Support Care Cancer (2013) 21:1461–1474
DOI 10.1007/s00520-013-1732-8

REVIEW ARTICLE

Pharmacological and non-hormonal treatment of hot flashes in breast cancer survivors: CEPO review and recommendations

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Received: 18 September 2012 / Accepted: 28 January 2013 / Published online: 23 February 2013

Abstract
Purpose Breast cancer patients frequently report hot flashes. Given that conventional hormone replacement therapy is generally contraindicated for them, other therapeutic modalities must be considered. The purpose of this review was to develop evidence-based recommendations on

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non-hormonal pharmacological interventions, including natural health products, for managing hot flashes in women undergoing treatment for breast cancer or with a history of breast cancer.
Methods A review of the scientific literature published between January 2000 and December 2011 was performed. A total of 26 randomized trials were identified.
Results Studies showed that serotonin–norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, antihypertensives and anticonvulsants significantly reduced the frequency and severity of hot flashes in breast cancer patients.
Conclusions Considering the evidence available to date, the CEPO recommends the following: (1) for breast cancer patients being treated with tamoxifen: (a) the use of venlafaxine, citalopram, clonidine, gabapentin and pregabalin be considered effective in treating hot flashes and (b) the use of paroxetine and fluoxetine be avoided, given that they may reduce the efficacy of tamoxifen; (2) for breast cancer patients not being treated with tamoxifen: (a) the use of venlafaxine, paroxetine, citalopram, clonidine, gabapentin and pregabalin be considered effective in treating hot flashes and (b) fluoxetine not be used to treat hot flashes, given that there is insufficient evidence for its therapeutic efficacy and (3) for breast cancer survivors, sertraline, phytoestrogens, black cohosh and St. John's wort not be used to treat hot flashes.

Keywords Hot flashes · Breast cancer · Antidepressants · Antihypertensives · Anticonvulsants · Natural health products

Introduction

According to recent Canadian statistics, an estimated 22,700 new breast cancer cases were expected to occur in Canada in 2012 [1]. Chemotherapy and hormone therapy, commonly used for treating breast cancer, are very effective but may induce adverse events such as premature menopause [2]. Between 60 and 65 % of women experiencing premature menopause have hot flashes, defined as "a subjective sensation of heat that is associated with objective signs of cutaneous vasodilation and a subsequent drop in core temperature" [2, 3]. This symptom is one of the major complaints about their treatment. It is strongly recommended that hot flashes be routinely assessed as a component of systematic symptom evaluation for breast cancer patients [4]. Assessment of hot flashes frequency, intensity, duration and impact on quality of life (QoL) is recommended for individualizing patient's treatment plan [4]. Usually, patients self-report their symptoms in a personal diary and according to the frequency and intensity of their symptoms, a hot flash score can be determined [3, 4]. This score can be calculated by multiplying the average frequency by the average intensity of the symptoms. Widely used and more reliable than only evaluating the change in frequency, the hot flash score correlates with patient QoL and allows indirect comparisons of different modalities [3].

In addition to the effect of treatment on hot flash frequency and score, impacts of this symptom are generally evaluated on seven additional aspects such as depression, interference with daily activities, mood, fatigue, QoL, sexual functioning and vasomotor symptoms. Different validated questionnaires are used for this purpose such as Hot Flash-Related Daily Interference Scale (HFRDIS), evaluating the degree to which hot flashes interfere with daily activities [5], Menopause-specific Quality Of Life (MENQOL), evaluating the impact of the menopause symptoms on patient QoL [6], Sexual Activity Questionnaire (SAQ), measuring the impact of hot flash on sexual functioning [7], and the modified Kupperman Index, evaluating menopausal symptoms [8].

For healthy menopausal women, hormone replacement therapy (HRT) was long considered to be the treatment of choice; however, it has been increasingly discarded since the publication of studies demonstrating the lack of cardiovascular benefits and the increased risks for cancer [4]. The Women's Health Initiative study assessed the major health risks and benefits of the combined hormone preparation (estrogen plus progestin) among healthy postmenopausal women [9]. This trial has been stopped prematurely because of the significant increase in invasive breast cancer and of an unfavourable risk/benefit ratio. Patients treated with combined hormone preparation had a 1.26-fold higher risk of developing breast cancer than placebo; however risk of developing endometrial or colon cancer remained unchanged or was reduced. Specifically aiming to evaluate the effect of HRT on breast cancer incidence, the Million Women Study found that patients using HRT had a significant elevated risk of developing breast cancer and to die from it [10]. However, in breast cancer survivors, the use of HRT remains controversial. While a meta-analysis [11] and the Stockholm trial [12] suggested that HRT had no significant effect on breast cancer recurrence, the HABITS (Hormonal replacement therapy after Breast cancer—Is iT Safe?) trial found that the risk of recurrence was higher in women taking HRT [13]. Because of this contradiction, it is widely recommended that HRT be avoided for breast cancer survivors [12, 14]. Nevertheless, in cases where hot flashes become bothersome or negatively affect patient QoL, a pharmacological and non-hormonal approach may be needed.

A literature search was performed to assess the efficacy and safety of the various pharmacological and non-hormonal treatments available for managing hot flashes in breast cancer patients and survivors. Evidence-based practice recommendations were subsequently developed by the CEPO.

Methods

A search of the scientific literature published from January 2000 to December 2011 was performed in PubMed with the following keywords: "hot flashes" (MeSH), "hot flash", "hot flush", "vasomotor symptoms", "climacteric symptoms", "menopausal symptoms", "treatment", "breast neoplasms" (MeSH) and "breast cancer". Only randomized controlled trials (RCTs) and meta-analyses published in English or French and reporting assessments of hot flash relief in breast cancer patients using non-hormonal treatments were considered. Economic analyses, retrospective studies, phase II studies, studies reporting only unplanned subgroup analyses and those assessing hot flash relief through homeopathic or alternative medicine approaches (i.e. acupuncture, paced respiration and behaviour therapy) were not considered. Abstracts from relevant international conferences held from 2008 to 2011 were reviewed and only those presenting results from RCTs were considered. Clinical practice guidelines and expert consensus statements issued by relevant international organizations and cancer agencies were identified. Levels of evidence (LOE) and strengths of recommendation were evaluated using the ASCO and ESMO grading system (Table 1). The original guideline was developed by a CEPO subcommittee, reviewed by independent external experts, and finally adopted by the CEPO.

