CYP2D6 inhibition by selective serotonin reuptake inhibitors: analysis of achievable steady-state plasma concentrations and the effect of ultrarapid metabolism at CYP2D6. Pharmacotherapy 22(8):1001–1006

Landgren MB, Bennink HJ, Helmond FA, Engelen S (2002) Dose–response analysis of effects of tibolone on climacteric symptoms. Br J Obstet Gynaecol 109(10):1109–1114

Lash TL, Cronin-Fenton D, Ahern TP, Rosenberg CL, Lunetta KL, Silliman RA, Hamilton-Dutoit S, Garne JP, Ewertz M, Sorensen HT, Pedersen L (2011a) Breast cancer recurrence risk related to concurrent use of SSRI antidepressants and tamoxifen. Acta oncologica (Stockholm, Sweden) 49(3):305–12

Lash TL, Cronin-Fenton D, Ahern TP, Rosenberg CL, Lunetta KL, Silliman RA, Garne JP, Sorensen HT, Hellberg Y, Christensen M, Pedersen L, Hamilton-Dutoit S (2011b) CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark. J Natl Cancer Inst 103(6):489–500

Laufer LR, Erlik Y, Meldrum DR, Judd HL (1982) Effect of clonidine on hot flashes in postmenopausal women. Obstet Gynecol 60(5):583–586

Leach MJ, Moore V (2012) Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database Syst Rev (Online) 9:CD007244, doi:10.1002/14651858.CD007244.pub2

Lethaby AE, Brown J, Marjoribanks J, Kronenberg F, Roberts H, Eden J (2007) Phytoestrogens for vasomotor menopausal symptoms. Cochrane database of systematic reviews (Online). (4):CD001395. doi:10.1002/14651858.CD001395.pub3

Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J (2013) Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database Syst Rev (Online) 12:CD001395, doi:10.1002/14651858.CD001395.pub4

Levis S, Strickman-Stein N, Ganjei-Azar P, Xu P, Doerge DR, Krischer J (2011) Soy isoflavones in the prevention of menopausal bone loss and menopausal

symptoms: a randomized, double-blind trial. Arch Intern Med 171(15):1363–1369, doi:10.1001/archinternmed.2011.330

Lewis JE, Nickell LA, Thompson LU, Szalai JP, Kiss A, Hilditch JR (2006) A randomized controlled trial of the effect of dietary soy and flaxseed muffins on quality of life and hot flashes during menopause. Menopause 13(4):631–642, doi:10.1097/01.gme.0000191882.59799.67

Li J, Godecke T, Chen SN, Imai A, Lankin DC, Farnsworth NR, Pauli GF, van Breemen RB, Nikolic D (2011) *In vitro* metabolic interactions between black cohosh (*Cimicifuga racemosa*) and tamoxifen via inhibition of cytochromes P450 2D6 and 3A4. Xenobiotica; the fate of foreign compounds in biological systems. doi:10.3109/00498254.2011.603385

Lipovac M, Chedraui P, Gruenhut C, Gocan A, Kurz C, Neuber B, Imhof M (2012) The effect of red clover isoflavone supplementation over vasomotor and menopausal symptoms in postmenopausal women. Gynecol Endocrinol 28(3):203–207, doi:10.3109/09513590.2011.593671

Lippert C, Seeger H, Wallwiener D, Mueck AO (2002) Tibolone versus 17beta-estradiol/norethisterone: effects on the proliferation of human breast cancer cells. Eur J Gynaecol Oncol 23(2):127–130

Liske E, Hänggi W, Henneicke von Zepelin HH, Boblitz N, Wüstenberg P, Rahlfs VW (2002) Physiological investigation of a unique extract of black cohosh (*Cimicifugae racemosae rhizoma*): a 6-month clinical study demonstrates no systemic estrogenic effect. J Womens Health Gend Based Med 11(2):163–174

Liu ZP, Yu B, Huo JS, Lu CQ, Chen JS (2001a) Estrogenic Effects of Cimicifuga racemosa (Black Cohosh) in Mice and on Estrogen Receptors in MCF-7 Cells. J Med Food 4(3):171–178

Liu J, Burdette JE, Xu H, Gu C, van Breemen RB, Bhat KP, Booth N, Constantinou AI, Pezzuto JM, Fong HH, Farnsworth NR, Bolton JL (2001b) Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms. J Agric Food Chem 49(5):2472–2479

Loibl S, Schwedler K, von Minckwitz G, Strohmeier R, Mehta KM, Kaufmann M (2007) Venlafaxine is superior to clonidine as treatment of hot flashes in breast cancer patients-a double-blind, randomized study. Ann Oncol 18(4):689–693

