Menopausal symptoms

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Nikolaos Burbos and Edward Morris

ABSTRACT

INTRODUCTION: Menopause is a physiological event. In the UK, the median age for onset of menopausal symptoms is 45.5 to 47.5 years. Although endocrine changes are permanent, menopausal symptoms such as hot flushes, which are experienced by about 70% of women, usually resolve with time, although they can persist for decades in some women. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of medical treatments for menopausal symptoms? What are the effects of non-prescribed treatments for menopausal symptoms? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2009 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 68 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: agnus castus, antidepressants, black cohosh, clonidine, oestrogens, phyto-oestrogens, progestogens, testosterone, and tibolone.

QUESTIONS

INTERVENTIONS

Key points

- In the UK, the median age for onset of menopausal symptoms is 45.5 to 47.5 years.

  Symptoms associated with the menopause include vasomotor symptoms, sleeplessness, mood changes, reduced energy levels, loss of libido, vaginal dryness, and urinary symptoms.

  Many symptoms, such as hot flushes, are temporary, but those resulting from reduced hormone levels, such as genital atrophy, may be permanent.

- Progestogens reduce menopausal vasomotor symptoms compared with placebo. However, the clinical usefulness of progestogens given alone for menopausal symptoms is limited by the unwanted adverse effects of the relatively high doses need to achieve relief of menopausal symptoms.

  Progestogens used alone or with oestrogens reduce vasomotor symptoms in perimenopausal women.

- Oestrogens reduce vasomotor and sexual symptoms, but, like progestogens, increase the risk of serious adverse effects.

  Oestrogens, used alone or with progestogens, reduce vasomotor, urogenital, and psychological symptoms, and improve quality of life compared with placebo over 3 to 6 months.

  However, oestrogens increase the risk of breast cancer, endometrial cancer, stroke, and venous thromboembolism.

  Oestrogens, used alone or with progestogens, do not seem to increase the risk of coronary heart disease.

  We don't know whether phyto-oestrogens, such as those in soy flour, reduce menopausal symptoms. Phyto-oestrogens have not been shown consistently to improve symptoms, and they may increase the risk of endometrial hyperplasia in perimenopausal women.

- CAUTION: Women with an intact uterus who are prescribed oestrogen replacement therapy should also take continuous or cyclical progestogens.
- Tibolone reduces vasomotor symptoms in postmenopausal women compared with placebo.

  Tibolone may improve sexual function compared with placebo or compared with combined oestrogens plus progestogens.

  However, we don't know if tibolone is more effective in reducing vasomotor symptoms than oestrogen and progestogen combined treatment.

  Tibolone may be associated with an increased risk of breast cancer recurrence in women previously treated surgically for breast cancer compared with placebo.
- Testosterone reduces sexual symptoms in postmenopausal women but does not seem to reduce vasomotor symptoms, compared with oestrogen HRT alone.
- Antidepressants may be more effective than placebo at relieving vasomotor symptoms in postmenopausal women in the short term. However, we don't know whether they are effective in the long term.
- We don't know whether clonidine, black cohosh, or agnus castus reduce menopausal symptoms.

DEFINITION

Menopause is defined as the end of the last menstrual period. A woman is deemed to be postmenopausal 1 year after her last period. For practical purposes, most women are diagnosed as menopausal after 1 year of amenorrhoea. Menopausal symptoms often begin in the perimenopausal years. The complex of menopausal symptomatology includes vasomotor symptoms (hot flushes), sleeplessness, mood changes, reduction in energy levels, loss of libido, vaginal dryness, and urinary symptoms.

INCIDENCE/ PREVALENCE

In the UK, the mean age for the start of the menopause is 50 years and 9 months. The median onset of the perimenopause is 45.5 to 47.5 years. One Scottish survey (6096 women aged 45–54 years) found that 84% of women had experienced at least one of the classic menopausal symptoms, with 45% finding one or more symptoms to be a problem. [1]

AETIOLOGY/ RISK FACTORS

Urogenital symptoms of menopause are caused by decreased oestrogen concentrations, but the cause of vasomotor symptoms and psychological effects is complex and remains unclear.

PROGNOSIS

Menopause is a physiological event. Timing of the natural menopause in healthy women may be determined genetically. Although endocrine changes are permanent, menopausal symptoms such as hot flushes, which are experienced by about 70% of women, usually resolve with time, although in some women they can persist for decades. [2] However, some symptoms, such as genital atrophy, may remain the same or worsen.

AIMS OF INTERVENTION

To reduce or prevent menopausal symptoms; and to improve quality of life, with minimum adverse effects of treatment.

OUTCOMES

Frequency and severity of vasomotor, urogenital, psychological, cognitive, and sleep symptoms; quality of life; adverse effects.

METHODS

Clinical Evidence search and appraisal March 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2009, Embase 1980 to March 2009, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2009, Issue 1 (1966 to date of issue). An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies apart from the HRT options where the minimum length of follow-up was at least 3 months. We excluded all studies described as “open”, “open label”, or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. Many of the RCTs identified were crossover trials, which may have important limitations because treatment effects may persist after crossover, con-

founding the results for each treatment. Where results are reported for comparisons with only pretreatment values, they have been omitted because these comparisons may be influenced in many (often unquantifiable) ways by factors other than treatment effect. Many RCTs assessing alleviation of symptoms with HRT are too small or do not have long enough follow-up to give useful information on adverse effects. Therefore, where we have found RCTs and systematic reviews specifically evaluating adverse effects, we have reported these in preference to any information from trials primarily examining benefits. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 31). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of medical treatments for menopausal symptoms?

OPTION TIBOLONE

Vasomotor symptoms
Compared with placebo Tibolone seems more effective at reducing the frequency and severity of hot flushes at 12 weeks (moderate-quality evidence).

Compared with oestrogen plus progestogen We don't know how tibolone and oestrogen plus progestogen compare at reducing hot flushes; results varied among RCTs (low-quality evidence).

Urogenital symptoms
Compared with placebo Tibolone may be more effective at increasing sexual fantasies and arousability at 3 months, but we don't know about other urogenital symptoms (very low-quality evidence).

Compared with oestrogen plus progestogen Tibolone seems more effective at reducing vaginal dryness, but it may be no more effective at improving sexual satisfaction (moderate-quality evidence).

Adverse effects
Compared with placebo Tibolone is associated with an increased risk of breast cancer recurrence in women previously treated surgically for breast cancer compared with placebo at a median of 3.1 years (high-quality evidence).

Note
We found no direct information from RCTs about the effects of tibolone on psychological, cognitive, and sleep symptoms, or quality of life.

For GRADE evaluation of interventions for menopausal symptoms, see table, p 31 .

Benefits:

Tibolone versus placebo:
We found four RCTs comparing tibolone versus placebo. [3] [4] [5] [6]

Vasomotor symptoms
The first RCT (82 women with menopausal symptoms) compared tibolone versus placebo, and had a crossover design without a washout period. It found that tibolone reduced a vasomotor symptom-severity score compared with baseline at 16 weeks, before the crossover point, but the RCT did not report how the effects of tibolone compared with placebo (results presented graphically; significance of difference between groups not assessed; P value not reported). [3]

The second RCT (775 women) compared four different doses of tibolone (0.625, 1.25, 2.5, and 5 mg/day) versus placebo. [4] It found that tibolone 1.25, 2.5, and 5 mg significantly reduced the frequency of hot flushes and sweating episodes compared with placebo at 12 weeks (assessed using symptom diaries, results presented graphically; P less than 0.0001). It found no significant difference in frequency of hot flushes and sweating episodes between tibolone 0.625 mg and placebo at 12 weeks (reported as not significant; P value not reported).

The third RCT (396 symptomatic postmenopausal women) compared tibolone 1.25 and 2.5 mg versus placebo. [5] It found that both doses of tibolone significantly reduced the frequency of hot flushes compared with placebo at 12 weeks (mean change in flushes/day: –9.7 with tibolone 2.5 mg

v –8.3 with tibolone 1.25 mg *v* –5.5 with placebo; for comparison with placebo: P less than 0.001 for tibolone 2.5 mg; P = 0.003 or less for tibolone 1.25 mg). The RCT also found that both doses of tibolone significantly reduced the severity of flushes at 12 weeks (mean change in severity scores: –1.7 with tibolone 2.5 mg *v* –0.9 with tibolone 1.25 mg *v* –0.3 with placebo; P less than 0.001 for both tibolone 2.5 mg and 1.25 mg *v* placebo).

Urogenital system
The fourth RCT (38 women) had a crossover design with no washout period, however, results from before the crossover point were not reported. [6] It found that tibolone significantly increased sexual fantasies and arousability over 3 months compared with placebo (sexual fantasy frequency from diary: 2.78 episodes/week with tibolone *v* 1.68 episodes/week with placebo; P less than 0.03; arousal frequency from diary: 12.08 episodes/week with tibolone *v* 9.05 episodes/week with placebo; P less than 0.01). We found no RCTs examining the effects of tibolone on urinary incontinence.

Psychological, cognitive, and sleep symptoms
None of the RCTs gave information on the effect of tibolone on psychological, cognitive, and sleep symptoms.

Quality of life
None of the RCTs gave information on the effect of tibolone on quality of life.

Tibolone versus oestrogen plus progestogen:
We found three RCTs comparing tibolone versus combined oestrogen and progestogen. [7] [8] [9]

Vasomotor symptoms
The first RCT (437 women with menopausal symptoms) compared combined oestrogen/progestogen versus tibolone. [7] It found that combined oestrogen/progestogen significantly reduced hot flushes after 48 weeks compared with tibolone (assessed using a 5-point scoring system [mean score 2.1 at baseline in both groups]: 1.56 with tibolone *v* 1.25 with combined HRT; P less than 0.001).

The second RCT (235 postmenopausal women) found no significant difference in vasomotor symptoms at 52 weeks between combined oestrogen/progestogen and tibolone (absolute values not reported; P value not reported). [8]

Urogenital system
The first RCT (437 women) found that tibolone significantly improved vaginal dryness from baseline compared with combined HRT (oestradiol plus norethisterone) after 48 weeks of treatment (assessed using a 5-point scoring system [mean score 2.1 at baseline in both groups]: 1.33 with tibolone *v* 1.27 with combined HRT; P less than 0.001). [7]

A further report of the first RCT also found that tibolone increased sexual satisfaction (as measured using McCoy's Sex Scale Questionnaire) compared with oestradiol plus norethisterone at 48 weeks, but that this difference was not significant (change in McCoy's sex scale from baseline: 3.85 with tibolone *v* 2.20 with combined HRT; reported as not significant, P value not reported). [10]

The third RCT (50 women attending a university gynaecology clinic) found that tibolone significantly improved sexual desire (measured using a questionnaire) compared with conjugated oestrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg at 12 months (proportion with improvement in sexual desire scores from baseline: 12/23 (23%) with tibolone *v* 3/21 (14%) with oestrogen plus medroxyprogesterone; P less than 0.05). The RCT also evaluated coital and orgasm frequency, and dyspareunia, but did not summarise the results (proportion of people with each total score reported only; significance of differences unclear). [9]

Psychological, cognitive, and sleep symptoms
None of the RCTs gave information on the effect of tibolone on psychological, cognitive, and sleep symptoms.

Quality of life
None of the RCTs gave information on the effect of tibolone on quality of life.

Harms:

Tibolone versus placebo:
Androgenic adverse effects
We found no good evidence of androgenic adverse effects, such as hair growth or greasiness of the skin.

Cardiovascular adverse effects
Two RCTs of short-term use found a 33% reduction in plasma high-density proteins with tibolone, [11] [12] although the long-term effects on cardiovascular disease are unknown.

Vaginal bleeding
One RCT reported that two women randomised to receive tibolone (at 1.25 and 5.0 mg/day doses) stopped treatment because of vaginal bleeding. [4] One non-randomised controlled trial found that the main adverse effect of tibolone was breakthrough bleeding, which occurred in about 10% of users. [13]

Breast cancer recurrence
We found one RCT (3148 women who had previously been treated surgically for breast cancer) evaluating the risk of breast cancer recurrence with tibolone compared with placebo. [14] The RCT, which was stopped early, found that tibolone was associated with a significantly higher rate of breast cancer recurrence compared with placebo at a median of 3.1 years (237/1556 [15%] with tibolone *v* 165/1542 [11%] with placebo; P = 0.001; HR 1.40, 95% CI 1.14 to 1.70).

