Management of menopausal symptoms in women with a history of breast cancer

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This guideline includes **Evidence Summaries** and **Recommendations** based on available evidence about the effectiveness and safety of different therapies for managing menopausal symptoms in women after breast cancer. The guideline provides health professionals and breast cancer patients with information to support decisions regarding the choice of particular therapies for the management of menopausal symptoms in the context of past or ongoing treatment for breast cancer.

Background

In Australia, the risk of a woman developing breast cancer in her lifetime is 1 in 8.[1] Women who have been treated for breast cancer are five times more likely to experience menopausal symptoms than women without breast cancer.[2] Recurrence of menopausal symptoms in postmenopausal women can follow the cessation of menopause hormone therapy, while the onset of menopausal symptoms can occur naturally in women approaching menopause at the time of diagnosis, or due to treatment-induced menopause (following chemotherapy or ovarian ablation/suppression) or the use of adjuvant endocrine therapy in premenopausal women.[3] A substantial proportion of Australian women diagnosed with breast cancer are diagnosed prior to menopause. In 2012, 35.7% of new cases of breast cancer were diagnosed in Australian women aged 20-54 years.[1] In a study of 578 Australian women with breast cancer who were seeking treatment for menopausal symptoms, 29% reported menopausal symptoms induced by chemotherapy, while 25% reported having menopausal symptoms induced by other treatments such as radiation, endocrine therapy, oophorectomy or hysterectomy.[4]

Menopausal symptoms in women whose symptoms are induced by breast cancer treatment are more severe than in women experiencing "natural" menopause.[5] Management of menopausal symptoms in women with a history of breast cancer is confounded in that systemic menopause hormone therapy, which is efficacious, is generally contraindicated in this patient group, and in particular, women with hormone sensitive disease.[6]

Clinical practice guidelines on the management of breast cancer in younger women and the management of early breast cancer were published previously, and noted that premature menopause is an adverse effect of ovarian ablation.[7-9] Those guidelines specifically addressed the issue of early menopause and breast cancer, and provided information and strategies for managing and treating menopausal symptoms in younger women with breast cancer. The aim of the current guideline is to provide evidence-based recommendations on the management of menopausal symptoms in all women (regardless of age) who have been treated for breast cancer.

Grading of Clinical Practice Recommendations

The recommendations included in this guideline are based on the summaries of evidence for the management of menopausal symptoms in women with a history of breast cancer. Practice Points and supporting information are also provided. Practice Points are based on expert opinion when the evidence to make a recommendation is insufficient or when the evidence is outside the scope of the systematic review.

All recommendations have been graded using the National Health and Medical Research Council (NHMRC) FORM methodology.[10] The NHMRC grades (A-D) assigned to the recommendations are intended to indicate the strength of the body of evidence underpinning the recommendations (refer to Table 1). Appendix 1 provides further detail of the NHMRC FORM grading methodology and the process undertaken in the grading of all recommendations contained in this guideline. See also Appendix 2 for Evidence summaries underpinning all recommendations.

Table 1: Definition of NHMRC grades of recommendations[10, 11]

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Clinical Practice Recommendations and Practice Points

The recommendations are based on evidence statements that were developed based on a body of evidence primarily including studies in women with a history of breast cancer, but also including additional studies in the general female menopausal population. Where evidence is lacking, expert opinion has been used to provide practice points.

As a general principle these guidelines support a step-wise approach based on relative safety of the implementation of the Recommendations, with regard to the specific menopausal symptoms experienced by a woman. Accordingly, the Recommendations presented first are those for non-pharmacological therapies, followed by Recommendations for pharmacological therapies. Recommendations regarding the use of hormone therapies are presented last, reflecting the fact that hormone therapies should be reserved for severe symptoms, unresponsive to non-hormonal therapies.

The following table provides links to the individual recommendations and practice points for the management of menopausal symptoms, which are listed below.

	Vasomotor Symptoms	Sleep disturbance	Vulvovaginal symptoms and sexual function
Non-pharmacological therapies	Cognitive behavioural therapy	Cognitive behavioural therapy	Non-hormonal vaginal gels
	Yoga	Relaxation therapy	Cognitive behavioural therapy
	Acupuncture	Hypnotherapy	Non-hormonal vaginal moisturisers
	Hypnotherapy	Acupuncture	
	Exercise	Vitamin E	Vaginal lubricants
	Black cohosh	Isoflavones	
	Homeopathy		
	Magnetic therapy		
	Omega-3 supplementation		
	Phytoestrogens		
Pharmacological	Venlafaxine	Desvenlafaxine	Topical lidocaine

therapies	Paroxetine Escitalopram Desvenlafaxine Clonidine Gabapentin Antidepressants Bupropion	Paroxetine Zolpidem Gabapentin	Ospemifene
Hormonal therapies	Menopause hormone therapy Tibolone Compounded hormones		Vaginal oestrogens Testosterone

Non-pharmacological therapies

Vasomotor symptoms

Number	Recommendation	Grade	Related evidence summaries
1	Purpose-designed cognitive behavioural therapy can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer.	C	ES8 ES41
2	Yoga can be considered for the management of vasomotor symptoms and sleep disturbance in women with a history of breast cancer noting there is inconsistent evidence regarding its effectiveness.	D	ES12 ES23 ES43

Number	Recommendation	Grade	Related evidence summaries
			ES53
3	Acupuncture and electro-acupuncture can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer noting there is inconsistent evidence regarding their effectiveness.	D	ES10 ES45
4	Purpose-designed hypnotherapy can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer.	D	ES9
5	Black cohosh is not recommended for the management of vasomotor symptoms in women with a history of breast cancer due to evidence that it is not effective.	B	ES13 ES48
6	Homeopathy is not recommended for the management of vasomotor symptoms in women with a history of breast cancer due to evidence that it is not effective.	B	ES14
7	Magnetic therapy is not recommended for the management of vasomotor symptoms in women with a history of breast cancer due to evidence that it is not effective.	C	ES16
8	Omega-3 supplementation is not recommended for the management of vasomotor symptoms in women with a history of breast cancer due to evidence that it is not effective.	C	ES47
9	Phytoestrogens are not recommended for the management of vasomotor symptoms as the efficacy and long-term safety in women with a history of breast cancer has not been established.	D	ES15 ES46
A	There is evidence that exercise has no effect on vasomotor symptoms in a general population, although there are other benefits of physical activity for women with a history of	Practice point	ES42 ES52

Number	Recommendation	Grade	Related evidence summaries
	breast cancer.		

Sleep disturbance

Number	Recommendation	Grade	Related evidence summaries
10	Purpose-designed cognitive behavioural therapy can be considered for the management of sleep disturbance in women with a history of breast cancer.	C	ES22
11	Relaxation therapy can be considered for the management of sleep disturbance in women with a history of breast cancer.	C	ES54
12	Purpose-designed hypnotherapy can be considered for the management of sleep disturbance in women with a history of breast cancer.	C	ES22
13	Acupuncture can be considered for the management of sleep disturbance in women with a history of breast cancer.	C	ES23
14	Vitamin E is not recommended for the management of sleep disturbance in women with a history of breast cancer due to evidence that it is not effective.	C	ES24
15	Isoflavones are not recommended for the management of sleep disturbance in women with a history of breast cancer due to evidence that they are not effective.	C	ES55

Vulvovaginal symptoms and sexual function

Number	Recommendation	Grade	Related evidence summaries
16	Non-hormonal vaginal gels can be considered for the treatment of vulvovaginal symptoms in women with a history of breast cancer.	C	ES27

Number	Recommendation	Grade	Related evidence summaries
17	Purpose-designed cognitive behavioural therapy can be considered for improving sexual function in women with a history of breast cancer.	C	ES28
B	Non-hormonal vaginal moisturisers can be considered for the treatment of vulvovaginal symptoms in women with a history of breast cancer.	Practice point	
C	Water-based or silicone-based vaginal lubricants can be used to enhance the comfort and ease of sexual intercourse.	Practice point	

Pharmacological therapies

Vasomotor symptoms

Number	Recommendation	Grade	Related evidence summaries
18	Venlafaxine (37.5 - 75 mg/day) can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer.	A	ES3 ES31
19	Paroxetine (10 - 20 mg/day) can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer who are not receiving tamoxifen. This recommendation is not generalisable to other SSRIs as there is insufficient evidence in women with a history of breast cancer that they have comparable effects on vasomotor symptoms.	B	ES2

Number	Recommendation	Grade	Related evidence summaries
	Note: Paroxetine interacts with tamoxifen and reduces the serum concentration of tamoxifen and metabolites.		
20	Escitalopram (10 - 20 mg/d) can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer, based on evidence from a general population of menopausal women. Note: Escitalopram may reduce the efficacy of tamoxifen by slowing metabolism to the active form. There is little evidence for clinical concern resulting from their concomitant use.	B	ES30
21	Desvenlafaxine (100 - 150 mg/d) can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer, based on evidence from a general population of menopausal women. Note: Desvenlafaxine may alter the serum concentration of tamoxifen and metabolites. There is little evidence for clinical concern resulting from their concomitant use.	B	ES32
22	Clonidine (0.10 - 0.15 mg/day) can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer.	B	ES3 ES5
23	Gabapentin (300 - 900 mg/day) can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer.	C	ES6
24	Bupropion is not recommended for the management of menopausal symptoms in women with a history of breast cancer due to	C	ES1 ES25

Number	Recommendation	Grade	Related evidence summaries
	evidence that it is not effective.		
D	The doses of antidepressants used for the management of vasomotor symptoms are not generally associated with increases in adverse sexual symptoms.	Practice point	ES25 ES57

Sleep disturbance

Number	Recommendation	Grade	Related evidence summaries
25	Desvenlafaxine (100 - 150 mg/d) can be considered for the management of sleep disturbance in women with a history of breast cancer, based on evidence from a general population of menopausal women. Note: Desvenlafaxine may alter the serum concentration of tamoxifen and metabolites. There is little evidence for clinical concern resulting from their concomitant use.	B	ES50
26	Paroxetine (10 - 20 mg/day) can be considered for the management of sleep disturbance in women with a history of breast cancer who are not receiving tamoxifen. This recommendation is not generalisable to other SSRIs as there is insufficient evidence that they have comparable effects on sleep disturbance. Note: Paroxetine interacts with tamoxifen and reduces the serum concentration of tamoxifen and metabolites.	C	ES17

Number	Recommendation	Grade	Related evidence summaries
27	The addition of zolpidem (10 mg/d) to an SSRI or SNRI can be considered for the management of sleep disturbance for women with a history of breast cancer.	C	ES19
28	Gabapentin (300 - 900mg/d) can be considered for the management of sleep disturbance in women with a history of breast cancer.	C	ES20
E	Gabapentin doses of up to 1200 mg/day can be considered for the alleviation of sleep disturbance in women with a history of breast cancer.	Practice point	

Vulvovaginal symptoms and sexual function

Number	Recommendation	Grade	Related evidence summaries
29	Topical lidocaine treatments to the vulvovaginal area can be considered for women with a history of breast cancer experiencing dyspareunia. Note: The treatment used in the included study was a 4% lidocaine solution applied to the vulvar vestibule for three minutes, followed by application of a silicone lubricant.	C	ES27
30	Ospemifene is not recommended for the management of vulvovaginal symptoms as the efficacy and long-term safety in women with a history of breast cancer has not been established.	C	ES65

Hormonal therapies

Vasomotor symptoms

Number	Recommendation	Grade	Related evidence summaries
31	Systemic menopause hormone therapy (oestrogen-only or combined oestrogen and progestogen) should generally be avoided in women with a history of breast cancer because it may increase the risk of new or recurrent breast cancer. Menopause hormone therapy may be considered in exceptional cases for women with a history of breast cancer with severe, intractable vasomotor symptoms. In these cases the potential risks and benefits should be discussed with the treatment team, and treatment should only proceed with the informed consent of the woman and at the lowest effective dose for that woman.	B	ES7 ES21 ES26 ES29 ES34 ES35 ES37 ES38 ES58 ES62
32	Tibolone should be avoided in women with a history of breast cancer because it increases the risk of new and recurrent breast cancer. Tibolone may be considered in exceptional cases for women with a history of breast cancer with severe, intractable vasomotor symptoms. In these cases the potential risks and benefits should be discussed with the treatment team, and treatment should only proceed with the informed consent of the woman and at the lowest effective dose for that woman.	B	ES7 ES21 ES26 ES29 ES33 ES51 ES61 ES67
33	Compounded hormones ('bioidentical' hormones) are not recommended for the management of menopausal symptoms in women with a history of breast cancer because the evidence of their effect is inconsistent and their safety after breast cancer is not known.	C	ES40

Number	Recommendation	Grade	Related evidence summaries
	Note: Compounded hormones are systemically absorbed and may contain high levels of sex steroids which may increase the risk of new or recurrent breast cancer.		

Vulvovaginal symptoms and sexual function

Number	Recommendation	Grade	Related evidence summaries
34	Vaginal oestrogens can be considered for the management of persistent vulvovaginal symptoms in women with a history of breast cancer who are non-responsive to non-hormonal vaginal gels or lubricants. A discussion of the potential risks and benefits between the woman and her treating team is recommended. Note: Vaginal oestrogen may be systemically absorbed. For women taking Aromatase Inhibitors this may result in measurable increases in circulating oestrogens. The clinical significance of systemic absorption is uncertain.	C	ES63
35	Exogenous testosterone is not recommended as a treatment to improve sexual function as the efficacy and long-term safety in women after breast cancer has not been established.	C	ES59 ES60 ES66

Summary of Evidence - Methodology

A Cancer Australia systematic review on the management of menopausal symptoms in women with a history of breast cancer was undertaken based on evidence published between January 2001 and November 2015. A systematic literature search was conducted in PubMed, Medline, EMBASE, PsychINFO, CINAHL and the Cochrane Library. A search of key menopause organisations, guidelines organisations, clinical trial websites and conference websites was also conducted.

This systematic review focused on evidence for the management of menopausal symptoms in the specific subgroup of women with a history of breast cancer. The systematic review did not include studies on the management of vasomotor symptoms in men who have a history of breast cancer. Outcome measures of interest were improvement or reduction of menopausal symptoms including vasomotor symptoms (hot flushes and/or night sweats); sleep disturbances; vulvovaginal symptoms including vaginal dryness, dyspareunia and sexual function; as well as psychological wellbeing, global quality of life, breast cancer recurrence and adverse events.

A total of 4157 citations were identified for review. Following application of the exclusion criteria, first to titles and abstracts, and then to full articles, and excluding studies with ≤ 10 participants in any one treatment arm, a total of 45 studies (41 RCTs, 1 sub-study and 3 updates) were identified as eligible. These citations addressed the primary research question: What is the effectiveness of interventions for the management of menopausal symptoms in women who have received treatment for breast cancer?

Following review of the evidence, it was revealed that a number of interventions of interest had no RCT evidence available specifically in the population of women who had received treatment for breast cancer. Interventions considered to be of interest were the antidepressants escitalopram and desvenlafaxine, the male hormone testosterone, and the menopausal hormone therapies vaginal oestrogen and compounded hormones (often referred to as 'bioidentical' hormones). Thus, an additional systematic review was undertaken to identify evidence for these interventions in the general female menopausal population, with available evidence from January 2001 to November 2015.

A systematic literature search was conducted in PubMed, Medline, EMBASE, PsychINFO and the Cochrane Library to identify relevant systematic reviews. A total of 589 citations were identified for review. Following application of the exclusion criteria, first to titles and abstracts, and then to full articles, a total of six relevant systematic reviews were identified: two for testosterone and one each for the other interventions. These citations addressed a secondary research question: What is the effectiveness of escitalopram, desvenlafaxine, testosterone, vaginal oestrogen and compounded hormones ('bioidentical hormones') for the management of menopausal symptoms in the general female menopausal population?

After careful consideration, it was recognised that clinical trial evidence from a general female menopausal population was generalisable to a breast cancer population. Consequently the Supplementary Evidence Review included studies of women experiencing menopausal symptoms in the general population treated with the same interventions considered in the primary Systematic Review with the addition of the interventions with no available evidence in the breast cancer population (escitalopram, desvenlafaxine, testosterone, vaginal oestrogen, and compounded hormones). The Supplementary Evidence Review supplements the evidence found in the Primary Systematic Review from the breast cancer population. Both of

these reviews support and inform the development of this clinical practice guideline.

Evidence Summaries were drafted based on the body of evidence identified for this guideline and these have been used to grade each recommendation. Of note, in both the Primary Systematic Review and Supplementary Evidence Review the studies on depression, anxiety, mood, global quality of life and mental health were of poor quality and the evidence was poorly reported. Consequently, for these symptoms no Evidence Summaries were developed in view of the poor quality of the studies: these symptoms were reported as secondary outcomes and the dosages of psychotropic medications used were below that needed to treat mental health conditions. Therefore for this guideline no recommendations have been made for the symptoms of depression, anxiety, mood, global quality of life and mental health.

Summary of Evidence - Introduction

There are a wide range of symptoms associated with menopause. While some of these appear to have a direct link with menopause, such as vasomotor symptoms and vulvovaginal symptoms, others may be linked to psychosocial factors such as age and social class, or to the occurrence of other menopausal symptoms. In a survey of 682 pre-, peri- and post-menopausal women, the strongest associations between menopausal symptoms were seen between depression, anxiety and sleep, cognitive difficulties and anxiety, and vasomotor, somatic and sleep symptoms.[12]

In a study of 200 women who had received treatment for breast cancer in the previous five years, hot flushes/sweating and sleep difficulties were the most commonly reported menopausal symptoms (85% and 86%, respectively).[13] In a study of 578 Australian women with breast cancer who were seeking treatment for menopausal symptoms, 65% reported moderate to severe hot flushes. Other symptoms commonly rated as moderate to severe included night sweats, difficulty sleeping and fatigue (58% each), and loss of libido (55%). Six percent of women were troubled by all five symptoms, while 9% were extremely troubled by four of the five symptoms.[4] Overall quality of life and the partner's quality of life have been shown to be significantly associated with all menopausal symptoms, with the highest correlations seen for vasomotor symptoms, depression, vaginal dryness and sexual problems.[13]

Summary of Evidence - Vasomotor symptoms

Vasomotor symptoms are the most common menopausal symptoms in women after breast cancer and include hot flushes and night sweats.

Thirty-nine studies (36 RCTs with three updated analyses or sub-studies) out of the 45 studies included in the primary systematic review reported on management of vasomotor symptoms in women with a history of breast cancer. Of these studies, all assessed the frequency, severity and/or problems/bother of hot flushes, with four trials also reporting on sweating and/or night sweats.

Twenty two systematic reviews and five RCTs identified in the supplementary Evidence Review reported the effect of one or more interventions on vasomotor symptoms.