Lopatka L, Totzke U, Schmid A, Käufeler R (2007) Die Traubensilberkerze in der Behandlung menopausaler Beschwerden - Ergebnisse einer Therapiebeobachtung mit Cimifemin(R) uno. Journal für Menopause 14(2):16–21

Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, Dose AM, Fischer T, Johnson C, Klatt NE, Bate WW, Rospond RM, Oesterling JE (1994a) Megestrol acetate for the prevention of hot flashes. N Engl J Med 331(6):347–352

Loprinzi CL, Goldberg RM, O'Fallon JR, Quella SK, Miser AW, Mynderse LA, Brown LD, Tschetter LK, Wilwerding MB, Dose M, Oesterling JE (1994b) Transdermal clonidine for ameliorating post-orchiectomy hot flashes. J Urol 151(3):634–636

Loprinzi CL, Pisansky TM, Fonseca R, Sloan JA, Zahasky KM, Quella SK, Novotny PJ, Rummans TA, Dumesic DA, Perez EA (1998) Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors. J Clin Oncol 16(7):2377–2381

Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, Novotny PJ, Dakhil SR, Rodger K, Rummans TA, Christensen BJ (2000) Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 356(9247):2059–2063, doi:10.1016/S0140-6736(00)03403-6

Loprinzi L, Barton DL, Sloan JA, Zahasky KM, Smith DA, Pruthi S, Novotny PJ, Perez EA, Christensen BJ (2002a) Pilot evaluation of gabapentin for treating hot flashes. Mayo Clin Proc 77(11):1159–1163

Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA, Halyard MY, Pruthi S, Novotny PJ, Rummans TA (2002b) Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 20(6):1578–1583

Loprinzi CL, Levitt R, Barton D, Sloan JA, Dakhil SR, Nikcevich DA, Bearden JD 3rd, Mailliard JA, Tschetter LK, Fitch TR, Kugler JW (2006) Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. J Clin Oncol 24(9):1409–1414

Loprinzi CL, Kugler JW, Barton DL, Dueck AC, Tschetter LK, Nelimark RA, Balcueva EP, Burger KN, Novotny PJ, Carlson MD, Duane SF, Corso SW, Johnson DB, Jaslowski AJ (2007) Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. J Clin Oncol 25(3):308–312, doi:10.1200/JCO.2006.07.5390

Loprinzi CL, Dueck AC, Khoyratty BS, Barton DL, Jafar S, Rowland KM Jr, Atherton PJ, Marsa GW, Knutson WH, Bearden JD 3rd, Kottschade L, Fitch TR (2009) A phase III randomized, double-blind, placebo-controlled trial of gabapentin in the management of hot flashes in men (N00CB). Ann Oncol 20(3):542–549

Loprinzi CL, Qin R, Balcueva EP, Flynn KA, Rowland KM Jr, Graham DL, Erwin NK, Dakhil SR, Jurgens DJ, Burger KN (2010) Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for alleviating hot flashes, N07C1. J Clin Oncol 28(4):641–647

Lundström E, Hirschberg AL, Söderqvist G (2011) Digitized assessment of mammographic breast density–effects of continuous combined hormone therapy, tibolone and black cohosh compared to placebo. Maturitas 70(4):361–364

Lupu R, Mehmi I, Atlas E, Tsai MS, Pisha E, Oketch-Rabah HA, Nuntanakorn P, Kennelly EJ, Kronenberg F (2003) Black cohosh, a menopausal remedy, does not have estrogenic activity and does not promote breast cancer cell growth. Int J Oncol 23(5):1407–1412

MacGregor CA, Canney PA, Patterson G, McDonald R, Paul J (2005) A randomised double-blind controlled trial of oral soy supplements versus placebo for treatment of menopausal symptoms in patients with early breast cancer. Eur J Cancer 41(5):708–714, doi:10.1016/j.ejca.2005.01.005

MacLennan AH, Broadbent JL, Lester S, Moore V (2009) Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane database of systematic reviews (Online). (4):CD002978

Mainini G, Torella M, Di Donna MC, Esposito E, Ercolano S, Correa R, Cucinella G, Stradella L, Luisi A, Basso A, Cerreto FV, Cicatiello R, Matteo M, De Franciscis P (2013) Nonhormonal management of postmenopausal women: effects of a red clover based isoflavones supplementation on climacteric syndrome and cardiovascular risk serum profile. Clin Exp Obstet Gynecol 40(3):337–341

Marchesoni D, Driul L, Ianni A, Fabiani G, Della Martina M, Zuiani C, Bazzocchi M (2006) Postmenopausal hormone therapy and mammographic breast density. Maturitas 53(1):59–64

Mirabi P, Mojab F (2013) The effects of valerian root on hot flashes in menopausal women. Iranian J Pharmaceut Res 12(1):217–222