Tibolone versus oestrogen plus progestogen:
The first RCT found that fewer women reported adverse effects with tibolone than with oestrogen plus norethisterone (74% with tibolone *v* 87% with oestrogen plus norethisterone; significance of difference not reported). [7] The most frequently reported adverse effects in both groups were breast tenderness, oedema, and nausea. The second RCT gave no information on adverse effects. [8] The third RCT found that the most common adverse effects reported were irregular bleeding, breast tenderness, and increase in facial hair. [9]

Comment: Data on the risk associated with the long-term use of tibolone, and on the effects on the endometrium, will be appraised in future updates.

Clinical guide:
Based on the evidence presented above, clinicians should avoid prescribing tibolone for women with known or suspected breast cancer, and those with a history of previous breast cancer. It remains reasonable to prescribe tibolone for women with no history of breast cancer, although we found no data from RCTs on the effects of tibolone on breast cancer risk in this group.

OPTION OESTROGENS ALONE

Vasomotor symptoms
Compared with placebo Oestrogen (oral, intranasal, topical, or via vaginal ring) is more effective at reducing the frequency of hot flushes and improving symptom scores (Kupperman Index; Greene Climacteric Scale) (moderate-quality evidence).

Compared with progestins We don't know how oestrogens and progestins compare at reducing vasomotor symptoms (low-quality evidence).

Compared with phyto-oestrogens We don't know how oestrogen alone and phyto-oestrogen (soy extract) compare at reducing vasomotor symptoms (very low-quality evidence).

Urogenital symptoms
Compared with placebo Oestrogen is more effective at reducing urinary tract infections, vaginal dryness, vaginal atrophy, and dyspareunia (high-quality evidence).

Different oestrogen preparations compared with each other Oestrogen tablets may be more effective than oestrogen rings at reducing vaginal dryness and dyspareunia, but not in reducing vaginal atrophy. Oestrogen rings may be more effective than oestrogen cream at improving pruritus, but not vaginal dryness or dyspareunia. Oestrogen tablets may be more effective than oestrogen cream at improving vaginal dryness, but not in improving dyspareunia (low-quality evidence).

Psychological, cognitive, and sleep symptoms
Compared with placebo We don't know whether oestrogen is more effective at improving cognitive scores. Oestrogen may be more effective at reducing depressed mood in women without a pre-existing diagnosis of depression; however, evidence is weak (very low-quality evidence).

Quality of life
Compared with placebo Oestrogen (oral or transdermal) is more effective at improving quality-of-life scores at 12 to 16 weeks (high-quality evidence).

Adverse effects

Compared with placebo Oestrogen seems to be associated with an increased risk of endometrial hyperplasia (in women who have not had a hysterectomy), breast cancer, venous thromboembolism, and stroke with long-term use (moderate-quality evidence).

For GRADE evaluation of interventions for menopausal symptoms, see table, p 31 .

Benefits:

Oestrogens alone versus placebo:

Vasomotor symptoms

We found one systematic review [15] and six subsequent RCTs. [16] [17] [18] [19] [20] [21] Three RCTs assessed newly developed delivery systems and lower doses of oestrogen preparations versus placebo: these preparations are not widely available and further data are required. [19] [20] [21]

The systematic review (search date 2002, 24 RCTs, 3329 women) found that oestrogen-only hormone replacement therapy (HRT) significantly reduced the frequency of hot flushes compared with placebo (3 RCTs, 365 women; WMD –14.8 flushes/week, 95% CI –20.9 flushes/week to –8.7 flushes/week; absolute numbers not reported). [15] Duration of trials ranged from 6 months to 3 years. The review also found that oestrogen-only HRT significantly reduced the proportion of women with hot flushes at the end of the study compared with placebo (3 RCTs, 959 women; 115/738 [16%] with oestrogen *v* 81/221 [37%] with placebo; OR 0.35, 95% CI 0.22 to 0.55).

The first subsequent RCT (2673 women entered, 2152 analysed) compared eight combinations of different doses of oral conjugated equine oestrogens (CEE; 0.625, 0.45, and 0.3 mg) either alone or plus different doses of medroxyprogesterone acetate (2.5 or 1.5 mg) versus placebo. [16] It found that daily doses of CEEs of 0.3, 0.45, or 0.625 mg alone significantly reduced vasomotor symptoms from weeks 3 to 12 compared with placebo (assessed using diary cards to record number and severity of hot flushes; 214 women; P less than 0.05; absolute results presented graphically). It found that CEE 0.625 mg alone significantly reduced the number of hot flushes by week 3 compared with oestrogen 0.45 and 0.3 mg (P less than 0.05; absolute results presented graphically).

The second subsequent RCT (165 women) compared two different doses of intranasal oestradiol (150 or 300 micrograms/day) versus placebo over 12 weeks. [17] Symptoms were assessed with diaries and the Kupperman Index. It found that both doses of oestrogen significantly reduced moderate-to-severe symptoms at 12 weeks compared with placebo (mean reduction from baseline in number of moderate-to-severe vasomotor symptoms/day: 9.39 with oestradiol 300 micrograms *v* 7.86 with oestradiol 150 micrograms *v* 5.22 with placebo; high dose *v* placebo P = 0.002; low dose *v* placebo P less than 0.001).

The third subsequent RCT (333 women) compared a vaginal ring releasing either 50 or 100 micrograms oestradiol daily versus a placebo vaginal ring for 12 weeks. [18] It found that both doses of oestradiol significantly reduced moderate-to-severe hot flushes and scores on the Greene Climacteric Scale after 12 weeks of treatment compared with placebo (hot flushes/week measured using 4-point scale in daily diary: 15.5 with oestradiol 50 micrograms *v* 8.3 with oestradiol 100 micrograms *v* 42.2 with placebo; P less than 0.05; reduction in Greene Climacteric Scale [score range 0–63]: 10.52 with oestradiol 50 micrograms *v* 10.72 with oestradiol 100 micrograms *v* 5.95 with placebo; P less than 0.002).

The fourth RCT (454 postmenopausal women, mean age 53 years) compared three different doses of transdermal oestradiol spray (one-, two-, and three-spray doses) versus placebo. [19] The RCT evaluated three different placebo groups to match the dosing used in the oestradiol groups. The RCT found that all three doses of oestradiol spray significantly reduced the frequency and severity of hot flushes compared with placebo at 12 weeks (reduction from baseline in flushes/day with three-spray dose: –8.44 with oestradiol *v* –5.32 with placebo; P less than 0.001; two-spray dose: –8.66 with oestradiol *v* –6.19 with placebo; P = 0.010; one-spray dose: –8.10 with oestradiol *v* –4.76 with placebo; P less than 0.001; reduction in flush severity scores with three-spray dose: from 2.58 to 1.50 with oestradiol *v* from 2.54 to 2.23 with placebo; P less than 0.001; two-spray dose: from 2.54 to 1.63 with oestradiol *v* from 2.29 to 2.00 with placebo; P = 0.041; reduction with one-spray dose: –1.04 with oestradiol v –0.26 with placebo; P less than 0.001; results not presented in same form for all doses). The analyses performed at 4 weeks found similar significant differences.

The fifth RCT (484 postmenopausal women, mean time of 8−9 years since last period) compared oestradiol gel at three doses (0.87, 1.7, or 2.6 g/day) versus placebo. [21] The RCT evaluated moderate-to-severe hot flushes each week for 12 weeks. It found that oestradiol 1.7 and 2.6 g both significantly reduced moderate-to-severe hot flushes at each evaluation from 3 weeks to 12 weeks (mean change in moderate-to-severe hot flushes/day: 3 weeks, –8.2 with oestradiol 1.7 g *v* –9.5 with oestradiol 2.6 g *v* –5.4 with placebo; P = 0.007 for 1.7 g *v* placebo, P less than 0.001 for 2.6 g *v* placebo; results from 4 to 12 weeks presented graphically, difference between groups reported

as significant, P value not reported). The RCT found that oestradiol 0.87 g significantly reduced moderate-to-severe hot flushes at each evaluation from 5 weeks to 12 weeks (mean change in moderate-to-severe hot flushes/day: 5 weeks: –7.7 with oestradiol 0.87 g *v* –5.5 with placebo; P less than 0.001; results from 6 to 12 weeks presented graphically, reported as significant, P value not reported).

The sixth RCT (200 postmenopausal women) compared a topical emulsion of oestradiol versus a placebo emulsion. [20] It found that oestradiol emulsion significantly reduced hot flush frequency and severity compared with placebo at 12 weeks (change from baseline in number of flushes/day: –11.1 with oestradiol *v* –7.2 with placebo; P = 0.001; change in severity of flushing: results presented graphically; P less than 0.001). Symptoms were assessed weekly; both flush frequency and severity showed significant improvement at each assessment from 3 weeks.

Urogenital system

We found two systematic reviews, [22] [23] and two subsequent RCTs, [17] [24] which assessed the effects of various preparations of oestrogen on urogenital symptoms. The first systematic review (search date 1998, 5 RCTs, 334 people) found a significant reduction in the incidence of urinary tract infection (UTI) with oral or vaginal oestrogen HRT compared with placebo or no treatment (OR for infection; no HRT *v* HRT: 2.51, 95% CI 1.48 to 4.25). [22] Vaginal oestrogens significantly reduced the risk of UTIs compared with oral oestrogens (P less than 0.008).

The second systematic review (search date 2006, 19 RCTs, 4162 women) performed an analysis of the effects of various vaginal preparations on urogenital symptoms (for full results see table 1, p 24). [23] One RCT (67 women) included in the review found that the oestrogen-containing ring significantly improved the proportion of women with freedom from dyspareunia (patient-assessed) compared with placebo after 12 weeks of treatment. [23] Another RCT (52 women) included in the review found significant reductions in pallor and friability (physician-assessed) with the oestrogen-containing ring compared with placebo. One RCT (159 women) included in the review assessing overall satisfaction with treatment found a significantly higher rate of satisfaction with oestrogen ring compared with placebo. One RCT (143 women) included in the review found no significant differences in tolerability between the two treatments. The review found that oestrogen-containing tablets significantly reduced (patient-assessed) burning and itching, dyspareunia, vaginal dryness, and vaginal atrophy compared with placebo (see table 1, p 24).

The first additional RCT (145 women) found that low-dose oestradiol reduced vaginal dryness at weeks 9 to 12 compared with placebo (86% of days free from vaginal dryness with oestradiol 1 mg *v* 76% with oestradiol 0.5 mg *v* 74% with placebo), but the significance of the difference between groups was not tested. [24]

The second additional RCT (165 women) compared the effects of two doses of intranasal oestradiol (150 or 300 micrograms/day) versus placebo on dyspareunia and "urinary troubles" (measured on a visual analogue scale). [17] It found that the 150 micrograms dose significantly reduced symptoms at 12 weeks compared with placebo (P less than 0.001), and that the 300 micrograms dose significantly reduced urogenital symptoms at 4 weeks compared with placebo (P = 0.014).

Psychological, cognitive, and sleep symptoms

We found three systematic reviews. [25] [26] [27] The first systematic review compared the effects of HRT versus placebo on menopausal depressed mood (search date 1995, 14 RCTs including several crossover RCTs, 12 cohort studies; duration of treatment ranged from 1 month to 2 years), [25] We found no RCTs of oestrogen treatment in women with clinically diagnosed depression. The first review found that oestrogen significantly reduced depressed mood (measured using different scales) compared with placebo or no treatment (P less than 0.0001). [25] Some of the included information was taken from cohort studies and should be interpreted with caution.