Vasomotor symptoms: Pharmacological interventions

Antidepressants

The results for the selective serotonin reuptake inhibitors (SSRIs) as a class were inconsistent and based on short-term studies only. One RCT (with a low risk of bias) in **women after breast cancer** found that paroxetine (10 or 20 mg/d for 4 weeks) significantly reduced hot flush frequency and severity during treatment compared with placebo.[14] However, three RCTs (with a low to moderate risk of bias) found that neither fluoxetine (20 mg/d for 4 weeks)[15] nor sertraline (25 to 100 mg/d for 4-6 weeks)[16, 17] had a consistent effect on hot flushes compared with placebo. [ES2]

In a population of **peri- and postmenopausal women**, two RCTs in a systematic review found that the SSRI escitalopram (10-20 mg/d for 8 weeks) significantly reduced hot flush frequency compared to placebo.[18] One of these RCTs (with a low risk of bias) was identified in one pooled analysis (with at least 14 bothersome vasomotor symptoms per week) found that 8 weeks of escitalopram (10 mg/d) significantly reduced vasomotor symptom frequency and bother compared with placebo.[19] [ES30]

Venlafaxine was the only serotonin-norepinephrine reuptake inhibitor (SNRI) assessed in the population of women experiencing menopausal symptoms after breast cancer. Two studies showed that venlafaxine significantly reduced hot flush frequency and severity in **women after breast cancer** compared with placebo: one RCT (with a low risk of bias) found that 12 weeks of venlafaxine at 75 mg/d (slow release) significantly reduced hot flush frequency and severity compared with placebo,[20] while a second study (with a moderate risk of bias) found that 14 weeks of venlafaxine at 37.5mg/d significantly reduced hot flush frequency and severity compared with placebo.[21] [ES3]

Venlafaxine was also found to have greater efficacy at reducing the frequency and severity of hot flushes than clonidine, and equivalent efficacy at reducing hot flushes compared with gabapentin and acupuncture. Three RCTs (with a low to moderate risk of bias) found that venlafaxine or clonidine reduced hot flush frequency and/or severity from baseline,[20, 22, 23] and in one RCT the improvement with venlafaxine was significantly greater than with clonidine.[23] One RCT (with a moderate risk of bias) found that 4 weeks of venlafaxine or gabapentin were associated with equivalent reductions in hot flash scores,[24] while another RCT (with a moderate risk of bias) found 12 weeks of venlafaxine or a course of acupuncture were associated with similar reductions in hot flash frequency and severity.[25] [ES3]

One RCT (with an low risk of bias) identified in a pooled analysis of **peri- and postmenopausal women** (with at least 14 bothersome vasomotor symptoms per week) found that 8 weeks of low-dose venlafaxine XR (37.5 mg/d for the first week, then 75 mg/d) significantly reduced vasomotor symptom frequency and bother compared with placebo.[19] [ES31]

One RCT (with a low risk of bias) **in menopause transition and postmenopausal women** found a significant reduction in vasomotor symptoms frequency and severity with venlafaxine (37.5mg/d for 1 week, then 75mg/d for 7 weeks) and with low dose oestradiol (0.5mg/d for 8 weeks) compared to placebo. Reduction of vasomotor symptoms frequency was greater in the low estradiol group (53%) compared to the venlafaxine group (48%). Reduction in vasomotor symptoms bother was found to be significant with the low oestradiol group compared to placebo, but not significant with the venlafaxine group compared to placebo.[19, 26] [ES35]

In a population of **postmenopausal women**, six RCTs in a systematic review found the SNRI desvenlafaxine (100 or 150 mg/d for 12 weeks) significantly reduced hot flush frequency compared to placebo[27] Seven RCTs (with an unclear risk of bias) identified in one Systematic Review (with a moderate risk of bias) **in postmenopausal women** (with at least seven moderate to severe hot flushes per day) found that 12 or more weeks of desvenlafaxine (≥100 mg/d) significantly reduced hot flush frequency and severity compared with placebo. Higher daily doses of 150mg and 200mg were associated with more adverse events and drug discontinuation.[28] [ES32]

One RCT (with a moderate risk of bias) in **women after breast cancer** found that 4 weeks of the atypical antidepressant bupropion (300 mg/day) had no statistically significant effect on the severity of hot flushes compared with placebo.[29] [ES1]

Sedatives

One RCT (with a moderate risk of bias) in **women after breast cancer** found that 5 weeks of SSRI/SNRI augmentation with zolpidem (10 mg/d) had no statistically significant additional effect on vasomotor symptoms compared with SSRI/SNRI augmentation with placebo.[30] [ES4]

Antihypertensives

One RCT (with a low risk of bias) in **women after breast cancer** found that the α-2 adrenergic receptor agonist clonidine (0.1 mg/d) significantly reduced the frequency and severity of hot flushes relative to placebo.[20] However, two RCTs (with a moderate risk of bias) found the reduction in vasomotor symptoms observed with clonidine was equivalent or less than the reduction observed with 75mg/d slow-release venlafaxine.[22, 23] [ES5]

Anticonvulsants

One RCT (with a moderate risk of bias) in **women after breast cancer** found that 4-8 weeks of the γ-aminobutyric acid analogue gabapentin (900 mg/d) was associated with a reduction in hot flush frequency and severity compared with placebo.[31] In addition, three RCTs (two with a moderate risk of bias and one with a high risk of bias) found that 4-12 weeks of gabapentin (900mg/d or 300mg/d) was associated with a significant reduction in hot flush frequency and severity compared to baseline.[24, 32, 33] In one of these RCTs, the effect size was equivalent to that observed with venlafaxine,[24] while in the other, the effect size was less than that observed with megestrol acetate.[32] [ES6]

Vasomotor symptoms: Hormonal interventions

Menopause hormone therapy

One RCT (with a low risk of bias) in **women after breast cancer** found that tibolone (2.5 mg/d) for up to 2.75 years significantly reduced the frequency and severity of hot flushes compared to placebo; however, tibolone was also shown to increase the risk of breast cancer recurrence.[34, 35]. One RCT (with a high risk of bias) of menopause hormone therapy (sequential or continuous combined oestrogen/progestogen) versus electro-acupuncture reported improvements with both interventions but did not report between-group differences.[36, 37] [ES7]

Four RCTs (with a high risk of bias) identified in a Systematic Review (with a low risk of bias) **in postmenopausal women** (including women surgically treated for breast cancer) found that tibolone (2.5 mg/d) significantly reduced hot flush frequency compared with placebo; however, tibolone was found to be less effective than hormone therapy.[38] [ES33]

Nine RCTs (with a low risk of bias) identified in a Systematic Review (with a low risk of bias) **in peri- and postmenopausal women** (not including women with breast cancer) found that oral hormone therapy (oestrogen and combined oestrogen/progestogen therapy) significantly reduced the frequency and severity of hot flushes compared with placebo.[39] [ES34]

Seven RCTs (with a low risk of bias) and two RCTs (with a high risk of bias) identified in a Systematic Review (with a low risk of bias) **in postmenopausal women** (at least seven hot flushes per day and/or at least 50 hot flushes per week) found that transdermal low-dose oestradiol (< 0.05 mg/d) significantly reduced hot flush frequency compared with placebo; greater reductions were seen with the higher dose range (0.029 mg/d to 0.045 mg/d) than the lower doses.[40] [ES37]

Five RCTs (with an unknown risk of bias) identified in a Systematic Review (with a moderate risk of bias) **in postmenopausal women** (natural or surgically induced) found that transdermal oestradiol gel preparations (0.25-1.5 mg/day) significantly reduced hot flush frequency and severity compared with placebo. The greatest effect was seen for dosing around 1mg/day but this also caused the greatest number of adverse events.[41] [ES38]

Compounded hormones

Compounded hormones are often referred to as 'bioidentical' hormones. In a population of **postmenopausal women**, three RCTs identified in a Systematic Review (with a moderate risk of bias) found inconsistent evidence of effect of compounded progesterone cream on vasomotor symptoms. One of the RCTs found a significant improvement in vasomotor symptoms severity for a compounded progesterone cream compared to placebo. Two of the RCTs found no significant difference in vasomotor symptoms severity between commercially available progesterone creams and placebo.[42] [ES40]

Other hormone therapies

Five RCTs (with a low risk of bias) identified in a Systematic Review (with a low risk of bias) **in postmenopausal women** with vulvovaginal dyspareunia and atrophy found that at 12 weeks, ospemifene (60 mg/d) significantly increased hot flushes compared with placebo.[43] [ES36]

In a population of **peri- and postmenopausal women**, two RCTs in a systematic review found that the addition of testosterone to menopause hormone therapy had no effect on vasomotor symptoms.[44] [ES39]

Vasomotor symptoms: Psychological and physical interventions

Cognitive behavioural therapy

One RCT (with a moderate risk of bias) in **women after breast cancer** found that purpose-designed cognitive behavioural therapy (CBT, 90min per week for 6 weeks) versus usual care had no effect on the frequency of hot flushes, but reduced the problem rating of hot flushes and night sweats.[45] In addition, another RCT (with a moderate risk of bias) found that purpose-designed group CBT in combination with physical exercise (2.5 to 3 hours per week) versus no intervention reduced the problem rating of hot flushes and night sweats.[46] [ES8]

One RCT (with an unknown risk of bias) identified in a Systematic Review (with a moderate risk of bias) **in peri- and postmenopausal women** found that CBT significantly reduced hot flushes and night sweats compared with no intervention.[47] [ES41]

Hypnotherapy

One RCT (with a moderate risk of bias) in **women after breast cancer** reported that a purpose-designed hypnotherapy protocol delivered once/week for 5 weeks reduced hot flush frequency and severity compared with no treatment.[48] [ES9]

Acupuncture

One RCT (with a low risk of bias) in **women after breast cancer** comparing acupuncture (needle inserted 0.5-3cm deep for 30min) to sham acupuncture (needle inserted 2-3mm deep for 30min) reported a reduction in frequency and severity of hot flushes.[49] However, two RCTs (with a moderate risk of bias) found no difference between acupuncture (needle inserted 5–20 mm deep for 20min or 0.25 to 0.5 inches deep) and sham acupuncture, in terms of frequency and severity of hot flushes.[50, 51] One RCT (with a low risk of bias) reported acupuncture (for 15-20min once a week) reduced the nuisance of hot flushes, but did not report between-group differences compared to sham acupuncture or no treatment.[52] [ES10]

Three RCTs (with a moderate to high risk of bias) comparing acupuncture with relaxation,[53, 54] menopause hormone therapy (sequential or continuous combined oestrogen/progestogen)[36, 37] or venlafaxine[25] did not report between-group differences. [ES10]

One RCT (with a moderate risk of bias) compared the effect of electro-acupuncture or Gabapentin with Sham acupuncture or placebo, for 8 weeks. Acupuncture produced a significantly greater placebo effect than gabapentin; but reported no statistically significant difference in hot flush frequency and severity compared to sham acupuncture.[55] [ES10]

Eight RCTs (with a high risk of bias) identified in a Systematic Review (with a low risk of bias) in peri- and postmenopausal women (including women with breast cancer) found that acupuncture significantly reduced hot flush severity, but not frequency, compared with sham acupuncture. Three RCTs (with a high risk of bias)

identified in the same Systematic Review found that hormone therapy significantly reduced hot flush frequency, but not severity, compared with acupuncture.[56] [ES45]

One additional RCT (with a low risk of bias) was published after the end of the literature search period. This trial enrolled **peri- and postmenopausal women** with no history of breast cancer and found no statistically significant difference in improvement in hot flush frequency and severity between acupuncture and sham acupuncture.[57] [ES45]

Relaxation therapy

One RCT (with a low risk of bias) in **women after breast cancer** reported reduced hot flush frequency and severity during relaxation therapy at one month (one hour session and a 20min tape to use once a day) versus no relaxation therapy.[58] Another RCT (with a high risk of bias) compared relaxation therapy with electro-acupuncture therapy but did not report between group differences.[53] [ES11]

Four RCTs (with a high risk of bias) identified in a Systematic Review (with a low risk of bias) **in peri- and postmenopausal women** (including women with breast cancer) found that 12 weeks of relaxation techniques did not significantly reduce hot flush frequency or severity compared with placebo/no treatment or acupuncture/superficial needling.[59] [ES44]

Yoga

One RCT (with a moderate risk of bias) in **women after breast cancer** found that an 8 week course of a "Yoga of awareness" program reduced the frequency and severity of hot flushes compared with no intervention.[60] [ES12]

In a population of peri- and postmenopausal **women after breast cancer**, one RCT (with moderate risk of bias) found that yoga with meditation (Hatha yoga, 90min/week for 12 weeks) significantly improved total menopausal symptoms compared to usual care.[61] [ES12]

One RCT (with a low risk of bias) **in menopause transition and postmenopausal women** found that yoga (90min weekly class for 12 weeks) did not significantly reduce vasomotor symptom frequency and bother compared with usual activity.[19, 62] One RCT (with an unknown risk of bias) identified in a Systematic Review (with a moderate risk of bias) **in menopausal women** (excluding trials exclusively conducted in women with breast cancer) found that 8 weeks of integrated yoga therapy (1 h/day, 5 days/week) significantly reduced vasomotor symptoms compared with exercise.[63] One additional RCT (with a high risk of bias) identified in a Systematic Review (with a low risk of bias;) **in peri- and postmenopausal women** (excluding women with breast cancer) found that there was no significant difference between yoga (up to 12 sessions) and exercise in reducing vasomotor symptoms.[64] [ES43]

Exercise

One RCT (with a low risk of bias) **in menopause transition and postmenopausal women** found that exercise (3 times per week of either treadmill, elliptical trainer, or stationary bicycle for 12 weeks) had no significant reduction in vasomotor symptoms frequency and bother compared to the usual activity control group.[65] A

meta-analysis of three RCTs (one low risk of bias, two with a high risk of bias), including Sternfeld et al (2014), identified in a Systematic Review (with a low risk of bias) **in peri- and postmenopausal women** (excluding women with breast cancer) found that exercise (of any type) did not significantly reduce the frequency of hot flushes/night sweats compared with no active treatment.[64] One RCT (with an unknown risk of bias) identified in a Systematic Review (with a moderate risk of bias) **in menopausal women** (excluding trials exclusively conducted in women with breast cancer) found that exercise did not significantly reduced vasomotor symptoms compared with no exercise or oestradiol.[63] [ES42]

Vasomotor symptoms: Complementary therapies

Black cohosh

Two RCTs (with a low to moderate risk of bias) in **women after breast cancer** reported no difference in the frequency or severity of hot flushes between black cohosh cohosh (1 capsule, Cimicifuga racemosa 20 mg BID) and placebo.[66, 67] Another RCT (with a high risk of bias) reported black cohosh (1 capsule, Cimicifuga racemosa, CR BNO 1055) plus tamoxifen (20mg/d) significantly reduced the frequency of hot flushes from baseline while tamoxifen alone did not, but between group differences were not reported.[68] [ES13]

Three RCTs (with a moderate risk of bias) identified in a Systematic Review (with a low risk of bias) **in peri- and postmenopausal women** (including women with breast cancer) found that black cohosh (40 mg/d) did not reduce vasomotor symptom frequency or bother compared with placebo.[69] [ES48]

Homeopathy

Two RCTs (with a low and high risk of bias) in **women after breast cancer** found no effect of homeopathy versus placebo on hot flush frequency or severity.[70, 71] [ES14]

Phytoestrogens

Three RCTs (with a low to high risk of bias) in **women after breast cancer** found no effect of phytoestrogens (tablets, 114 mg of isoflavonids or soybean beverage or 235 mg of soy extract with 17.5 mg of Isoflavines 70mg/d) versus placebo on the Kupperman Index (which includes assessment of hot flushes) or the frequency or severity of hot flushes.[72-74] [ES15]

Fifteen RCTs (with an unknown risk of bias) identified in a Systematic Review (with a moderate risk of bias) **in peri- and early postmenopausal women** (with hot flushes and at least one co-occurring symptom) found an inconsistent benefit of soy and other isoflavones on vasomotor symptoms compared with placebo and other nutritional comparators.[75] [ES46]

Omega 3

One RCT (with a low risk of bias) in **menopause transition and postmenopausal women** found that 12 weeks of omega-3 supplement (1.8 grams daily: EPA; 425mg, DHA; 100mg, omega-3 90mg) did not significantly improve vasomotor symptoms frequency or bother compared to placebo.[19, 76] [ES47]

Magnetic therapy

One RCT (with a moderate risk of bias) in **women after breast cancer** found that 3 days of magnetic therapy (6 magnets on acupuncture pressure sites per participant) had no effect on the severity of hot flushes compared with placebo, while placebo was reported to have had a greater effect than magnetic therapy on frequency of hot flushes.[77] [ES16]

Summary of Evidence - Sleep disturbance

Sleep disturbance is a common menopausal symptom in women after breast cancer and includes poor quality of sleep, restless sleep, sleepiness, trouble sleeping, difficulty sleeping, interrupted sleep, unrefreshing sleep and insomnia.

Nineteen RCTs out of the 45 studies included in the primary systematic review reported sleep disturbance outcomes during treatment for menopausal symptoms in women after breast cancer. Only two studies had sleep disturbance as a primary outcome measure; all other studies reported sleep disturbance symptoms as a secondary outcome, or as an adverse event.

Five systematic reviews and three RCTs identified in the supplementary evidence review reported the effect of one or more interventions on sleep disturbance.

Sleep disturbance: Pharmacological interventions

Antidepressants

The results for SSRIs as a class were inconsistent. One RCT (with a low risk of bias) in **women after breast cancer** found that paroxetine (10 or 20 mg/d for 9 weeks) was associated with an improvement in sleep compared with placebo,[14] while another RCT (with a low risk of bias) in women after breast cancer with fluoxetine (20 mg/d for 9 weeks) did not report between-group differences for sleep disturbance compared with placebo.[15] [ES17]

In a population of **peri- and postmenopausal women**, one RCT in a systematic review found that the SSRI escitalopram (10-20 mg/d for 8 weeks) had no statistically significant effect on sleep disturbance compared to placebo.[18] [ES49]

Venlafaxine was the only SNRI assessed in the population of women experiencing menopausal symptoms after breast cancer. One RCT (with a moderate risk of bias) in **women after breast cancer** found no difference in sleep disturbance between venlafaxine 75 mg/d and placebo.[21] [ES18]

Three RCTs (one with a low risk of bias and two with a moderate risk of bias) compared venlafaxine with clonidine [20, 22, 23] and only one of the three studies found an improvement in sleep for venlafaxine compared with clonidine.[22] One additional RCT (with a moderate risk of bias) reported no statistical comparison for sleep disturbance between venlafaxine and acupuncture.[25] [ES18]

In a population of **postmenopausal women**, three RCTs in a systematic review found the SNRI desvenlafaxine (100 or 150 mg/d for 12 weeks) significantly reduced the number of night-time awakenings compared to placebo.[27] [ES50]

Sedatives

One RCT (with a moderate risk of bias) in **women after breast cancer** receiving an SSRI or SNRI for vasomotor symptoms found an improvement in sleep disturbance with 5 weeks augmentation with zolpidem (10 mg/d) compared with augmentation with placebo.[30] [ES19]

Anticonvulsants

One RCT (with a moderate risk of bias) in **women after breast cancer** reported that the γ-aminobutyric acid analogue gabapentin (300mg/d or 900mg/d) had no effect on sleep compared with placebo.[31] [ES20] One RCT (with a moderate risk of bias) reported that gabapentin (900mg/d for 4 weeks) also had no effect on sleep compared with venlafaxine (75mg/d for 4 weeks);[24] however, another RCT (with a moderate risk of bias) reported that gabapentin (900mg/d for 12 weeks) improved sleep quality compared with Vitamin E (800 IU/d for 12 weeks).[33] [ES20]

Sleep disturbance: Hormonal interventions

Menopause hormone therapy

One RCT (with a low risk of bias) in **women after breast cancer** found that tibolone (2.5mg/d) was associated with an improvement in sleep quality compared with placebo (LIBERATE study).[35] An earlier analysis from the LIBERATE study reported insomnia as an adverse event, but did not report between-group differences.[34] Another RCT (with a high risk of bias) found that menopause hormone therapy (oestradiol ± progestogen) improved sleep compared with no treatment.[78] [ES21]

One RCT (with a moderate risk of bias) assessed the effect of menopause hormone therapy (sequential or continuous combined oestrogen/progestogen) and acupuncture on sleep, and found that hormone therapy improved sleep relative to baseline, but did not report between-group differences.[37] [ES21]

One RCT (with a high risk of bias) identified in a Systematic Review (with a low risk of bias) **in postmenopausal women** (including women surgically treated for breast cancer) found that tibolone (2.5 mg/d for more than two years) did not reduce the frequency of insomnia compared with placebo.[38] [ES51]

Sleep disturbance: Psychological and physical interventions

Cognitive behavioural therapy

One RCT (with a moderate risk of bias) in **women after breast cancer** found that CBT (90min per week for 6 weeks) significantly improved sleep problems compared with usual care.[45] [ES22]

One RCT (with a low risk of bias) in **women after breast** reported a statistically significant improvement in sleep efficiency scores and sleep latency scores with cognitive behavioural therapy for insomnia (CBTI, 30-60min once a week for 6 weeks) compared to behavioural placebo treatment (BPT); but found no significant improvement on wake after sleep onset scores or number of awakenings with CBTI compared to BPT.[79] [ES22]

Hypnotherapy

One RCT (with a moderate risk of bias) in **women after breast cancer** found that hypnotherapy (once a week for 5 weeks) improved sleep compared with no treatment.[48] [ES22]

Relaxation therapy

One small RCT (with an unknown risk of bias) identified in a Systematic Review (with a moderate risk of bias) **in menopausal women** (excluding trials exclusively conducted in women with breast cancer) found that relaxation therapy significantly improved sleep symptoms compared with waitlist control.[63] [ES54]

Acupuncture

One RCT (with a low risk of bias) in **women after breast cancer** found that acupuncture significantly improved sleep compared with sham acupuncture or no treatment.[52] [ES23]

Yoga

One RCT (with a moderate risk of bias) in **women after breast cancer** found that yoga significantly improved sleep disturbance compared with no intervention.[60] [ES23]

One RCT (with an unknown risk of bias) identified in a Systematic Review (with a moderate risk of bias) **in menopausal women** (excluding trials exclusively conducted in women with breast cancer) found that yoga significantly improved sleep symptoms but there was no significant difference between the effect of yoga and exercise on sleep symptoms.[63] One RCT (with a low risk of bias;) **in menopause transition and postmenopausal women** found that yoga (90min weekly class for 12 weeks) significantly improved insomnia symptoms compared with usual activity.[19, 62] [ES53]

Exercise

Two RCTs (with an unknown risk of bias) identified in a Systematic Review (with a moderate risk of bias) **in menopausal women** (excluding trials exclusively conducted in women with breast cancer) found that physical activity/exercise had no significant effect on sleep symptoms.[63] One RCT (with a low risk of bias) in menopause transition and postmenopausal women found that exercise (3 times per week of treadmill, elliptical trainer, or stationary bicycle for 12 weeks) significantly improved sleep quality and insomnia symptoms compared to the usual activity control group.[19, 65] [ES52]

Sleep disturbance: Complementary therapies

Phytoestrogens

One RCT (with an unknown risk of bias) identified in a Systematic Review (with a moderate risk of bias) **in peri- and early postmenopausal women** (with hot flushes and at least one co-occurring symptom) found that an isoflavone combination significantly reduced insomnia at 12 weeks; other trials found that soy and other isoflavones did not significantly improve sleep symptoms.[75] [ES55]

Omega-3 fatty acids

One RCT (with a low risk of bias) in peri- and postmenopausal women reported no significant effect on sleep quality and insomnia with omega-3 fatty acid supplementation compared to placebo.[76] [ES56]

Vitamin E

One RCT (with a moderate risk of bias) in **women after breast cancer** found that Vitamin E (800 IU/d for 12 weeks) was inferior to gabapentin (900mg/d for 12 weeks) at reducing sleep disturbance.[33] [ES24]

Summary of Evidence - Vulvovaginal symptoms and sexual function

Changes in vulvovaginal symptoms are a common menopausal symptom in women after breast cancer and include vaginal dryness and atrophy, pain or discomfort during intercourse (vaginal symptoms or dyspareunia), sexual desire (libido), sexual activity (frequency or habit), sexual pleasure and orgasm.