Moorman PG, Grubber JM, Millikan RC, Newman B (2003) Antidepressant medications and their association with invasive breast cancer and carcinoma *in situ* of the breast. Epidemiology 14(3):307–314

Moraska AR, Atherton PJ, Szydlo DW, Barton DL, Stella PJ, Rowland KM Jr, Schaefer PL, Krook J, Bearden JD, Loprinzi CL (2010) Gabapentin for the management of hot flashes in prostate cancer survivors: a longitudinal continuation Study-NCCTG Trial N00CB. J Support Oncol 8(3):128–132

Mori S, Chang JT, Andrechek ER, Matsumura N, Baba T, Yao G, Kim JW, Gatza M, Murphy S, Nevins JR (2009) Anchorage-independent cell growth signature identifies tumors with metastatic potential. Oncogene 28(31):2796–2805

Mueck AO, Lippert C, Seeger H, Wallwiener D (2003) Effects of tibolone on human breast cancer cells and human vascular coronary cells. Arch Gynecol Obstet 267(3):139–144

Murkies AL, Lombard C, Strauss BJ, Wilcox G, Burger HG, Morton MS (1995) Dietary flour supplementation decreases post-menopausal hot flushes: effect of soy and wheat. Maturitas 21(3):189–195

Nagamani M, Kelver ME, Smith ER (1987) Treatment of menopausal hot flashes with transdermal administration of clonidine. Am J Obstet Gynecol 156(3):561–565

Nahas PE, Nahas-Neto J, De Luca L, Traiman P, Pontes A, Dalben I (2004) Benefits of soy germ isoflavones in postmenopausal women with contraindication for conventional hormone replacement therapy. Maturitas 48(4):372–380, doi:10.1016/j.maturitas.2003.09.026

Nahas EA, Nahas-Neto J, Orsatti FL, Carvalho EP, Oliveira ML, Dias R (2007) Efficacy and safety of a soy isoflavone extract in postmenopausal women: a randomized, double-blind, and placebo-controlled study. Maturitas 58(3):249–258, doi:10.1016/j.maturitas.2007.08.012

Nakano K, Pinnow E, Flaws JA, Sorkin JD, Gallicchio L (2012) Reproductive history and hot flashes in perimenopausal women. J Womens Health (Larchmt) 21(4):433–439, doi: 0.1089/jwh.2011.2999

NAMS (2012) The 2012 hormone therapy position statement of: The North American Menopause Society. Menopause 19(3):257–271, doi:10.1097/gme.0b013e31824b970a

Nappi RE, Malavasi B, Brundu B, Facchinetti F (2005) Efficacy of *Cimicifuga racemosa* on climacteric complaints: a randomized study versus low-dose transdermal estradiol. Gynecol Endocrinol 20(1):30–35

Narod SA (2011) Hormone replacement therapy and the risk of breast cancer. Nat Rev Clin Oncol 8(11):669–676

Naumenko VS, Kondaurova EM, Popova NK (2011) On the role of brain 5-HT7 receptor in the mechanism of hypothermia: comparison with hypothermia mediated via 5-HT1A and 5-HT3 receptor. Neuropharmacology 61(8):1360–1365, doi:10.1016/j.neuropharm.2011.08.022