The second and third reviews compared the effects of oestrogen versus placebo on cognitive function in postmenopausal women. [26] [27]

The second review (search date 1996, 6 RCTs, 4 non-randomised controlled trials, 9 observational studies) found that studies were too weak to allow reliable conclusions to be drawn, and it is not reported further. [26]

The third systematic review (search date 2006, 16 RCTs including 4 RCTs also in the second review, 10,114 postmenopausal women) evaluated the effect of HRT on cognitive function, and compared oestrogen alone or oestrogen plus progestogen versus placebo. [27] Five of the RCTs included evaluated global cognitive scores; the review analysed each type of score separately. The review found no significant difference in Cambridge Cognitive Examination for Mental Disorders of the Elderly (CAMCOG) scores, Modified Mini-Mental State Examination (3MSE) scores, or Folstein

Mini-Mental State Examination scores between oestrogen alone and placebo at the end of follow-up, between 20 weeks and 6 years (CAMCOG scores, 20 weeks: 1 RCT, 115 women; mean difference +0.60, 95% CI –0.62 to +1.82; 3MSE scores, 6 years: 1 RCT; number of women not reported; mean difference –0.45, 95% CI –0.99 to +0.09; Folstein Mini-Mental State Examination, 3 years: 1 RCT, 373 women; mean difference –0.10, 95% CI –0.34 to +0.14; absolute values not reported for any outcome). The review found that, at 1 year, oestrogen significantly reduced cognitive function scores (3MSE scores, higher scores better) compared with placebo (WMD –0.44, 95% CI –0.73 to –0.16, absolute values not reported). The review found no significant difference in the proportion of people with a diagnosis of mild cognitive impairment between groups at 5 years (1 RCT: 76/1463 [5%] with oestrogen *v* 58/1479 [4%] with placebo; OR 1.34, 95% CI 0.95 to 1.90). Eight smaller RCTs identified by the review were analysed separately and examined different types of cognitive function test (verbal memory and language tests, visual tests, and speed and dexterity tests). Most of these analyses showed no significant difference in test scores between oestrogen and placebo; however, the authors stated that there were too few people in the analyses to determine whether HRT has a beneficial or harmful effect.

Quality of life

We found no systematic review. We found one RCT comparing transdermal oestradiol versus placebo, [28] and one RCT comparing oral oestradiol versus placebo. [29] The first RCT (242 postmenopausal women) found that oestradiol transdermal patches (50 micrograms/24 hours) significantly improved quality of life compared with placebo patches at 12 weeks (change in Nottingham Health Profile scores: −58.2 with oestradiol *v* −17.3 with placebo; P = 0.0003). [28]

The second RCT (82 women aged 40–60 years) found that oral oestradiol significantly improved quality-of-life scores compared with placebo at 16 weeks (Kupperman Index: 8.6 with oestradiol *v* 18.1 with placebo; P = 0.0015; Green Index psychological subscore: 8.0 with oestradiol *v* 16.7 with placebo; P = 0.0037; Green Index somatic subscore: 3.3 with oestradiol *v* 5.4 with placebo; P = 0.0026; Green Index vasomotor subscore: 4.5 with oestradiol *v* 9.4 with placebo; P = 0.0003). [29]

Different oestrogen preparations versus each other:

Urogenital symptoms

We found one systematic review (search date 2006, 19 RCTs, 4162 women), which performed an analysis of the effects of various vaginal preparations on urogenital symptoms (for full results see table 1, p 24). [23] Oestrogen-containing tablets significantly improved vaginal dryness and dyspareunia (all patient-assessed) compared with oestrogen-containing rings. One RCT (170 women) included in the review found no significant difference in vaginal atrophy between these two vaginal preparations. The review also found a significant improvement in pruritus with the oestrogen ring compared with oestrogen cream. However, there were no significant differences in improvement in vaginal dryness and dyspareunia (patient assessed) between the oestrogen ring and oestrogen cream. One RCT (48 women) included in the review found that oestrogen tablets significantly improved vaginal dryness compared with placebo, but found no significant difference in dyspareunia between groups (both outcomes patient assessed). The review found no significant differences between groups (ring *v* cream, ring *v* tablets, tablets *v* cream, and tablets *v* placebo) in dysuria, nocturia, urgency, urge incontinence, soreness and irritation, loss of libido, vaginitis, endometrial hyperplasia, proliferation of the endometrium, or increasing endometrial thickness as assessed by ultrasound.

Oestrogens alone versus progestins:

Vasomotor symptoms

We found one RCT (43 women with menopausal symptoms) that compared oral oestrogen alone versus progestin (medroxyprogesterone 150 mg depot for 25 days/month). [30] It found a similar reduction in vasomotor symptoms between treatments at 3 months (P value not reported; absolute results presented graphically).

Oestrogens alone versus phyto-oestrogens:

See benefits of phyto-oestrogens, p 18 .

Harms:

Oestrogens versus placebo

The most important long-term adverse effects with oestrogens are increased risk of venous thromboembolic disease (see HRT in review on secondary prevention of ischaemic cardiac events), endometrial cancer, and breast cancer. [17] [22] [23] [24]

Weight gain

Women often report an increase in weight when starting oestrogen, but we found no evidence from RCTs that oestrogen causes clinically important weight gain in the long term. One systematic review (search date 1998; 22 RCTs) found no significant difference in body weight between oestrogen

alone and placebo or no treatment at 3 months to 4 years (9 RCTs, 10,194 women: WMD +0.03 kg, 95% CI –0.61 kg to +0.67 kg). [31]

Endometrial cancer

We found one systematic review (search date 2008, 45 RCTs) comparing unopposed oestrogen versus placebo, which assessed endometrial hyperplasia. [32] It found that low-dose oestrogen significantly increased endometrial hyperplasia at 18 to 24 months, but it found no significant difference between groups at 12 months (12 months [4 RCTs]: 13/980 [1.3%] with low-dose oestrogen *v* 2/519 [0.4%] with placebo; OR 2.84, 95% CI 0.97 to 8.29; 18–24 months [6 RCTs]: 34/627 [5%] with low-dose oestrogen *v* 5/266 [2%] with placebo; OR 2.42, 95% CI 1.19 to 4.92). The review found that moderate-dose oestrogen significantly increased endometrial hyperplasia at 12 months, 18–24 months, and 3 years (12 months [5 RCTs]: 89/606 [15%] with moderate-dose oestrogen *v* 2/638 [less than 1%] with placebo; OR 8.4, 95% CI 5.5 to 12.9; 18–24 months [6 RCTs]: 103/290 [36%] with moderate-dose oestrogen *v* 4/337 [1%] with placebo; OR 11.9, 95% CI 7.8 to 18.1; 3 years [1 RCT]: 74/119 [62%] with moderate-dose oestrogen *v* 2/119 [2%] with placebo; OR 16, 95% CI 9.3 to 27.5). The review found that high-dose oestrogen significantly increased endometrial hyperplasia compared with placebo at 12 and at 18–24 months (12 months [1 RCT]: 26/60 [43%] with oestrogen *v* 1/60 [2%] with placebo; OR 10.7, 95% CI 4.6 to 25.1; 18–24 months [1 RCT]: 32/60 [53%] with oestrogen *v* 1/60 [2%] with placebo; OR 13.1, 95% CI 5.9 to 29). The review did not perform an analysis of the effect of unopposed oestrogen on endometrial cancer, as only one case occurred, which was in the placebo group of one of the RCTs. The review found that both cyclical and continuous treatment with progestogen significantly reduced rates of endometrial hyperplasia compared with oestrogen alone, and it found no significant difference in endometrial hyperplasia or endometrial cancer between combined therapy and placebo (see harms of oestrogens plus progestogens, p 10). One non-systematic review (4 RCTs, more than 20,000 women) found no significant difference between combined HRT and placebo in risk of endometrial cancer (RR 0.76, 95% CI 0.45 to 1.31). [33]

Breast cancer

One systematic review (search date not reported; 51 RCTs, more than 160,000 women) found that HRT (oestrogen alone or oestrogen plus progestogen; see harms section of oestrogens plus progestogens, p 10) significantly increased the relative risk of breast cancer by 2.3% (95% CI 1.1% to 3.6%) each year. [34] Five or more years after HRT was stopped, there was no significant excess of breast cancer. One non-systematic review of four large RCTs (more than 20,000 women) found that long-term combined HRT or oestrogen-only HRT significantly increased the risk of developing breast cancer compared with placebo (RR 1.27, 95% CI 1.03 to 1.56). [33] One RCT (postmenopausal women aged 50–79 years of age who had undergone hysterectomy, with or without oophorectomy) found no significant difference in the incidence of breast cancer during a mean follow-up period of 7.1 years between conjugated equine oestrogens (CEE) 0.625 mg daily and placebo (129/5310 [2%] with CEE *v* 161/5429 [3%] with placebo; HR 0.82, 95% CI 0.62 to 1.04, P = 0.09). [35]

Colorectal cancer

One non-systematic review (4 RCTs, more than 20,000 women) found that long-term combined HRT or oestrogen significantly decreased the risk of colorectal cancer (RR 0.64, 95% CI 0.45 to 0.92). [33]

Fractures

One non-systematic review (4 RCTs, more than 20,000 women) found that long-term combined HRT or oestrogen significantly decreased the risk of fractured neck of femur (RR 0.72, 95% CI 0.52 to 0.98; see harms of HRT in review on fracture prevention in postmenopausal women). [33]

Cardiovascular adverse effects

We found three systematic reviews evaluating cardiovascular complications of HRT. [36] [37] [38] All the reviews compared either oestrogen alone, or oestrogen plus progestogen, versus placebo or no treatment. The reviews did not report results for oestrogen alone. The systematic reviews identified many RCTs in common; among them they identified 44 different RCTs.

The first systematic review (search date 2004; 28 RCTs, 39,769 people, 3 RCTs included men) found that oestrogen alone or oestrogen plus progestogen significantly increased the proportion of people with any stroke and ischaemic stroke compared with no HRT (any stroke: 534/19,735 [3%] with HRT *v* 406/20,034 [2%] with no HRT; OR 1.29, 95% CI 1.13 to 1.47; ischaemic stroke: OR 1.29, 95% CI 1.06 to 1.56; absolute numbers not reported). [36] However there was no significant difference in haemorrhagic stroke between oestrogen alone or oestrogen plus progestogen and no HRT (OR 1.07, 95% CI 0.65 to 1.75, absolute numbers not reported). [36] The review also found that HRT significantly increased the severity of stroke compared with no HRT (OR for death or dependency after a stroke 1.56, 95% CI 1.11 to 2.20, absolute numbers not reported).

The second systematic review (search date 2008, 31 RCTs, 41,113 women) found that HRT significantly increased cerebrovascular events (stroke or TIA) and venous thromboembolism compared with control (cerebrovascular events: 581/23,116 [3%] with HRT *v* 453/20,433 [2%] with control; OR 1.24, 95% CI 1.09 to 1.41; venous thromboembolism: 360/22,540 [2%] with HRT *v* 187/19,841 [1%] with control; OR 2.05, 95% CI 1.44 to 2.92). [37] The review found no significant difference in coronary heart disease events (including MI) between HRT and control (841/22,945 [4%] with HRT *v* 795/20,214 [4%] with placebo; OR 1.00, 95% CI 0.90 to 1.11).

The third systematic review (search date 2007, 9 RCTs, 7 case control studies, and one prospective cohort study) compared HRT versus placebo, and assessed the risk of venous thromboembolism by study design, route of administration of oestrogen preparation, and clinical risk factors. [38] Analysis of data from RCTs (38,779 women; 3 RCTs of oestrogen alone; 3 RCTs of combined HRT; 3 RCTs of either oestrogen alone or combined HRT) found that HRT significantly increased venous thromboembolism compared with placebo (OR 2.1, 95% CI 1.4 to 3.1; P = 0.03; absolute numbers not reported).The review identified no RCTs assessing the effect of transdermal oestrogen preparations on venous thromboembolism risk. Two RCTs identified by the review found that the presence of one pro-thrombotic mutation (factor V Leiden or prothrombin G20210A) increased the risk of VTE in the oestrogen-only group and in the oestrogen plus progestogen group compared with placebo (oestrogen only: OR 3.5, 95% CI 0.2 to 11.1; oestrogen plus progestogen: OR 5.2, 95% CI 2.8 to 9.8). The same RCTs also found that, for women with BMI greater than 25 kg/m^2, the risk of VTE was significantly higher with oestrogen only and oestrogen plus progestogen preparations compared with placebo (oestrogen only: OR 3.3, 95% CI 1.9 to 5.6; oestrogen plus progestogen: OR 4.7, 95% CI 3.1 to 7.1).

Oestrogens alone versus progestins:
The RCT reported that no significant complications occurred over the short trial period. [30]

Oestrogens alone versus phyto-oestrogens:
See harms of phyto-oestrogens, p 18 .

Comment:

Clinical guide:
Based on the evidence of important adverse effects, there has been a change in prescribing attitude towards HRT. Before starting HRT, it is now considered important for prescribers to discuss with women the excess risks associated with HRT. Based on the evidence presented under harms, above, it remains important that women with an intact uterus who are prescribed any form of systemic oestrogen take either continuous or cyclic progestogens.