Table 1 Levels of evidence and grades of recommendation

Levels of evidence	
Level	Type of evidence
I	Evidence demonstrated by means of meta-analyses of well-designed controlled trials or large randomized trials with clear-cut results (low false-positive and false-negative errors, high power)
II	Evidence demonstrated by means of small randomized trials with uncertain results (high false-positive and false-negative errors, low power)
III	Evidence demonstrated by means of nonrandomized concurrent cohort comparisons with contemporaneous controls
IV	Evidence demonstrated by means of nonrandomized historical cohort comparisons
V	Evidence demonstrated by means of case series without controls
Grades of recommendation	
Grade	Recommendation
A	Supported by level I evidence or multiple level II, III or IV trials presenting concordant observations
B	Supported by level II, III or IV trials presenting generally concordant observations
C	Supported by level II, III or IV trials presenting non-concordant observations
D	Supported by little or no empiric evidence

Adapted from Cook et al. [63]

Results

Literature review results

A total of 26 RCTs were selected. These included 11 RCTs evaluating the efficacy of serotonin–norepinephrine reuptake inhibitors (SNRIs) or selective serotonin reuptake inhibitors (SSRIs) [15–25] (Table 2), one RCT evaluating the efficacy of antihypertensive agents [26] and five RCTs evaluating the efficacy of anticonvulsant agents [27–31] (Table 3), and nine RCTs evaluating the efficacy of natural health products [32–40] (Table 4). Sample size of the individual studies ranged from 46 to 420 breast cancer patients or survivors.

Efficacy of SNRIs and SSRIs

- Venlafaxine

  Five RCTs evaluated the efficacy of venlafaxine for treating hot flashes in breast cancer survivors [15–19]. In 2007, Carpenter et al. demonstrated that breast cancer survivors taking venlafaxine 37.5 mg/day for 4 weeks had a significant reduction in physiological (22 % versus 0 %) and in self-reported (42 % versus 18 %) hot flash frequency compared with placebo ($p<0.001$ for both; LOE II) [15]. Patients who experienced more than a 50 % decrease in hot flash frequency showed significant improvements from baseline in fatigue ($p=0.007$), mental health ($p=0.02$), sleep disturbance ($p=0.03$) and vitality ($p=0.048$). However, compared with placebo, patients taking venlafaxine reported significantly more dry mouth ($p<0.001$), constipation ($p=0.001$) and headache ($p=0.007$).

  In 2000, Loprinzi et al. showed that after 4 weeks of treatment with different doses of venlafaxine (37.5, 75 or 150 mg/day) or a placebo, median hot flash frequency in breast cancer survivors was reduced from baseline by 30 to 58 % for patients taking venlafaxine and by 19 % for patients receiving placebo ($p<0.001$ for each venlafaxine dose compared to placebo; LOE II) [16]. Median hot flash score was also reduced by 37 to 61 %, depending on the venlafaxine dose taken, compared to 27 % in patients receiving placebo ($p<0.001$). Dry mouth, nausea, decreased appetite and constipation were significantly higher in patients treated with venlafaxine. Improvements in libido, depressive symptoms and QoL were reported with venlafaxine.

  Three RCTs compared the efficacy of venlafaxine with that of clonidine for treating hot flashes in breast cancer survivors [17–19]. In 2011, Boekhout et al. demonstrated

Table 2 Summary of results: SNRIs and SSRIs

Study	Treatment	n	Breast cancer history (% patient)	Duration (weeks)	Variations				Adverse events
					Frequency	*p* value	Score	*p* value	
Venlafaxine versus placebo									
Carpenter et al. [15] (crossover study)	Venlafaxine 37.5 mg/d	26	100 %	14	−22 %	<0.001	–	–	Constipation, headache, dry mouth
	Placebo (c)	26	100 %		0 %		–		–
Loprinzi et al. [16]	Venlafaxine 37.5 mg/d	56	–	4	−30 %	<0.001	−37 %	<0.001	Dry mouth, nausea, decreased appetite, constipation
	Venlafaxine 75 mg/d	55	–		−46 %		−61 %		
	Venlafaxine 150 mg/d	54	–		−58 %		−61 %		
	Placebo (c)	56	–		−19 %		−27 %		–
Venlafaxine versus clonidine									
Boekhout et al. [17]	Venlafaxine 75 mg/d	41	100 %	12	–	–	−41 %	<0.001	Nausea, constipation, decreased appetite
	Clonidine 0.1 mg/d	41	100 %		–		−26 %	0.045	–
	Placebo (c)	20	100 %		–		−29 %	–	–
Buijs et al. [18] (crossover study)	Venlafaxine 75 mg/d	49	100 %	18	–	–	−49 %	0.55	Taste alteration, decreased appetite, nausea, constipation
	Clonidine 0.1 mg/d (c)	51	100 %		–		−55 %		Itching, pain
Loibl et al. [19] (crossover study)	Venlafaxine 75 mg/d	40	100 %	4	−57 %	0.025	−11.4 U/day	0.043	Nausea, dry mouth, tiredness, restless sleep
	Clonidine 0.15 mg/d (c)	40	100 %		−37 %		−8.9 U/day		Dry mouth, tiredness, restless sleep
Paroxetine versus placebo									
Stearns et al. [20] (crossover study)	Paroxetine 10 mg/d	37	78 %	8	−41 %	0.0006	−46 %	0.0008	Nausea
	Placebo (c)	39	79 %		−14 %		−14 %		
	Paroxetine 20 mg/d	38	82 %		−52 %	0.002	−56 %	0.004	
	Placebo (c)	37	86 %		−27 %		−29 %		
Fluoxetine versus placebo									
Loprinzi et al. [21] (crossover study)	Fluoxetine 20 mg/d	40	–	8	−42%[a]	0.54	−50%[a]	0.35	–
	Placebo (c)	41	–		−31 %		−36 %		–
Sertraline versus placebo									
Wu et al. [22]	Sertraline 25 mg/d	24	95 %	4	−37 %	0.322	−32 %	0.384	–
	Placebo (c)	22	95 %		−22 %		−22 %		–
Kimmick et al. [23] (crossover study)	Sertraline 50 mg/d	33	100 %	12	−1.6 HF/week	0.90	−3.2 U/week	0.70	–
	Placebo (c)	29	100 %		−1.5 HF/week		−4.6 U/week		–
Citalopram versus placebo									
Barton et al. [24]	Citalopram 10 mg/d	54	35 %	6	−46 %	<0.001	−49 %	≤0.002	–
	Citalopram 20 mg/d	56	37 %		−43 %		−50 %		–