Nesheim BI, Saetre T (1981) Reduction of menopausal hot flushes by methyldopa. A double blind crossover trial. Eur J Clin Pharmacol 20(6):413–416
Neßelhut T, Schellhase C, Dietrich R, Kuhn W (1993) Untersuchungen zur proliferativen Potenz von Phytopharmaka mit östrogenähnlicher Wirkung bei Mammakarzinomzellen. Arch Gynecol Obstet 254(1–4):817–818
Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J (2006) Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. Ann Intern Med 145(12):869–79, doi:145/12/869
Nikander E, Kilkkinen A, Metsa-Heikkila M, Adlercreutz H, Pietinen P, Tiitinen A, Ylikorkala O (2003) A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. Obstet Gynecol 101(6):1213–1220
Nisslein T, Freudenstein J (2004) Concomitant administration of an isopropanolic extract of black cohosh and tamoxifen in the *in vivo* tumor model of implanted RUCA-I rat endometrial adenocarcinoma cells. Toxicol Lett 150(3):271–275
Obi N, Chang-Claude J, Berger J, Braendle W, Slanger T, Schmidt M, Steindorf K, Ahrens W, Flesch-Janys D (2009) The use of herbal preparations to alleviate climacteric disorders and risk of postmenopausal breast cancer in a German case–control study. Cancer Epidemiol Biomarkers Prev 18(8):2207–2213
Oktem M, Eroglu D, Karahan HB, Taskintuna N, Kuscu E, Zeyneloglu HB (2007) Black cohosh and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized trial. Adv Ther 24(2):448–61, doi:622
Oliveira SS, Del Giglio AB, Lerner TG, Zanellato RM, Tiemi L, Reifur L, Santi PX, Del Giglio A (2013) Paullinia cupana for control of hot flashes in breast cancer patients: a pilot study. Einstein 11(4):435–438
Osmers R, Friede M, Liske E, Schnitker J, Freudenstein J, Henneicke von Zepelin HH (2005) Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. Obstet Gynecol 105(5):1074–1083
Pandya KJ, Raubertas RF, Flynn PJ, Hynes HE, Rosenbluth RJ, Kirshner JJ, Pierce HI, Dragalin V, Morrow GR (2000) Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. Ann Intern Med 132(10):788–793, doi:200005160–00004 [pii]
Pandya KJ, Thummala AR, Griggs JJ, Rosenblatt JD, Sahasrabudhe DM, Guttuso TJ, Morrow GR, Roscoe JA (2004) Pilot study using gabapentin for tamoxifen-induced hot flashes in women with breast cancer. Breast Cancer Res Treat 83 (1):87–89, doi:10.1023/B:BREA.0000010676.54597.22
Pandya KJ, Morrow GR, Roscoe JA, Zhao H, Hickok JT, Pajon E, Sweeney TJ, Banerjee TK, Flynn PJ (2005) Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. Lancet 366(9488):818–824, doi:10.1016/S0140-6736(05)67215-7
Park H, Parker GL, Boardman CH, Morris MM, Smith TJ (2011) A pilot phase II trial of magnesium supplements to reduce menopausal hot flashes in breast cancer patients. Support Care Cancer 19(6):859–863, doi:10.1007/s00520-011-1099-7
Penotti M, Fabio E, Modena AB, Rinaldi M, Omodei U, Vigano P (2003) Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. Fertil Steril 79(5):1112–1117
Perez DG, Loprinzi CL, Barton DL, Pockaj BA, Sloan J, Novotny PJ, Christensen BJ (2004) Pilot evaluation of mirtazapine for the treatment of hot flashes. J Support Oncol 2(1):50–56
Perez DG, Loprinzi CL, Sloan J, Novotny P, Barton D, Carpenter L, Smith D, Christensen B, Rummans T (2006) Pilot evaluation of bupropion for the treatment of hot flashes. J Palliat Med 9(3):631–637, doi:10.1089/jpm.2006.9.631
Pinkerton JV, Constantine G, Hwang E, Cheng RF (2013) Desvenlafaxine compared with placebo for treatment of menopausal vasomotor symptoms: a 12-week, multicenter, parallel-group, randomized, double-blind, placebo-controlled efficacy trial. Menopause 20(1):28–37, doi:10.1097/gme.0b013e31826421a8
Pinkerton JV, Kagan R, Portman D, Sathyanarayana R, Sweeney M, Breeze I (2014) Phase 3 randomized controlled study of gastroretentive gabapentin for the treatment of moderate-to-severe hot flashes in menopause. Menopause 21(6):567–573, doi:10.1097/GME.0b013e3182a7c073
Pockaj BA, Loprinzi CL, Sloan JA, Novotny PJ, Barton DL, Hagenmaier A, Zhang H, Lambert GH, Reeser KA, Wisbey JA (2004) Pilot evaluation of black cohosh for the treatment of hot flashes in women. Cancer Invest 22(4):515–521
Pockaj BA, Gallagher JG, Loprinzi CL, Stella PJ, Barton DL, Sloan JA, Lavasseur BI, Rao RM, Fitch TR, Rowland KM, Novotny PJ, Flynn PJ, Richelson E, Fauq AH (2006) Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. J Clin Oncol 24(18):2836–2841