OPTION OESTROGENS PLUS PROGESTOGENS

Vasomotor symptoms
Compared with placebo Oestrogens plus progestogens are more effective at reducing hot flushes and night sweats (high-quality evidence).

Compared with tibolone We don't know how oestrogen plus progestogen and tibolone compare at reducing hot flushes; results varied among RCTs (low-quality evidence).

Compared with phyto-oestrogens We don't know how oestrogen plus medroxyprogesterone acetate and phyto-oestrogen (pueraria lobata) compare at reducing vasomotor symptoms (very low-quality evidence).

Urogenital symptoms
Compared with placebo Oestrogens plus progestogens seem more effective at reducing vaginal dryness, but we don't know about urinary frequency or nocturia (moderate-quality evidence).

Compared with tibolone Oestrogen plus progestogen seems less effective at reducing vaginal dryness, but it may be equally effective at improving sexual satisfaction (moderate-quality evidence).

Psychological, cognitive, and sleep symptoms
Compared with placebo We don't know whether oestrogens plus progestogens are more effective at improving cognitive scores, reducing new diagnoses of mild cognitive impairment, or improving mental health or depressive symptom scores (low-quality evidence).

Quality of life
Compared with placebo We don't know whether oestrogens plus progestogens are more effective at improving quality-of-life scores (low-quality evidence).

Different preparations of oestrogen plus progestogen versus each other We don't know whether transdermal oestrogen plus medroxyprogesterone is more effective at improving quality-of-life scores (low-quality evidence).

Adverse effects
Compared with placebo Long-term use of oestrogens plus progestogens seems to be associated with an increased risk of breast cancer, stroke, thromboembolism, and gall-bladder disease (moderate-quality evidence).

For GRADE evaluation of interventions for menopausal symptoms, see table, p 31 .

Benefits:

Oestrogens plus progestogens versus placebo:
Vasomotor symptoms
We found one systematic review, [15] two subsequent RCTs [16] [39] comparing oestrogens plus progestogens versus placebo, and one subsequent RCT comparing oestrogen plus drospirenone (a new progestogen preparation) versus placebo. [40] The systematic review (search date 2001, 21 RCTs, 2511 women, follow-up 3–36 months) included comparisons of progesterone-plus-oestrogen HRT versus placebo. [15] It found that progesterone plus oestrogen significantly reduced hot flushes compared with placebo (94/678 [14%] with progesterone plus oestrogen *v* 126/279 [45%] with placebo; OR 0.10, 95% CI 0.04 to 0.25). [15]

The first subsequent RCT (2673 women entered, 2152 analysed) compared eight combinations of different doses of oral conjugated equine oestrogens (CEE; 0.625, 0.45, and 0.3 mg) either alone or plus different doses of medroxyprogesterone acetate (2.5 or 1.5 mg) versus placebo. [16] It found that daily doses of 0.3, 0.45, or 0.625 mg CEE plus medroxyprogesterone acetate 2.5 mg daily significantly reduced vasomotor symptoms from weeks 3 to 12 compared with placebo (P less than 0.05). There was no significant difference in the number or severity of hot flushes between different doses of medroxyprogesterone acetate. The second subsequent RCT (16,608 postmenopausal women with an intact uterus aged 50–79 years) found that CEE 0.625 mg daily plus medroxyprogesterone acetate 2.5 mg daily significantly reduced the proportion of women with hot flushes and night sweats compared with placebo (proportion with relief from hot flushes: 86% with oestrogen plus medroxyprogesterone *v* 58% with placebo; OR 4.40, 95% CI 3.40 to 5.71; proportion with relief from night sweats: 78% with oestrogen plus medroxyprogesterone *v* 57% with placebo; OR 2.58, 95% CI 2.04 to 3.26, absolute figures not reported for either outcome). [39] The third RCT (90 postmenopausal women) found that oestradiol plus drospirenone significantly reduced the number of hot flushes compared with placebo from 3 to 16 weeks (reduction in number of hot flushes: 48% with placebo *v* 84% with oestrogen plus drospirenone; P less than 0.001; absolute numbers not reported). [40]

Urogenital system
We found three RCTs. [41] [39] [40] The first RCT (136 women) found that low-dose transdermal oestrogen 25 micrograms daily plus norethisterone acetate significantly reduced vaginal dryness and dyspareunia over 6 months compared with placebo (measured on a 100 mm visual analogue scale, vaginal dryness: 32.4 mm with oestrogen *v* 50.5 mm with placebo; dyspareunia: 20.5 mm with oestrogen *v* 34.2 mm with placebo; P less than 0.001). [41]

The second RCT (16,608 postmenopausal women with an intact uterus, aged 50–79 years) compared CEE 0.625 mg daily plus medroxyprogesterone acetate 2.5 mg daily versus placebo. [39] The RCT found that oestrogen significantly reduced the proportion of women with vaginal or genital dryness (proportion of women reporting improvement in vaginal dryness: 74% with oestrogen plus medroxyprogesterone *v* 55% with placebo; OR 2.40, 95% CI 1.90 to 3.02, absolute numbers not reported). [39]

The third RCT (90 postmenopausal women) found a similar reduction in urinary frequency and nocturia with oestradiol plus drospirenone and with placebo, but it did not assess the significance of the difference between groups (change from baseline in proportion with urinary frequency: 40% to 17% with oestradiol plus drospirenone *v* 30% to 16% with placebo; proportion with nocturia: 29% to 14% with oestradiol plus drospirenone *v* 22% to 14% with placebo; absolute numbers not reported). [40] See harms, below, for effects of oestrogen/oestrogen plus progestogen on the incidence of urinary incontinence.

Psychological, cognitive, and sleep symptoms
We found one systematic review assessing the effect of oestrogen plus progestogens on cognitive function of postmenopausal women. [27] One large RCT in the review (reported in 2 publications) also assessed the effect of oestrogen plus progesterone on mental health and depression symptoms. [42] [43]

The systematic review (search date 2006, 16 RCTs, 10,114 women) analysed the effects of oestrogen-only and oestrogen-plus-progestogen preparations on cognitive function of postmenopausal women. [27]

The review found that oestrogen plus progestogen significantly lowered scores of cognitive function (Modified Mini-Mental State Examination [3MSE] score; lower scores were worse) compared with placebo at 3 and 4 years' follow-up (1 RCT, 4344 postmenopausal women; 3 years: WMD −0.36, 95% CI –0.61 to –0.11; P = 0.0046; 4 years: WMD –0.52, 95% CI –0.81 to –0.23; P = 0.00042; absolute values not reported). At 1, 2, and 5 years, the review found no significant difference between groups, although the scores were lower with HRT. The review also found no significant difference between groups in the proportion of people with a diagnosis of mild cognitive impairment at 4 years (AR: 56/2229 [3%] with HRT *v* 55/2303 [2%] with placebo; OR 1.05, 95% CI 0.75 to 1.54). Two other RCTs identified by the review were analysed separately and examined disparate types of cognitive test (verbal memory and language tests, visual tests, and speed and dexterity tests). Most of these analyses showed no significant difference in test scores between oestrogen and placebo; however, the authors stated that these provided insufficient evidence to determine whether HRT has a beneficial or harmful effect.

The RCT assessing mental health (16,608 postmenopausal women with an intact uterus aged 50–79 years) compared CEE 0.625 mg daily plus medroxyprogesterone acetate 2.5 mg daily versus placebo. [42] It found that oestrogen plus progestin did not significantly improve mental health or depressive symptoms (assessed using the RAND 36-Item Health Survey) compared with placebo after 1 year (range of RAND mental health and depression subscores at 1 year [all expressed as change from baseline]: –0.1 to +0.6 with oestrogen plus progestin *v* –0.1 to +0.7 with placebo; P = 0.40–0.81). However, it did find significant improvements in sleep disturbance (mean change of scores from baseline: 0.5 with oestrogen plus progestin *v* 0.1 with placebo; P less than 0.001). [43] Applicability of the large RCT may be limited because the average age of women enrolled in the study (63.3 years) was much older than that of women who typically start HRT. [42]

Quality of life
We found one RCT. [42] The large RCT (described above) did not report an overall quality-of-life score, but instead reported separate subscores of the RAND 36-Item Health Survey. It found that oestrogen plus progestin did not significantly improve general health, social functioning, vitality, or sexual satisfaction compared with placebo after 1 year (range of RAND quality-of-life subscores at 1 year [all expressed as change from baseline]: from –1.9 to +0.2 with oestrogen plus progestin *v* from –2.3 to 0 with placebo; P = 0.08–0.76). [42] However, it did find that oestrogen plus progestin significantly improved physical functioning and bodily pain subscores compared with placebo at 1 year (mean change in physical functioning subscore: −0.6 with oestrogen plus progestin *v* −1.4 with placebo; P less than 0.001; change in bodily pain subscore: +0.1 with oestrogen plus progestin *v* −1.8 with placebo; P less than 0.001). However, the generalisability of these results may be limited (see comment below). [43]

Different preparations of oestrogens plus progestogens versus each other:
Quality of life
We found one RCT (74 women with an intact uterus and ovaries, 2–7 years after menopause), which found similar improvements in quality of life with either oral CEE (0.625 mg/day for four 4-week cycles) plus medroxyprogesterone acetate (10 mg for the last 12 days of each cycle) or with continuous transdermal oestradiol-17beta (50 micrograms twice weekly for four 4-week cycles) plus medroxyprogesterone acetate (10 mg for the last 12 days of each cycle). [44]

Oestrogens plus progestogens versus tibolone:
See benefits of tibolone, p 3 .

Oestrogens plus progestogens versus phyto-oestrogens:
See benefits of phyto-oestrogens, p 18 .

Harms:

Oestrogens plus progestogens versus placebo:
Minor/general adverse effects
The review gave no information on adverse effects. [15] Three RCTs assessed the harms of oestrogen plus progestogens. [39] [45] [46] The first RCT (321 women who had undergone hysterectomy and were already taking CEEs) compared continuous progestogen (norgestrel) versus placebo. [45] It found no difference in adverse effects of treatments (including weight gain and bloating). The second RCT (875 women) compared various oestrogen/progestogen combinations over 3 years. [46] It found that the addition of progestogen to oestrogen significantly increased breast discomfort compared with oestrogen alone (OR 1.92, 95% CI 1.16 to 3.09). The third RCT found that oestrogen alone (see harms of oestrogens alone, p 5) or oestrogen plus progesterone significantly increased the proportion of women with urinary incontinence at 1 year compared with placebo, with the risk highest for stress incontinence (RR for stress incontinence with oestrogen alone 2.15, 95% CI 1.77 to 2.62; with oestrogen plus progesterone 1.87, 95% CI 1.61 to 2.18; absolute figures not reported). The RCT also found that oestrogen plus progesterone significantly increased the proportion of women with breast tenderness, genital discharge, and headache compared with placebo (breast

tenderness: 9% with oestrogen plus progesterone *v* 2% with placebo; OR 4.26, 95% CI 3.59 to 5.04; genital discharge: 4% with oestrogen plus progesterone *v* 1% with placebo; OR 4.47, 95% CI 3.44 to 5.81; headache: 6% with oestrogen plus progesterone *v* 5% with placebo; OR 1.26, 95% CI 1.08 to 1.46, absolute figures not reported for any outcome). [39]

Endometrial cancer
We found one systematic review (search date 2008, 45 RCTs, total number of women not reported), which found no significant difference in endometrial cancer between combined HRT (oestrogen plus either cyclical or continuous progestogen) and placebo at times from 3 to 5 years (for continuous combined HRT, at 5 or more years: 27/8506 [0.3%] with combined HRT *v* 31/8102 [0.4%] with placebo; OR 0.83, 95% CI 0.49 to 1.39; for cyclical medroxyprogesterone acetate 10 mg, at 3 years: 1 RCT, 0/118 [0%] with combined HRT *v* 1/119 [1%] with placebo; OR 0.33, 95% CI 0.01 to 8.27; for cyclical progesterone 200 mg, at 3 years: 1 RCT, 0/120 [0%] with combined HRT *v* 1/119 [1%] with placebo; OR 0.33, 95% CI 0.01 to 8.13). [32] The review also found that oestrogens plus progestogens (either cyclical or continuous) significantly reduced endometrial hyperplasia compared with oestrogens alone, and found no significant difference in endometrial hyperplasia between combined therapy and placebo (meta-analysis not performed owing to varying doses of oestrogens and progestogens used; data reported from individual RCTs only). The largest RCT in the systematic review (16,608 postmenopausal women, described in benefits section above) also found no significant difference between combined HRT and placebo in the risk of gynaecological tumours (see table 2, p 25). [47]

Breast cancer
A further report of the large RCT (16,608 postmenopausal women) described in the benefits section above [42] [43]) found that oestrogen plus progesterone increased the risk of breast cancer and, in women who developed breast cancer, it significantly increased the size of tumours and the risk of tumour spread compared with placebo (increase in size of tumour: 1.7 cm with treatment *v* 1.5 cm with placebo; P = 0.04; increase in risk of tumour spread: 25% with treatment *v* 16% with placebo; P = 0.04; (see table 2, p 25). [48]

Cardiovascular events
We found three systematic reviews (search date 2004; 28 RCTs, 39,769 people, 3 RCTs included men; [36] search date 2008, 31 RCTs, 41,113 women; [37] and search date 2007, 9 RCTs, 7 case control studies, and one prospective cohort study [38]) evaluating cardiovascular complications of HRT. All of the reviews compared either oestrogen alone or oestrogen plus progestogen versus placebo or no treatment. The reviews did not report results separately for combined HRT. The reviews found that HRT significantly increased cerebrovascular events (stroke and TIA) and venous thromboembolism compared with placebo. See harms of oestrogens alone, p 5 for full details of the results of these reviews.