Table 2 (continued)

Study	Treatment	n	Breast cancer history (% patient)	Duration (weeks)	Variations			Adverse events
					Frequency	*p* value	Score	*p* value	
	Citalopram 30 mg/d	55	35 %		−50 %		−55 %		–
	Placebo (c)	83	31 %		−20 %		−23 %		–
Kalay et al. [25]	Citalopram 20 mg/d	25	–	8	–	–	−37 %	0.001	Somnolence, perspiration, palpitations, dry mouth
	Placebo (c)	25	–		–		−13 %		–

c comparator, *d* day, *HF* hot flash, *mg* milligram, *n* number of patients, *U* unit, – data not available

[a] Crossover analysis showed that patients taking fluoxetine had further reductions in hot flash frequency (19 %; $p=0.01$) and score (24 %; $p=0.02$) compared with placebo

that during the 12 weeks of treatment, breast cancer patients taking venlafaxine 75 mg/day had a 41 % hot flash score reduction compared with placebo ($p<0.001$); those taking clonidine 0.1 mg/day had a 26 % reduction ($p=0.045$; LOE II) [17]. Compared with patients receiving placebo, those taking venlafaxine experienced significantly more nausea ($p=0.02$) and constipation ($p=0.04$). Loss of appetite occurred more frequently with venlafaxine compared with clonidine ($p=0.003$). Sexual function and sleep quality were similar in both groups.

In 2009, Buijs et al. published a crossover study which showed no difference in the mean reduction in hot flash score between breast cancer patients taking venlafaxine 75 mg/day and those taking clonidine 0.1 mg/day after 8 weeks of treatment (49 % versus 55 %; $p=0.55$; LOE II) [18]. After 2 weeks, patients taking venlafaxine reported taste alteration, appetite loss, nausea and constipation, whereas patients taking clonidine reported pain and itching. After 8 weeks, fewer depressive symptoms were observed in the venlafaxine group compared to baseline ($p=0.001$), while no change was observed in the clonidine group. Neither treatment had an impact on sexual function.

In 2007, Loibl et al. demonstrated that venlafaxine 75 mg/day was significantly more effective than clonidine 0.15 mg/day in reducing hot flash frequency (57 % versus 37 %; $p=0.025$) and score (11.4 versus 8.9 U/day; $p=0.043$) in breast cancer patients (LOE II) [19]. In both groups, the most common adverse events were dry mouth, tiredness and restless sleep. Nausea was more frequently reported by patients taking venlafaxine compared to clonidine ($p=0.05$).

- Paroxetine

  In 2005, Stearns et al. showed that paroxetine 10 or 20 mg/day significantly reduced hot flash frequency (40.6 % versus 13.7 %; $p=0.0006$ and 51.7 % versus 26.6 %; $p=0.002$) and score (45.6 % versus 13.7 %; $p=0.0008$ and 56.1 % versus 28.8 %; $p=0.004$) compared with placebo in women among which more than 80 % were breast cancer survivors (LOE II) [20]. Efficacy was similar between the two doses, but women were less likely to discontinue low-dose paroxetine. Adverse events that may have been related to paroxetine were mostly mild and mainly included nausea. Sleep improvements were reported with low-dose paroxetine compared with placebo ($p=0.01$).

- Fluoxetine

  In 2002, Loprinzi et al. published a crossover study and showed that after the first 4 weeks of treatment, no variation in hot flash frequency or score was observed between breast cancer patients treated with fluoxetine 20 mg/day and those receiving placebo (LOE II) [21]. Nevertheless, subsequent analysis of the crossover data

Table 3 Summary of results: antihypertensives and anticonvulsants

Study	Treatment	n	Breast cancer history (% patient)	Duration (weeks)	Variations				Adverse events
					Frequency	*p* value	Score	*p* value	
Clonidine versus placebo									
Pandya et al. [26]	Clonidine 0.1 mg/d	99	100 %	8	−37 %	0.006	−50 %	0.006	Sleeping difficulties
	Placebo (c)	99	100 %		−17 %		−26 %		–
Gabapentin versus other medications (venlafaxine, vitamin E or placebo)									
Bordeleau et al. [27] (crossover study)	Gabapentin 900 mg/d	34	100 %	4	–	–	−66 % (for both)[a]	<0.001	Dizziness, increased appetite
	Venlafaxine 75 mg/d	32	100 %		–				Nausea, appetite loss, constipation, difficulty achieving orgasms
Biglia et al. [28]	Gabapentin 900 mg/d	60	100 %	12	−57%[b]	–	−67%[b]	–	Somnolence, dizziness, dry mouth, nervousness, weight gain
	Vitamin E 800 IU/d (c)	55	100 %		−10 %		−7 %		–
Loprinzi et al. [29]	Gabapentin 900 mg/d	55	84 %	4	−49 %	0.61	−60 %	0.37	Nervousness
	Antidepressants+Gabapentin 900 mg/d (c)	58	78 %		−54 %		−56 %		–
Pandya et al. [30]	Gabapentin 300 mg/d	139	100 %	8	−30 %	0.0006[c]	–31 %	0.007[c]	–
	Gabapentin 900 mg/d	144	100 %		−44 %		–46 %		
	Placebo (c)	137	100 %		−15 %		–15 %		–
Pregabalin versus placebo									
Loprinzi et al. [31]	Pregabalin 150 mg/d	69	35 %	6	−59 %	0.007	−65 %	0.009	Dizziness, trouble concentrating
	Pregabalin 300 mg/d	69	44 %		−61 %	0.007	−71 %	0.007	Dizziness, cognitive difficulties, weight gain, somnolence, coordination problems, trouble concentrating, blurred/double vision
	Placebo (c)	69	41 %		−36 %	–	−50 %	–	–

c comparator, *d* day, *mg* milligram, *n* number of patients, *IU* international unit, – data not available

[a] Reduction from baseline averaged over both treatments and treatment periods

[b] No direct statistical comparison has been done between the two experimental arms. Only patients treated with gabapentin have demonstrated significant reductions of hot flash frequency and score compared to baseline ($p<0.05$)