Porch JV, Lee IM, Cook NR, Rexrode KM, Burin JE (2002) Estrogen-progestin replacement therapy and breast cancer risk: the Women's Health Study (United States). Cancer Causes Control 13(9):847–854
Powell SL, Godecke T, Nikolic D, Chen SN, Ahn S, Dietz B, Farnsworth NR, van Breemen RB, Lankin DC, Pauli GF, Bolton JL (2008) In vitro serotonergic activity of black cohosh and identification of Nω-methylserotonin as a potential active constituent. J Agric Food Chem 56(24):11718–11726
Powles TJ, Hickish T (1995) Breast cancer response to hormone replacement therapy withdrawal. Lancet 345(8962):1442
Prentice RL, Chlebowski RT, Stefanick ML, Manson JE, Langer RD, Pettinger M, Hendrix SL, Hubbell FA, Kooperberg C, Kuller LH, Lane DS, McTiernan A, O'Sullivan MJ, Rossouw JE, Anderson GL (2008) Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. Am J Epidemiol 167(12):1407–1415, doi:10.1093/aje/kwn090
Preskorn SH, Shah R, Neff M, Golbeck AL, Choi J (2007) The potential for clinically significant drug-drug interactions involving the CYP 2D6 system: effects with fluoxetine and paroxetine versus sertraline. J Psychiatr Pract 13(1):5–12
Pritchard KI (2010) Do selective serotonin receptor inhibitor antidepressants reduce tamoxifen's effectiveness and increase the risk of death from breast cancer? Breast Cancer Res 12(Suppl 4):S18, doi:10.1186/bcr2747
Pruthi S, Qin R, Terstreip SA, Liu H, Loprinzi CL, Shah TR, Tucker KF, Dakhil SR, Bury MJ, Carolla RL, Steen PD, Vuky J, Barton DL (2012) A phase III, randomized, placebo-controlled, double-blind trial of flaxseed for the treatment of hot flashes: North Central Cancer Treatment Group N08C7. Menopause 19(1):48–53, doi:10.1097/gme.0b013e318223b021
Quella SK, Loprinzi CL, Sloan J, Novotny P, Perez EA, Burch PA, Antolak SJ Jr, Pisansky TM (1999) Pilot evaluation of venlafaxine for the treatment of hot flashes in men undergoing androgen ablation therapy for prostate cancer. J Urol 162(1):98–102
Quella SK, Loprinzi CL, Barton DL, Knost JA, Sloan JA, LaVasseur BI, Swan D, Krupp KR, Miller KD, Novotny PJ (2000) Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial. J Clin Oncol 18(5):1068–1074
Radhakrishnan G, Rashmi NA, Vaid NB (2009) Evaluation of isoflavone rich soy protein supplementation for postmenopausal therapy. Pak. J Nutr 8(7):1009–1017
Rauš K, Brucker C, Gorkow C, Wuttke W (2006) First-time proof of endometrial safety of the special black cohosh extract (*Actaea* or *Cimicifuga racemosa extract*) CR BNO 1055. Menopause 13(4):678–691, doi:10.1097/01.gme.0000196813.34247.e2
Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, Edwards BK, Berry DA (2007) The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 356(16):1670–1674, doi:10.1056/NEJMsr070105
Rebar RW, Spitzer IB (1987) The physiology and measurement of hot flushes. Am J Obstet Gynecol 156(5):1284–1288
Rebbeck TR, Troxel AB, Norman S, Bunin GR, DeMichele A, Baumgarten M, Berlin M, Schinnar R, Strom BL (2007) A retrospective case–control study of the use of hormone-related supplements and association with breast cancer. Int J Cancer 120(7):1523–1528
Reddy SY, Warner H, Guttuso T Jr, Messing S, DiGrazio W, Thornburg L, Guzick DS (2006) Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. Obstet Gynecol 108(1):41–48, doi:10.1097/01.AOG.0000222383.43913.ed
Reed SD, Newton KM, LaCroix AZ, Grothaus LC, Grieco VS, Ehrlich K (2008) Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (HALT) Study. Menopause 15(1):51–58
Rice S, Amon A, Whitehead SA (2007) Ethanolic extracts of black cohosh (Actaea racemosa) inhibit growth and oestradiol synthesis from oestrone sulphate in breast cancer cells. Maturitas 56(4):359–367
Rockwell S, Liu Y, Higgins SA (2005) Alteration of the effects of cancer therapy agents on breast cancer cells by the herbal medicine black cohosh. Breast Cancer Res Treat 90(3):233–239
Rosenberg J, Larsen SH (1991) Hypothesis: pathogenesis of postmenopausal hot flush. Med Hypotheses 35(4):349–350
Ross SM (2012) Menopause: a standardized isopropanolic black cohosh extract (remifemin) is found to be safe and effective for menopausal symptoms. Holist Nurs Pract 26(1):58–61