The largest RCT in the reviews (16,608 postmenopausal women, described in benefits section above) reported similar results, finding that HRT significantly increased venous thromboembolism and stroke compared with placebo (for full results see table 2, p 25). However, it did find that HRT caused a small significant increase in the combined outcome of non-fatal MI or cardiac death compared with placebo.

Gallbladder disease
One RCT (22,579 women) found that oestrogen alone and oestrogen plus progesterone significantly increased risk of gallbladder disease compared with placebo (HR for any gallbladder event: oestrogen alone 1.67, 95% CI 1.35 to 2.06; oestrogen plus progesterone 1.59, 95% CI 1.28 to 1.97; absolute numbers not reported). [49]

Oestrogens plus progestogens versus tibolone:
See harms of tibolone, p 3 .

Oestrogens plus progestogens versus phyto-oestrogens:
See harms of phyto-oestrogens, p 18 .

Comment:

Clinical guide:
Based on the evidence for harms associated with oestrogen (see harms of oestrogens alone, p 5), it remains important that women with an intact uterus who are prescribed any form of oestrogen take either continuous or cyclical progestogens. Applicability of the large RCT may be limited, because the average age of women enrolled in the study (63.3 years) is much older than that of women who typically start HRT. [42]

OPTION PROGESTOGENS ALONE

Vasomotor symptoms
Compared with placebo Progestogens (oral and transdermal) may be more effective in reducing vasomotor symptoms (low-quality evidence).

Compared with oestrogens We don't know how medroxyprogesterone and oestrogens compare at reducing vasomotor symptoms (low-quality evidence).

Note
We found no direct information from RCTs about the effects of progestogens alone in the treatment of urogenital symptoms in women with menopausal symptoms. Progestogens are seldom given alone, as the high doses of progestogens required for improvement of menopausal symptoms are associated with adverse effects.

For GRADE evaluation of interventions for menopausal symptoms, see table, p 31 .

Benefits:

Progestogens versus placebo:
Vasomotor symptoms
We found no systematic review. We found three RCTs comparing oral progestogens versus placebo, [50] [51] [52] two RCTs comparing transdermal progesterone versus placebo, [53] [54] and one RCT comparing oral progestogens versus oral oestrogen. [30] The three RCTs comparing oral progestogens alone versus placebo (all 24 weeks or less in duration) all found that progestogens significantly reduced vasomotor symptoms (see table 3, p 26). [50] [51] [52] However, the RCTs had crossover comparisons, which makes it difficult to draw conclusions. The two RCTs comparing transdermal progesterone alone versus placebo found different results. [53] [54] The first RCT found that progesterone significantly reduced vasomotor symptoms compared with placebo (see table 3, p 26). [53] The second RCT found no significant difference in vasomotor symptoms (assessed using the Greene Climacteric Scale) between treatments (see table 3, p 26). [54]

Urogenital system
We found no RCTs evaluating the effects of progestogens alone on urinary incontinence, the lower genital tract, or libido.

Psychological, cognitive, and sleep symptoms
We found one RCT (80 women). [54] It found no significant difference in depression or anxiety symptoms after 12 weeks between transdermal progesterone and placebo (see table 3, p 26).

Quality of life
We found one RCT, which found no significant difference between transdermal progesterone and placebo for each of four quality-of-life domains. [54]

Progestogens versus oestrogens:
See benefits of oestrogens alone, p 5 .

Harms:

Progestogens versus placebo:
The RCTs gave no information on harms. [50] [51] [52] [53] [54] See also harms of oral progestogen in the reviews on menorrhagia and premenstrual syndrome.

Progestogens versus oestrogens:
See harms of oestrogens alone, p 5 .

Comment:

Clinical guide:
Progestogens are seldom given alone, which makes it difficult to isolate their effects. When given without oestrogen, doses of progestogens were high, the lowest dose being medroxyprogesterone 20 mg acetate daily. The adverse effects associated with these high doses of progestogens limit the clinical usefulness of progestogens given alone for menopausal symptoms.

OPTION ANTIDEPRESSANTS

Vasomotor symptoms
Compared with placebo Antidepressants (SSRIs, selective noradrenaline reuptake inhibitors [SNRIs], veralipride, and desvenlafaxine) may be more effective at reducing vasomotor symptom severity in the short term. However, the significance of the effect for some antidepressants depended on the analysis undertaken (very low-quality evidence).

Note
We found no direct information from RCTs about the effects of antidepressants in the treatment of urogenital symptoms; psychological, cognitive, and sleep symptoms; or quality of life, in women with menopausal symptoms.

For GRADE evaluation of interventions for menopausal symptoms, see table, p 31 .

Benefits:

Antidepressants versus placebo:

Vasomotor symptoms

We found one systematic review [55] and one subsequent RCT, [56] which assessed the effects of antidepressants on the number and severity of hot flushes.

The systematic review (search date 2005, 10 RCTs, 998 women) carried out a meta-analysis of selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline (norepinephrine) reuptake inhibitors (SNRIs). The review found that SSRIs/SNRIs significantly reduced the mean number of daily hot flushes compared with placebo (6 RCTs, 744 women; WMD –1.13, 95% CI –1.70 to –0.57). However, four of the six RCTs were in women with breast cancer who were also receiving a selective oestrogen receptor modulator. A subgroup analysis found that the reduction in the number of hot flushes was not significant for SSRI/SNRI alone compared with placebo (2 RCTs, 180 women; WMD –0.17, 95% CI –1.41 to +1.07). However, SSRI/SNRI plus selective oestrogen receptor modulator significantly reduced hot flushes compared with placebo (4 RCTs, 564 women; WMD –1.40, 95% CI –1.97 to –0.82). The review also included three RCTs (50, 40, and 30 women) comparing veralipride 100 mg daily versus placebo, but did not carry out a meta-analysis of these results. [55] Two RCTs found that veralipride significantly reduced the frequency and severity of hot flushes compared with placebo (P less than 0.05 for both RCTs). The third RCT found a reduction from baseline in frequency of hot flushes for both veralipride and placebo, and found no between-group differences (P value not reported).

The subsequent RCT (458 postmenopausal women) compared desvenlafaxine at two doses (100 and 150 mg/day) versus placebo. [56] It found that desvenlafaxine at both doses significantly reduced the number and severity of hot flushes compared with placebo at 12 weeks (change in number of moderate and severe hot flushes/day: −7.1 with desvenlafaxine 100 mg *v* −7.0 with desvenlafaxine 150 mg *v* −5.8 with placebo; for comparison with placebo: P = 0.005 for desvenlafaxine 100 mg, P = 0.012 for desvenlafaxine 150 mg; change in daily hot flush severity score [possible range not reported]: –0.65 with desvenlafaxine 100 mg *v* –0.66 with desvenlafaxine 150 mg *v* –0.33 with placebo; P less than 0.001 for both desvenlafaxine 100 and 150 mg *v* placebo).

Urogenital symptoms

We found no systematic review or RCTs.

Psychological, cognitive, and sleep symptoms

We found no systematic review or RCTs.

Quality of life

We found no systematic review or RCTs.

Harms:

Antidepressants versus placebo:

The review found that the most common adverse effects reported with SSRIs or SNRIs were dry mouth, decreased appetite, nausea, constipation, and drowsiness (no other details reported). [55] The review reported that gastrointestinal adverse effects, mastodynia, and galactorrhoea were more common with veralipride than with placebo. Antidepressants as a group can cause many central nervous system adverse effects, including sedation and agitation, as well as urinary and vision problems, liver dysfunction, and cardiac dysrhythmias (see antidepressants in review on depression in adults [drug and other physical treatments]). The subsequent RCT found that desvenlafaxine significantly increased nausea compared with placebo (AR: 76/301 [25%] people with desvenlafaxine *v* 11/151 [7%] with placebo; P less than 0.001). [56] One woman taking venlafaxine developed hypertension, while another taking placebo reported bronchospasm. Rates of other adverse events observed such as dizziness, insomnia, diarrhoea, and hypertension did not differ significantly with placebo.

Comment:

Clinical guide:

The SSRI/SNRI classes of antidepressants may alleviate severe menopausal symptoms in women unable or unwilling to take hormonal medications. Evidence suggests that there is no long-term effect, and so the short-term benefits should be balanced against the adverse effect of these drugs.

OPTION CLONIDINE

Vasomotor symptoms

Compared with placebo We don't know whether clonidine is more effective in reducing hot flushes at 4 weeks compared with placebo (very low-quality evidence).

Note

We found no direct information from RCTs about the effects of clonidine on sexual function, psychological symptoms, or quality of life.

For GRADE evaluation of interventions for menopausal symptoms,
see table , p 31

.

Benefits:

Clonidine versus placebo:
Vasomotor symptoms
We found one systematic review (search date 2005, 4 RCTs, 446 women with 4 weeks' follow-up, and 228 women with 8 weeks' follow-up) on the effects of clonidine on menopausal symptoms. [55] The review found that clonidine 0.05 to 0.15 mg daily significantly reduced the mean number of daily hot flushes at 4 and 8 weeks compared with placebo (4 weeks: 4 RCTs, 446 women, WMD –0.95, 95% CI –1.44 to –0.47; 8 weeks: 2 RCTs, 218 women, WMD –1.63, 95% CI –2.76 to –0.50). However, two of the four RCTs were in women with breast cancer who were also receiving a selective oestrogen receptor modulator. A subgroup analysis found that the reduction in the number of hot flushes was not significant at 4 weeks in women receiving only clonidine compared with placebo (2 RCTs, 130 women; WMD –0.53, 95% CI –2.09 to +1.04). The review did not carry out a subgroup analysis of women receiving only clonidine after 8 weeks' treatment.

Urogenital system
We found no systematic review or RCTs.

Psychological, cognitive, and sleep symptoms
We found no systematic review or RCTs.

Quality of life
We found no systematic review or RCTs.

Harms:

Clonidine versus placebo:
Minor adverse effects:
The review reported the main adverse effects as dry mouth, constipation, insomnia, headache, and drowsiness (no further details reported). [55]

Comment:

Clinical guide:
Most RCTs on the effect of clonidine on vasomotor symptoms are considered of poor or moderate quality. The length of follow-up of the individual RCTs does not support a long-term effect. Further research with high-quality RCTs is required.

OPTION TESTOSTERONE

Urogenital symptoms
Testosterone plus oestrogen-containing HRT compared with oestrogen-containing HRT alone Testosterone plus oestrogen-containing HRT may be more effective in improving sexual function scores compared with oestrogen-containing HRT alone (low-quality evidence).

Psychological, cognitive, and sleep symptoms
Testosterone plus oestrogen-containing HRT compared with oestrogen-containing HRT alone We don't know whether testosterone (oral methyltestosterone) plus oestrogen-containing HRT is more effective than oestrogen-containing HRT alone at improving cognition at 16 weeks compared with oestrogen-containing HRT alone (low-quality evidence).

Note
We found no direct information from RCTs on whether testosterone alone is better than no active treatment, or on the effects of testosterone on quality of life in women with menopausal symptoms.

For GRADE evaluation of interventions for menopausal symptoms, **see table, p 31** .