Twelve RCTs (reported in 13 studies) out of the 45 studies included in the primary systematic review were identified that reported sexual functioning outcomes during treatment for vasomotor symptoms in women with a history of breast cancer. Only one pilot study assessed sexual functioning as a primary outcome measure, while all other studies reported sexual functioning as a secondary outcome or as an adverse event or side effect of treatment.

Eight systematic reviews and one RCT were identified in the supplementary Evidence review reported the effect of treatment on sexual function. As each systematic review reported the effects of a different intervention, they are described individually by intervention type.

Vulvovaginal symptoms and sexual function: Pharmacological interventions

Antidepressants

Neither the SSRIs nor an atypical antidepressant had an effect on sexual function. Three RCTs (two with a low and one with a moderate risk of bias) in **women after breast cancer** reported no difference after 4-12 weeks of treatment with bupropion 300 mg/d, fluoxetine 20 mg/d, or paroxetine 10-20 mg/d on sexual function compared with placebo.[14, 15, 29] [ES25]

Two RCTs (one with a low and one with a moderate risk of bias) reported no significant differences in sexual functioning for the SNRI venlafaxine compared with clonidine,[20, 22] while another RCT (with a moderate risk of bias) reported an increased difficulty achieving orgasm for venlafaxine (75mg/d) compared with gabapentin (300mg/d or 900mg/d).[24] [ES25]

In a population of **peri- and postmenopausal women**, one RCT in a systematic review found that the SSRI escitalopram (10-20 mg/d for 8 weeks) had no statistically significant effect on libido compared to placebo.[18] [ES57]

Vaginal gel

One RCT (with a low risk of bias) in **women after breast cancer** found that 12 weeks treatment with a vaginal pH-balanced gel was associated with a statistically significant improvement in a range of vaginal symptoms, compared with placebo.[80] [ES27]

Topical lidocaine

One RCT (with a low risk of bias) in **women after breast cancer** found that 8 weeks with topical lidocaine treatment (4% solution for 3 minutes) was associated with a statistically significant improvement in vulvovaginal symptoms including dyspareunia, compared to placebo.[81] [ES27]

Vulvovaginal symptoms and sexual function: Hormonal interventions

Menopause hormone therapy

One RCT (with a low risk of bias) in **women after breast cancer** found an improvement in sexual behaviour and vaginal dryness for tibolone (2.5 mg/d for 2.75 years) compared with placebo,[35] while two RCTs (with a high risk of bias) found inconsistent effects of menopause hormone therapy (oestradiol ± progestogen) on sexual enjoyment, sexual activity and discomfort compared with no treatment.[78, 82] [ES26]

One RCT (with a low risk of bias) in **menopause transition and postmenopausal women** found that 8 weeks of low-dose oestradiol (0.5mg/day) or venlafaxine (37.5mg/day for 1 week and 75mg/day for 7 weeks) did not significantly altered sexual function (measured with Female Sexual Function Index) compared to placebo; but venlafaxine significantly improved vaginal dryness compared to the placebo group.[83] [ES58]

Twenty seven RCTs (with a moderate risk of bias) identified in a systematic review (with a low risk of bias) **in postmenopausal women** found that menopause hormone therapy (oestrogen transdermal patch 0.014 mg/day; gel 0.87 g/d, gel 1.7 g/d, 2.6 g/d; oestrogen spray 150mcg/day or 300mcg/day; oestrogen vaginal ring 50mcg/day or 100mcg/day or conjugated equine estrogen 0.625mg plus medroxyprogesterone acetate 2.5mg daily; for 12 weeks) did not significantly improve sexual function (composite score) compared with control; but did show a small to moderate benefit in sexual function compared to control.[84] [ES62]

Four RCTs (with a high risk of bias) identified in a Systematic Review (with a low risk of bias) **in postmenopausal women** (including women surgically treated for breast cancer) found that tibolone (2.5 mg/d for more than two years) did not significantly reduce vaginal dryness or dyspareunia compared with placebo. [38] [ES61]

Vaginal oestrogen therapy

In a population of **postmenopausal women**, nineteen RCTs identified in a Systematic Review (with a low risk of bias) **in postmenopausal women** with vaginal atrophy found that at least three months of vaginally administered oestrogen rings, creams and tablets were equally effective at relieving the symptoms of vaginal atrophy, better than placebo.[85] Fourteen RCTs and prospective comparative studies (with a high risk of bias) identified in a Systematic Review (with a low risk of bias) in postmenopausal women with genitourinary syndrome of menopause (excluding women with breast cancer) found that vaginal oestrogen was more effective than placebo in the relief of vaginal dryness, itching, and dyspareunia.[86] [ES63]

Other hormone therapies

In a population of **peri- and postmenopausal women**, nine RCTs analysed in a Systematic Review (with a low risk of bias) found a statistically significant improvement in sexual function with testosterone in combination with menopause hormone therapy versus menopause hormone therapy alone.[44] [ES59]

Thirty five RCTs identified in a Systematic Review (with a low risk of bias) **in postmenopausal women** (with an unknown history of breast cancer) found a statistically significant improvement in sexual function with therapy containing testosterone versus therapy without testosterone.[87] [ES60]

Two RCTs (with a low risk of bias) identified in a Systematic Review (with a low risk of bias) **in postmenopausal women** with vulvovaginal dyspareunia and atrophy found that oral ospemifene (60 mg/d) significantly reduces dyspareunia compared with placebo.[43] Twenty seven RCTs (with a moderate risk of bias) identified in a systematic review (with a low risk of bias**) in postmenopausal women** found that selective oestrogen receptor modulators (SERMs) (bazedoxifene 20 mg alone or plus conjugated estrogens 0.45mg or 0.625mg daily; for 12 weeks) did not significantly improve sexual function (composite score) compared with control; but showed a small benefit in sexual function when compared with control.[84] [ES65]

Vulvovaginal symptoms and sexual function: Psychological and physical interventions

Cognitive behavioural therapy

One RCT (with a moderate risk of bias) in **women after breast cancer** found that CBT alone or in combination with physical exercise improved sexual function compared with wait list controls.[46] [ES28]

Hypnotherapy

One RCT (with a moderate risk of bias) in **women after breast cancer** found that a 5-week course of hypnotherapy had no statistically significant effect on the impact of hot flushes on sexuality compared with no treatment.[48] [ES28]

Vulvovaginal symptoms and sexual function: Complementary therapies

Phytoestrogens

Six RCTs (with a high risk of bias) identified in a Systematic review (with a moderate risk of bias) **in menopausal women** found that soy isoflavones had an uncertain effect on vaginal dryness and dyspareunia compared to placebo.[88] [ES64]

Summary of Evidence - Depression and anxiety

Twenty-four RCTs out of the 45 studies included in the primary systematic review reported on psychological outcomes (which included depression and anxiety) during treatment for menopausal symptoms in women with a history of breast cancer. Although 21 studies used validated instruments to measure different aspects of psychological wellbeing, only six used measures recommended for use in a breast cancer population.

No systematic reviews were identified in the supplementary evidence review that included reporting of depression or anxiety as an outcome of interest.

Due to the poor quality of the identified studies (e.g. study/outcome design, low statistical power, and inappropriate patient populations) formal Evidence Summaries have not been developed for depression and anxiety. However, a summary of the findings from the included studies is presented below.

Depression and anxiety: Pharmacological interventions

Antidepressants

Neither the SSRIs nor the atypical antidepressant bupropion had an effect on depression in **women after breast cancer**. Four RCTs found no statistically significant effect on depression, compared with placebo, for bupropion (300mg/d for 4 weeks, with a moderate risk of bias),[29] fluoxetine (20mg/d for 4 weeks, with a low risk of bias),[15] paroxetine (10mg/d for 4 weeks, with a low risk of bias),[14] and sertraline (50mg/d for 6 weeks, with a moderate risk of bias).[16] In addition, two of these RCTs found no effect on anxiety of paroxetine and sertraline compared with placebo.[14, 16]

Venlafaxine was the only SNRI assessed in the population of women experiencing menopausal symptoms after breast cancer and was only compared with other active treatments. One RCT (with a moderate risk of bias) in **women after breast cancer** found that the group treated with venlafaxine (75mg/d for 8 weeks) had a statistically significant improvement in depression compared with baseline, but no change was observed in the clonidine (0.05mg/d for 8 weeks) group compared with baseline.[22] An additional RCT (with a low risk of bias) found that venlafaxine (75mg/d for 12 weeks) had a statistically significant reduction in anxiety compared with clonidine (0.1mg/d), but found statistically significant increased depression in the venlafaxine group compared with the clonidine group.[20]

One RCT (with a moderate risk of bias) found that venlafaxine (75mg/d for 12 weeks) had a similar statistically significant effect on depression compared with acupuncture (30 min twice/week for 4 weeks, then once/week for 8 weeks).[25]

One RCT (with a moderate risk of bias) found no statistically significant difference on depression between zolpidem augmentation of an SSRI or SNRI (10mg/d for 5 weeks) compared with placebo augmentation of an SSRI or SNRI.[30]

Anticonvulsants

One RCT (with a moderate risk of bias) in **women after breast cancer** reported a significant reduction in anxiety for the γ-aminobutyric acid analogue gabapentin (300mg/d and 900mg/d for 4 and 8 weeks) compared with placebo.[89]

Depression and anxiety: Hormonal interventions

Menopause hormone therapy

One RCT (with a high risk of bias) in **women after breast cancer** found a statistically significant improvement for both depression and anxiety in the menopause hormone therapy group (oestradiol ± progestogen) at 6 and 12 months compared with baseline. In the no treatment group there was a statistically significant improvement in anxiety at 12 months compared to baseline. Between group differences were not reported.[78]

One RCT (with a low risk of bias) in **women after breast cancer** found no statistically significant difference in anxiety for tibolone (2.5mg/d for a mean of 2.5 years) compared with placebo.[35]

Depression and anxiety: Psychological and physical interventions

Cognitive behavioural therapy

One RCT (with a moderate risk of bias) in **women after breast cancer** reported no significant difference from baseline for depression or anxiety between CBT and physical exercise (PE), or between CBT+PE and a wait list control group.[46] However, another RCT (with a moderate risk of bias) found a statistically significant improvement in depressed mood and anxiety for CBT compared with usual care.[45]

Hypnotherapy

One RCT (with a moderate risk of bias) in **women after breast cancer** found a statistically significant improvement in depression and anxiety for hypnotherapy compared with no treatment.[48]

Relaxation therapy

One RCT (with a low risk of bias) in **women after breast cancer** found no statistically significant difference in anxiety for relaxation therapy compared with no treatment.[58]

Depression and anxiety: Complementary therapies

Homeopathy

One RCT (with a low risk of bias) in **women after breast cancer** found no statistically significant difference in depression or anxiety between homeopathy and placebo.[70]

Phytoestrogens

One RCT (with a moderate risk of bias) in **women after breast cancer** found no statistically significant difference in depression or anxiety between phytoestrogens and placebo.[72]

Summary of Evidence - Mood and emotional wellbeing

Twenty-four RCTs out of the 45 studies included in the primary systematic review reported on psychological outcomes (which included mood and emotional wellbeing) during treatment for menopausal symptoms in women with a history of breast cancer. Although 21 studies used validated instruments to measure different aspects of psychological wellbeing, only six used measures recommended for use in a breast cancer population.

Two systematic reviews of testosterone were identified in the supplementary evidence review that included reporting of mood or emotional wellbeing as an outcome of interest.

Due to the poor quality of the identified studies (e.g. study/outcome design, low statistical power, and inappropriate patient populations) formal Evidence Summaries have not been developed for mood and emotional wellbeing. However, a summary of the findings from the included studies is presented below.

Mood and emotional wellbeing: Pharmacological interventions

Antidepressants

Venlafaxine, an SNRI, was the only antidepressant assessed for mood in **women after breast cancer**. One RCT (with a moderate risk of bias) found no statistically significant difference in effect on mood between venlafaxine (37.5mg/twice per day) and clonidine (0.075mg/twice per day for 4 weeks), but reported that venlafaxine significantly improved mood compared with baseline.[23]

One RCT (with a moderate risk of bias) found a statistically significant reduction on negative mood for venlafaxine (75mg/d for 21 days) compared with gabapentin (900mg/d for 22 days).[24]

One RCT (with a moderate risk of bias) found a significant improvement on emotional wellbeing for the SSRI sertraline (25-100mg/d for 4 weeks) compared with placebo,[17] while another RCT (with a moderate risk of bias) found no significant difference on emotional wellbeing between the SNRI venlafaxine (37.5mg/d or 75mg/d for 6 weeks) and placebo.[21]

Mood and emotional wellbeing: Hormonal interventions

Menopause hormone therapy

One RCT (with a low risk of bias) in **women after breast cancer** found a statistically significant improvement in depressed mood for tibolone (2.5mg/d for a mean of 2.5 years) compared with placebo.[35]

Other hormone therapies

In a population of **peri- and postmenopausal women**, two RCTs in a systematic review found that the addition of testosterone to menopause hormone therapy had no effect on overall wellbeing.[44] In a population of **postmenopausal women**, nine RCTs found that testosterone reduced personal distress, but other RCTs in the systematic review found that testosterone had no effect on anxiety (four RCTs) or depressed mood (five RCTs).[87]

Mood and emotional wellbeing: Psychological and physical interventions

Yoga

One RCT (with a moderate risk of bias) in **women after breast cancer** found a significant improvement in mood for a yoga of awareness program at 3 month follow-up compared with a waitlist control.[60]

Acupuncture

One RCT (with a high risk of bias) in **women after breast cancer** found improved mood for electro-acupuncture (EA) compared to baseline, but did not report between group differences for EA compared with applied relaxation. Psychological wellbeing significantly improved for both treatment groups compared to baseline, but between group differences were not reported.[54]

Summary of Evidence - Mental health

Twenty-four RCTs out of the 45 studies included in the primary systematic review reported on psychological outcomes (which included assessment of mental health) during treatment for menopausal symptoms in women with a history of breast cancer. Although 21 studies used validated instruments to measure different aspects of psychological wellbeing, only six used measures recommended for use in a breast cancer population.

No systematic reviews were identified in the supplementary evidence review that included reporting of mental health as an outcome of interest.

Due to the poor quality of the identified studies (e.g. study/outcome design, low statistical power, and inappropriate patient populations) formal Evidence Summaries have not been developed for mental health. However, a summary of the findings from the included studies is presented below.

Mental health: Pharmacological interventions

Antidepressants

Three RCTs (with a moderate risk of bias) in **women after breast cancer** found no statistically significant differences in mental health between the SNRI venlafaxine (37.5mg/d or 75mg/d) and placebo,[21] clonidine (0.05mg/d),[22] and gabapentin (900mg/d).[24] Another RCT (with a moderate risk of bias) found an equivalent statistically significant improvement in mental health and menopause-specific quality of life for venlafaxine (75mg/d) and acupuncture (30min/twice a week).[25]

Anticonvulsants

One RCT (with a moderate risk of bias) in **women after breast cancer** found a significant improvement in mental health for gabapentin (900mg/d) compared with baseline, but found no statistically significant improvement for vitamin E (800IU/d) compared with baseline. The study did not report change from baseline between group differences.[33]

Mental health: Psychological and physical interventions

Cognitive behavioural therapy

One RCT (with a moderate risk of bias) in **women after breast cancer** found no statistically significant improvement in mental health between CBT alone, or in combination with physical exercise, compared with wait list controls.[46] However, another RCT (with a moderate risk of bias) found a statistically significant improvement in mental health for CBT compared with usual care.[45]

Summary of Evidence - Global quality of life

This guideline uses the term "global quality of life" to refer to the overall wellbeing of an individual, including physical, cognitive, emotional and social functioning and wellbeing, work, and general health.

Eleven RCTs out of the 45 studies included in the primary systematic review reported the outcome of global quality of life during treatment of vasomotor symptoms in women with a history of breast cancer. Only one study reported quality of life as a primary outcome measure, while the remaining 10 studies reported quality of life as a secondary outcome measure, and frequently quality of life scores were not clearly presented.

No systematic reviews were identified in the supplementary evidence review that included reporting of global quality of life as an outcome of interest.

Due to the poor quality of the identified studies (eg, study/outcome design, low statistical power, and inappropriate patient populations) formal Evidence Summaries have not been developed for global quality of life. However, a summary of the findings from the included studies is presented below.

Global quality of life: Pharmacological interventions

Antidepressants

Four RCTs in **women after breast cancer** found no statistically significant effects on global quality of life between the SSRI and atypical antidepressants bupropion (300mg/d for 4 weeks, with a moderate risk of bias);[29] fluoxetine (20mg/d for 4 weeks, with a low risk of bias);[15] paroxetine (10mg/d for 4 weeks, with a low risk of bias);[14] and sertraline (50mg/d for 6 weeks, with a moderate risk of bias),[16] compared with placebo.

Sedatives

One RCT (with a moderate risk of bias) in **women after breast cancer** found a statistically significant improvement in global quality of life for SSRI/SNRI augmented with zolpidem (10mg/d) compared with SSRI/SNRI augmented with placebo.[30]

Global quality of life: Hormonal interventions

Menopause hormone therapy

One RCT (with a moderate risk of bias) in **women after breast cancer** found a statistically significant improvement in global quality of life for menopause hormone therapy (oestradiol ± progestogen) at 6 and 12 months compared with baseline, but no significant improvement for no menopause hormone therapy compared with baseline; between group differences were not reported.[78] Another RCT (with a high risk of bias) found a statistically significant improvement in global quality of life for menopause hormone therapy (sequential or continuous combined oestrogen/progestogen) and electro-acupuncture compared with baseline, but no significant difference between groups.[37]

Global quality of life: Psychological and physical interventions

Physical interventions

One RCT (with a low risk of bias) in **women after breast cancer** found no significant improvement in global quality of life between relaxation therapy and no treatment.[58]

Global quality of life: Complementary therapies

Three RCTs (two with a low risk of bias and one with a moderate risk of bias) in **women after breast cancer** found no statistically significant difference in global quality of life between homeopathy,[70] soy isoflavones [74] or magnetic therapy [77] and placebo.

Summary of Evidence - Breast cancer recurrence

This guideline uses the term "breast cancer recurrence" to refer to the occurrence of breast cancer in any location of the body after treatment for an initial breast cancer.

All 45 studies included in the primary systematic review were reviewed for information on breast cancer recurrence. Three studies of menopause hormone therapy reported formal data analyses on breast cancer recurrence, while three studies of other therapies reported cancer occurrence (not necessarily breast cancer recurrence) with no formal analysis.

Two systematic reviews, one of testosterone and another one of tibolone, identified in the supplementary Evidence Review included reporting of breast cancer recurrence as an outcome of interest.

Menopause hormone therapy

There was no level I evidence from systematic reviews regarding the recurrence of breast cancer in **women after breast cancer** who were administered menopause hormone treatments.

One RCT (with a high risk of bias) in women after breast cancer found that menopause hormone therapy (sequential or continuous combined oestrogen/progestogen) was associated with a significantly higher rate of new breast cancer events compared with no treatment, resulting in the early termination of this study.[90] One RCT (with a high risk of bias) of menopause hormone therapy (combined oestradiol/medroxyprogesterone) in women after breast cancer was terminated early due to safety concerns related to breast cancer recurrence.[91] One RCT (with a low risk of bias) in women after breast cancer found that tibolone (2.5 mg/d) was associated with a significantly higher rate of new breast cancer events compared with no treatment.[34] [ES29]

Three RCTs in a Systematic Review (with a low risk of bias) in postmenopausal women reported that tibolone was associated with a significant reduction in breast cancer occurrence compared to placebo, but no significant difference in breast cancer occurrence compared to menopause hormone therapy. The authors acknowledge that the follow-up duration in these studies may be insufficient to fully assess the risk of breast cancer associated with tibolone.[38] [ES67]

Other hormone therapies

Thirty-five RCTs analysed in a Systematic Review (with a low risk of bias) **in peri- and postmenopausal women** (natural or surgically-induced, with or without a history of breast cancer) did not report the effect of long term use of testosterone. The authors acknowledged that testosterone should be used with caution as the dose, duration, safety and long-term effects have not been established.[44] [ES66]

Strengths and Weaknesses of the Evidence

There are limitations within the evidence base of the Primary Systematic Review and the Supplementary Evidence Review **[SR2]** that was used to inform the recommendations in women with a history of breast cancer. For some interventions, RCTs that specifically assessed menopausal symptoms in the population of women with a history of breast cancer were not identified. Across many of the studies identified, the clinical importance of the magnitude of observed effects was difficult to interpret and this has limited the strength of the conclusions that can be drawn.

Overall, the Primary Systematic Review undertaken for this guideline provides level II evidence for the treatment of vasomotor symptoms (hot flushes and night sweats) in women previously treated for breast cancer. Improvement in vasomotor symptoms was the primary outcome investigated by the majority of the studies, with improvement in other symptoms typically assessed as secondary outcomes. As such, studies were generally powered for detecting changes in vasomotor symptoms only and were insufficiently powered to detect a difference in secondary outcomes. Further, treatment doses were specifically chosen for efficacy in treating vasomotor symptoms and not for the secondary outcomes; thus, drug dosage and duration of treatment may not have been sufficient to elicit a significant effect for outcomes other than vasomotor symptoms. Some interventions were supported only by a single study. Further studies with larger study samples and greater methodological rigour are needed to assess treatments for sleep disturbance, sexual function, psychological wellbeing and global quality of life.