Ross RK, Paganini-Hill A, Wan PC, Pike MC (2000) Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 92(4):328–332

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 288(3):321–333

Rostock M, Fischer J, Mumm A, Stammwitz U, Saller R, Bartsch HH (2011) Black cohosh (Cimicifuga racemosa) in tamoxifen-treated breast cancer patients with climacteric complaints - a prospective observational study. Gynecol Endocrinol 27(10):844–848

Roth AJ, Scher HI (1998) Sertraline relieves hot flashes secondary to medical castration as treatment of advanced prostate cancer. Psychooncology 7(2):129–132, doi:10.1002/(SICI)1099-1611(199803/04)7:2<129::AID-PON294>3.0.CO;2-T

Ruhlen RL, Haubner J, Tracy JK, Zhu W, Ehya H, Lamberson WR, Rottinghaus GE, Sauter ER (2007) Black cohosh does not exert an estrogenic effect on the breast. Nutr Cancer 59(2):269–277

Ruhlen RL, Sun GY, Sauter ER (2008) Black Cohosh: Insights into its Mechanism(s) of Action. Integrative medicine insights 3:21–32

Saadati N, Mohammadjafari R, Natanj S, Abedi P (2013) The effect of gabapentin on intensity and duration of hot flashes in postmenopausal women: a randomized controlled trial. Global J Health Sci 5(6):126–130, doi:10.5539/gjhs.v5n6p126

Sammartino A, Di Carlo C, Mandato VD, Bifulco G, Di Stefano M, Nappi C (2003) Effects of genistein on the endometrium: ultrasonographic evaluation. Gynecol Endocrinol 17(1):45–49

Saxena T, Lee E, Henderson KD, Clarke CA, West D, Marshall SF, Deapen D, Bernstein L, Ursin G (2010) Menopausal hormone therapy and subsequent risk of specific invasive breast cancer subtypes in the California Teachers Study. Cancer Epidemiol Biomarkers Prev 19(9):2366–2378

Scambia G, Mango D, Signorile PG, Anselmi Angeli RA, Palena C, Gallo D, Bombardelli E, Morazzoni P, Riva A, Mancuso S (2000) Clinical effects of a standardized soy extract in postmenopausal women: a pilot study. Menopause 7(2):105–111

Schellenberg R, Saller R, Hess L, Melzer J, Zimmermann C, Drewe J, Zahner C (2012) Dose-dependent effects of the *Cimicifuga racemosa* extract Ze 450 in the treatment of climacteric complaints: a randomized, placebo-controlled study. Evid Based Complement Alternat Med 2012:260301, doi:10.1155/2012/260301

Schow DA, Renfer LG, Rozanski TA, Thompson IM (1998) Prevalence of hot flushes during and after neoadjuvant hormonal therapy for localized prostate cancer. South Med J 91(9):855–857

Scurlock H, Meehan J (1996) Galactorrhea after treatment with paroxetine. J Serot Res 4:271–272

Secreto G, Chiechi LM, Amadori A, Miceli R, Venturelli E, Valerio T, Marubini E (2004) Soy isoflavones and melatonin for the relief of climacteric symptoms: a multicenter, double-blind, randomized study. Maturitas 47(1):11–20

Seidlová-Wuttke D, Hesse O, Jarry H, Christoffel V, Spengler B, Becker T, Wuttke W (2003) Evidence for selective estrogen receptor modulator activity in a black cohosh (*Cimicifuga racemosa*) extract: comparison with estradiol-17beta. Eur J Endocrinol 149(4):351–362

Seidlová-Wuttke D, Pitzel L, Thelen P, Wuttke W (2006) Inhibition of 5α-reductase in the rat prostate by *Cimicifuga racemosa*. Maturitas 55:S75–S82, doi:10.1016/j.maturitas.2006.06.019

Seidlova-Wuttke D, Thelen P, Wuttke W (2006) Inhibitory effects of a black cohosh (Cimicifuga racemosa) extract on prostate cancer. Planta Med 72(6):521–526

Sevior DK, Hokkanen J, Tolonen A, Abass K, Tursas L, Pelkonen O, Ahokas JT (2010) Rapid screening of commercially available herbal products for the inhibition of major human hepatic cytochrome P450 enzymes using the N-in-one cocktail. Xenobiotica 40(4):245–254, doi:10.3109/00498251003592683

Sharma P, Wisniewski A, Braga-Basaria M, Xu X, Yep M, Denmeade S, Dobs AS, DeWeese T, Carducci M, Basaria S (2009) Lack of an effect of high dose isoflavones in men with prostate cancer undergoing androgen deprivation therapy. J Urol 182(5):2265–2272, doi:10.1016/j.juro.2009.07.030

Silverman BG, Siegelmann-Danieli N, Braunstein R, Kokia ES (2011) Trends in breast cancer incidence associated with reductions in the use of hormone replacement therapy. Cancer Epidemiol 35(1):11–16

Simon JA, Portman DJ, Kaunitz AM, Mekonnen H, Kazempour K, Bhaskar S, Lippman J (2013) Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. Menopause 20(10):1027–1035, doi:10.1097/GME.0b013e3182a66aa7

Singh MS, Francis PA, Michael M (2011) Tamoxifen, cytochrome P450 genes and breast cancer clinical outcomes. Breast (Edinburgh, Scotland) 20(2):111–8, doi:10.1016/j.breast.2010.11.003

Singh SP, Wahajuddin, Raju KS, Ali MM, Kohli K, Jain GK (2012) Reduced bioavailability of tamoxifen and its metabolite 4-hydroxytamoxifen after oral administration with biochanin A (an isoflavone) in rats. Phytother Res 26(2):303–307, doi:10.1002/ptr.3652