[c] Difference in percentage change in frequency and severity from baseline to week 8

Table 4 Summary of results: natural health products

Study	Treatment	n	Breast cancer history (% patient)	Duration (weeks)	Variations			
					Frequency	*p* value	Score	*p* value
Phytoestrogens, isoflavones and other derivatives versus placebo								
Pruthi et al. [32]	Flaxseed 7.5 g/d	94	50 %	6	−29 %	0.90	−4.9 U/d	0.29
	Placebo (c)	94	52 %		−25 %		−3.5 U/d	
MacGregor et al. [33]	Isoflavones 70 mg/d	36	100 %	12	–	–	–	0.806[a]
	Placebo (c)	36	100 %		–		–	
Nikander et al. [34]	Phytoestrogens 114 mg/d	32	100 %	3	–	–	–	0.992[b]
	Placebo (c)	32	100 %		–		–	
Van Patten et al. [35]	Isoflavones 90 mg/d	78	100 %	12	–		–30 %	ns
	Placebo (c)	79	100 %		–		–40 %	
Quella et al. [36]	Phytoestrogens 150 mg/d	87	100 %	8	–	–	−44 %[c], −21 %[c], −35 %[c]	0.78
	Placebo (c)	88	100 %		–		−40 %[c], −22 %[d], −35 %[e]	
Black cohosh versus placebo								
Pockaj et al. [37]	Black cohosh 40 mg/d	66	59 %	8	–	–	−15 %	0.10
	Placebo (c)	65	69 %		–		−31 %	
Jacobson et al. [38]	Black cohosh 40 mg/d	42	100 %	2 months	−27 % overall	0.86	–	–
	Placebo (c)	43	100 %				–	
Tamoxifen versus tamoxifen + black cohosh								
Hernandez et Pluchino [39]	Tamoxifen 20 mg/d+black cohosh 40 mg/d	90	100 %	60 days	46.7 %[d]	–	–	–
	Tamoxifen 20 mg/d (c)	46	100 %		–		–	
St. John's wort versus placebo								
Al-Akoum et al. [40]	St. John's wort 900 mg/d	22	55 %	3 months	−2.3 HF/d	0.11	−3.8 U/d	0.10
	Placebo (c)	25	68 %		−1 HF/d		−1.8 U/d	

c comparator, *d* day, *HF* hot flash, *mg* milligram, *n* number of patients, *ns* not significant, *U* unit, – data not available, *g* gram

[a] Treatment with isoflavone did not result in significant differences in menopausal symptoms scores compared to placebo (hot flashes and sweating)

[b] Reductions in Kupperman index score were evaluated following two treatments; no difference was observed compared to placebo (15.5 % versus 14.7 %)

[c] Percentage of patients having ≤25 %, 25 to 50 %, and ≥50 % reduction in hot flash score, respectively

[d] Percentage of patients free of hot flashes

showed that fluoxetine was associated with significant reduction in hot flash frequency (19 %; $p=0.01$) and score (24 %; $p=0.02$). Additional analysis confirmed the superiority of fluoxetine over placebo, even when adjusted for potential confounding factors such as depression, tamoxifen use and age. Compared with placebo, fluoxetine treatment did not induce further toxicity and had no significant impact on libido, depressive symptoms and QoL.

- Sertraline

  Two RCTs evaluated the efficacy of sertraline for treating hot flashes in breast cancer survivors [22, 23]. In 2009, Wu et al. found no difference in hot flash frequency or score between breast cancer patients treated with sertraline 25 mg/day or placebo (LOE II) [22]. No serious drug-related adverse events were associated with the use of sertraline. Most adverse events were mild to moderate and resolved by themselves or by lowering doses. Treatment with sertraline had no significant impact on patient QoL.

  In 2006, Kimmick et al. showed no difference in hot flash frequency or score between patients treated with sertraline 50 mg/day or placebo (LOE II) [23]. The adverse events most frequently reported in the sertraline group were nausea (28 %), diarrhea (20 %), fatigue/malaise (12 %) and anxiety/nervousness (12 %); their incidence was similar in the placebo group. Even though sertraline had no significant impact on patient QoL, the majority of patients preferred sertraline over placebo.

- Citalopram

  Two RCTs evaluated the efficacy of citalopram for treating hot flashes in breast cancer survivors [24, 25]. In 2010, Barton et al. demonstrated that after 6 weeks of treatment, breast cancer patients receiving citalopram 10, 20 or 30 mg/day had statistically significant reductions in hot flash frequency (46, 43 and 50 % versus

20 %, respectively; $p<0.001$) and score (49, 50 and 55 % versus 23 % respectively; $p\leq0.002$) compared to placebo (LOE II) [24]. No significant difference was observed between the three doses. No citalopram-related toxicity and no impact on patient QoL were reported. Nevertheless, significant improvement in anxiety ($p\leq0.01$) and reduction in hot flash interference in daily life ($p<0.01$) were observed in patients taking citalopram 20 mg/day.

In 2007, Kalay et al. reported that after 8 weeks of treatment with citalopram 20 mg/day, women not taking HRT had significant reductions in hot flash score compared with placebo (37 % versus 13 %; $p=0.001$; LOE II) [25]. Adverse events such as somnolence, increased perspiration, palpitations and dry mouth were observed with citalopram. A significant improvement in physical well-being was observed in patients taking citalopram ($p=0.001$). However, no difference was reported for sexual functioning and patient QoL.

Efficacy of antihypertensive drugs

- Clonidine

  In 2000, Pandya et al. found that breast cancer patients receiving clonidine 0.1 mg/day had a greater reduction in hot flash frequency (37 % versus 17 %; $p=0.006$) and score (50 % versus 26 %; $p=0.006$) than patients receiving placebo (LOE II) [26]. Patients taking clonidine were more likely to report difficulty sleeping (41 % versus 21 %; $p=0.02$). Improvements in QoL were observed after 8 weeks of treatment with clonidine ($p=0.02$).