A key limitation of the literature assessed in the Supplementary Evidence Review undertaken for this guideline is the varying ways that treatment was administered and outcomes were measured in the studies included in the systematic reviews. This prevented synthesis of the findings, and several analyses were based on a small number of studies. Additionally, the systematic reviews pooled the effects of the treatments of interest with other treatments, such as escitalopram with other SSRIs, and testosterone with oestrogen, making it difficult to identify the individual treatment effects. Conversely, the Supplementary Evidence Review on compounded hormones only investigated one form of treatment, compounded progesterone cream, when compounded oestrogen and compounded androgens may also be used to treat menopausal symptoms.

For many of the therapies included in these guidelines there is little or no evidence for their long-term safety in peri- and postmenopausal women. In particular, the use of testosterone, SERMs and compounded hormones in this population is not informed by long-term studies. Tibolone may be associated with an increased risk of breast cancer, although the evidence is drawn from a limited number of trials and there is some inconsistency in the effects observed. In addition, all of the therapies included in these guidelines, both pharmacological and non-pharmacological, have specific contraindications and adverse event profiles that should inform the consideration of their benefits and harms for individual women.

Unanswered Questions Regarding Treatments of Interest

Is the use of menopause hormone therapy safe in women who have been treated for breast cancer?

An increased risk of breast cancer recurrence has been reported in a number of RCTs examining the use of menopause hormone therapy for menopausal symptoms. Tibolone was shown to significantly increase the risk of breast cancer recurrence compared with placebo (HR 1.40; 95% CI 1.14, 1.17),[34, 35] while oestrogen was shown to significantly increase the risk of breast cancer events (HR 3.5; 95% CI 1.5, 8.1).[90] Another study showed no increase in breast cancer recurrence with oestrogen compared with no menopause hormone therapy; however, the trial was stopped early due to an increased hazard of breast cancer.[91]

The use of menopause hormone therapy to treat menopausal symptoms in women who have been treated for breast cancer should generally be avoided, and be limited to cases where symptoms are resistant to treatment and the quality of life benefit outweighs the potential risk. Informed consent should be sought from the woman, and the decision to use MHT should be made in conjunction with the treating oncology team and counselling regarding the potential increased risk of breast cancer recurrence.[3]

Is the use of testosterone effective and safe in women who have been treated for breast cancer?

Based on the findings of the supplementary systematic review conducted for this guideline, the use of testosterone with oestrogen may have a beneficial effect on sexual functioning and no effect on vasomotor symptoms in the general female menopausal population, but may also affect lipid profiles and increase the incidence of acne and hirsutism.[44, 87] There was some evidence that testosterone had a beneficial effect on personal distress, although the authors noted that the quality of the evidence for that outcome was imprecise and at risk of bias.[87] An RCT conducted in women who had survived cancer (not limited to breast) who had decreased libido found no benefit of transdermal testosterone over placebo.[92]

Thus, the effectiveness and safety of testosterone for the treatment of menopausal symptoms in women who have been treated for breast cancer are highly uncertain. It should also be noted that testosterone is not approved by the Therapeutic Goods Administration (TGA) for the treatment of menopausal symptoms.

Is the use of compounded hormones ('bioidentical' hormones) hormones effective and safe in women who have been treated for breast cancer?

A recent cross-sectional study has estimated that 6% of Australian women aged 50–69 years have used compounded hormones at some time, with 2% being current.[93] A systematic review of studies in the general female postmenopausal population found that two RCTs showed no benefit of compounded hormone (a standardised, manufactured progesterone cream) over placebo when vasomotor symptoms were measured using a validated scale, while another found that a compounded progesterone cream (which could not be replicated) significantly improved self-reported severity of vasomotor symptoms.[42] Safety data from the included studies was limited; vaginal spotting was reported in a small number of patients in two RCTs while a

third RCT noted there was no significant difference between treatment and placebo for headaches or vaginal spotting.[42] Compounded hormones are systemically absorbed and may contain high levels of sex steroids which may increase the risk of new or recurrent breast cancer. It should be noted that compounded hormones have not been studied in women who have received treatment for breast cancer, and compounded hormones are not registered with the TGA.

Is the use of laser therapy for vulvovaginal symptoms effective and safe in women who have been treated for breast cancer?

CO2 laser therapy is an emerging treatment for vulvovaginal atrophy. Preliminary in vitro and ex vivo studies have found that use of laser therapy can result in the remodelling of vaginal tissue. [94, 95] To date, only a small number of observational studies have been performed using CO2 laser therapy in post-menopausal women. These studies have reported significant improvements in vulvovaginal symptoms, sexual function and quality of life over up to 12 weeks of follow-up.[96-98] The results of these studies should be interpreted with caution as they have not included an appropriate control, such as sham laser treatment or active control with hormone treatments, which is necessary to address the substantial placebo response that is common in trials investigating female sexual dysfunction.[99] As the studies have been of short duration, they have not established the long-term durability of the effect, or the long-term safety of vaginal laser therapy. In addition, no studies have been carried out in women with a history of breast cancer. Further research of a higher methodological standard is required to establish the efficacy and safety of laser therapy for the management of vulvovaginal atrophy.

International Guidelines

Eleven international guidelines that included recommendations relevant to the treatment of menopausal symptoms in women who have been treated for breast cancer were identified during the literature search for this guideline. Details of all relevant recommendations made by others are provided in the Cancer Australia Primary Systematic Review, Appendix H.

Ongoing and Additional Trials of Interest

Clinical trials registries were searched to identify any ongoing studies among women with menopausal symptoms who were treated for breast cancer. The following trials were identified (full details can be found in Section 3.9 of the systematic review):

- NCT01908270: A single blind RCT (Germany) in women treated for breast cancer with a score of ≥ 5 on the Menopausal Rating Scale (MRS) comparing yoga with usual care. The study has been completed but no published results were available at the time the systematic review was undertaken. N=40.
- NCT02091765: A RCT (the Netherlands) in women treated for breast cancer with menopausal symptoms comparing an internet-based cognitive behavioural therapy intervention with a minimal intervention control group. N=160.
- NCT01275807: An open-label RCT (Italy) in women with breast cancer receiving endocrine therapy and experiencing menopausal symptoms comparing acupuncture with self-case. N=210.
- NCT01900418: A single-blind RCT (US) in women with breast cancer receiving endocrine therapy with mild joint pain/symptoms comparing walking with no intervention. N=80.
- NCT00156416: A single-blind, pilot study RCT (US) in women with breast cancer and amenorrhoea secondary to breast cancer treatment, as well as menopausal symptoms comparing mindfulness medication with attention. N=60.
- NCT01246427: A double-blind RCT (France) in women receiving at least 1 month of adjuvant therapy for breast cancer who are experiencing menopausal symptoms comparing the homeopathic drug BRN01 with placebo. N=138.
- NCT02672189: A RCT (the Netherlands) of Internet-based CBT for breast cancer patients with climacteric symptoms. N=265.
- NCT01573442: A double-blind RCT (US) of subcutaneous testosterone in the adjuvant treatment of postmenopausal women with aromatase inhibitor induced arthralgias. N=224.
- ACTRN12615000083594: A double-blind RCT (Australia) investigating the efficacy and safety of intra-vaginal testosterone for the treatment of vulvo-vaginal atrophy associated with aromatase inhibitor therapy in women with breast cancer. N=100

After the literature searches were concluded, an additional Australian trial on the use of water-based and silicon based lubricants in women after breast cancer was published.[100] The randomised crossover trial found no significant difference in total sexual discomfort between water-based and silicon based lubricants. However; a post hoc analysis showed that, pain/discomfort during penetration improved more with silicone-based lubricant use than with water-based lubricant.

Drug Contraindications and Side Effects

Adverse events were poorly and inconsistently reported by the Primary Systematic Review and the Supplementary Evidence Review; therefore this guideline has presented selected information from the Therapeutic Goods Administration (August 2016) regarding the safety of pharmaceuticals commonly used by women who have had breast cancer, including the pharmaceuticals assessed by the Primary Evidence Base. For full details on the safety of these drugs, see the product information on the Australia Register of Therapeutic Goods website.

Table 2. Selected safety information from the Australia Register of Therapeutic Goods approved product information (August 2016) on pharmaceuticals used by women with a history of breast cancer [101]

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
Anastrozole	Breast cancer	Pregnancy or lactation	Hot flushes Asthenia Headache Nausea Vomiting Rash Weakness Joint pain, stiffness / arthritis Vaginal dryness and bleeding Hair thinning (alopecia), Allergic reactions Diarrhoea	Drugs metabolised by cytochrome P450 1A2, 2C8/9, 3A4 Tamoxifen	Not recommended for use in children or in pre-menopausal women. Potential risks associated with patients with renal and hepatic impairment. May cause a reduction in bone mineral density, therefore women with osteoporosis or at risk of osteoporosis should be monitored. Should not be co-administered with oestrogen-containing products as these would negate its pharmacological action.

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
			Somnolence Carpel Tunnel Syndrome Sensory disturbances Increases in liver enzymes Anorexia Hypercholesterolaemia Bone pain Myalgia		
Bupropion	Nicotine dependence	Seizure disorders CNS tumour Abrupt withdrawal from benzodiazepines or alcohol Current or previous diagnosis of bulimia or anorexia nervosa Monoamine oxidase inhibitors (MAOIs)	Fever Asthenia Insomnia Headache Dizziness Agitation, anxiety Tremor Concentration disturbance Depression Dry mouth Gastrointestinal	May interact with drugs known to affect the CYP2B6 isoenzyme Drugs which require activation by CYP2D6 (e.g. tamoxifen) may have reduced efficacy Co-administration of drugs known to induce (e.g. carbamazepine, phenobarbital) or inhibit (e.g. valproate) metabolism may affect its activity	Bupropion is associated with a dose-related risk of seizures, therefore the recommended dose must not be exceeded. Used with caution in patients with renal and hepatic impairments and used with extreme caution in patients with severe hepatic cirrhosis. Care and monitoring should be taken for the emergence of significant depressive symptoms or suicidal ideation in patients, especially patients with a history of psychiatric illness .

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
			disturbance Abdominal pain Constipation Hypersensitivity reactions Visual disturbance Taste disorders		Care should be taken in patients with a recent history of myocardial infarction or unstable heart disease.

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
Citalopram	Major depression Obsessive-compulsive disorder	Monoamine oxidase inhibitors Linezolid Pimozide Congenital long QT syndrome	Migraine Abnormal accommodation Taste perversion Amnesia Apathy Depression Increased appetite Aggravated depression Saliva increased Increased / decreased weight Postural hypotension, hypotension Tachycardia Polyuria Amenorrhoea Sweating Drowsiness Dry mouth Nausea	Drugs that prolong the QT interval Selegiline (selective MAO-B inhibitor) Pimozide Serotonergic drugs Hepatic enzymes	Clinical worsening and suicide risk associated with psychiatric disorders Care, monitoring and more frequent ECG monitoring should be taken with patients at higher risk of developing prolongation of the QT interval. Caution should be taken in patients concomitantly treated with oral anticoagulants, medicinal products known to affect platelet function as well as in patients with a past history of abnormal bleeding or predisposing conditions. Used with caution in patients with a history of seizures. Care should be taken with diabetic patients as their insulin and glucose responses may be modified. Care should be taken with elderly patients who are a group at risk of hyponatraemia

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
					Review use and dose if patients develop akathisia within the first few weeks of treatment. Withdrawal symptoms when treatment is discontinued are common
Clonidine	Hypertension Renal hypertension Migraine prophylaxis Menopausal flushing	Bradyarrhythmia	Dizziness Sedation Orthostatic hypotension Dry mouth Depression Sleep disorder Dizziness, sedation Headache Constipation Nausea Salivary gland pain Vomiting Erectile dysfunction Fatigue	Antihypertensive agents Nonsteroidal anti-inflammatory drugs can reduce the therapeutic effect of clonidine Substances with α2-adrenergic receptor blocking properties (e.g. phentolamine), may abolish the α2-adrenergic receptor mediated effects of clonidine in a dose-dependent way Concomitant administration of drugs with a negative chronotropic or dromotropic effect (i.e. β-blockers or digitalis glycosides) can cause bradycardiac rhythm	Special care should be exercised in treating patients who have a history of depression or who have advanced cerebrovascular disease. Diabetic patients should be monitored for a possible increase in their requirements of anti-diabetic therapy. Caution should be used in patients with mild to moderate bradyarrhythmia such as low sinus rhythm, with disordered of cerebral or puerperal perfusion, polyneuropathy and constipation. Careful consideration for dosage is required in patients with renal insufficiency. Monitoring is required in patients with heart failure or severe coronary heart disease

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
				disturbances Tricyclic antidepressants or neuroleptics with □-receptor blocking effects	Termination of oral therapy should be gradual. Warnings should be given to patients who wear contact lenses that treatment may cause decreased lacrimation.
Desvenlafaxine	Major depression, including the prevention of relapse	Monoamine oxidase inhibitors	**Very common (>10%)** Nausea Dry Mouth Constipation Fatigue Dizziness Headache Insomnia Hyperhidrosis *for side effects occurring in between 1% and 10% of patients please see specific PI	Monoamine oxidase inhibitors Caution advised for CNS-active drugs Other agents that affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs etc.)	Clinical worsening and suicide risk associated with psychiatric disorders. Used cautiously in patients with a history or family history of mania or hypomania. The development of syndromes like serotonin syndrome (SS) or Neuroleptic Malignant Syndrome (NMS) may occur. Close monitoring of patients with raised intra-ocular pressure or patients at risk for acute narrow-angle glaucoma. All patients should have regular monitoring of blood pressure. With caution exercised in treating patients with underlying conditions that might be

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
					compromised by increases in blood pressure. Caution is advised for patients with cardiovascular, cerebrovascular, or lipid metabolism disorders due to increases in blood pressure and heart rate. Risk of bleeding events associated with concomitantly using drugs that affect coagulation or bleeding (e.g. NSAIDs, aspirin) Care should be taken with elderly patients or patients taking diuretics who are a group at risk of hyponatraemia.
Escitalopram	Major depression Social anxiety disorder (social phobia) General anxiety disorder Obsessive com	Escitalopram or any of the excipients Monoamine oxidase inhibitors Pimozide	Nausea Headache Insomnia Diarrhoea Dry mouth Dizziness Somnolence Anorexia	Monoamine oxidase inhibitors serotonergic agents Pimozide	Clinical worsening and suicide risk associated with psychiatric disorders. Review use and dose if patients develop akathisia within the first few weeks of treatment. Caution should be taken in patients concomitantly treated with oral anticoagulants, medicinal products known to affect platelet

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
	pulsive disorder		Libido decreased Appetite decreased Agitation Impotence Yawning Fatigue Sweating Anorgasmia Ejaculation disorder / failure		function as well as in patients with a past history of abnormal bleeding or predisposing conditions. Care should be taken with elderly patients who are a group at risk of hyponatraemia Used with caution in patients with a history of seizures. Care should be taken with diabetic patients as their insulin and glucose responses may be modified. Used cautiously in patients with a history or family history of mania or hypomania.
Exemestane	Oestrogen receptor-positive breast cancer	Pregnancy or lactation	**Very common (>10%)** Pain Fatigue Abdominal pain Nausea Hepatic enzyme increased (including ALT	No formal drug interaction studies have been carried out	Should not be co-administered with oestrogen-containing products as these would negate its pharmacological action. Should not be administered to women with premenopausal endocrine status. Care and monitoring should be taken with

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
			increased, GGT increased) Blood bilirubin increased Serum alkaline phosphatase increase Dizziness Headache Depression Insomnia Hot flushes Sweating Lymphocyte decrease *for side effects occurring in between 1% and 10% of patients please see specific PI		women who have/at risk of osteoporosis as bone mineral density and fracture risk may be impacted.
Fluoxetine	Major depression Obsessive compulsive disorder	Monoamine oxidase inhibitors Should not be used in combination with	**Very common (>10%)*** Fatigue (includes asthenia) Diarrhoea	Tryptophan, Warfarin, Pimozide, Serotonergic drugs Drugs metabolised by cytochrome P450 3A4 and P450 (CYP2D6)	Clinical worsening and suicide risk associated with psychiatric disorders. Possibility of fractures should be considered during treatment.

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
	Premenstrual dysphoric disorder (PMDD)	Pimozide	Nausea Anxiety and nervousness Dizziness Headache Insomnia Somnolence Tremor *for side effects occurring in between 1% and 10% of patients please see specific PI	Highly protein bound drugs Tamoxifen may have reduced efficacy	The development of serotonin syndrome may occur. Caution should be taken for patients with conditions such as congenital long QT syndrome; acquired long QT syndrome; a family history of QT prolongation; or other conditions that predispose to arrhythmias or increased exposure to fluoxetine . Care should be taken with patients with a history of seizures. Caution should be taken for patients with concomitant illness, especially diseases or conditions that could affect metabolism or haemodynamic responses (e.g. recent history of myocardial infarction, cirrhosis of the liver, renal impairment, diabetes, acute narrow-angle glaucoma, abnormal bleeding).
Gabapentin	Epilepsy Neuropathic pain	Hypersensitivity to gabapentin	**Side effects occurring in >5% of participants*** Fatigue	Cimetidine Antacids may reduce gabapentin bioavailability	Antiepileptic drugs, including gabapentin, increase the risk of suicidal thoughts or behaviours in patients

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
			Nausea Vomiting Somnolence Dizziness Ataxia Nystagmus Headache Tremor Diplopia Asthenia Diarrhoea Peripheral oedema *for side effects occurring in between 1% and 5% of patients please see specific PI		taking these drugs for any indication. Caution should be taken in patients who have mixed seizure disorders that include absence seizures.
Letrozole	Hormone receptor positive breast cancer in post menopa	Premenopausal endocrine status Pregnancy Lactation	**Very common (>10%)*** High cholesterol / Hypercholesterolaemia Hot flushes	There is minimal data on the interaction between Letrozole and other drugs. Metabolism of Letrozole may be influenced by	Caution and supervision of patients with renal and hepatic impairment. Should not be co-administered with tamoxifen, other anti-estrogens or estrogen-containing therapies as

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
	usal women		Increased sweating Arthralgia Fatigue (including asthenia and malaise) *for side effects occurring in between 1% and 10% of patients please see specific PI	drugs known to affect the CYP3A4 and CYP2A6 enzymes.	these may diminish the pharmacological action. Monitoring of overall bone health is recommended during treatment.
Megestrol acetate	Palliative treatment of recurrent inoperable or metastatic carcinoma of the breast	As a diagnostic test for pregnancy	Weight gain Increased appetite Nausea Vomiting Edema Breakthrough uterine bleeding	No information is available regarding interactions with food, alcohol or other drugs	Use with caution in patients with a history of thromboembolic disease or diabetes mellitus. Not recommended for use during the first four months of pregnancy.
Paroxetine	Major depression Obsessive compulsive disorder Panic disorder	Monoamine oxidase inhibitors Should not be used in combination with Pimozide or Thioridazine	The most commonly observed adverse events associated with use and not seen at an equivalent incidence among placebo treated patients: Nausea	Medicines that interfere with haemostasis (NSAIDs, aspirin, warfarin etc.) Drugs affecting hepatic metabolism	Clinical worsening and suicide risk associated with psychiatric disorders. Caution and supervision of patients with renal/hepatic impairment and diabetes. Caution should be taken

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
	Social anxiety disorder /Social Phobia Generalised Anxiety Disorder Post-traumatic Stress Disorder		Somnolence Sweating Tremor Asthenia Dry mouth Insomnia Sexual dysfunction Dizziness Constipation Diarrhoea Decreased appetite For further side effects please see specific PI.	Drugs metabolised by cytochrome P450 3A4/2D6 Serotonergic drugs Tamoxifen may have reduced efficacy	in the co-administration of tricyclic antidepressants. Used cautiously in patients with a history or family history of mania or hypomania. Possibility of fractures should be considered during treatment. Caution should be observed with patients with cardiac conditions, epilepsy, seizures and glaucoma. Caution should be taken in patients concomitantly treated with oral anticoagulants, medicinal products known to affect platelet function as well as in patients with a past history of abnormal bleeding or predisposing conditions. Care should be taken with elderly patients who are a group at risk of hyponatraemia.
Pregabalin	Epilepsy Neuropathic	Galactose intolerance Lapp lactase	**Very common (>10%)*** Dizziness	Pregabalin undergoes negligible metabolism in	Antiepileptic drugs, including gabapentin, increase the risk of suicidal thoughts or

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
	pain	deficiency Glucose-galactose malabsorption	Somnolence *for side effects occurring in between 1% and 10% of patients please see specific PI	humans and is unlikely to produce pharmacokinetic interactions.	behaviours in patients taking these drugs for any indication. Caution should be taken for patients with congestive heart failure.
Sertraline	Major depression Social anxiety disorder Premenstrual dysphoric disorder Obsessive compulsive disorder in children	Monoamine oxidase inhibitors Pimozide	**Very common (>10%)*** Fatigue Tremor Nausea Insomnia Somnolence *for side effects occurring in between 1% and 10% of patients please see specific PI	Pimozide Drugs that prolong the QT interval Serotonergic drugs Medicines that interfere with haemostasis Drugs highly bound to plasma proteins Drugs metabolised by CYP enzymes	The development of syndromes like serotonin syndrome or Neuroleptic Malignant Syndrome has been reported Clinical worsening and suicide risk associated with psychiatric disorders. Caution should be taken in patients concomitantly treated with oral anticoagulants, medicinal products known to affect platelet function as well as in patients with a past history of abnormal bleeding or predisposing conditions. Care should be taken with elderly patients who are a group at risk of hyponatraemia.