Benefits:

Testosterone versus placebo:
We found no systematic review or RCTs.

Testosterone plus oestrogen versus placebo:
We found no systematic review or RCTs.

Testosterone plus oestrogen-containing HRT versus oestrogen-containing HRT alone:
We found one systematic review (search date 2003, 1957 peri- and postmenopausal women) [57] and one subsequent RCT, [58] which compared testosterone plus oestrogen-containing HRT versus oestrogen-containing HRT alone.

Vasomotor symptoms
The systematic review found no clinically relevant data in the identified RCTs for meta-analysis. [57] The review found that descriptive data analysis found no consistent evidence of an effect of testosterone on menopausal symptoms (3 RCTs, vasomotor symptoms assessed using validated questionnaires). [57]

Urogenital system
The systematic review found that testosterone plus oestrogen-containing HRT significantly improved sexual responsiveness and libido compared with oestrogen-containing HRT alone (sexual responsiveness; 2 RCTs, 238 women: SMD 0.45, 95% CI 0.19 to 0.71; libido; 3 RCTs, 315 women: SMD 0.42, 95% CI 0.18 to 0.66). [57] The review found a significant improvement in a composite sexual function score with testosterone plus oestrogen-containing HRT compared with oestrogen-containing HRT alone (SMD 0.41, 95% CI 0.15 to 0.67). However, the review found no significant difference between treatments in improvement in sexual activity or frequency and satisfaction (sexual activity; 2 RCTs, 97 women: SMD 1.01, 95% CI 0.42 to 1.60; satisfaction; 1 RCT, 77 women: SMD 0.98, 95% CI 0.24 to 1.72). The subsequent RCT (562 women receiving oestrogen-containing HRT) compared testosterone (300 micrograms daily transdermally by a patch worn on the abdomen) plus oestrogen versus placebo patches plus oestrogen over a 24-week period. [58] Improvements were assessed using a weekly symptom log and validated symptom questionnaires (the Profile of Female Sexual Function and Personal Distress Scale). The questionnaire measured seven domains of sexual function (sexual desire, pleasure, arousal, orgasm, responsiveness, concerns, and self-image). Responses were scored on a 6-point scale for each item in each domain (1 = always to 6 = never). Treatment differences were expressed as difference in 4-week frequency of sexual activity, desire, and distress at week 24. The RCT found that testosterone plus oestrogen-containing HRT significantly improved total satisfying sexual activity, sexual desire, and personal distress at 24 weeks compared with oestrogen-containing HRT alone (satisfying sexual activity: treatment difference 0.99, 95% CI 0.20 to 1.79; P = 0.015; sexual desire: treatment difference 4.09, 95% CI 0.79 to 7.38; P = 0.015; personal distress: treatment difference –5.49, 95% CI –10.47 to –0.51; P = 0.03). [58]

Psychological, cognitive, and sleep symptoms
One RCT included in the systematic review found no significant difference in improvement in cognition over 16 weeks between oral methyltestosterone 2.5 mg daily plus oestrogen-containing HRT and oestrogen-containing HRT alone, which was assessed with identical pictures and shape memory (identical pictures: difference in means –0.42, 95% CI –1.20 to +0.36; shape memory: difference in means +0.03, 95% CI –0.74 to +0.80). [57] However, this RCT included only 40 people, and so it may have been too small to detect a clinically important difference. [57]

Quality of life
We found no systematic review or RCTs.

Harms:

Testosterone versus placebo:
We found no systematic review or RCTs.

Testosterone plus oestrogen versus placebo:
We found no systematic review or RCTs.

Testosterone plus oestrogen-containing HRT versus oestrogen-containing HRT alone:
Androgenic adverse effects
One RCT (218 women) included in the review analysed the androgenic adverse effects of testosterone when taken with oestrogen-containing HRT. [57] The RCT found no significant differences in hirsutism and acne after 16 weeks' treatment between testosterone plus oestrogen-containing HRT and oestrogen-containing HRT alone (hirsutism: WMD +0.40, 95% CI –0.15 to +0.95; acne: WMD +0.10, 95% CI –0.03 to +0.23; absolute numbers not reported). The subsequent RCT (562 women) also found no significant differences in hirsutism and acne after 24 weeks' treatment between the two treatments (hirsutism: 16/283 [5.7%] with testosterone plus oestrogen *v* 18/279 [6.5%] with oestrogen alone; acne: 17/283 [6.0%] with testosterone plus oestrogen *v* 17/279 [6.1%] with oestrogen alone; both reported as not significant; P values not reported). [58]

Comment:

The RCTs included in the review had inconsistent washout periods and attrition bias. Randomisation and blinding were generally considered of good quality. Of the 23 RCTs included the review, none was of sufficient quality to provide reliable information about menopausal symptoms.

QUESTION What are the effects of non-prescribed treatments for menopausal symptoms?

OPTION AGNUS CASTUS

Note
We found no direct information from RCTs about agnus castus in the treatment of women with menopausal symptoms.

For GRADE evaluation of interventions for menopausal symptoms, see table, p 31 .

Benefits: We found no systematic review or RCTs of agnus castus in women with menopausal symptoms.

Harms: We found no RCTs.

Comment: None.

OPTION BLACK COHOSH

Note
We found no direct information from RCTs about black cohosh in the treatment of women with menopausal symptoms.

For GRADE evaluation of interventions for menopausal symptoms, see table , p 31 .

Benefits: We found no systematic review or RCTs of black cohosh in women with menopausal symptoms.

Harms: We found no RCTs.

Comment: A temporal association between the start of treatment with black cohosh and adverse effects on the liver has been reported. [59] In the UK, the European Medicines Agency (EMLA) and Medicines and Healthcare products Regulatory Agency (MHRA) have issued guidance that women taking black cohosh, who develop signs and symptoms suggestive of hepatic impairment, should stop taking the drug and contact their doctor immediately.

OPTION PHYTO-OESTROGENS

Vasomotor symptoms
Compared with placebo We don't know whether phyto-oestrogens (soy isoflavone extracts, soy dietary supplements, red clover, or other phyto-oestrogens) are more effective at reducing vasomotor symptoms (very low-quality evidence).

Compared with oestrogen alone We don't know how phyto-oestrogen (soy extract) and oestrogen alone compare at reducing vasomotor symptoms (very low-quality evidence).

Compared with oestrogen plus progestogen We don't know how phyto-oestrogen (pueraria lobata) and oestrogen plus medroxyprogesterone acetate compare at reducing vasomotor symptoms (very low-quality evidence).

Urogenital symptoms
Compared with placebo We don't know whether phyto-oestrogens (soy protein or red clover extract) are more effective at improving vaginal dryness or libido (very low-quality evidence).

Psychological, cognitive, and sleep symptoms
Compared with placebo We don't know whether phyto-oestrogens are more effective in improving psychological symptoms or cognitive function at 3 to 6 months (very low-quality evidence)

Adverse effects
Compared with placebo Isoflavone may be associated with an increased risk of endometrial hyperplasia in women at 5 years compared (low-quality evidence).

Note
We found no direct information from RCTs about the effects of phyto-oestrogens on quality of life in women with menopausal symptoms.

For GRADE evaluation of interventions for menopausal symptoms, see table, p 31 .

Benefits:

Phyto-oestrogens versus placebo:

Vasomotor symptoms

We found one systematic review [60] and one additional RCT. [61] The systematic review (search date 2007, 31 RCTs, 2730 postmenopausal women) evaluated food products or dietary supplements containing high levels of phyto-oestrogens for management of hot flushes and night sweats. [60] Most of the RCTs identified were small pilot studies that evaluated disparate types of phyto-oestrogen with no standardised dosing, and therefore the review did not perform a meta-analysis for most comparisons. As a consequence the review was unable to draw any firm conclusions as to whether any phyto-oestrogen preparation was effective. We have reported the results of the included RCTs that met *Clinical Evidence* inclusion criteria separately (see table 4, p 27 for full results). The review grouped the trials by whether they included soy dietary supplements (flour, powders, or drinks: 6 RCTs), soy isoflavone extracts (usually tablets; 6 RCTs), red clover extracts (tablets; 6 RCTs), or other phyto-oestrogens (extracts of genistein, pueraria lobata, hops, or flaxseed).

For soy isoflavone supplements, five of the RCTs (485 women) found no significant difference between supplements and placebo in hot flush frequency at times from 12 weeks to 2 years. One RCT (104 women) found than soy powder supplements significantly reduced hot flush frequency compared with placebo. The review found seven RCTs that met our inclusion criteria, comparing soy supplements versus placebo, and evaluating hot flush frequency or severity (see table 4, p 27 for full results). Four of the RCTs (393 women) evaluated hot flush frequency, with two of these RCTs (150 women) finding that soy supplements reduced hot flush frequency compared with placebo, and the remaining two RCTs (243 women) finding no significant difference between groups. Four RCTs evaluated hot flush severity, with two of these RCTs (287 women) finding that soy supplements improved hot flush severity compared with placebo, and the remaining two RCTs (111 women) finding no significant difference between groups.

For red clover extracts, the review performed a meta-analysis of five RCTs (400 women) comparing a standard red clover extract (promensil) with placebo, and found no significant difference in the frequency of hot flushes at 12 to 16 weeks. The remaining RCT (60 women) comparing red clover extract versus placebo was not included in the analysis as it used a non-standard extract, and it did not assess significance.

For other phyto-oestrogens, three RCTs (278 women) found no significant difference in hot flush severity between various dietary phyto-oestrogens and placebo at times from 12 weeks to 1 year. One RCT (90 women) found that genistein extract significantly reduced hot flush frequency compared with placebo at 1 year, and one further RCT (52 women) found no significant difference in hot flush frequency between a linseed diet and a placebo (wheat) diet at 12 weeks.

The additional RCT (crossover, 51 women) compared a daily dietary supplement containing no phyto-oestrogens versus a supplement containing soy protein 34 mg. [61] It found that, at 6 weeks, soy protein reduced the severity (P less than 0.001) but not the frequency of vasomotor symptoms.

Urogenital system

We found two RCTs. [62] [63] The first RCT (94 women) found no significant difference between soy protein and placebo in improvement in vaginal dryness (P = 0.1) and libido (P = 0.38) after 3 months. [63] Severity of symptoms before and after treatment was assessed using a 4-point subjective rating scale (0 = none to 3 = severe).

The second RCT (60 women, 90-day crossover study of red clover isoflavone) found that red clover isoflavone significantly improved vaginal cytology (measured using the karyopyknotic index) after 90 days' treatment compared with placebo (mean karyopyknotic score after 90 days [baseline of 6.1]: 45.6 with isoflavone *v* 3.6 with placebo; P less than 0.05). [62]

Psychological, cognitive, and sleep symptoms

We found two RCTs. [63] [64] The first RCT (94 women) found no significant difference in improvement in psychological symptoms — including irritability, depression, anxiousness, and sleeplessness — at 3 months between soy protein and placebo (reported as not significant; P values not reported). [63] Severity of symptoms before and after treatment was assessed using a 4-point subjective rating scale (0 = none to 3 = severe).

The second RCT (78 women) was a crossover study of two 6-month treatment phases of isoflavone 60 mg or placebo, with a 1-month washout phase between treatments. [64] Cognitive performance was assessed with pairs-recall test. The RCT found a significant increase in the number of pairs recalled correctly with red clover compared with placebo (pairs recalled correctly: 6.5 with phyto-oestrogen *v* 6.2 with placebo; P = 0.04). The RCT also found a significant improvement in the backwards recall of digits with red clover compared with placebo (5.9 with phyto-oestrogen *v* 5.4 with placebo; P = 0.05). However, there was no significant difference in the forwards recall of digits

between red clover and placebo (6.5 with phyto-oestrogen *v* 6.5 with placebo; P = 0.98). The RCT found no other significant differences in the other domains of cognitive function — including the digit symbol, digit span, or visual scanning test — between red clover and placebo. Mood was also assessed with the Beck Depression Inventory, Spielberg State-Trait Anxiety Inventory, and Profile of Mood States. The RCT found that red clover significantly improved depression and mood compared with placebo (Beck Depression Inventory score: 7.6 with phyto-oestrogen *v* 9.7 with placebo; P = 0.01; global score for the Profile of Mood States: 34 with phyto-oestrogen *v* 41 with placebo; P = 0.01).

Quality of life
We found no systematic review or RCTs.