Efficacy of anticonvulsant drugs

- Gabapentin

  Four RCTs evaluated the efficacy of gabapentin for treating hot flashes in breast cancer survivors [27–30]. In 2010, Bordeleau et al. showed a statistically significant reduction in hot flash score in patients treated with gabapentin 900 mg/day and in patients treated with venlafaxine 75 mg/day compared with baseline values (66 % reduction; $p<0.001$; LOE II) [27]. Treatment crossover was planned after 28 days and following crossover, significantly more patients preferred venlafaxine over gabapentin (68 % versus 32 %; $p=0.01$). No grade 3 or 4 treatment-related adverse events were reported. However, treatment with venlafaxine was associated with increased appetite loss ($p=0.003$), nausea ($p=0.02$) and constipation ($p=0.05$), and with fewer negative mood changes ($p=0.01$) compared with gabapentin. On the other hand, gabapentin was associated with increased appetite ($p=0.001$) and dizziness ($p=0.005$). More difficulty achieving orgasms was noted with venlafaxine ($p=0.002$).

  In 2009, Biglia et al. assessed the efficacy and tolerability of gabapentin 900 mg/day compared with vitamin E for controlling vasomotor symptoms in breast cancer patients (LOE II) [28]. After 12 weeks, gabapentin resulted in significant reductions in hot flash frequency and score from baseline (57 % and 67 %; $p<0.05$ for both). The effect of vitamin E was considered fairly small by the authors with a 10 % reduction in hot flash frequency and a 7 % reduction in hot flash score. The most common gabapentin-related adverse events were somnolence and dizziness. Dry mouth, nervousness and modest weight gains were also observed. Patient QoL and sleep quality were significantly improved with gabapentin ($p<0.05$ for both).

  In 2007, Loprinzi et al. showed that combining an antidepressant and gabapentin was not more effective than gabapentin alone in reducing hot flash frequency (49 % versus 54 %; $p=0.61$) and score (60 % versus 56 %; $p=0.37$; LOE II) [29]. Despite a trend for difference in nervousness and negative mood changes among the two treatment arms, incidence of adverse events and impact on QoL were similar in both groups.

  In 2005, Pandya et al. demonstrated that breast cancer patients treated with gabapentin 300 or 900 mg/day had significant reductions in hot flash frequency (30 and 44 % versus 15 %; $p=0.0006$) and severity score (31 and 46 % versus 15 %; $p=0.007$) between baseline and week 8, compared with placebo (LOE I) [30]. Only the higher dose of gabapentin was associated with significant decreases in hot flash frequency and severity ($p<0.0001$). Use of gabapentin was associated with improved appetite and reduced pain.

- Pregabalin

  In 2010, Loprinzi et al. demonstrated that breast cancer patients treated with pregabalin 75 and 150 mg twice daily for 6 weeks had significant reductions from baseline in hot flash frequency (59 and 61 % versus 36 %; $p=0.007$ for both) and score (65 and 71 % versus 50 %; $p=0.009$ and $p=0.007$, respectively), compared to placebo (LOE I) [31]. Treatment with pregabalin induced more dizziness, cognitive difficulties, undesirable weight gain, somnolence, coordination difficulties, trouble concentrating and concerns regarding blurred or double vision. Changes in these adverse events were mostly significant with the higher dose of pregabalin. Treatment with pregabalin had no effect on patient QoL, but a reduction in hot flash interference in daily life was observed. Patients treated with pregabalin were much

more satisfied with their hot flash control than those receiving placebo ($p \leq 0.0001$).

Efficacy of natural health products

- Phytoestrogens, isoflavones and other derivatives

  Five RCTs evaluated the efficacy of phytoestrogens and their derivatives for treating hot flashes in breast cancer survivors [32–36]. In 2012, Pruthi et al. found that flaxseed 7.5 g/day had no further effect on the mean reduction of hot flash frequency (29 % versus 25 %; $p=0.90$) and score (4.9 versus 3.5 U/day; $p=0.29$) compared with placebo (LOE II) [32]. Patients in both groups reported abdominal distension, flatulence, diarrhea and nausea. Patients taking flaxseed had significantly less grade 1 pruritus than patients taking placebo ($p=0.04$). No difference was observed between the groups concerning mood, QoL and hot flash interference in daily life, except for leisure interference for which an improvement was observed in patients taking flaxseed ($p=0.03$).

  In 2005, MacGregor et al. observed that breast cancer patients taking soy phytoestrogens 35 (isoflavones 70 mg/day) had no significant reductions in menopausal symptoms scores (hot flashes and sweating) compared with placebo (LOE II) [33]. Toxicity of soy phytoestrogens was mild, primarily gastrointestinal and not significantly different from that of placebo. Furthermore, soy phytoestrogen did not improve patient QoL.

  In 2003, Nikander et al. demonstrated in a crossover study that breast cancer patients treated with phytoestrogens 114 mg/day (including soy isoflavones, glycitein, daidzein and genistein) had a significant reduction in Kupperman index from baseline (15.5 %; $p=0.002$), but not different from that observed in the placebo arm (14.7 %; $p=0.992$; LOE II) [34]. Neither hot flashes nor any other components of the Kupperman index were relieved with phytoestrogens when evaluated separately. Moreover, phytoestrogens had no impact on patient working capacity, depression, anxiety and self-confidence.

  In 2002, Van Patten et al. found no significant difference in the 24-hour hot flash score reduction in breast cancer patients treated daily with a soy beverage containing 90 mg isoflavones or with a placebo rice beverage (30 % versus 40 %; p=not significant; LOE II) [35]. Mild gastrointestinal adverse events were reported in both groups but were more frequent and severe in the soy beverage arm.

  In 2000, Quella et al. demonstrated that breast cancer survivors treated with soy phytoestrogens 150 mg/day had no reduction in hot flash score from baseline compared with placebo ($p=0.78$; LOE II) [36]. However, 36 % of patients receiving placebo reported that hot flash frequency had been reduced by half compared with to 24 % of patients receiving soy phytoestrogens ($p=0.01$). Incidence of adverse events was similar in both groups.

- Black cohosh

  Three RCTs evaluated the efficacy of black cohosh for treating hot flashes in breast cancer patients [37–39]. In 2006, Pockaj et al. showed no significant difference in mean hot flash frequency (17 % versus 26 %; $p=0.36$) and score (20 % versus 27 %; $p=0.53$) in women with a history of breast cancer or a perceived increased risk of breast cancer treated with black cohosh 40 mg/day compared to placebo (difference between the fourth treatment week and baseline; LOE II) [37]. After 4 weeks, a crossover was allowed, which did not show any benefit for black cohosh ($p=0.98$). Black cohosh was well tolerated and did not affect patient QoL.