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
					Possibility of fractures should be considered during treatment. Caution should be observed with patients with diabetes, seizures and glaucoma.
Tamoxifen	Breast cancer	Pregnancy	Hot flushes Nausea and vomiting	Coumarin type anticoagulants Cytotoxic agents Rifampicin CYP2D6 inhibitors Fluoxetine and Paroxetine	An increased incidence of endometrial changes including hyperplasia, polyps and cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported. Used cautiously in patients with existing leucopenia or thrombocytopenia.
Testosterone	Male hypogonadism Male testosterone deficiency	Suspected carcinoma of the prostate or breast (in men) Pregnancy and lactation Patients with nephrosis or nephrotic phase of nephritis Hypercalcaemis accompanying malignant	**Very common (>10%)** Administration site reactions **Common (>1% and <10%)** Headache Prostatic disorders Gynaecomastia Mastodynia	Insulin Anticoagulants Corticosteroids Oxyphenbutazone Cyclosporin Barbiturates and other enzyme inducers	Androgens may accelerate the progression of sub-clinical prostate cancer and benign prostatic hyperplasia. Care and monitoring should be taken for patients with myocardial or renal dysfunction, hypertension, migraine, diabetes or epilepsy due to fluid retention.

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
		tumours	Dizziness Paraesthesia Amnesia Hyperaesthesia Mood disorders Hypertension Diarrhoea Alopecia Urticaria		
Tibolone	Menopause symptoms Bone mineral density loss	Known, suspected or history of breast cancer Estrogen-dependent malignant tumours Pregnancy and lactation Undiagnosed genital bleeding Untreated endometrial hyperplasia Previous or current venous thro	None occurring with an incidence of at least 10% **Common (>1% and <10%)** Lower abdominal pain Abnormal hair growth Genital discharge Endometrial wall thickening Postmenopausal or vaginal Hemorrhage Breast tenderness	May enhance the effect of anticoagulants CYP3A4 substrates CYP3A4 inducing compounds St John's Wort	Tibolone increases the risk of ischaemic stroke from the first year of treatment. Care and monitoring should be taken for women with conditions such as Leiomyoma or endometriosis, risk factors for thromboembolic disorders and estrogen dependent tumours, hypertensions, liver disorders, diabetes, chloelithiasis, migraines, systemic lupus erythematosus, history of endometrial hyperplasia, epilepsy, asthma and otosclerosis.

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
		mboembolism, thrombophilic disorders, Any history of arterial thromboembolic disease Liver disease Porphyria	Genital pruritus Vaginal candidiasis Pelvic pain Cervical dysplasia Vulvovaginitis		
Vaginal oestrogen	Climacteric symptoms	Pregnancy and lactation Known, suspected or history of breast cancer Other undiagnosed breast pathology Oestrogen-dependent neoplasia Abnormal genital bleeding Venous thromboembolism, Arterial thromboembolic disease,	**Very common (>10%)** Breast pain **Common (>1% and <10%)** Abnormal uterine bleeding Tenderness Enlargement Discharge Leucorrhoea Arthralgias Leg cramp Alopecia Changes in weight	CYP3A4 inducers or inhibitors St John's Wort Antihypertensive agents	Increases the risk of stroke, deep vein thrombosis and pulmonary embolism. The use of unopposed oestrogens in women with an intact uterus has been associated with an increased risk of endometrial cancer. Caution and monitoring of patients with a history of cardiac or renal dysfunction due to fluid retention.

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
		Severe uncontrolled hypertension Liver dysfunction	Increased triglycerides Vaginitis Depression		
Venlafaxine	Major depression General anxiety disorder Social anxiety disorder Panic disorder	Monoamine oxidase inhibitors	None occurring with an incidence of at least 10% **Common(>1% and <10%)** Headache, Nausea Insomnia, Drowsiness Asthenia / fatigue Hypertension, vasodilation Appetite decreased Vomiting Serum cholesterol increased Weight loss Abnormal dreams Dry mouth Paraesthesia	Drugs that prolong the QT interval Monoamine oxidase inhibitors Other agents that affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs etc.) St John's Wort	Clinical worsening and suicide risk associated with psychiatric disorders. The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome-like reaction may occur. Caution should be observed with patients with diabetes, hypertension, unstable heart disease and glaucoma. Caution should be taken for patients with risk factors for QTc prolongation.

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
			Tremor Yawning Abnormality of accommodation, mydriasis Visual disturbance Anorgasmia Urination impaired Dizziness, Weakness Constipation Sweating Nervousness		
Zolpidem	Insomnia	Obstructive sleep apnoea Myasthenia gravis Severe hepatic insufficiency Severe pulmonary insufficiency Children under 18 years of age Prior or	Headache Drowsiness Dizziness Diarrhoea	CNS depressants Imipramine Hepatic enzyme inhibitors and inducers	Continuous long-term use of Zolpidem is not recommended and should not exceed four weeks. Care should be taken in patients with hepatic, renal, memory impairment.

Generic name (brand names)	Indications	Contraindications	Common side effects (occurring in ≥1% of patients)	Drug interactions	Precautions / Comments
		concomitant intake with alcohol			

Evidence Matrix

This evidence matrix provides an "at-a-glance" summary of the findings of the evidence review grouped by class of treatment and symptom.

Table 3: Evidence matrix based on primary and supplementary systematic reviews

Legend:

Evidence of effect	Evidence of no effect	Limited evidence	No evidence

Note: Bold text refers to evidence from studies in women with breast cancer, and non-bold text refers to evidence from general menopausal populations.

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
Bupropion	**Limited evidence of no effect on hot flush severity with bupropion** [ES1]	**No evidence** Insomnia is a common side effect	**Limited evidence of no effect on sexual function with bupropion** [ES25]	Not reported
Fluoxetine	**Limited evidence of an inconsistent effect on hot flushes with fluoxetine** [ES2]	**Limited evidence of no effect in sleep disturbance with fluoxetine** [ES17] Insomnia is a common side effect	**Limited evidence of no effect on sexual function with fluoxetine** [ES25] Sexual dysfunction is a common side effect	Not reported
Paroxetine	**Limited evidence for reduction in hot flush frequency and severity with paroxetine** [ES2]	**Limited evidence for improvement in sleep disturbance with paroxetine** [ES17]	**Limited evidence of no effect on sexual function with paroxetine** [ES25]	Not reported
Sertraline	**Limited evidence of an inconsistent effect on hot**	**No evidence** Insomnia is a	**No evidence**	Not reported

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
	flushes with sertraline [ES2]	common side effect		
Venlafaxine	**Evidence for reduction in frequency and severity of hot flushes with venlafaxine** [ES3] **Evidence that venlafaxine and clonidine are equally effective at reducing the frequency and severity of hot flushes** [ES3] **Limited evidence that gabapentin and venlafaxine have similar effectiveness [ES6]** Evidence for reduction in vasomotor symptom frequency and bother with venlafaxine [ES31]	**Limited evidence of no effect of venlafaxine on sleep** [ES18] Insomnia is a common side effect	**Limited evidence of no effect on sexual function with venlafaxine** [ES25]	Not reported
Zolpidem (augmented with SSRI/SNRI)	**Limited evidence of no additional effect on**	**Limited evidence that adding zolpidem to an**	**No evidence**	Not reported

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
	vasomotor symptoms with zolpidem when combined with an SSRI or SNRI [ES4]	**SSRI or SNRI improves sleep** [ES19] TGA approved treatment for insomnia		
Escitalopram	Evidence for reduction in vasomotor symptom frequency and bother with escitalopram [ES30]	Limited evidence of no effect on sleep disturbance with escitalopram [ES49] Insomnia is a common side effect	Limited evidence of no effect on sexual function with escitalopram [ES57] Sexual dysfunction is a possible side effect	Not reported
Desvenlafaxine	Evidence for reduction in hot flush frequency with desvenlafaxine [ES32]	Evidence for reduction in the number of night-time awakenings with desvenlafaxine [ES50] Insomnia is a common side effect	No evidence Sexual dysfunction is a possible side effect	Not reported
Clonidine	**Evidence for reduction in frequency and severity of hot flushes with cloni dine. Evidence that this effect is comparable to**	**No evidence**	**No evidence**	Not reported

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
	the effect achieved with venlafaxine. [ES5]			
Gabapentin	**Limited evidence for reduction in hot flush frequency and severity with gabapentin** [ES6] **Limited evidence that gabapentin and venlafaxine have similar effectiveness** [ES6]	**Limited evidence of an inconsistent effect of gabapentin on sleep disturbance** [ES20]	**No evidence**	Not reported
Oestrogen/progesterone	**Limited evidence that menopause hormone therapy reduces hot flushes** [ES7] Evidence for reduction in hot flush frequency and severity with menopause hormone therapy [ES34]	**Evidence that menopause hormone therapy improves sleep quality** [ES21]	**Limited evidence of inconsistent effect of menopause hormone therapy on sexual function** [ES26] Evidence of no effect on sexual function with menopause hormone therapy [ES62]	**Evidence that menopause hormone therapy increase breast cancer recurrence** [ES29]
Tibolone	**Limited evidence that tibolone reduces the frequency and severity of hot flushes** [ES7]	**Limited evidence that tibolone improves sleep quality** [ES21]	**Limited evidence of improved sexual function with tibolone** [ES26]	**Evidence that tibolone increase breast cancer recurrence** [ES29]

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
	Evidence for reduction in hot flush frequency with tibolone [ES33]	Limited evidence of no effect on insomnia with tibolone [ES51]	Evidence of no effect on vaginal dryness and dyspareunia with tibolone [ES61]	Limited evidence that tibolone reduces breast cancer recurrence [ES67]
Oral low-dose oestradiol	Limited evidence for reduction in hot flush frequency and severity with oestradiol [ES35] Limited evidence for reduction in hot flush bother with oestradiol [ES35]	No evidence	No evidence Limited evidence of no effect on sexual function with low-dose oestradiol [ES58]	Increased risk of breast cancer recurrence*
Low-dose oestradiol / low-dose transdermal oestradiol	Evidence for a reduction in hot flush frequency with low-dose transdermal oestradiol [ES37]	No evidence	Limited evidence of no effect on sexual function with low-dose oestradiol [ES58]	Increased risk of breast cancer recurrence*
Transdermal oestradiol	Evidence for a reduction in hot flush frequency and severity with transdermal oestradiol [ES38]	No evidence	No evidence	Increased risk of breast cancer recurrence*
Ospemifene / SERMs	Evidence for increase in hot flushes with the selective oestrogen receptor modulator,	No evidence	Evidence for decreased dyspareunia with ospemifene [ES65]	Not reported

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
	ospemifene [ES36]		Limited evidence of no effect in sexual function (composite score) with SERMs [ES65]	
Testosterone in combination with systemic menopause hormone therapy	Limited evidence of no additional effect on vasomotor symptoms with testosterone added to menopause hormone therapy [ES39]	No evidence	Evidence that testosterone improves sexual function [ES59]	No evidence of the effect of testosterone on breast cancer recurrence [ES66]
Testosterone (with or without menopause hormone therapy)	No evidence	No evidence	Evidence of improvement in sexual function with testosterone [ES60]	Not reported
Compounded hormones	Limited evidence of inconsistent effect of compounded progesterone cream on vasomotor symptoms [ES40]	No evidence	No evidence	Not reported
Vaginal pH-balanced gel	**No evidence**	**No evidence**	**Limited evidence for improved vaginal symptoms with vaginal gel [ES27]**	Not reported
Lidocaine gel	**No evidence**	**No evidence**	**Limited evidence for improved dyspareunia and vulvovaginal**	Not reported

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
			symptoms with lidocaine [ES27]	
Vaginal oestrogen	No evidence	No evidence	Evidence that vaginally administered oestrogen relieves vaginal dryness and itching [ES63] Evidence for a reduction in vaginal dryness, itching and burning, and dyspareunia with vaginal oestrogen [ES63]	Not reported
CBT or CBTI	**Evidence that CBT alone reduces the problem rating of hot flushes and night sweats** [ES8] Limited evidence of reduction in hot flushes and night sweats with CBT [ES41]	**Limited evidence that CBT improves sleep** [ES22]	**Limited evidence for improved sexual function with CBT alone** [ES28]	Not reported
Hypnotherapy	**Limited evidence for reduction in frequency and severity of hot flushes with a purpose-designed hypnotherapy**	**Limited evidence that hypnotherapy improve sleep** [ES22]	**Limited evidence that hypnotherapy has no effect on sexual function** [ES28]	Not reported

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
	protocol [ES9]			
Relaxation therapy	**Limited evidence of reduction in hot flush frequency and severity with short-term relaxation therapy** [ES11] Limited evidence of no effect on vasomotor symptoms with relaxation [ES44]	**No evidence** Limited evidence of improvement on sleep with relaxation therapy [ES54]	**No evidence**	Not reported
Physical exercise	**Limited evidence that physical exercise in combination with CBT reduces the problem rating of hot flushes and night sweats** [ES8] Evidence of no effect on vasomotor frequency and bother with exercise [ES42]	**No evidence** Limited evidence of an inconsistent effect on sleep symptoms with exercise [ES52]	**Limited evidence for improved sexual function with CBT in combination with exercise** [ES28]	Not reported
Yoga	**Limited evidence for reduction in frequency and severity of hot flushes with yoga** [ES12]	**Limited evidence that yoga improves sleep** [ES23]	**No evidence**	Not reported

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
	Limited evidence for improvement of total menopausal symptoms with Yoga and meditation [ES12] Limited evidence of an inconsistent effect on vasomotor symptoms with yoga [ES43]	Limited evidence that yoga improve sleep symptoms [ES53]		
Acupuncture	**Limited evidence of an inconsistent effect of acupuncture on the frequency and severity of hot flushes** [ES10] Limited evidence for an inconsistent effect on vasomotor symptoms with acupuncture [ES45]	**Limited evidence that acupuncture improves sleep** [ES23]	**No evidence**	Not reported
Magnetic therapy	**Limited evidence of no effect on hot flushes frequency or severity with magnetic therapy**	**No evidence**	**No evidence**	Not reported

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
	[ES16]			
Homeopathy	**Evidence of no effect on hot flush frequency or severity with homeopathy** [ES14]	**No evidence**	**No evidence**	Not reported
Black cohosh	**Evidence of no effect on severity or frequency of hot flushes with black cohosh** [ES13] Evidence of no effect on vasomotor symptoms with black cohosh [ES48]	**No evidence**	**No evidence**	Not reported
Phytoestrogens / isoflavones	**Evidence of no effect on hot flush frequency or severity with phytoestrogens** [ES15] Limited evidence of an inconsistent effect on vasomotor symptoms with other isoflavones [ES46]	**No evidence** Limited evidence of no effect on sleep symptoms with isoflavones [ES55]	**No evidence** Limited evidence of an inconsistent effect on vaginal dryness and dyspareunia with soy isoflavones [ES64]	Not reported

Intervention	Vasomotor symptoms	Sleep disturbance	Vulvovaginal Symptoms and Sexual function	Breast cancer recurrence
Omega-3 supplementation	Limited evidence of no effect on vasomotor symptoms with omega-3 fatty acid supplementation [ES47]	No evidence Limited evidence of no effect on sleep quality and insomnia with omega-3 fatty acid supplementation [ES56]	No evidence	Not reported
Vitamin E	**No evidence**	**Limited evidence of no effect on sleep disturbance by Vitamin E** [ES24]	**No evidence**	Not reported

* The WHI study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo.

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External Review

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Additional Information

Guideline development process

Topics for guideline development are determined in consultation with key stakeholders including experts in relevant disciplines and consumer representatives. A specific multidisciplinary Working Group, including consumers, is established and is involved in all aspects of guideline development. A systematic evidence review is undertaken for each guideline. All members are asked to declare any conflicts of interest and these declarations are recorded. The content of the guideline is not influenced by any external funding body. The guideline is reviewed externally by key stakeholders and the wider community and endorsement is sought from relevant professional colleges and groups in Australia.

Copyright statements

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Appendix 1: Grading Methodology

To accurately assess the strength of evidence available, the NHMRC methodology (FORM) was used in this clinical practice guideline to formulate and grade recommendations. The aim of this approach by NHMRC is to assist clinical practice guideline developers with a structured process for evaluating the evidence base corresponding to a particular key clinical question, in the context of the setting in which it is to be applied.

The grading methodology allows for both the quality of the evidence and the strength of recommendations to be determined. Where insufficient evidence exists to formulate a grade, a practice point may be assigned instead. The NHMRC grading framework allows for these practice points to be included when developers consider it is important to provide non-evidence-based guidance.

The NHMRC Recommendation Form sets out the basis for rating five key components of the 'body of evidence' for each recommendation. These components are:

1. The evidence base, in terms of the number of studies, level of evidence and quality of studies (risk of bias)
2. The consistency of the study results
3. The potential clinical impact of the proposed recommendation
4. The generalisability of the body of evidence to the target population for the guideline
5. The applicability of the body of evidence to the Australian healthcare context.

The first two components describe the internal validity of the study data in support of efficacy (for an intervention), accuracy (for a diagnostic test), or strength of association (for a prognosis or aetiological question). As suggested, the third component gives the likely clinical impact of the proposed recommendation. The final two components assess external factors that may influence the effectiveness of the proposed recommendation in practice, in terms of generalisability of study results to the intended target population for the guideline and setting of the proposed recommendation, and applicability to the Australian (or other local) health care system.[11]

These described components should be rated according to the body of evidence matrix (refer to Table 3). The matrix system is used to summarise the rating of the five key components which allows each recommendation to be assigned an overall NHMRC Grade of Recommendation (A-D).[10]

Table 4: NHMRC body of evidence matrix[11]

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence basea	One or more level I studies with a low risk of bias or several level II studies with a low	One or more level I studies with a moderate or high risk of bias, one or two level II studies	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of	Level IV studies, or level I to III studies/SRs with a high risk of bias

Component	A	B	C	D
	risk of bias	with a low risk of bias or several level III studies with a low risk of bias	bias	
Consistencyb	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impactc	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer	Population/s studied in the body of evidence are similar to the target population for the guideline: some studies were in women treated for breast cancer and some studies were in a general menopausal population	Population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population: all studies were in a general menopausal population	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery	Applicable to Australian healthcare context with few caveats: most studies were conducted in Australia or developed countries with similar levels of health service delivery	Probably applicable to Australian healthcare context with some caveats: some studies were conducted in Australia or developed countries with similar levels of health service delivery	Not applicable to Australian healthcare context: studies were conducted in settings not relevant to the Australian health system

SR = systematic review; several = more than two studies

a Level of evidence determined from the NHMRC hierarchy

b If only one study is present, component is ranked as 'not applicable'

c If there is evidence of no effect rank this component as 'not applicable'.

There is also capacity to note any other relevant factors that were considered by the guideline developers and the respective working group when judging the body of evidence and developing the wording of the recommendation.

The NHMRC grades given (A-D) are intended to indicate the strength of the body of evidence underpinning the recommendation (refer to Table 5). Grade A or B recommendations are generally based on a body of evidence that can be trusted to guide clinical practice, whereas Grades C or D recommendations must be applied cautiously to individual clinical and organisational circumstances and should be interpreted with care. A recommendation cannot be graded A or B unless evidence base and consistency of the evidence are both rated A and B respectively.[11]

Table 5: Definition of NHMRC grades of recommendations[10, 11]

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

By referring to the summaries of evidence in combination with the NHMRC body of evidence matrix, a grade for each recommendation was derived from the respective grades allocated to the five key components. Grading the components of evidence base, consistency, clinical impact, generalisability and applicability, was undertaken by the working group members, who discussed each section, and based on consensus achieved across the working group, arrived at these ratings.

The use of the NHMRC evidence table hierarchy table, categorises the respective study level according to the study design (refer to Table 6). This is used to determine the respective grades for evidence base and consistency of the recommendation.

Implementing the NHMRC Evidence Hierarchy, each included study in a systematic review should be assessed according to the following three dimensions of evidence:

1. Strength of evidence (level of evidence, quality of evidence (risk of bias) and statistical precision
2. Size of effect (assessing the clinical importance of the findings of each study and hence addressing the

clinical impact component of the body of evidence matrix.

3. Relevance of evidence (translation of research evidence into clinical practice and is potentially the most subjective of the evidence assessments).[10, 11]

Table 6: NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question[10, 11]

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening intervention
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorando mised controlled trial(i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorando mised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised, experimental trial

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening intervention
	• Cohort study • Case-control study • Interrupted time series with a control group				• Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Appendix 2: Evidence Summaries

The Evidence Summaries are based on the evidence base identified in the Cancer Australia systematic reviews conducted for this guideline. Further details are available in the Cancer Australia systematic reviews and the Summary of Evidence sections. The systematic reviews focused on evidence for the management of menopausal symptoms in women who have received treatment for breast cancer and the general female menopausal population for the same interventions plus selected ones that have not been previously researched in a breast cancer population.