Phyto-oestrogens versus oestrogen alone:
Vasomotor symptoms
We found one systematic review (search date 2007, 31 RCTs, 2730 postmenopausal women), which identified one RCT comparing phyto-oestrogen (soy extract) versus oestrogen plus placebo. [60] The RCT found no significant difference between groups in vasomotor symptom severity (see table 4, p 27 for full results).

Urogenital symptoms
We found no systematic review or RCTs.

Psychological, cognitive, and sleep symptoms
We found no systematic review or RCTs.

Quality of life
We found no systematic review or RCTs.

Phyto-oestrogens versus oestrogens plus progestogens:
Vasomotor symptoms
We found one systematic review (search date 2007, 31 RCTs, 2730 postmenopausal women), which identified one RCT comparing phyto-oestrogen (pueraria lobata) versus oestrogen plus medroxyprogesterone acetate. [60] The RCT found no significant difference between groups in vasomotor symptom severity (see table 4, p 27 for full results).

Urogenital symptoms
We found no systematic review or RCTs.

Psychological, cognitive, and sleep symptoms
We found no systematic review or RCTs.

Quality of life
We found no systematic review or RCTs.

Harms:

Phyto-oestrogens versus placebo:
See table 4, p 27 for full details of adverse effects in the RCTs identified by the systematic review. [60] Two of the RCTs (179 women) identified by the first systematic review found no significant difference in rates of adverse effects between phyto-oestrogens and placebo. One smaller RCT in the review (24 women) found that soy powder significantly increased overall adverse effects compared with placebo. One RCT in the review (80 women) found no significant difference in endometrial thickening between groups. Three RCTs in the review (163 women) found that phyto-oestrogens significantly increased the vaginal maturation index compared with placebo. The RCT on the effects of phyto-oestrogens on psychological symptoms of menopause gave no information on adverse effects. [64]

Endometrial hyperplasia
One RCT (376 women) found that isoflavone 150 mg daily significantly increased the proportion of women with endometrial hyperplasia at 5 years compared with placebo (6/154 [4%] with isoflavone *v* 0/165 [0%] with placebo; P less than 0.05). [65] There was also one case of complex hyperplasia in the phyto-oestrogen group, and none in the placebo group (reported as not significant). It should be noted that the dose used in this study is considered by some agencies to be above the standard recommended dose of phyto-oestrogen of 80 mg daily.

Phyto-oestrogens versus oestrogen alone:
The RCT identified by the review found that oestrogen significantly increased endometrial thickness compared with soy extract (see table 4, p 27 for full details). [60]

Phyto-oestrogens versus oestrogens plus progestogens:
The RCT identified by the review gave no information on adverse effects. [60]

Comment: Few studies have specifically investigated adverse effects of phyto-oestrogens. Results of studies are difficult to interpret because phyto-oestrogen preparations are not standardised.

GLOSSARY

Beck Depression Inventory Standardised scale to assess depression. This instrument consists of 21 items to assess the intensity of depression. Each item is a list of four statements (rated 0, 1, 2, or 3), arranged in increasing severity, about a particular symptom of depression. The range of scores possible are 0 = least severe depression to 63 = most severe depression. It is recommended for people aged 13–80 years. Scores of more than 12 or 13 indicate the presence of depression.
Greene Climacteric Scale A numerical index that scores 21 menopausal symptoms in three domains: psychological, somatic, and vasomotor. Each symptom is rated from 0 to 3 where 0 = no symptoms and 3 = extreme symptoms.
Kupperman Index A numerical index that scores 11 menopausal symptoms: hot flushes, paraesthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia or myalgia, headache, palpitations, and formication. Each symptom is rated from 0 to 3 according to severity and symptoms (where 0 = no symptoms and 3 = most severe), weighted and the total sum calculated. The maximum score is 51 points.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Spielberger's 20-item State-trait Anxiety Inventory scores range from 20 to 80, where 20 equals not feeling like that at all (state anxiety) or ever (trait anxiety) and 80 would equal feeling like that very much (state anxiety) or always (trait anxiety).
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antidepressants One RCT added, which found that desvenlafaxine reduced the frequency and severity of hot flushes compared with placebo at 12 weeks. [56] In previously reported evidence, the significance of the effect for some antidepressants depended on the analysis undertaken. Effects of antidepressants on vasomotor symptoms remain unclear. Categorisation unchanged (Unknown effectiveness).
Oestrogens alone Three RCTs evaluating vasomotor symptoms added. [19] [20] [21] All three RCTs found that oestrogen reduced hot-flush frequency and severity compared with placebo. One systematic review added, which found no significant difference in new diagnoses of mild cognitive impairment or in cognitive scores between HRT and placebo. [27] One systematic review added, which found that oestrogen significantly increased endometrial hyperplasia compared with placebo. [32] Two systematic reviews added comparing HRT (oestrogen alone, or combined with progestogen) versus placebo, which evaluated cardiovascular adverse effects. [37] [38] The first systematic review found that HRT significantly increased stroke compared with placebo but found no difference in cardiac events between groups. [37] The second systematic review found that HRT significantly increased venous thromboembolism compared with placebo. [38] Categorisation unchanged (Trade-off between benefits and harms).
Oestrogens plus progestogens One RCT added found that oestrogen plus drospirenone (a new progestogen preparation) reduced hot flushes and urinary symptoms compared with placebo. [40] One systematic review added that found inconsistent results suggesting that HRT may worsen cognitive scores compared with placebo, but which noted that there was insufficient data to judge whether HRT had a positive or negative effect on cognition. [27] One systematic review added found no significant difference in endometrial cancer or hyperplasia between oestrogen plus progestogen and placebo. [32] Two systematic reviews added comparing HRT (oestrogen alone or combined with progestogen) versus placebo, which evaluated cardiovascular adverse effects. [37] [38] The first systematic review found that HRT significantly increased stroke compared with placebo, but found no difference in cardiac events between groups. [37] The second systematic review found that HRT significantly increased venous thromboembolism compared with placebo. [38] Categorisation unchanged (Trade-off between benefits and harms).
Phyto-oestrogens One systematic review added, which identified several small RCTs. [60] Owing to disparate preparations and trial methods it was unable to draw firm conclusions about the effectiveness of phyto-oestrogens in alleviating hot flushes. Categorisation unchanged (unknown effectiveness).
Tibolone Two RCTs added comparing tibolone versus placebo. The first RCT found that tibolone (both 1.25 and 2.5 mg) reduced the frequency and severity of hot flushes at 12 weeks. [5] The second RCT evaluated the risk of breast cancer recurrence with tibolone, and was stopped early after finding that tibolone significantly increased the rate of breast cancer at a median follow-up of 3.5 years. [14] Categorisation changed (from Beneficial to Trade-off between benefits and harms).

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Edward P Morris
Consultant in Obstetrics and Gynaecology
Norfolk and Norwich University Hospital
Norwich
UK

Nikolaos Burbos
Department of Obstetrics and Gynaecology
Norfolk and Norwich University Hospital
Norwich
UK

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Disclaimer

TABLE 1 **Summary of data on comparisons of oestrogen-containing intravaginal preparations.** [23]

Event	Absolute numbers	Odds ratio
Oestrogen ring v placebo		
Improvement in dyspareunia (1 RCT, 67 women)	30/33 (91%) with oestrogen ring *v* 15/34 (44%) with placebo	12.67, 95% CI 3.23 to 49.67
Absence of pallor (1 RCT, 52 women)	21/25 (84%) with oestrogen ring *v* 14/27 (52%) with placebo	4.88, 95% CI 1.32 to 18.05
Absence of friability (1 RCT, 52 women)	18/21 (86%) with oestrogen ring *v* 9/20 (45%) with placebo	7.33, 95% CI 1.63 to 33.08
Overall satisfaction with treatment (1 RCT, 159 women)	50 micrograms oestrogen: 84/90 (93%) with ring *v* 56/69 (81%) with placebo	0.31, 95% CI 0.11 to 0.86
	100 micrograms oestrogen: 88/89 (99%) with ring *v* 56/69 (81%) with placebo	0.05, 95% CI 0.01 to 0.38
Tolerability (pain during intercourse: 1 RCT, 143 women)	50 micrograms oestrogen: 23/82 (28%) with ring *v* 15/61 (25%) with placebo	0.58, 95% CI 0.17 to 2.01
	100 micrograms oestrogen: 17/75 (23%) with ring *v* 15/61 (25%) with placebo	0.43, 95% CI 0.11 to 1.64
Oestrogen tablet v placebo		
Proportion with burning and itching (2 RCTs, 774 women)	89/385 (23%) with oestrogen tablet *v* 249/389 (64%) with placebo	0.15, 95% CI 0.10 to 0.20
Proportion with dyspareunia (2 RCTs, 716 women)	105/358 (29%) with oestrogen tablet *v* 256/358 (72%) with placebo	0.17, 95% CI 0.12 to 0.23
Proportion with vaginal dryness (3 RCTs, 1140 women)	108/568 (19%) with oestrogen tablet *v* 423/572 (74%) with placebo	0.08, 95% CI 0.06 to 0.10
Proportion with vaginal atrophy (2 RCTs, 1256 women)	129/626 (21%) with oestrogen tablet *v* 454/630 (72%) with placebo	0.09, 95% CI 0.07 to 0.12
Oestrogen ring v oestrogen tablet		
Improvement or cure of vaginal dryness (2 RCTs, 397 women)	155/235 (66%) with ring *v* 124/162 (77%) with tablet	0.40, 95% CI 0.24 to 0.64
Improvement or cure of dyspareunia (3 RCTs, 567 women)	200/347 (58%) with ring *v* 147/220 (67%) with tablet	0.53, 95% CI 0.36 to 0.78
Absence of vaginal atrophy symptoms (1 RCT, 170 women)	47/112 (42%) with ring *v* 22/58 (38%) with tablet	1.18, 95% CI 0.62 to 2.27
Oestrogen ring v oestrogen cream		
Improvement in pruritus (2 RCTs, 341 women)	159/203 (78%) with ring *v* 81/138 (59%) with cream	2.71, 95% CI 1.66 to 4.43
Improvement in vaginal dryness (2 RCTs, 341 women)	165/203 (81%) with ring *v* 107/138 (76%) with cream	1.29, 95% CI 0.75 to 2.22

Event	Absolute numbers	Odds ratio
Improvement in dyspareunia (2 RCTs, 341 women)	145/203 (71%) with ring *v* 108/138 (78%) with cream	0.69, 95% CI 0.41 to 1.14
Oestrogen tablet v oestrogen cream		
Improvement or cure in vaginal dryness (1 RCT, 48 women)	12/24 (50%) with tablet *v* 3/24 (13%) with cream	7.00, 95% CI 1.64 to 29.85
Improvement or cure in dyspareunia (1 RCT, 48 women)	8/24 (33%) with tablet *v* 3/24 (13%) with cream	3.50, 95% CI 0.11 to 2.58

TABLE 2 **Harms of oestrogen: summary data regarding stroke, breast, ovarian, and endometrial cancer incidence from the Women s Health Initiative Trial** [47] [48] [67]

Event type		Cumulative absolute risk with oestrogen plus progesterone *v* placebo	Hazard ratio
Breast cancer [48]	Total cancers	245/8506 (3%) with oestrogen plus progesterone *v* 185/8102 (2%) with placebo	1.24, 95% CI 1.02 to 1.50
	Invasive cancers	199/8506 (2.3%) with oestrogen plus progesterone *v* 150/8102 (1.9%) with placebo	1.24, 95% CI 1.01 to 1.54
	In situ cancers	47/8506 (0.6%) with oestrogen plus progesterone *v* 37/8102 (0.5%) with placebo	1.18, 95% CI 0.77 to 1.82
Ovarian cancer [47]	Total cancers	20/8506 (0.2%) with oestrogen plus progesterone *v* 12/8102 (0.1%) with placebo	1.58, 95% CI 0.77 to 3.24
Endometrial cancer [47]	Total cancers	27/8506 (0.3%) with oestrogen plus progesterone *v* 31/8102 (0.4%) with placebo	0.81, 95% CI 0.48 to 1.36
Stroke [67]	Total strokes	151/8506 (2%) with oestrogen plus progesterone *v* 107/8102 (1%) with placebo	1.31, 95% CI 1.02 to 1.68
	Ischaemic stroke	125/8506 (1.5%) with oestrogen plus progesterone *v* 81/8102 (1.0%) with placebo	1.44, 95% CI 1.09 to 1.90
	Haemorrhagic stroke	18/8506 (0.2%) with oestrogen plus progesterone *v* 20/8102 (0.2%) with placebo	0.82, 95% CI 0.43 to 1.56
Thromboembolic disease [68]	Deep vein thrombosis	123/8506 (1.4%) with oestrogen plus progesterone *v* 59/8102 (0.7%) with placebo	1.95, 95% CI 1.43 to 2.67
	Pulmonary embolism	86/8506 (1.0%) with oestrogen plus progesterone *v* 38/8102 (0.4%) with placebo	2.13, 95% CI 1.39 to 3.25
Coronary heart disease [42]	Non-fatal MI and death due to coronary heart disease	164/8506 (0.4%) with oestrogen plus progesterone *v* 122/8102 (0.3%) with placebo	1.29, 95% CI 1.02 to 1.63