  In 2001, Jacobson et al. found that breast cancer survivors treated with black cohosh 40 mg/day for 2 months had no reduction in hot flash frequency and intensity compared with placebo with an overall decline in the mean number of hot flashes from baseline of 27 % ($p=0.86$; LOE II) [38]. Significant improvement in sweating was observed in the black cohosh group ($p= 0.04$). Severe adverse events, such as cases requiring hysterectomy and breast cancer recurrence, were observed in the black cohosh arm.

  In 2003, Hernandez-Munoz and Pluchino found that 46.7 % of breast cancer survivors treated with tamoxifen and black cohosh 20 mg/day were free of hot flashes (LOE II) [39]. However, severe hot flashes were reported by 24.4 % of patients treated with tamoxifen and black cohosh and by 73.9 % of patients treated with tamoxifen alone ($p< 0.01$).

- St. John's wort

  In 2009, Al-Akoum et al. found no difference in the reduction of daily hot flash frequency (2.3 versus 1.0; $p= 0.11$) and score (3.8 versus 1.8 U/day; $p=0.10$) in breast cancer survivors treated with St. John's wort 900 mg/day or placebo for 12 weeks (LOE II) [40]. After 3 months, significant improvements in menopause-specific QoL ($p=0.01$) and reductions in sleep problems ($p=0.05$) were reported in the St. John's wort arm. Adverse events such as fatigue, dry mouth and abnormal sweating were more common in the placebo group than in the St. John's wort group.

Discussion

Menopause is unfortunately a reality that no woman can escape. For the majority of menopausal women, hot flashes are among the most bothersome symptoms. In healthy women, this symptom disappears within 4 to 5 years from the

onset of menopause. However, among breast cancer survivors, it is usually more intense and more frequent and can significantly affect QoL [41]. HRT is a treatment option that may be considered for the majority of women, but is generally contraindicated for breast cancer patients and survivors.

Usual management of breast cancer include endocrine treatment or chemotherapy. Both treatments cause an estrogen deprivation that can lead to a premature menopause, resulting in more severe and prolonged menopausal symptoms [3, 42]. Tamoxifen is one of the most used treatments for breast cancer. In breast cancer patients initiating tamoxifen treatment, the pattern of hot flashes is typically a gradual increase over the first 2 to 3 months, followed by a plateau and a slow dissipation [43]. Among the selected studies, most included breast cancer patients treated with tamoxifen. Only five studies presented results from unplanned analysis of the effectiveness of the different nonhormonal hot flashes treatments according to concomitant tamoxifen intake [20, 24, 31, 32, 38]. All concluded that the effectiveness of these treatments was not influenced by tamoxifen.

Efficacy of SNRIs and SSRIs

Historically, SNRIs and SSRIs have been recognized mainly for their effects on depression, obsessive-compulsive disorders and anxiety. However, for the purpose of this review, 11 RCTs evaluating the efficacy of these agents in hot flashes treatment in breast cancer patients were included [15–25]. Overall, studies demonstrated that treatment with venlafaxine (37.5 to 150 mg/day), paroxetine (10 to 20 mg/day) or citalopram (10 to 30 mg/day) led to significant reductions in hot flash frequency (from 14 to 58 %) and score (from 26 to 51 %) compared to placebo [15–20, 24, 25]. No direct comparison between treatments could be made due to the heterogeneity in study populations. Furthermore, methodological weaknesses, such as low statistical power, high frequency of treatment dropout and non-optimal treatment compliance, were frequently observed. One study showed a very modest improvement in hot flash frequency and score in breast cancer survivors with the use of fluoxetine compared to placebo but only after treatment crossover [21]. The short duration of the study and the absence of a washout period before crossover may have significantly affected the outcomes observed.

It is fascinating to observe that all the selected studies compared the efficacy of SNRIs or SSRIs with that of placebo. It would be interesting to compare these with each other in order to establish their superiority in efficacy. In most of the reviewed evidence, reductions in hot flash frequency and score were also observed in patients receiving placebo. These reductions were consistent with the finding that 4 weeks treatment with placebo generally led to a reduction in hot flash frequency of more than 25 % in menopausal patients [2]. Few studies compared venlafaxine efficacy with that of other agents such as clonidine or gabapentin [17–19, 27] and only one showed a significant improvement in hot flash frequency and score with venlafaxine [27].

Generally, SNRIs and SSRIs induce significant adverse events such as dry mouth, nausea, constipation and appetite problems. In addition, some of these drugs are known to inhibit cytochrome P450 2D6 activity, an enzyme involved in tamoxifen metabolism [44]. Consequently, the use of drugs such as fluoxetine and paroxetine must not be prescribed concomitantly with tamoxifen because they are known to reduce endoxifen plasma concentration. Analyses derived from the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial suggested that there was no strong evidence available to conclude that these drugs should be avoided in women treated with tamoxifen [45]. However, current clinical practice guidelines are more cautious and still recommend that fluoxetine and paroxetine should not be prescribed to women treated with tamoxifen [42, 46–48].

Efficacy of antihypertensive and anticonvulsant agents

One study showed that clonidine 0.1 mg/day significantly reduced hot flash frequency and score, compared with placebo, in breast cancer patients [26]. Improved QoL was showed in favour of clonidine despite increased sleep disturbances.

Efficacy of anticonvulsants was evaluated in five RCTs using different comparative treatments, including antidepressants, vitamin E or placebo [27–31]. Studies showed that treating hot flashes in breast cancer patients with gabapentin 900 mg/day or pregabalin 150 mg/day led to significant reductions in hot flash frequency and score. Treatment with gabapentin compared to vitamin E provided approximately a six- to tenfold reduction in hot flash frequency and score [28]. Gabapentin given concurrently with antidepressants provided no further benefit on hot flash relief [29]. Furthermore, a study showed that breast cancer patients experiencing hot flashes preferred treatment with venlafaxine than with gabapentin [27]. Adverse events were generally observed with high doses of anticonvulsants and mainly included dizziness, poor appetite, dry mouth, nervousness, weight gain and difficulty concentrating.

The studies reviewed were generally of short duration (4 to 12 weeks) and included no long-term data. Because of heterogeneity in the study population, it was not possible to compare these medications with each other. Well-designed RCTs are needed to position these drugs within a treatment continuum. Absence of treatment comparison affect their value in clinical practice, given that some clinical guidelines

and expert consensus statements consider anticonvulsant drugs to be both first-line or second-line treatments for hot flashes [42, 48–50].