ES1

One RCT (with a moderate risk of bias; Brazil) in women after breast cancer found that 4 weeks of bupropion (300 mg/day) had no statistically significant effect on the severity of hot flushes compared with placebo.[29]

ES2

One RCT (with a low risk of bias; USA) in **women after breast cancer** found that paroxetine (10 or 20 mg/d for 4 weeks) significantly reduced hot flush frequency and severity compared with placebo.[14]

Three RCTs (with a low to moderate risk of bias; USA) in **women after breast cancer** found that neither fluoxetine (20 mg/d for 4 weeks)[15] nor sertraline (25 to 100 mg/d for 4-6 weeks)[16, 17] had a consistent effect on hot flushes compared with placebo.

ES3

One RCT (with low risk of bias; the Netherlands) in **women after breast cancer** found that 12 weeks of venlafaxine at 75 mg/d (slow release) significantly reduced hot flush frequency and severity compared with placebo.[20]

One RCT (with moderate risk of bias; USA) in **women after breast cancer** found that 14 weeks of venlafaxine at 37.5mg/d significantly reduced hot flush frequency and severity compared with placebo.[21]

One RCT (with a low risk of bias; the Netherlands) in **women after breast cancer** found that venlafaxine (75mg/d for 12 weeks) was equally effective as clonidine (0.1mg/d for 12 weeks) at reducing hot flush frequency and severity.[20]

One cross-over RCT (with a moderate risk of bias; the Netherlands) in **women after breast cancer** found that venlafaxine (75mg/d for 8 weeks) was equally effective as clonidine (0.1mg/d for 8 weeks) at reducing hot flush frequency and severity.[22]

One RCT (with a moderate risk of bias; Germany) in **women after breast cancer** found that venlafaxine (75mg/d for 4 weeks) was more effective than clonidine (0.15mg/d for 4 weeks) at reducing the frequency of hot flushes.[23]

One RCT (with a moderate risk of bias; Canada) in **women after breast cancer** found that 4 weeks of venlafaxine (37.5mg/d for 7 days and 75mg/d for 21 days) or gabapentin (300mg/d for 3 days, 900mg/d for 3 days, and 1200mg/d for 22 days) were associated with equivalent reductions in hot flash scores.[24]

One RCT (with a moderate risk of bias; USA) in **women after breast cancer** found 12 weeks of venlafaxine (37.5mg/d for 1 week and 75mg/d for 11 weeks) or a course of acupuncture (twice per week for 4 weeks, and once per week for 8 weeks) were associated with similar reductions in hot flash frequency and severity.[25]

ES4

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** found that augmentation of an SSRI or SNRI with 5 weeks of zolpidem (10mg/d) has no statistical significant additional effect on vasomotor symptoms compared to placebo.[30]

ES5

One RCT (with a low risk of bias; the Netherlands) **in women after breast cancer** found that clonidine (0.1 mg/d) significantly reduced the frequency and severity of hot flushes relative to placebo.[20]

ES6

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** found that 4-8 weeks of gabapentin (900 mg/d) was associated with a reduction in hot flush frequency and severity compared with placebo.[31]

Three RCTs (two with a moderate risk of bias and one with a high risk of bias; Canada, Iran, Italy) **in women after breast cancer** found that 4-12 weeks of gabapentin (900mg/d or 300mg/d) was associated with a significant reduction in hot flush frequency and severity compared with baseline[24, 32, 33] and one of the RCTs found a significant reduction in hot flush frequency between groups.[32] In one of these RCTs the effect size was equivalent to that observed with venlafaxine (37.5mg/d for 7 days and 75mg/d for 21 days,[24] and in another the effect size was less than that observed with megestrol acetate (40mg/d)[32].

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** found that 8 weeks of gabapentin (300g/day for 3 days, then 900mg/day for 8 weeks) did not significantly reduce hot flush frequency and severity compared with placebo, but the gabapentin group experienced improvement in hot flushes compared with baseline.[55]

ES7

One RCT (with a low risk of bias; multinational) **in women after breast cancer** found that tibolone (2.5 mg/d) for up to 2.75 years significantly reduced the frequency and severity of hot flushes compared with placebo.[34, 35]

One RCT (with high risk of bias; Sweden) **in women after breast cancer** found that menopause hormone therapy (sequential or combined oestrogen/progestogen for 24 months) and electro-acupuncture (for 12 weeks) statistically significantly reduced the number of night-time hot flushes over 2 years[37]. Menopause hormone therapy appeared to be more effective than electro-acupuncture although between□group

statistical significance was not reported[36, 37].

ES8

One RCT (with a moderate risk of bias; UK) **in women after breast cancer** found that purpose-designed group CBT (90min per week for 6 weeks) alone versus usual care had no effect on the frequency of hot flushes, but reduced the problem rating of hot flushes and night sweats.[45]

One RCT (with a moderate risk of bias; the Netherlands) **in women after breast cancer** found that purpose-designed group CBT (90min per week for 6 weeks) in combination with physical exercise (2.5 to 3 hours per week) compared with no intervention reduced the problem rating of hot flushes and night sweats.[46]

ES9

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** reported that a purpose-designed hypnotherapy protocol delivered once/week for 5 weeks reduced hot flush frequency and severity compared with no treatment.[48]

ES10

One RCT (with a low risk of bias; Norway) **in women after breast cancer** comparing acupuncture (needle inserted 0.5-3cm deep for 30min) with sham acupuncture (needle inserted 2-3mm deep for 30min), reported a reduction in frequency and severity of hot flushes with acupuncture.[49]

Two RCTs (with a moderate risk of bias; Sweden, USA) **in women after breast cancer** found no difference between acupuncture (needle inserted 5–20 mm deep for 20min or 0.25 to 0.5 inches deep) and sham acupuncture, in terms of frequency and severity of hot flushes.[50, 51]

One RCT (with a low risk of bias; Denmark) **in women after breast cancer** reported acupuncture (for 15-20min once a week) reduced the nuisance of hot flushes, but did not report between-group differences compared with sham or no treatment.[52]

One RCT (with a high risk of bias; USA) **in women after breast cancer** found that acupuncture (for 12 weeks) and venlafaxine (75mg/d for 12 weeks) were equally effective at reducing the frequency and severity of hot flushes.[25]

One RCT (with a high risk of bias; Sweden) **in women after breast cancer** found that electro-acupuncture (for 12 weeks) and menopause hormone therapy (for 24 months) were effective at reducing night-time hot flushes compared to baseline.[36, 37]

One RCT (with a high risk of bias; Sweden) **in women after breast cancer** found electro-acupuncture (for 12 weeks) and applied relaxation (for 12 weeks) were equally effective at decreasing the frequency of hot flushes and improving the Kuppermann Index compared to baseline.[53, 54]

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** found that electro-acupuncture

(twice per week for 2 weeks, then once per week for 6 weeks) reported no statistically significant difference in hot flush frequency and severity compared with sham acupuncture, but electro-acupuncture was more effective at improving hot flush frequency and severity compared with baseline than the sham acupuncture, placebo and gabapentin groups (300mg/d for 2 weeks, then 900mg/day for 6 weeks).[55]

ES11

One RCT (with a low risk of bias; UK) **in women after breast cancer** reported reduced hot flush frequency and severity during relaxation therapy treatment at one month (one hour session and a 20min tape to use once a day) versus no treatment.[58]

ES12

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** found that an 8-week yoga program reduced the frequency and severity of hot flushes compared with no intervention.[60]

One RCT (with a moderate risk of bias; Germany) **in women after breast cancer** reported significant improvement in total menopausal symptoms with yoga and meditation (Hatha yoga, 90min/week for 12 weeks) compared with usual care.[61]

ES13

Two RCTs (with a low to moderate risk of bias; both from USA) **in women after breast cancer** reported no difference in severity and frequency of hot flushes between black cohosh (1 capsule, Cimicifuga racemosa 20 mg BID) and placebo.[66, 67]

One RCT (with a high risk of bias; Venezuela) **in women after breast cancer** compared tamoxifen (20mg/d) with black cohosh (1 capsule, Cimicifuga racemosa, CR BNO 1055) for 12 months, but did not adequately report data on the frequency or severity of hot flushes.[68]

ES14

Two RCTs (with a low and high risk of bias; UK and USA respectively) **in women after breast cancer** found no effect of homeopathy (in tablet, granule, or liquid form) compared with placebo on hot flush frequency or severity.[70, 71]

ES15

Three RCTs (with a low to high risk of bias; Canada, Finland, UK) **in women after breast cancer** found no effect of phytoestrogens (tablets, 114 mg of isoflavonoids or soybean beverage or 235 mg of soy extract with 17.5 mg of Isoflavones 70mg/d) versus placebo on the Kupperman's Index, as well as no effect on the frequency or severity of hot flushes.[72-74]

ES16

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** found that 3 days of magnetic therapy (6 magnets on acupuncture pressure sites per participant) had no effect on the severity of hot flushes compared with placebo, while placebo was reported to have had a greater effect on frequency of hot flushes compared with magnetic therapy.[77]

ES17

One RCT (with a low risk of bias; USA) **in women after breast cancer** found that paroxetine (10 or 20 mg/d for 9 weeks) was associated with an improvement in sleep compared with placebo.[14]

One RCT (with a low risk of bias; USA) **in women after breast cancer** found that there fewer reports on trouble sleeping in the fluoxetine (20 mg/d) arm at 9 weeks relative to baseline, but did not report between group differences for sleep disturbance compared with placebo.[15]

ES18

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** found no difference in sleep disturbance between venlafaxine 75 mg/d and placebo.[21]

Three RCTs (one with a low risk of bias and two with a moderate risk of bias; Germany, the Netherlands) **in women after breast cancer** compared venlafaxine versus clonidine (Boekhout 2011, Buijs 2009, Loibl 2007), and only one of the three studies found an improvement in sleep for venlafaxine compared to clonidine.[22]

One RCT (with a moderate risk of bias; USA) **in women after breast** reported no statistical comparison between venlafaxine versus acupuncture.[25]

ES19

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** receiving an SSRI or SNRI for vasomotor symptoms found an improvement in sleep disturbance with 5 weeks of zolpidem (10 mg/d) augmentation compared with placebo.[30]

ES20

One RCT (with a moderate risk of bias: USA) **in women after breast cancer** reported that gabapentin (300mg/d or 900mg/d) had no effect on sleep compared to placebo.[31]

One cross-over RCT (with a moderate risk of bias; Canada) **in women after breast cancer** reported that gabapentin (900mg/d for 4 weeks) had no difference in sleeplessness compared to venlafaxine (75mg/d for 4 weeks).[24]

One RCT (with a moderate risk of bias; Italy) **in women after breast cancer** reported that gabapentin (900mg/d for 12 weeks) improved sleep quality (measured using the Pittsburgh Sleep Quality Index score) compared to Vitamin E (800 IU/d for 12 weeks).[33]

ES21

One RCT (with a low risk of bias; multinational) **in women after breast cancer** found that tibolone (2.5mg/d) was associated with an improvement in sleep quality compared with placebo (LIBERATE study) (Sismondi 2011). An earlier analysis from the LIBERATE study reported insomnia as an adverse event, but did not report between-group differences.[34]

One RCT (with a high risk of bias; Sweden) **in women after breast cancer** found menopause hormone therapy (2mg of oestradiol with different progestogens) improved sleep compared with no treatment.[78] One RCT (with a moderate risk of bias; Sweden) **in women after breast cancer** found that menopause hormone therapy (for 24 months) and electro-acupuncture (for 12 weeks) improved sleep relative to baseline, but did not report between group differences.[37]

ES22

One RCT (with a moderate risk of bias; UK) **in women after breast cancer** found that CBT (90min per week for 6 weeks) significantly improved sleep compared with usual care.[45]

One RCT (with a low risk of bias; USA) **in women after breast cancer** reported a statistically significant improvement in sleep efficiency scores and sleep latency scores with cognitive behavioural therapy for insomnia (CBTI, 30-60min once a week for 6 weeks) compared with behavioural placebo treatment (BPT); but found no significant improvement on wake after sleep onset scores or number of awakenings with CBTI compared with BPT.[79]

One RCT (with moderate risk of bias; USA) **in women after breast cancer** found that hypnotherapy (once a week for 5 weeks) improved sleep compared with no treatment .[48]

ES23

One RCT (with moderate risk of bias; USA) **in women after breast cancer** found that an 8-week yoga program significantly improved sleep compared with no intervention.[60]

One RCT (with low risk of bias; Denmark) **in women after breast cancer** found that acupuncture (for 15-20min once a week) significantly improved sleep compared with sham-acupuncture and no treatment groups, but did not report between-group differences from baseline.[52]

ES24

One RCT (with moderate risk of bias; Italy) **in women after breast cancer** found that gabapentin (900mg/d for 12 weeks) improved sleep quality (measured using the Pittsburgh Sleep Quality Index score, PSQI), compared with Vitamin E (800 IU/d for 12 weeks) which had no effect on the PSQI score.[33]

ES25

Three RCTs (two with low and one with a moderate risk of bias; Brazil; two from USA) **in women after breast**

cancer reported no difference in sexual function as measured by the ASEX, BDI single item, MOS SPI or SAQ, after 4-12 weeks of treatment with antidepressants, including bupropion 300 mg/d[29], fluoxetine 20 mg/d[15] or paroxetine 10-20 mg/d[14] compared with placebo.

One cross-over RCT (with a low risk of bias; the Netherlands) **in women after breast cancer** found that neither venlafaxine (75mg/d for 8 weeks) nor clonidine (0.1mg/d for 8 weeks) had an effect on sexual activity as measured by the Sexual Activity Questionnaire Scales.[22]

One RCT (with a moderate risk of bias; the Netherlands) **in women after breast cancer** found no differences in sexual function as measured by the Sexual Activity Questionnaire for venlafaxine (75mg/d for 12 weeks), clonidine (0.1mg/d for 12 weeks) or placebo.[20]

One RCT (with moderate risk of bias; Canada) **in women after breast cancer** reported increase in difficulty achieving orgasm as measured using a symptom diary for venlafaxine (75mg/d) compared to gabapentin (300mg/d or 900mg/d).[24]

ES26

One RCT (with a low risk of bias; multinational) **in women after breast cancer** found an improvement in sexual behaviour and vaginal dryness for tibolone (2.5 mg/d for 2.75 years) compared with placebo.[35]

Two RCTs (with a high risk of bias; Sweden, UK) **in women after breast cancer** found inconsistent effects of menopause hormone therapy on sexual enjoyment, sexual activity and discomfort compared with no treatment control.[78, 82]

ES27

One RCT (with a low risk of bias; South Korea) **in women after breast cancer** found that 12 weeks with a non-hormonal vaginal gel was associated with a statistically significant improvement in a range of vaginal symptoms, compared with placebo.[80]

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** found that 8 weeks of topical lidocaine treatment (4% solution for 3 minutes) was associated with a statistically significant improvement in vulvovaginal symptoms including dyspareunia, compared with placebo.[81]

ES28

One RCT (with a moderate risk of bias; the Netherlands) **in women after breast cancer** found that CBT alone or in combination with physical exercise improves sexual function compared with wait list control.[46]

One RCT (with a moderate risk of bias; USA) **in women after breast cancer** found that a 5 weeks course of hypnotherapy had no statistically significant effect on the impact of hot flushes on sexuality compared to no treatment control.[48]

ES29

One RCT (with a low risk of bias; multinational) in **women after breast cancer** found that tibolone (2.5 mg/d) was associated with a significantly higher rate of new breast cancer events compared with no treatment.[34]

One RCT (with a high risk of bias; Sweden) of menopause hormone therapy (combined oestradiol/medroxyprogesterone) in **women after breast cancer** was terminated early due to safety concerns related to breast cancer recurrence.[91]

One RCT (with a high risk of bias; Sweden) in **women after breast cancer** found that menopause hormone therapy (sequential or continuous combined oestrogen/progestogen) was associated with a significantly higher rate of new breast cancer events compared with no treatment, resulting in the early termination of this study.[90]

ES30

Two RCTs (overall risk of bias of included studies not reported; both USA identified in one Systematic Review (with a low risk of bias; USA; Shams 2014)[18] **in peri- and postmenopausal women** (women with breast cancer were not included) found that 8 weeks of escitalopram (10-20 mg/d) significantly reduced hot flush frequency compared with placebo. One of these RCTs (with a low risk of bias), also identified in one pooled analysis in **peri- and postmenopausal women** (with at least 14 bothersome vasomotor symptoms per week), found that 8 weeks of escitalopram (10 mg/d) significantly reduced vasomotor symptom frequency and bother compared with placebo.[19, 102]

ES31

One RCT (with a low risk of bias; USA) identified in a pooled analysis **in peri- and postmenopausal women** (with at least 14 bothersome vasomotor symptoms per week) found that 8 weeks of low-dose venlafaxine XR (37.5 mg/d for the first week, then 75 mg/d) significantly reduced vasomotor symptom frequency and bother compared with placebo.[19, 26]

ES32

Six RCTs (all with a low risk of bias; countries not reported) identified in one Systematic Review (with a low risk of bias; Sun 2013) **in postmenopausal women** (healthy with an unknown breast cancer history) found that 12 weeks of desvenlafaxine (100 mg or 150 mg daily) significantly reduced hot flush frequency compared with placebo.[27]

Seven RCTs (with an unclear risk of bias; Europe, North America, South Africa) identified in one Systematic Review (with a moderate risk of bias; Berhan 2014) in **postmenopausal women** (with at least seven moderate to severe hot flushes per day) found that 12 or more weeks of desvenlafaxine (≥100 mg/d) significantly reduced hot flush frequency and severity compared with placebo.[28]

ES33

Four RCTs (with a high risk of bias; Austria, Denmark, Spain, Sweden, Switzerland, the Netherlands, Turkey, UK, USA) identified in a Systematic Review (with a low risk of bias; Formoso et al 2012) in **postmenopausal**

women (including women surgically treated for breast cancer) found that tibolone (2.5 mg/d) significantly reduced hot flush frequency compared with placebo.[38]

ES34

Nine RCTs (overall risk of bias of included studies not reported; France, Norway, Russia, two from UK, four from USA) identified in a Systematic Review (with a low risk of bias; MacLennan et al 2004) in **peri- and postmenopausal women** (not including women with breast cancer) found that oral hormone therapy (oestrogen and combined oestrogen/progestogen therapy) significantly reduced the frequency and severity of hot flushes compared with placebo.[39]

ES35

One RCT (with a low risk of bias; USA) **in menopause transition and postmenopausal women** found a significant reduction in vasomotor symptom frequency and severity with low dose oestradiol (0.5mg/d for 8 weeks) and with venlafaxine (37.5mg/d for 1 week, then 75mg/d for 7 weeks) compared with placebo. Reduction of vasomotor symptom frequency was greater in the low estradiol group (53%) compared with the venlafaxine group (48%). Reduction in vasomotor symptom bother was found to be significant with the low oestradiol group compared with placebo, but not significant with the venlafaxine group compared with placebo.[19, 26]

ES36

Five RCTs (all with a low risk of bias; Finland, four from USA) identified in a Systematic Review (with a low risk of bias; Cui et al 2013) in **postmenopausal women** with vulvovaginal dyspareunia and atrophy found that at 12 weeks, ospemifene (60 mg/d) significantly increased hot flushes compared with placebo.[43]

ES37

Seven RCTs (with a low risk of bias; USA) and two RCTs (with a high risk of bias; Italy, USA) identified in a Systematic Review (with a low risk of bias; Corbelli et al 2014) in **postmenopausal women** (at least seven hot flushes per day and/or at least 50 hot flushes per week) found that transdermal low-dose oestradiol (< 0.05 mg/d) significantly reduced hot flush frequency compared with placebo; greater reductions were seen with the higher dose range (0.029 mg/d to 0.045 mg/d) than the lower doses.[40]

ES38

Five RCTs (with an unknown risk of bias; locations not reported) identified in a Systematic Review (with a moderate risk of bias; Derzko et al 2016) in **postmenopausal women** (natural or surgically induced) found that transdermal oestradiol gel preparations (0.25-1.5 mg/day) significantly reduced hot flush frequency and severity compared with placebo. The greatest effect was seen with dosing around 1mg/day but this also caused the greatest number of adverse events.[41]

ES39

Two RCTs (overall risk of bias of included studies not reported; both from USA) analysed in a Systematic Review (with a low risk of bias; Somboonporn et al 2005) **in peri- and postmenopausal women** (natural or surgically-induced, with or without a history of breast cancer) found no significant differences in vasomotor symptoms between combined testosterone and menopause hormone therapy versus menopause hormone therapy alone.[44]

ES40

Three RCTs (one with a low and two with moderate risk of bias; Australia, UK, USA) identified in a Systematic Review (with a moderate risk of bias; Whelan et al 2013) **in postmenopausal women** reported on compounded progesterone cream and vasomotor symptoms. One of the RCTs found a significant improvement in vasomotor symptom severity for a compounded progesterone cream compared with placebo, while two of the RCTs found no significant difference in vasomotor symptom severity between commercially available progesterone creams and placebo.[42]

ES41

One RCT (with an unknown risk of bias; UK) identified in a Systematic Review (with a moderate risk of bias; Velez Toral 2014) in **peri- and postmenopausal women** found that CBT (120 min per week for 4 weeks) significantly reduced hot flushes and night sweats compared with no intervention.[47]

ES42

One RCT (with a low risk of bias: USA) **in menopause transition and postmenopausal women** found that exercise (3 times per week of either treadmill, elliptical trainer, or stationary bicycle for 12 weeks) had no significant reduction in vasomotor symptom frequency and bother compared with the usual activity control group.[19, 65]