Speroff L, Gass M, Constantine G, Olivier S (2008) Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. Obstet Gynecol 111(1):77–87, doi:10.1097/01.AOG.0000297371.89129.b3

Spetz AC, Fredriksson MG, Hammar ML (2003) Hot flushes in a male population aged 55, 65, and 75 years, living in the community of Linköping. Sweden Menopause 10(1):81–87

St Germain A, Peterson CT, Robinson JG, Alekel DL (2001) Isoflavone-rich or isoflavone-poor soy protein does not reduce menopausal symptoms during 24 weeks of treatment. Menopause 8(1):17–26

Stearns V, Isaacs C, Rowland J, Crawford J, Ellis MJ, Kramer R, Lawrence W, Hanfelt JJ, Hayes DF (2000) A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors. Ann Oncol 11(1):17–22

Stearns V, Beebe KL, Iyengar M, Dube E (2003) Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA 289(21):2827–2834, doi:10.1001/jama.289.21.2827

Stearns V, Slack R, Greep N, Henry-Tilman R, Osborne M, Bunnell C, Ullmer L, Gallagher A, Cullen J, Gehan E, Hayes DF, Isaacs C (2005) Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. J Clin Oncol 23(28):6919–6930, doi:10.1200/JCO.2005.10.081

Steingart A, Cotterchio M, Kreiger N, Sloan M (2003) Antidepressant medication use and breast cancer risk: a case–control study. Int J Epidemiol 32(6):961–966

Stevenson JC, Hodis HN, Pickar JH, Lobo RA (2011) HRT and breast cancer risk: a realistic perspective. Climacteric 14(6):633–636

Stoll W (1987) Phytotherapeutikum beeinflusst atrophisches Vaginalepithel. Doppelblindversuch Cimicifuga vs Östrogenpräparat Therapeutikon 1:23–31

Sturdee DW, Pines A, International Menopause Society Writing G, Archer DF, Baber RJ, Barlow D, Birkhauser MH, Brincat M, Cardozo L, de Villiers TJ, Gambacciani M, Gompel AA, Henderson VW, Kluft C, Lobo RA, MacLennan AH, Marsden J, Nappi RE, Panay N, Pickar JH, Robinson D, Simon J, Sitruk-Ware RL, Stevenson JC (2011) Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. Climacteric 14(3):302–320, doi:10.3109/13697137.2011.570590

Stute P, Nisslein T, Gotte M, Kamischke A, Kiesel L, Klockenbusch W (2007) Effects of black cohosh on estrogen biosynthesis in normal breast tissue in vitro. Maturitas 57(4):382–391

Suvanto-Luukkonen E, Koivunen R, Sundstrom H, Bloigu R, Karjalainen E, Haiva-Mallinen L, Tapanainen JS (2005) Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study. Menopause 12(1):18–26, doi:00042192-200512010-00006

Tarim E, Bagis T, Kilicdag E, Erkanli S, Aslan E, Kuscu E (2002) Moclobemide in the treatment of hot flashes in postmenopausal women. Adv Ther 19(6):258–265

Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR (2003) Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial. JAMA 290(2):207–214, doi:10.1001/jama.290.2.207

Turkington RW (1972) Prolactin secretion in patients treated with various drugs: phenothiazines, tricyclic antidepressants, reserpine, and methyldopa. Arch Intern Med 130(3):349–354

Uebelhack R, Blohmer JU, Graubaum HJ, Busch R, Gruenwald J, Wernecke KD (2006) Black Cohosh and St. John's Wort for climacteric complaints: A randomized trial. Obstetr Gynecol 107(2):247–255

Upmalis DH, Lobo R, Bradley L, Warren M, Cone FL, Lamia CA (2000) Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. Menopause 7(4):236–242

van de Weijer PH, Barentsen R (2002) Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. Maturitas 42(3):187–93, doi:S0378512202000804 [pii]

Van Patten CL, Olivotto IA, Chambers GK, Gelmon KA, Hislop TG, Templeton E, Wattie A, Prior JC (2002) Effect of soy phytoestrogens on hot flashes in