Efficacy of natural health products

Natural health products, especially those derived from medicinal plants, have very complex molecular compositions, and studies generally included non-clinically validated substances or composites in which no dose–response relationships were observed. In the selected studies, none of the tested natural health products significantly reduced hot flash frequency or score in breast cancer patients [32–40].

No study assessing the efficacy of phytoestrogens and their derivatives for treating hot flashes in breast cancer patients was positive [32–36]. Phytoestrogens are known to have estrogenic or anti-estrogenic activities depending on their dosage [51]. A potential risk for hormone-related adverse events, such as endometrial hyperplasia and breast cancer, is of concern because phytoestrogens have been demonstrated to act as weak estrogen agonists [52]. None of the reviewed studies assessed the impact of phytoestrogen intake on breast cancer survival and recurrence. Data on phytoestrogen safety and survival benefits are inconsistent. This is generally due to differences in study design and populations and the presence of confounding factors [53–55]. Safety of phytoestrogens was evaluated in a meta-analysis that included 174 RCTs [52]. No difference in overall incidence of adverse events was shown between the phytoestrogens and control arms (36.7 % versus 38 %; $p=0.20$). However, a significantly higher incidence of gastrointestinal toxicity was observed with phytoestrogens (17.8 % versus 13.4 %; $p=0.003$).

Three RCTs evaluated the efficacy of black cohosh and showed no significant benefit for reducing hot flash frequency and score in breast cancer patients [37–39]. Black cohosh may cause major adverse events, such as constipation, arrhythmia, weight gain, abdominal cramps, endometrial hyperplasia and vaginal bleeding. An in vitro study suggested that black cohosh may also interfere with tamoxifen activity [56]. However, other studies concluded that this natural health product is a reasonable and safe treatment for breast cancer patients [57–61]. In 2004, the *Collège des médecins du Québec* and *Ordre des pharmaciens du Québec* jointly evaluated the safety of different natural health products and suggested that patients taking black cohosh concurrently with other medications should be closely monitored by their physicians or pharmacists [62]. Furthermore, no benefit was reported with St. John's wort for reducing hot flash frequency and severity in breast cancer patients and adverse events, such as constipation, dry mouth and abnormal sweating, were observed [40]. As with black cohosh, St. John's wort may decrease tamoxifen efficacy and may interfere with other medications used for cancer-associated conditions such as depression, anxiety, coagulation disorders or heart diseases. Thus, monitoring patients taking St. John's wort is highly recommended [62].

Conclusion and recommendations

For breast cancer survivors, regaining a normal QoL is key to their well-being. Hot flashes, whether natural or induced by anticancer therapy, may make it difficult to achieve this objective. The frequency, severity and duration of hot flashes, along with their interference in daily life and their impact on QoL, are important parameters to consider in treatment decisions. Studies have shown that antidepressants (venlafaxine, paroxetine, citalopram and fluoxetine), antihypertensives (clonidine) and anticonvulsants (gabapentin and pregabalin) significantly reduce hot flash frequency and severity. However, the use of natural health products such as phytoestrogens, black cohosh and St. John's wort for hot flash treatment is not supported.

In order to set realistic expectations for women choosing a non-hormonal modality for alleviating hot flashes, it is important to point out that the differences between the interventions and placebos, though significant, are sometimes quite small. Also women who do not have breast cancer may not benefit completely from non-hormonal modality since none of these therapies approaches the efficacy of hormone therapy in reducing hot flashes.

Considering the evidence available to date, the CEPO recommends the following:

1. For breast cancer patients *being treated with tamoxifen*:
   a. The use of venlafaxine, citalopram, clonidine, gabapentin and pregabalin be considered effective in treating hot flashes (grade B recommendation).
   b. The use of paroxetine and fluoxetine be avoided, given that they may reduce the efficacy of tamoxifen (grade D recommendation).
2. For breast cancer patients *not being treated with tamoxifen*:
   a. The use of venlafaxine, paroxetine, citalopram, clonidine, gabapentin and pregabalin be considered effective in treating hot flashes (grade B recommendation).
   b. Fluoxetine not be used to treat hot flashes, given that there is insufficient evidence for its therapeutic efficacy (grade D recommendation).
3. For breast cancer survivors, sertraline, phytoestrogens (including isoflavones and other phytoestrogen derivatives), black cohosh and St. John's wort not be used to treat hot flashes (grade A recommendation).

Acknowledgements The CEPO is a group of oncology specialists that reports to the Direction québécoise de cancérologie du ministère de la Santé et des Services sociaux du Québec. La Direction québécoise de cancérologie provided funding for the work reported in this article, which is an adaptation of CEPO's original clinical practice guideline published in June 2012, available in French at www.msss.gouv.qc.ca/cancer. The CEPO would like to thank Jamil Asselah MD, Montreal General Hospital (MUHC); Amélie Chartier B.Pharm./M.Sc./BCOP, Montreal General Hospital (MUHC); Renée Simon MD, Hôpital Charles LeMoyne; Dominique Synnott MD, Hôpital du Sacré-Cœur de Montréal and Lucie Vaillancourt MD, Hôpital du St-Sacrement (CHU de Québec) for their contribution as external reviewers for the original clinical practice guideline.

Disclosure The authors have no financial conflicts of interest to declare.