A meta-analysis of three RCTs (one low risk of bias, two with a high risk of bias; Finland, two from USA), including Sternfeld et al (2014), identified in a Systematic Review (with a low risk of bias; Daley et al 2014) **in peri- and postmenopausal women** (excluding women with breast cancer) found that exercise (of any type) did not significantly reduce the frequency of hot flushes/night sweats compared with no active treatment.[64, 65]

One RCT (with an unknown risk of bias; USA) identified in a Systematic Review (with a moderate risk of bias; Woods et al 2014) **in menopausal women** (excluding trials exclusively conducted in women with breast cancer) found that exercise did not significantly reduce vasomotor symptoms compared with no exercise or oestradiol.[63]

ES43

One RCT (with a low risk of bias; USA; Newton 2014 and Guthrie 2015) **in menopause transition and postmenopausal women** found that yoga (90min weekly class for 12 weeks) did not significantly reduce vasomotor symptom frequency and bother compared with usual activity.[19]

One RCT (with an unknown risk of bias; India) identified in a Systematic Review (with a moderate risk of bias;

Woods et al 2014) **in menopausal women** (excluding trials exclusively conducted in women with breast cancer) found that 8 weeks of integrated yoga therapy (1 h/day, 5 days/week) significantly reduced vasomotor symptoms compared with exercise.[63]

One additional RCT (with a high risk of bias; USA) identified in a Systematic Review (with a low risk of bias; Daley et al 2014) **in peri- and postmenopausal women** (excluding women with breast cancer) found that there was no significant difference between yoga (up to 12 sessions) and exercise in reducing vasomotor symptoms.[64]

ES44

Four RCTs (overall risk of bias of included studies not reported; Sweden, UK, USA) identified in a Systematic Review (with a low risk of bias; Saensk et al 2014) in **peri- and postmenopausal women** (including women with breast cancer) found that 12 weeks of relaxation techniques did not significantly reduce hot flush frequency or severity compared with placebo/no treatment or acupuncture/superficial needling.[59]

ES45

Nine RCTs (overall risk of bias of included studies not reported; Denmark, Korea, Norway, Sweden, five from USA) identified in a Systematic Review (with a low risk of bias; Dodin et al 2013) in **peri- and postmenopausal women** (including women with breast cancer) found that acupuncture significantly reduced hot flush severity, but not frequency, compared with sham acupuncture. Three RCTs (with a high risk of bias; China, Sweden) identified in the same Systematic Review found that hormone therapy significantly reduced hot flush frequency, but not severity, compared with acupuncture.[56]

One RCT (with a low risk of bias; Australia) in peri- and postmenopausal women reported no statistically significant difference in hot flush frequency or severity for acupuncture compared with sham acupuncture (10 treatments over 8 weeks for both).[57]

ES46

15 RCTs (with an unknown risk of bias; Brazil, Canada, Ecuador, Iran, Italy, Japan, Korea, Taiwan, UK, USA) identified in a Systematic Review (with a moderate risk of bias; Thomas 2014) in **peri- and early postmenopausal women** (with hot flushes and at least one co-occurring symptom) found an inconsistent benefit of soy and other isoflavones on vasomotor symptoms compared with placebo and other nutritional comparators.[75]

ES47

One RCT (with a low risk of bias; USA) **in menopause transition and postmenopausal women** found that 12 weeks of omega-3 supplement (1.8 grams daily: EPA; 425mg, DHA; 100mg, omega-3 90mg) did not significantly improve vasomotor symptoms frequency or bother compared with placebo.[19, 76]

ES48

Five RCTs (overall risk of bias of included studies not reported; Switzerland, four from USA) identified in a Systematic Review (with a low risk of bias; Leach and Moore 2012) in **peri- and postmenopausal women** (including women with breast cancer) found that black cohosh (40 mg/d) did not reduce vasomotor symptom frequency or bother compared with placebo.[69]

ES49

One RCT (overall risk of bias of included study not reported; USA) identified in a Systematic Review (with a low risk of bias; Shams et al 2014) **in peri- and postmenopausal women** found that escitalopram had no statistical effect on sleep disturbance compared to placebo.[18]

ES50

Three RCTs (with a low risk of bias; all USA) identified in a Systematic Review (with a low risk of bias; Sun et al 2013) **in postmenopausal women** (healthy with an unknown breast cancer history) found that 12 weeks of desvenlafaxine (100mg or 150mg daily) significantly reduced the number of night-time awakenings compared with placebo.[27]

ES51

One RCT (overall risk of bias of included studies not reported; multinational: Asia, Australia, Europe, USA) identified in a Systematic Review (with a low risk of bias; Formoso et al 2012) **in postmenopausal women** (including women surgically treated for breast cancer) found that tibolone (2.5 mg/d for more than two years) did not reduce the frequency of insomnia compared with placebo.[38]

ES52

Two RCTs (with an unknown risk of bias; India, USA) identified in a Systematic Review (with a moderate risk of bias; Woods et al 2014) **in menopausal women** (excluding trials exclusively conducted in women with breast cancer) found that physical activity/exercise had no significant effect on sleep symptoms.[63]

One RCT (with a low risk of bias: USA) **in menopause transition and postmenopausal women** found that exercise (3 times per week of treadmill, elliptical trainer, or stationary bicycle for 12 weeks) significantly improved sleep quality and insomnia symptoms compared to the usual activity control group.[19, 65]

ES53

One RCT (with an unknown risk of bias; India) identified in a Systematic Review (with a moderate risk of bias; Woods 2014) **in menopausal women** (excluding trials exclusively conducted in women with breast cancer) found that yoga significantly improved sleep symptoms compared to baseline, but there was no significant difference between the effect of yoga and exercise on sleep symptoms.[63]

One RCT (with a low risk of bias; USA) **in menopause transition and postmenopausal women** found that yoga (90min weekly class for 12 weeks) significantly improved insomnia symptoms compared with usual activity. [19, 62]

ES54

One small RCT (with an unknown risk of bias; USA) identified in a Systematic Review (with a moderate risk of bias; Woods et al 2014) in **menopausal women** (excluding trials exclusively conducted in women with breast cancer) found that relaxation therapy significantly improved sleep symptoms compared with a waitlist control.[63]

ES55

One RCT (with an unknown risk of bias; Italy) identified in a Systematic Review (with a moderate risk of bias; Thomas et al 2014) in **peri- and early postmenopausal women** (with hot flushes and at least one co-occurring symptom) found that an isoflavones combined with magnolia bark extract, magnesium, lactobacillus, calcium and Vitamin D3 significantly reduced insomnia at 12 weeks compared to calcium and Vitamin D3 alone; other trials in this systematic review found that soy and other isoflavones did not significantly improve sleep symptoms.[75]

ES56

One RCT (with a low risk of bias; USA) **in peri- and postmenopausal women** reported no significant effect on sleep quality and insomnia with omega-3 fatty acid supplementation compared to placebo.[76]

ES57

One RCT (overall risk of bias of included studies not reported; USA) identified in a Systematic Review (with a low risk of bias; Shams et al 2014) **in peri- and postmenopausal women** reported no significant effect on libido with escitalopram compared to placebo.[18]

ES58

One RCT (with a low risk of bias; USA) **in menopause transition and postmenopausal women** found that 8 weeks of low-dose oestradiol (0.5mg/day) or venlafaxine (37.5mg/day for 1 week and 75mg/day for 7 weeks) did not significantly altered sexual function (measured with Female Sexual Function Index) compared to placebo; but venlafaxine significantly improved vaginal dryness compared to the placebo group.[83]

ES59

Nine RCTs (overall risk of bias of included studies not reported; Australia, USA and multinational) identified in a Systematic Review (with a low risk of bias; Somboonporn et al 2005) **in peri- and postmenopausal women** (natural or surgically-induced, with or without a history of breast cancer) found a statistically significant improvement in sexual function with testosterone in combination with menopause hormone therapy compared with menopause hormone therapy alone.[44]

ES60

Thirty five RCTs (various locations) identified in a Systematic Review (with a low risk of bias; Elraiyah et al 2014) **in postmenopausal women** (with an unknown history of breast cancer) found a statistically significant improvement in sexual function with therapy containing testosterone compared with therapy without testosterone.[87]

ES61

Four RCTs (with a high risk of bias; multinational: Asia, Australia, Europe, USA) identified in a Systematic Review (with a low risk of bias; Formoso et al 2012) **in postmenopausal women** (including women surgically treated for breast cancer) found that tibolone (2.5 mg/d for more than two years) did not significantly reduce vaginal dryness or dyspareunia compared with placebo.[38]

ES62

Twenty seven RCTs (overall risk of bias of included studies not reported; 30 countries in Asia, Australia, Europe, South America, USA) identified in a systematic review (with a low risk of bias, Nastri el al 2013) **in postmenopausal women** found that menopause hormone therapy (oestrogen transdermal patch 0.014 mg/day; oestrogen gel 0.87 g/d, oestrogen gel 1.7 g/d, 2.6 g/d; oestrogen spray 150mcg/day or 300mcg/day; oestrogen vaginal ring 50mcg/day or 100mcg/day or conjugated equine estrogen 0.625mg plus medroxyprogesterone acetate 2.5mg daily; for 12 weeks) did not significantly improve sexual function (composite score) compared with control, but did show a small to moderate benefit in sexual function compared with control.[84]

ES63

Nineteen RCTs (overall risk of bias of included studies not reported; Australia, Europe, North America, Thailand) identified in a Systematic Review (with a low risk of bias; Suckling et al 2006) **in postmenopausal women** with vaginal atrophy (without a history of hormone-dependent neoplasia) found that at least three months of vaginally administered oestrogen rings, creams or tablets were each equally effective at relieving the symptoms of vaginal atrophy, while being more effective than placebo.[85]

Fourteen RCTs and prospective comparative studies (seven with a low risk of bias, six with a moderate risk of bias and one with a high risk of bias; Europe, Israel, UK, USA) identified in a Systematic Review (with a low risk of bias; Rahn et al 2014) in **postmenopausal women** with genitourinary syndrome of menopause (excluding women with breast cancer) found that vaginal oestrogen was more effective than placebo in the relief of vaginal dryness, itching, and dyspareunia.[86]

ES64

Six RCTs (overall risk of bias of included studies not reported; locations not reported) identified in a Systematic review (with a moderate risk of bias; Ghazanfarpour et al 2015) in **menopausal women** found that soy isoflavones had an uncertain effect on vaginal dryness and dyspareunia compared to placebo.[88]

ES65

Two RCTs (USA) identified in a Systematic Review (with a low risk of bias; Cui et al 2013) in **postmenopausal women** with vulvovaginal dyspareunia and atrophy found that oral ospemifene (60 mg/d) significantly reduces dyspareunia compared with placebo.[43]

Twenty seven RCTs (overall risk of bias of included studies not reported; Brazil, Denmark, Estonia, Italy, Poland, Romania, Sweden, Taiwan, the Netherlands, USA and multinational) identified in a systematic review (with a low risk of bias, Nastri el al 2013) **in postmenopausal women** found that SERMs (bazedoxifene 20 mg alone or plus conjugated estrogens 0.45mg or 0.625mg daily; for 12 weeks) did not significantly improve sexual function (composite score) compared with control; but showed a small benefit in sexual function when compared with control.[84]

ES66

Thirty-five RCTs (overall risk of bias of included studies not reported; Australia, Brazil, Canada, Italy, Sweden, UK, USA and multinational) identified in a Systematic Review (with a low risk of bias; Somboonporn et al 2005) **in peri- and postmenopausal women** (natural or surgically-induced, with or without a history of breast cancer) did not report the effect of long term use of testosterone. The authors acknowledged that testosterone should be used with caution as the dose, duration, safety and long-term effects have not been established.[44]

ES67

Two RCT (overall risk of bias of included studies not reported; multinational and USA) in a Systematic Review (with a low risk of bias; Formoso et al 2012) **in postmenopausal women** reported that tibolone (1.25 mg/day) was associated with a significant reduction in breast cancer occurrence compared with placebo.[38]

Two RCTs (overall risk of bias of included studies not reported; Brazil and USA) in a Systematic Review (with a low risk of bias; Formoso et al 2012) **in postmenopausal women** reported no significant difference in the risk of breast cancer with tibolone (2.5 mg/day) compared to placebo.[38]

Four RCTs (overall risk of bias of included studies not reported; multinational: Chile, Europe, USA) in a Systematic Review (with a low risk of bias; Formoso et al 2012) **in postmenopausal women** reported no significant difference in breast cancer occurrence for tibolone (2.5 and 1.25 mg/day) compared with menopause hormone therapy. The authors acknowledge that the follow-up duration in these studies may be insufficient to fully assess the risk of breast cancer associated with tibolone.[38]

Appendix 3: Recommendation Grading Forms

Recommendation 1 - CBT for vasomotor symptoms

Evidence summaries

- ES8
- ES41

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Duijts 2012	Breast cancer	CBT	II	moderate	the Netherlands
Mann 2012	Breast cancer	CBT	II	moderate	UK
Velez Toral 2014	Menopause	CBT	I	moderate	UK

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	one level I study with a moderate risk of bias, two level II studies with a moderate risk of bias
2. Consistency	C	some inconsistency reflecting genuine uncertainty around clinical question
3. Clinical impact	D	slight or restricted
4. Generalisability	B	population/s studied in the body of evidence are similar to the target population for the guideline: some studies were in women treated for breast cancer and some studies were in a general menopausal population
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Purpose-designed cognitive behavioural therapy can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer.	**GRADE OF RECOMMENDATION** **C**

Recommendation 2 and Practice Point A - Physical activity for vasomotor symptoms and sleep disturbance

Evidence summaries - Yoga

- ES12
- ES23
- ES43
- ES53

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Carson 2009	Breast cancer	Yoga	II	moderate	USA
Cramer 2015	Breast cancer	Yoga	II	moderate	Germany
Daley 2014	Menopause	Yoga	I	low	USA
Woods 2014	Menopause	Yoga	I	moderate	India
Newton 2014	Menopause	Yoga	II	low	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	A	one level I study and one level II study with a low risk of bias, one level I and two level II studies with a moderate risk of bias
2. Consistency	D	evidence is inconsistent
3. Clinical impact	D	slight or restricted
4. Generalisability	B	population/s studied in the body of evidence are similar to the target population for the guideline

Component	Rating	Description
5. Applicability	B	applicable to Australian healthcare context with few caveats

Recommendation

	GRADE OF RECOMMENDATION
Yoga can be considered for the management of vasomotor symptoms and sleep disturbance in women with a history of breast cancer noting there is inconsistent evidence regarding its effectiveness. Practice Point A: There is evidence that exercise has no effect on vasomotor symptoms in a general population, although there are other benefits of physical activity for women with a history of breast cancer.	**D**

Recommendation 2 : Acupuncture and electro-acupuncture for vasomotor symptoms

Evidence summaries: acupuncture

- ES10
- ES45

Study characteristics: acupuncture

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Bokmand 2013	Breast cancer	acupuncture	II	low	Denmark
Deng 2007	Breast cancer	acupuncture	II	moderate	USA
Hervik 2009	Breast cancer	acupuncture	II	low	Norway
Liljegren 2012	Breast cancer	acupuncture	II	moderate	Sweden

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Walker 2010	Breast cancer	acupuncture	II	high	USA
Dodin 2013	Menopause	acupuncture	I	low	Denmark, Korea, Norway, Sweden, USA
Ee 2016	Menopause	acupuncture	II	low	Australia

Evidence summaries - electro-acupuncture

- ES10

Study characteristics - electro-acupuncture

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Frisk 2008/Frisk 2012	Breast cancer	electro-acupuncture	II	high	Sweden
Mao 2015	Breast cancer	electro-acupuncture	II	moderate	USA
Nedstrand 2005/Nedstrand 2006	Breast cancer	electro-acupuncture	II	high	Sweden

Recommendation matrix

Component	Rating	Description
1. Evidence base	A	one level I study with a low risk of bias, two level II studies with a low risk of bias, three level II studies with a moderate risk of bias, three level II studies with a high risk of bias
2. Consistency	D	evidence is inconsistent
3. Clinical impact	C	moderate
4. Generalisability	B	population/s studied in the body of evidence are similar to the target population for the guideline: some studies were in women treated for breast cancer and some

Component	Rating	Description
		studies were in a general menopausal population
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Acupuncture and electro-acupuncture can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer noting there is inconsistent evidence regarding their effectiveness.	**GRADE OF RECOMMENDATION** **D**

Recommendation 4: Hypnotherapy for vasomotor symptoms

Evidence summaries

- ES9

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Elkins 2008	Breast cancer	hypnotherapy	II	moderate	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	C	one level II study with a moderate risk of bias
2. Consistency	N/A	one study only
3. Clinical impact	D	slight or restricted
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all

Component	Rating	Description
		studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Purpose-designed hypnotherapy can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer.	**GRADE OF RECOMMENDATION** **D**

Recommendation 5: Black cohosh for vasomotor symptoms

Evidence summaries

- ES13
- ES48

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Hernandez Munoz 2003	Breast cancer	black cohosh	II	high	Venezuela
Jacobson 2001	Breast cancer	black cohosh	II	low	USA
Pockaj 2006	Breast cancer	black cohosh	II	moderate	USA
Leach and Moore 2012	Menopause	black cohosh	I	low	Switzerland, USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	A	one level I study with a low risk of bias, one level II study with a low risk of bias, one level II study with a moderate risk of bias, one level II study with a high risk of bias
2. Consistency	A	all studies consistent

Component	Rating	Description
3. Clinical impact	N/A	none
4. Generalisability	B	population/s studied in the body of evidence are similar to the target population for the guideline: some studies were in women treated for breast cancer and some studies were in a general menopausal population
5. Applicability	B	applicable to Australian healthcare context with few caveats: most studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

	GRADE OF RECOMMENDATION
Black cohosh is not recommended for the management of vasomotor symptoms in women with a history of breast cancer due to evidence that it is not effective.	**B**

Recommendation 6: Homeopathy for vasomotor symptoms

Evidence summaries

- ES14

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Jacobs 2005	Breast cancer	homeopathy	II	high	USA
Thompson 2005	Breast cancer	homeopathy	II	low	UK

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	one level II study with a low risk of bias, one level II study with a high risk of bias

Component	Rating	Description
2. Consistency	A	all studies consistent
3. Clinical impact	N/A	none
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Homeopathy is not recommended for the management of vasomotor symptoms in women with a history of breast cancer due to evidence that it is not effective.	**GRADE OF RECOMMENDATION** **B**

Recommendation 7: Magnetic therapy for vasomotor symptoms

Evidence summaries

- ES16

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Carpenter 2002	Breast cancer	magnetic therapy	II	moderate	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	C	one level II study with a moderate risk of bias
2. Consistency	N/A	One study only
3. Clinical impact	N/A	none

Component	Rating	Description
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Magnetic therapy is not recommended for the management of vasomotor symptoms in women with a history of breast cancer due to evidence that it is not effective.	**GRADE OF RECOMMENDATION** **C**

Recommendation 8: Omega-3 supplementation for vasomotor symptoms

Evidence summaries

- ES47

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Cohen 2014	Menopause	omega-3 supplementation	II	low	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	one level II study with a low risk of bias
2. Consistency	N/A	One study only
3. Clinical impact	N/A	none

Component	Rating	Description
4. Generalisability	C	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population: all studies were in a general menopausal population
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

	GRADE OF RECOMMENDATION
Omega-3 supplementation is not recommended for the management of vasomotor symptoms in women with a history of breast cancer due to evidence that it is not effective.	C

Recommendation 9: Phytoestrogens for vasomotor symptoms

Evidence summaries

- ES46
- ES15

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
MacGregor 2005	Breast cancer	isoflavones	II	low	UK
Nikander 2003	Breast cancer	isoflavones	II	moderate	Finland
Van Patten 2002	Breast cancer	soy isoflavones	II	high	Canada
Thomas 2014	Menopause	soy and other isoflavones	I	moderate	Brazil, Canada, Ecuador, Iran, Italy, Japan, Korea, Taiwan, UK, USA

Study name	Population	Intervention	Level of study	Risk of Bias	Country

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	one level I study with a moderate risk of bias, one level II study with a low risk of bias, one level II study with a moderate risk of bias and one level II study with a high risk of bias
2. Consistency	C	some inconsistency reflecting genuine uncertainty around clinical question
3. Clinical impact	D	slight or restricted
4. Generalisability	B	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
5. Applicability	B	applicable to Australian healthcare context with few caveats: most studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Phytoestrogens are not recommended for the management of vasomotor symptoms as the efficacy and long-term safety in women with a history of breast cancer has not been established.	**GRADE OF RECOMMENDATION** **d**

Recommendation 10: CBT for sleep disturbance

Evidence summaries

- ES22

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Mann 2012	Breast cancer	CBT	II	moderate	UK
Matthews 2014	Breast cancer	CBT	II	low	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	one II study with a low risk of bias, one level II study with a moderate risk of bias
2. Consistency	C	some inconsistency reflecting genuine uncertainty around clinical question
3. Clinical impact	C	moderate
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Purpose-designed cognitive behavioural therapy can be considered for the management of sleep disturbance in women with a history of breast cancer.	**GRADE OF RECOMMENDATION** **C**