postmenopausal women with breast cancer: a randomized, controlled clinical trial. J Clin Oncol 20(6):1449–1455
Vázquez SM, Pignataro O, Luthy IA (1999) α_2-adrenergic effect on human breast cancer MCF-7 cells. Breast Cancer Res Treat 55(1):41–49
Vermes G, Banhidy F, Acs N (2005) The effects of remifemin on subjective symptoms of menopause. Adv Ther 22(2):148–154
Vitolins MZ, Griffin L, Tomlinson WV, Vuky J, Adams PT, Moose D, Frizzell B, Lesser GJ, Naughton M, Radford JE Jr, Shaw EG (2013) Randomized trial to assess the impact of venlafaxine and soy protein on hot flashes and quality of life in men with prostate cancer. J Clin Oncol 31(32):4092–4098, doi:10.1200/JCO.2012.48.1432
von Schoultz E, Rutqvist LE (2005) Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. J Natl Cancer Inst 97(7):533–535
Waldinger MD, Berendsen HH, Schweitzer DH (2000) Treatment of hot flushes with mirtazapine: four case reports. Maturitas 36(3):165–168
Wang PS, Walker AM, Tsuang MT, Orav EJ, Levin R, Avorn J (2001) Antidepressant use and the risk of breast cancer: a non-association. J Clin Epidemiol 54(7):728–734, doi: S0895-4356(00)00354-1
Weiss LK, Burkman RT, Cushing-Haugen KL, Voigt LF, Simon MS, Daling JR, Norman SA, Bernstein L, Ursin G, Marchbanks PA, Strom BL, Berlin JA, Weber AL, Doody DR, Wingo PA, McDonald JA, Malone KE, Folger SG, Spirtas R (2002) Hormone replacement therapy regimens and breast cancer risk. Obstet Gynecol 100(6):1148–1158
Wernli KJ, Hampton JM, Trentham-Dietz A, Newcomb PA (2009) Antidepressant medication use and breast cancer risk. Pharmacoepidemiol Drug Saf 18 (4):284–290, doi:10.1002/pds.1719
Wren BG, Brown LB (1986) A double-blind trial with clonidine and a placebo to treat hot flushes. Med J Aust 144(7):369–370
Wu MF, Hilsenbeck SG, Tham YL, Kramer R, Elledge RM, Chang JC, Friedman LC (2009) The efficacy of sertraline for controlling hot flashes in women with or at high risk of developing breast cancer. Breast Cancer Res Treat 118(2):369–375, doi:10.1007/s10549-009-0425-y
Wuttke W, Seidlová-Wuttke D, Gorkow C (2003) The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. Maturitas 44(Suppl 1):S67–S77
Wuttke W, Gorkow C, Seidlova-Wuttke D (2006) Effects of black cohosh (Cimicifuga racemosa) on bone turnover, vaginal mucosa, and various blood parameters in postmenopausal women: a double-blind, placebo-controlled, and conjugated estrogens-controlled study. Menopause 13(2):185–196
Yang HM, Liao MF, Zhu SY, Liao MN, Rohdewald P (2007) A randomised, double-blind, placebo-controlled trial on the effect of Pycnogenol on the climacteric syndrome in peri-menopausal women. Acta Obstet Gynecol Scand 86(8):978–985, doi:10.1080/00016340701446108
Ye YB, Wang ZL, Zhuo SY, Lu W, Liao HF, Verbruggen M, Fang S, Mai HY, Chen YM, Su YX (2012) Soy germ isoflavones improve menopausal symptoms but have no effect on blood lipids in early postmenopausal Chinese women: a randomized placebo-controlled trial. Menopause 19(7):791–798, doi:10.1097/gme.0b013e31823dbeda
Zava DT, Dollbaum CM, Blen M (1998) Estrogen and progestin bioactivity of foods, herbs, and spices. Proc Soc Exp Biol Med 217:369–378
Zbuk K, Anand SS (2012) Declining incidence of breast cancer after decreased use of hormone-replacement therapy: magnitude and time lags in different countries. J Epidemiol Community Health 66(1):1–7
Zeng Z, Liu Y, Liu Z, You J, Chen Z, Wang J, Peng Q, Xie L, Li R, Li S, Qin X (2013) CYP2D6 polymorphisms influence tamoxifen treatment outcomes in breast cancer patients: a meta-analysis. Cancer Chemother Pharmacol 72(2):287–303, doi:10.1007/s00280-013-2195-9
Zhang L, Khan IA, Willett KL, Foran CM (2003) *In vivo* effects of black cohosh and genistein on estrogenic activity and lipid peroxidation in Japanese Medaka (Oryzias latipes). J Herb Pharmacother 3(3):33–50
Ziaei S, Kazemnejad A, Zareai M (2007) The effect of vitamin E on hot flashes in menopausal women. Gynecol Obstet Invest 64(4):204–207, doi:10.1159/000106491
Zichella L, Falaschi P, Fioretti P, Melis GB, Cagnacci A, Gambacciani M, Mancini S (1986) Effects of different dopamine agonists and antagonists on post-menopausal hot flushes. Maturitas 8(3):229–237
Zierau O, Bodinet C, Kolba S, Wulf M, Vollmer G (2002) Antiestrogenic activities of *Cimicifuga racemosa* extracts. J Steroid Biochem Mol Biol 80(1):125–130