References

1. Comité Directeur de la Société Canadienne du Cancer. Statistiques Canadiennes sur le Cancer 2012. Société Canadienne du Cancer, Toronto
2. Boekhout AH, Beijnen JH, Schellens JH (2006) Symptoms and treatment in cancer therapy-induced early menopause. Oncologist 11(6):641–654. doi:10.1634/theoncologist.11-6-641
3. Debourdeau P, Bachelot T, Zammit C, Aletti M, Gallineau C, Gligorov J (2004) Treatment of hot flashes in women with a previous diagnosis of breast cancer. Bull Cancer 91(4):339–349
4. Dalal S, Zhukovsky DS (2006) Pathophysiology and management of hot flashes. J Support Oncol 4(7):315–320, 325
5. Carpenter JS (2001) The hot flash related daily interference scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. J Pain Symptom Manag 22(6):979–989
6. Hilditch JR, Lewis J, Peter A, van Maris B, Ross A, Franssen E, Guyatt GH, Norton PG, Dunn E (1996) A menopause-specific quality of life questionnaire: development and psychometric properties. Maturitas 24(3):161–175
7. Thirlaway K, Fallowfield L, Cuzick J (1996) The sexual activity questionnaire: a measure of women's sexual functioning. Qual Life Res 5(1):81–90
8. Wiklund I, Holst J, Karlberg J, Mattsson LA, Samsioe G, Sandin K, Uvebrant M, von Schoultz B (1992) A new methodological approach to the evaluation of quality of life in postmenopausal women. Maturitas 14(3):211–224
9. 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
10. Beral V (2003) Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 362(9382):419–427
11. Col NF, Hirota LK, Orr RK, Erban JK, Wong JB, Lau J (2001) Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. J Clin Oncol 19(8):2357–2363
12. von Schoultz E, Rutqvist LE (2005) Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. J Natl Cancer Inst 97(7):533–535. doi:10.1093/jnci/dji071
13. Holmberg L, Anderson H (2004) HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. Lancet 363(9407):453–455. doi:10.1016/S0140-6736(04)15493-7
14. Holmberg L, Iversen OE, Rudenstam CM, Hammar M, Kumpulainen E, Jaskiewicz J, Jassem J, Dobaczewska D, Fjosne HE, Peralta O, Arriagada R, Holmqvist M, Maenpaa J (2008) Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. J Natl Cancer Inst 100(7):475–482. doi:10.1093/jnci/djn058
15. 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
16. 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
17. 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. doi:10.1200/JCO.2010.33.1298
18. 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
19. 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. doi:10.1093/annonc/mdl478
20. 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
21. Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA, Halyard MY, Pruthi S, Novotny PJ, Rummans TA (2002) Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 20(6):1578–1583
22. 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
23. 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
24. 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. doi:10.1200/JCO.2009.26.6379
25. Kalay AE, Demir B, Haberal A, Kalay M, Kandemir O (2007) Efficacy of citalopram on climacteric symptoms. Menopause 14(2):223–229. doi:10.1097/01.gme.0000243571.55699.4a
26. 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

27. 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. doi:10.1200/JCO.2010.29.9230
28. Biglia N, Sgandurra P, Peano E, Marenco D, Moggio G, Bounous V, Tomasi Cont N, Ponzone R, Sismondi P (2009) Non-hormonal treatment of hot flushes in breast cancer survivors: gabapentin vs. vitamin E. Climacteric 12(4):310–318. doi:10.1080/13697130902736921
29. 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
30. 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
31. 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. doi:10.1200/JCO.2009.24.5647
32. 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
33. 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
34. 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
35. 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
36. 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
37. 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. doi:10.1200/JCO.2005.05.4296
38. 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
39. Hernandez Munoz G, Pluchino S (2003) Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer. Maturitas 44(Suppl 1):S59–S65
40. 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
41. Loibl S, Lintermans A, Dieudonne AS, Neven P (2011) Management of menopausal symptoms in breast cancer patients. Maturitas 68(2):148–154. doi:10.1016/j.maturitas.2010.11.013
42. Boutet G (2012) Management of hot flushes for breast cancer survivors. Gynecol Obstet Fertil 40(4):241–254. doi:10.1016/j.gyobfe.2012.02.015
43. Clemons M, Clamp A, Anderson B (2002) Management of the menopause in cancer survivors. Cancer Treat Rev 28(6):321–333
44. 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
45. Pal (2010) CYP2D6 testing falls short as predictor of adjuvant tamoxifen efficacy http://www.cancernetwork.com/conference-reports/sabcs2010/content/article/10165/1756542. Accessed 30 janvier 2012
46. National Institute for Clinical Excellence (2009) Early and locally advanced breast cancer: diagnosis and treatment. National Collaborating Centre for Cancer
47. National Comprehensive Cancer Network (2011) NCCN Guidelines Version 2.2011 Breast cancer
48. Hickey M, Saunders C, Partridge A, Santoro N, Joffe H, Stearns V (2008) Practical clinical guidelines for assessing and managing menopausal symptoms after breast cancer. Ann Oncol 19(10):1669–1680. doi:10.1093/annonc/mdn353
49. Reid RL, Blake J, Abramson B, Khan A, Senikas V, Fortier M (2009) Menopause and osteoporosis update 2009. J Obstet Gynaecol Can 222:S1–S47
50. American Association of Clinical Endocrinologists (2006) Medical guidelines for clinical practice for the diagnostic and treatment of menopause
51. Chang YC, Parker J, Dooley WC (2006) Hot flash therapies in breast cancer survivors. Support Cancer Ther 4(1):38–48. doi:10.3816/SCT.2006.n.030
52. Tempfer CB, Froese G, Heinze G, Bentz EK, Hefler LA, Huber JC (2009) Side effects of phytoestrogens: a meta-analysis of randomized trials. Am J Med 122(10):939–946. doi:10.1016/j.amjmed.2009.04.018, e939
53. Velentzis LS, Woodside JV, Cantwell MM, Leathem AJ, Keshtgar MR (2008) Do phytoestrogens reduce the risk of breast cancer and breast cancer recurrence? What clinicians need to know. Eur J Cancer 44(13):1799–1806. doi:10.1016/j.ejca.2008.05.019
54. Limer JL, Speirs V (2004) Phyto-oestrogens and breast cancer chemoprevention. Breast Cancer Res 6(3):119–127. doi:10.1186/bcr781bcr781
55. Duffy C, Cyr M (2003) Phytoestrogens: potential benefits and implications for breast cancer survivors. J Womens Health (Larchmt) 12(7):617–631. doi:10.1089/154099903322404276
56. 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. doi:10.3109/00498254.2011.603385
57. 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. doi:10.3109/09513590.2010.538097
58. 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. doi:10.1139/Y07-111
59. 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
60. Borrelli F, Ernst E (2008) Black cohosh (Cimicifuga racemosa) for menopausal symptoms: a systematic review of its efficacy. Pharmacol Res 58(1):8–14. doi:10.1016/j.phrs.2008.05.008
61. Huntley A (2004) The safety of black cohosh (Actaea racemosa, Cimicifuga racemosa). Expert Opin Drug Saf 3(6):615–623
62. Collège des médecins du Québec et Ordre des pharmaciens du Québec (2004) Les produits de santé naturels: Pour mieux conseiller vos patients. document de référence 1–25
63. Cook DJ, Guyatt GH, Laupacis A, Sackett DL (1992) Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 102(4 Suppl):305S–311S