Recommendation 11: Relaxation therapy for sleep disturbance

Evidence summaries

- ES54

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Woods 2014	Menopause	relaxation therapy	I	moderate	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	One level I study with a moderate risk of bias
2. Consistency	N/A	one study only
3. Clinical impact	C	moderate
4. Generalisability	C	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population: all studies were in a general menopausal population
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Relaxation therapy can be considered for the management of sleep disturbance in women with a history of breast cancer.	**GRADE OF RECOMMENDATION**
	C

Recommendation 12: Hypnotherapy for sleep disturbance

Evidence summaries

- ES22

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Elkins 2008	Breast cancer	hypnotherapy	II	moderate	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	C	one level II study with a moderate risk of bias
2. Consistency	N/A	one study only
3. Clinical impact	C	moderate
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Purpose-designed hypnotherapy can be considered for the management of sleep disturbance in women with a history of breast cancer.	**GRADE OF RECOMMENDATION**
	C

Recommendation 13: Acupuncture for sleep disturbance

Evidence summaries

- ES23

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Bokmand	Breast cancer	acupuncture	II	low	Denmark

Study name	Population	Intervention	Level of study	Risk of Bias	Country
2013					

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	one level II study with a low risk of bias
2. Consistency	N/A	one study only
3. Clinical impact	C	moderate
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Acupuncture can be considered for the management of sleep disturbance in women with a history of breast cancer.	**GRADE OF RECOMMENDATION**
	C

Recommendation 14: Vitamin E for sleep disturbance

Evidence summaries

- ES24

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Biglia 2009	Breast cancer	Vitamin E	II	moderate	Italy

Study name	Population	Intervention	Level of study	Risk of Bias	Country
		800 IU/d			

Recommendation matrix

Component	Rating	Description
1. Evidence base	C	one level II study with a moderate risk of bias
2. Consistency	N/A	one study only
3. Clinical impact	N/A	none
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Vitamin E is not recommended for the management of sleep disturbance in women with a history of breast cancer due to evidence that it is not effective.	**GRADE OF RECOMMENDATION** **C**

Recommendation 15: Isoflavones for sleep disturbance

Evidence summaries

- ES55

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Thomas 2014	Menopause	soy and other isoflavones	I	moderate	Italy

Study name	Population	Intervention	Level of study	Risk of Bias	Country

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	One level I study with a moderate risk of bias
2. Consistency	N/A	one study only
3. Clinical impact	N/A	none
4. Generalisability	C	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population: all studies were in a general menopausal population
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

	GRADE OF RECOMMENDATION
Isoflavones are not recommended for the management of sleep disturbance in women with a history of breast cancer due to evidence that they are not effective.	C

Recommendation 16: Non-hormonal vaginal gels for vulvovaginal symptoms

Evidence summaries

- ES27

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Lee 2011	Breast cancer	non-hormonal vaginal gel	II	low	South Korea

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	one level II study with a low risk of bias
2. Consistency	N/A	one study only
3. Clinical impact	C	moderate
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

	GRADE OF RECOMMENDATION
Non-hormonal vaginal gels can be considered for the treatment of vulvovaginal symptoms in women with a history of breast cancer. Practice Point B: Non-hormonal vaginal moisturisers can be considered for the treatment of vulvovaginal symptoms in women with a history of breast cancer. Practice point C: Water-based or silicone-based vaginal lubricants can be used to enhance the comfort and ease of sexual intercourse.	**C**

Recommendation 17: CBT for sexual function

Evidence summaries

- ES28

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Duijts 2012	Breast cancer	CBT	II	moderate	The Netherlands

Recommendation matrix

Component	Rating	Description
1. Evidence base	C	one level II study with a moderate risk of bias
2. Consistency	N/A	one study only
3. Clinical impact	C	moderate
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

	GRADE OF RECOMMENDATION
Purpose-designed cognitive behavioural therapy can be considered for improving sexual function in women with a history of breast cancer.	C

Recommendation 18: Venlafaxine for vasomotor symptoms

Evidence summaries

- ES3
- ES31

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Boekhout 2011	Breast cancer	venlafaxine 75mg/d (slow release)	II	low	the Netherlands
Bordeleau 2010	Breast cancer	venlafaxine 37.5-75mg/d	II	moderate	Canada
Buijs 2009	Breast cancer	venlafaxine 75mg/d	II	moderate	the Netherlands
Carpenter 2007	Breast cancer	venlafaxine 37.5mg/d	II	moderate	USA
Loibl 2007	Breast cancer	venlafaxine 75mg/d	II	moderate	Germany
Walker 2010	Breast cancer	venlafaxine 37.5-75mg/d	II	moderate	USA
Joffe 2014	Menopause	venlafaxine 37.5-75mg/d	II	low	USA

Recommendation matrix

Component	Rating	Description
1.Evidence base	B	two level II studies with a low risk of bias, five level II studies with a moderate risk of bias
2.Consistency	A	all studies consistent
3.Clinical impact	B	substantial
4.Generalisability	A	evidence directly generalisable to target population
5.Applicability	A	directly applicable to Australian healthcare context

Recommendation

Venlafaxine (37.5 - 75 mg/day) can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer.	**GRADE OF RECOMMENDATION**
	A

Recommendation 19: Paroxetine for vasomotor symptoms

Evidence summaries: paroxetine

- ES2

Study characteristics: paroxetine

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Stearns 2005	Breast cancer	paroxetine 10-20 mg/d	II	low	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	one level II study with a low risk of bias
2. Consistency	N/A	one study only

Component	Rating	Description
3. Clinical impact	B	substantial
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	B	evidence applicable to Australian healthcare context with few caveats
Other factors(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)		

Recommendation

	GRADE OF RECOMMENDATION
Paroxetine (10 - 20 mg/day) can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer who are not receiving tamoxifen. This recommendation is not generalisable to other SSRIs as there is insufficient evidence in women with a history of breast cancer that they have comparable effects on vasomotor symptoms. Note: Paroxetine interacts with tamoxifen and reduces the serum concentration of tamoxifen and metabolites.	**B**

Recommendation 20: Escitalopram for vasomotor symptoms

Evidence summaries

- ES30

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Shams 2014	Menopause	escitalopram 10-20 mg/d	I	low	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	A	one level I study with a low risk of bias
2. Consistency	A	all studies consistent
3. Clinical impact	B	substantial
4. Generalisability	C	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population: all studies were in a general menopausal population
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

	GRADE OF RECOMMENDATION
Escitalopram (10–20 mg/d) can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer, based on evidence from a general population of menopausal women. Note: Escitalopram may reduce the efficacy of tamoxifen by slowing metabolism to the active form. There is little evidence for clinical concern resulting from their concomitant use.	**B**

Recommendation 21: Desvenlafaxine for vasomotor symptoms

Evidence summaries

- ES32

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Sun 2013	Menopause	desvenlafaxine 100-150 mg/day	I	low	not reported
Berhan 2014	Menopause	desvenlafaxine ≥100 mg/d	I	moderate	Europe, North America, South Africa

Recommendation matrix

Component	Rating	Description
1. Evidence base	A	one level I study with a low risk of bias, one level I study with a moderate risk of bias
2. Consistency	B	most studies consistent and inconsistency may be explained
3. Clinical impact	B	substantial
4. Generalisability	C	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population: all studies were in a general menopausal population
5. Applicability	B	evidence applicable to Australian healthcare context with few caveats

Recommendation

Desvenlafaxine (100–150 mg/d) can be considered for the management of moderate to severe vasomotor symptoms in	**GRADE OF RECOMMENDATION**

women with a history of breast cancer, based on evidence from a general population of menopausal women. Note: Desvenlafaxine may alter the serum concentration of tamoxifen and metabolites. There is little evidence for clinical concern resulting from their concomitant use.	**B**

Practice point D: Antidepressants and sexual symptoms

Evidence summaries

- ES25
- ES57

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Boekhout 2011	Breast cancer	venlafaxine 75mg/d (slow release)	II	low	the Netherlands
Bordeleau 2010	Breast cancer	venlafaxine 37.5-75mg/d	II	moderate	Canada
Buijs 2009	Breast cancer	venlafaxine 75mg/d	II	moderate	the Netherlands
Loprinzi 2002	Breast cancer	fluoxetine 20 mg/d	II	low	USA
Nunez 2013	Breast cancer	bupropion 300 mg/d	II	moderate	Brazil
Stearns 2005	Breast cancer	paroxetine 10-20 mg/d	II	low	USA

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Shams 2014	Menopause	escitalopram 10-20 mg/d	I	low	USA

Practice Point D:

The doses of antidepressants used for the management of vasomotor symptoms are not generally associated with increases in adverse sexual symptoms.

Recommendation 22: Clonidine for vasomotor symptoms

Evidence summaries

- ES3
- ES5

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Boekhout 2011	Breast cancer	clonidine 0.1mg/d	II	low	the Netherlands
Buijs 2009	Breast cancer	clonidine 0.1mg/d	II	moderate	the Netherlands
Loibl 2007	Breast cancer	clonidine 0.15mg/d	II	moderate	Germany

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	one level II study with a low risk of bias, two level II studies with a moderate risk of bias
2. Consistency	B	most studies consistent and inconsistency may be explained
3. Clinical impact	B	substantial
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context

Recommendation

Clonidine (0.10 - 0.15 mg/day) can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer.	**GRADE OF RECOMMENDATION** **B**

Recommendation 23: Gabapentin for vasomotor symptoms

Evidence summaries

- ES6

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Pandya 2005	Breast cancer	gabapentin 900 mg/d	II	moderate	USA
Bordeleau 2010	Breast cancer	gabapentin	II	moderate	Canada

Study name	Population	Intervention	Level of study	Risk of Bias	Country
		300-900 mg/d			
Ahimahalle 2012	Breast cancer	gabapentin 300 mg/d	II	high	Iran
Biglia 2009	Breast cancer	gabapentin 900 mg/d	II	moderate	Italy
Mao 2015	Breast cancer	gabapentin 300-900 mg/d	II	moderate	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	C	Four level II studies with a moderate risk of bias, one level II study with a high risk of bias
2. Consistency	C	some inconsistency reflecting genuine uncertainty around clinical question
3. Clinical impact	B	Substantial
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

Other factors (Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)

Recommendation

Gabapentin (300 - 900 mg/day) can be considered for the management of moderate to severe vasomotor symptoms in	**GRADE OF RECOMMENDATION**

women with a history of breast cancer.	C

Recommendation 24: Bupropion for menopausal symptoms

Evidence summaries

- ES1
- ES25

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Nunez 2013	Breast cancer	bupropion 300 mg/d	II	moderate	Brazil

Recommendation matrix

Component	Rating	Description
1. Evidence base	C	one level II study with a moderate risk of bias
2. Consistency	N/A	one study only
3. Clinical impact	D	slight or restricted
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	B	applicable to Australian healthcare context with few caveats

Recommendation

Bupropion is not recommended for the management of menopausal symptoms in women with a history of breast cancer due to evidence that it is not effective.	**GRADE OF RECOMMENDATION** **C**

Recommendation 25: Desvenlafaxine for sleep disturbance

Evidence summaries

- ES50

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Sun 2013	Menopause	desvenlafaxine 100-150mg/d	I	low	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	A	one level I study with a low risk of bias
2. Consistency	A	all studies consistent
3. Clinical impact	B	substantial
4. Generalisability	C	population/s studied in body of evidence different to target population for guideline, but it is clinically sensible to apply this evidence to target population: all studies were in a general menopausal population
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Desvenlafaxine (100 - 150 mg/d) can be considered for the management of sleep disturbance in women with a history of	**GRADE OF RECOMMENDATION**

breast cancer, based on evidence from a general population of menopausal women. Note: Desvenlafaxine may alter the serum concentration of tamoxifen and metabolites. There is little evidence for clinical concern resulting from their concomitant use.	**B**

Recommendation 26: Paroxetine for sleep disturbance

Evidence summaries

- ES17

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Stearns 2005	Breast cancer	paroxetine 10-20 mg/d	II	low	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	B (paroxetine)	one level II study with a low risk of bias
2. Consistency	N/A	One study only
3. Clinical impact	C	moderate
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Component	Rating	Description

Recommendation

Paroxetine (10 - 20 mg/day) can be considered for the management of sleep disturbance in women with a history of breast cancer who are not receiving tamoxifen. This recommendation is not generalisable to other SSRIs as there is insufficient evidence that they have comparable effects on sleep disturbance. Note: Paroxetine interacts with tamoxifen and reduces the serum concentration of tamoxifen and metabolites.	**GRADE OF RECOMMENDATION** **C**

Recommendation 27: Zolpidem augmentation for sleep disturbance in women taking an SSRI or SNRI

Evidence summaries

- ES19

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Joffe 2010	Breast cancer	zolpidem 10 mg/d	II	moderate	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	C	one level II study with a moderate risk of bias

Component	Rating	Description
2. Consistency	N/A	one study only
3. Clinical impact	C	moderate
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

	GRADE OF RECOMMENDATION
The addition of zolpidem (10 mg/d) to an SSRI or SNRI can be considered for the management of sleep disturbance for women with a history of breast cancer.	C

Recommendation 28: Gabapentin for sleep disturbance and Practice Point E

Evidence summaries

- ES20

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Biglia 2009	Breast cancer	gabapentin 900 mg/d	II	moderate	Italy
Bordeleau	Breast cancer	gabapentin	II	moderate	Canada

Study name	Population	Intervention	Level of study	Risk of Bias	Country
2010		900 mg/d			
Pandya 2005	Breast cancer	gabapentin 300–900 mg/d	II	moderate	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	C	three level II studies with a moderate risk of bias
2. Consistency	C	Some inconsistency reflecting genuine uncertainty around clinical question
3. Clinical impact	C	Moderate
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

	GRADE OF RECOMMENDATION
Gabapentin (300– 900mg/d) can be considered for the management of sleep disturbance in women with a history of breast cancer. Practice point E: Gabapentin doses of up to 1200 mg/day can be considered for the alleviation of sleep disturbance in women with a history of breast cancer.	**C**

Recommendation 29: Topical lidocaine for vulvovaginal symptoms

Evidence summaries

- ES27

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Goetsch 2015	Breast cancer	topical lidocaine	II	moderate	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	C	one level II study with a moderate risk of bias
2. Consistency	N/A	one study only
3. Clinical impact	C	moderate
4. Generalisability	A	population/s studied in body of evidence are the same as the target population for the guideline: all studies were in women treated for breast cancer
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Topical lidocaine treatments to the vulvovaginal area can be considered for women with a history of breast cancer experiencing dyspareunia.	**GRADE OF RECOMMENDATION**

Note: The treatment used in the included study was a 4% lidocaine solution applied to the vulvar vestibule for three minutes, followed by application of a silicone lubricant.	C

Recommendation 30: Ospemifene for vulvovaginal symptoms

Evidence summaries

- ES65

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Cui 2013	Menopause	ospemifene 60 mg/d	I	low	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	A	one level I study with a low risk of bias
2. Consistency	B	most studies consistent and inconsistency may be explained
3. Clinical impact	C	moderate
4. Generalisability	D	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
5. Applicability	A	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Component	Rating	Description

Recommendation

Ospemifene is not recommended for the management of vulvovaginal symptoms as the efficacy and long-term safety in women with a history of breast cancer has not been established.	**GRADE OF RECOMMENDATION** **C**

Recommendation 31: Menopause Hormone Therapy for menopausal symptoms

Evidence summaries

- ES7
- ES21
- ES26
- ES29
- ES34
- ES35
- ES37
- ES38
- ES58
- ES62

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Frisk 2008/2012 (HABITS)	Breast cancer	MHT	II	high	Sweden
Von Schoultz 2005; Fahlen	Breast cancer	MHT	II	high	Sweden

Study name	Population	Intervention	Level of study	Risk of Bias	Country
2011					
Marsden 2001	Breast cancer	MHT	II	high	UK
Holmberg 2004	Breast cancer	MHT	II	high	Sweden
Corbelli 2014	Menopause	oestradiol < 0.05 mg/d	I	low	Italy, USA
Derzko 2016	Menopause	MHT	I	moderate	North America, Europe
MacLennan 2004	Menopause	MHT	I	low	Europe, Russia, USA
Nastri 2013	Menopause	MHT	I	low	multinational
Joffe 2014	Menopause	oestradiol 0.5mg/d	II	low	USA
Reed 2014	Menopause	oestradiol 0.5mg/d	II	low	USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	A	three level I studies with a low risk of bias, one level I study with a moderate risk of bias, one level II study with a low risk of bias and four level II studies with a high risk of bias.
2. Consistency	B	most studies consistent and inconsistency may be

Component	Rating	Description
		explained
3. Clinical impact	B	substantial
4. Generalisability	B	population/s studied in the body of evidence are similar to the target population for the guideline
5. Applicability	B	applicable to Australian healthcare context with few caveats

Recommendation

	GRADE OF RECOMMENDATION
Systemic menopause hormone therapy (oestrogen-only or combined oestrogen and progestogen) should generally be avoided in women with a history of breast cancer because it may increase the risk of new or recurrent breast cancer. Menopause Hormone Therapy may be considered in exceptional cases for women with a history of breast cancer with severe, intractable vasomotor symptoms. In these cases the potential risks and benefits should be discussed with the treatment team, and treatment should only proceed with the informed consent of the woman and at the lowest effective dose for that woman.	**B**

Recommendation 32: Tibolone for menopausal symptoms

Evidence summaries

- ES7
- ES21
- ES26
- ES29

- ES33
- ES51
- ES61
- ES67

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Kenemans 2009/Sismondi 2011 (LIBERATE)	Breast cancer	Tibolone	II	Low	Multinational
Formoso 2012	Menopause	Tibolone	I	Low	Multinational

Recommendation matrix

Component	Rating	Description
1. Evidence base	A	one level I study with a low risk of bias and one level II study with a low risk of bias
2. Consistency	B	most studies consistent and inconsistency may be explained
3. Clinical impact	B	substantial
4. Generalisability	B	population/s studied in the body of evidence are similar to the target population for the guideline
5. Applicability	B	applicable to Australian healthcare context with few caveats

Recommendation

Tibolone should be avoided in women with a history of breast cancer because it increases the risk of new and recurrent breast cancer. Tibolone may be considered in exceptional cases for women with a history of breast cancer with severe, intractable vasomotor symptoms. In these cases the potential risks and benefits should be discussed with the treatment team, and treatment should only proceed with the informed consent of the woman and at the lowest effective dose for that woman.	**GRADE OF RECOMMENDATION** **B**

Recommendation 33: Compounded hormones for menopausal symptoms

Evidence summaries

- ES40

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Whelan 2013	Menopause	Compounded progesterone cream	I	moderate	Australia, UK, USA

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	One level I study with a moderate risk of bias
2. Consistency	D	evidence is inconsistent

Component	Rating	Description
3. Clinical impact	C	moderate
4. Generalisability	D	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
5. Applicability	A	directly applicable to Australian healthcare context

Recommendation

	GRADE OF RECOMMENDATION
Compounded hormones ('bioidentical' hormones) are not recommended for the management of menopausal symptoms in women with a history of breast cancer because the evidence of their effect is inconsistent and their safety after breast cancer is not known. Note: Compounded hormones are systemically absorbed and may contain high levels of sex steroids which may increase the risk of new or recurrent breast cancer.	**C**

Recommendation 34: Vaginal oestrogen for vulvovaginal symptoms

Evidence summaries

- ES63

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Rahn 2014	Menopause	vaginal	I	low	Europe, Israel,

Study name	Population	Intervention	Level of study	Risk of Bias	Country
		oestrogen			UK, USA
Suckling 2006	Menopause	vaginal oestrogen	I	low	Australia, Europe, North America, Thailand

Recommendation matrix

Component	Rating	Description
1. Evidence base	A	two level I studies with a low risk of bias
2. Consistency	B	most studies consistent and inconsistency may be explained
3. Clinical impact	C	moderate
4. Generalisability	C	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population: all studies were in a general menopausal population
5. Applicability	B	directly applicable to Australian healthcare context: all studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Vaginal oestrogens can be considered for the management of persistent vulvovaginal symptoms in women with a history of breast cancer who are non-responsive to non-hormonal vaginal gels or lubricants. A discussion of the potential risks and benefits between the woman and her treating team is recommended.

GRADE OF RECOMMENDATION

Note: Vaginal oestrogen may be systemically absorbed. For women taking Aromatase Inhibitors this may results in measurable increases in circulating oestrogens. The clinical significance of systemic absorption is uncertain.	**C**

Recommendation 35: Testosterone for sexual function

Evidence summaries

- ES59
- ES60
- ES66

Study characteristics

Study name	Population	Intervention	Level of study	Risk of Bias	Country
Elraiyah 2014	Menopause	testosterone	I	low	multinational
Somboonporn 2005	Menopause	testosterone	I	low	multinational

Recommendation matrix

Component	Rating	Description
1. Evidence base	B	two level I studies with a low risk of bias; no evidence of safety or efficacy in a breast cancer population
2. Consistency	B	most studies consistent and inconsistency may be explained
3. Clinical impact	C	moderate
4. Generalisability	D	Population/s studied in body of evidence differ to target

Component	Rating	Description
		population and hard to judge whether it is sensible to generalise to target population
5. Applicability	B	applicable to Australian healthcare context with few caveats: most studies were conducted in Australia or developed countries with similar levels of health service delivery

Recommendation

Exogenous testosterone is not recommended as a treatment to improve sexual function as the efficacy and long-term safety in women with a history of breast cancer has not been established.	**GRADE OF RECOMMENDATION** **C**