TABLE 3 **Placebo-controlled RCTs evaluating the effect of progestogens on vasomotor symptoms** [50] [51] [52] [53] [54]

Trial	Comparison	Outcome	Difference
Loprinzi [50]	Oral medroxyprogesterone acetate 200 mg twice daily *v* placebo (crossover) for 9 weeks; 97 women	50% reduction in daily hot flush frequency at 4 weeks (pre-crossover)	34/48 (71%) with medroxyprogesterone acetate *v* 12/49 (24%) with placebo; RR 2.9, 95% CI 1.71 to 4.89; NNT 3, 95% CI 2 to 4
Aslaksen [51]	Oral medroxyprogesterone acetate 100 mg twice daily *v* placebo (crossover) for 24 weeks; 21 women	Free from hot flushes at end of study	18/21 (86%) with medroxyprogesterone acetate *v* 7/21 (33%) with placebo; RR for no flushes 2.60, 95% CI 1.37 to 4.83; NNT 2, 95% CI 2 to 3
		Free from sweating	18/21 (86%) with medroxyprogesterone acetate *v* 3/21 (14%) with placebo; RR for no sweating 6.0, 95% CI 2.1 to 17.4; NNT 2, 95% CI 1 to 2
Schiff [52]	Oral medroxyprogesterone acetate 20 mg daily *v* placebo (crossover) for 24 weeks; 27 women	Percentage reduction in hot flushes at 12 week crossover to alternative treatment	74% with medroxyprogesterone acetate *v* 26% with placebo; P less than 0.05
Leonetti [53]	Transdermal progesterone cream 20 mg *v* placebo for 1 year; 102 women	Improvement or resolution of vasomotor symptoms as determined by review of weekly symptom diaries (43 women were assigned to treatment group and 47 were assigned to placebo. Thirty women in the treatment group and 26 in the placebo group initially complained of vasomotor symptoms)	25/30 (83%) with transdermal progesterone *v* 5/26 (19%) with placebo; RR 1.5, 95% CI 1.1 to 2.0; NNT 4, 95% CI 2 to 9
Wren [54]	Transdermal progesterone cream 32 mg daily *v* placebo for 12 weeks; 80 women	Greene Climacteric Scale and the Menopause Quality of Life Questionnaire	Median change in Greene Climacteric Scale (vasomotor symptoms) from baseline: –1.0 with progesterone *v* 0 with placebo; P = 0.07

TABLE 4 **Summary of results from individual RCTs and meta-analyses from systematic review of phyto-oestrogens** [60]

Population	Outcome, Interventions and Absolute results	Statistical analysis	Comments
Soy dietary supplements versus placebo			
104 postmenopausal women, mean ages 52−53 years results from single RCT	**Number of flushes/day, 12 weeks** 60 g soy powder (76 mg isoflavones) placebo (60 g casein)	Mean difference −1.59 flushes in favour of soy powder, 95% CI −1.95 flushes to −1.2 flushes P less than 0.01	**Comment:** Absolute values not reported **Adverse effects:** Reported no significant difference in overall adverse effects between groups
241 postmenopausal women, mean age 51 years results from single RCT	**Number and severity of flushes/day, 2 years** soy drink with lower isoflavones (42 mg/day) soy drink with higher isoflavones (58 mg/day) placebo	Reported as not significant P value not reported	**Comment:** Absolute values not reported **Adverse effects:** No information given
52 postmenopausal women, mean ages 53.6−54.6 years results from single RCT 3-armed trial	**Percentage reduction in number of hot flushes, 12 weeks** 22% with soy diet (53 mg isoflavones/day) 41% with linseed diet (high in isoflavones) 51% with placebo (wheat diet)	Reported as not significant P value not reported Unclear which comparison was used for assessing significance	**Comment:** Crossover design Results reported from before the crossover point The quantity of isoflavones in the linseed diet was not reported This RCT is also reported below (see other phyto-oestrogens *v* placebo) **Adverse effects:** The RCT found that the soy diet increased the vaginal maturation index by more than placebo or linseed diet but did not report the significance of the difference (103% with soy diet *v* 6% with linseed diet *v* 11% with placebo)
24 postmenopausal women, aged 45−60 years results from single RCT	**Number of flushes/week, 12 weeks** 29 with soy powder drink (60 g/day) 46 flushes/week with placebo (casein powder drink)	Reported as not significant P value not reported	**Adverse effects:** The RCT found that soy significantly increased the rate of adverse effects compared with placebo (75% with soy diet *v* 17% with placebo; P less than 0.001).
99 postmenopausal women, mean age 53 years results from single RCT	**Menoquol vasomotor symptom severity score; Number of flushes/day; Flushing severity (from 1, none, to 7, severe), all at 16 weeks** soy flour muffins (42 mg isoflavones/day) flaxseed muffins (50 mg lignans/day) placebo	Reported as not significant P value not reported Unclear which comparison was used for assessing significance	**Comment:** This RCT is also reported below (see other phyto-oestrogens versus placebo) **Adverse effects:** No information given
69 postmenopausal women, median age 50 years results from single RCT	**Proportion of people with reduced frequency, duration, and severity of flushes; Number of flushes/week; Number of sweats/week, 24 weeks** higher-dose soy protein (80.4 mg isoflavones/day) lower-dose soy protein (4.4 mg isoflavones/day) placebo	Reported as not significant for all outcomes P values not reported Unclear which comparisons were used for assessing significance	**Adverse effects:** No information given
Soy extracts, given as capsules or tables, versus placebo			
75 postmenopausal women, mean ages 52−54 years results from single RCT	**Proportion with reduced hot flushes, 25 weeks** 74% with standardised soy extract (33 mg isoflavones/day) 43% with placebo **Proportion with reduced night sweats, 25 weeks** 68% with standardised soy extract (33 mg isoflavones/day) 46% with placebo	P = 0.007 for hot flushes P = 0.049 for night sweats	**Comment:** The RCT also evaluated the Greene vasomotor scale, and symptom severity. It found no significant difference in either between groups (reported as not significant; absolute numbers and P value not reported) **Adverse effects:** The RCT found no significant difference in vaginal maturation index between groups (reported as not significant; absolute values and P value not reported)

Population	Outcome, Interventions and Absolute results	Statistical analysis	Comments
36 postmenopausal women, mean age 51 years results from single RCT	**Number of flushes/week, 12 weeks** standardised soy extract capsules (60 mg isoflavones/day) placebo	Reported as not significant P value not reported	**Comment:** Crossover design Results reported from before the crossover point **Adverse effects:** The RCT found no significant difference in the vaginal maturation index between groups (reported as not significant; absolute values and P value not reported)
36 postmenopausal women, mean ages 57−59 years results from single RCT	**Greene vasomotor symptom severity score, 12 weeks** soy supplement capsules (60 mg isoflavones/day) placebo	Reported as not significant. P value not reported	**Adverse effects:** No information given
75 postmenopausal women, mean ages 53−53.9 years results from single RCT	**Reduction in number of flushes/day, 16 weeks** 61% with soy extract capsules (70 mg isoflavones/day) 21% with placebo **Proportion who responded to treatment (those with at least 50% reduction in number of flushes/day), 16 weeks** 66% with soy extract capsules 34% with placebo	Significance not assessed for reduction in flushes P less than 0.005 for proportion who responded	**Adverse effects:** The RCT found no significant difference in the rate of adverse effects between groups (reported as not significant; P value not reported)
80 postmenopausal women, mean ages 48−49 years results from single RCT	**Kupperman vasomotor symptom severity score, 16 weeks** 8.2 with soy capsules (100 mg isoflavones/day) 9.9 with placebo	P less than 0.01	**Adverse effects:** The RCT found no significant difference in endometrial thickness between groups (reported as not significant; P value not reported)
207 postmenopausal women, mean ages 52−54 years results from single RCT	**Reduction in hot flush severity/week, 12 weeks** 34% with soy extract tables (50 mg of genistein and daidzin/day) 21% with placebo	P = 0.01 for hot flush severity The RCT also assessed hot flush frequency and night sweats, and found no significant difference between groups (flush frequency: P = 0.078; night sweats: reported as not significance, P value not reported; no absolute data reported for either outcome)	**Adverse effects:** Comparison of rates in both groups not reported
Red clover extracts versus placebo			
300 postmenopausal women, mean ages in RCTs ranged from 51.1 to 54.5 years 5 RCTs in this analysis	**Number of hot flushes/day, 12−16 weeks** standard red clover extract (promensil 40 mg or 80 mg) placebo	WMD −0.57 flushes/day in favour of red clover extract, 95% CI −1.76 flushes/day to +0.62 flushes/day	
282 postmenopausal women, mean ages in RCTs ranged from 51 to 52 years 2 RCTs in this analysis	**Reduction in number of hot flushes from baseline, 12−16 weeks** standard red clover extract (promensil 40 mg or 80 mg) placebo	WMD +20.15, 95% CI −12.08 to +52.38	**Comment:** The estimate of effect size is imprecise
30 postmenopausal women, mean ages 51−52 years results from single RCT	**Risk of improvement in hot flush severity, 16 weeks** standard red clover extract (promensil 40 mg) placebo	OR 47.7, 95% CI 2.4 to 967.4	**Comment:** The estimate of effect size is imprecise
252 postmenopausal women, mean age 52 years	**Vasomotor symptom severity score, 12 weeks** standard red clover extract (promensil) placebo	WMD +0.1, 95% CI −1.5 to +1.7	

Population	Outcome, Interventions and Absolute results	Statistical analysis	Comments
60 postmenopausal women results from single RCT	**Kupperman Index for hot flushes (severity scored as a percentage), 12 weeks** 15% with red clover extract 98% with placebo **Kupperman Index for night sweats (severity scored as a percentage), 12 weeks** 30% with red clover extract 93% with placebo Absolute numbers not reported	Significance not assessed for either outcome	**Comment:** Crossover design Results reported from before the crossover point
Other phyto-oestrogens versus placebo			
90 postmenopausal women, mean ages 51−52 years results from single RCT 3-arm trial; the remaining arm evaluated continuous HRT	**Reduction in number of hot flushes/day, 1 year** genistein extract (54 mg isoflavones/day) placebo Absolute values not reported	24% greater reduction with genistein compared with placebo P less than 0.01	**Adverse effects:** The RCT found no significant difference in endometrial thickness between groups (reported as not significant; absolute values and P value not reported)
subgroup of 112 women with symptoms at the start of the trial (full RCT evaluated 199 postmenopausal women, mean ages 54−55 years) results from single RCT	**Menoquol hot flush and sweat severity scores, 1 year** flaxseed dietary supplement (in bread and ground grains, containing 21,071 micrograms lignans) placebo wheatgerm supplement (low in lignans) Absolute values not reported	Reported as no significant difference; P value not reported	**Adverse effects:** No information given
67 postmenopausal women, mean ages 52−53 results from single RCT	**Kupperman hot flush severity score, 12 weeks** lower dose hop extract (containing 100 micrograms lignans) higher dose hop extract (containing 250 micrograms lignans) placebo	Reported no significant difference; unclear which comparison was used for assessing significance P value not reported	**Adverse effects:** No information given
52 postmenopausal women, mean ages 53.6−54.6 years results from single RCT 3-arm trial	**Percentage reduction in number of hot flushes, 12 weeks** 22% with soy diet (53 mg isoflavones/day) 41% with linseed diet (high in isoflavones) 51% with placebo (wheat diet)	Reported as not significant Unclear which comparison was used for assessing significance; P value not reported	**Comment:** Crossover design Results reported from before the crossover point The quantity of isoflavones in the linseed diet was not reported This RCT is also reported below (see soy dietary supplements versus placebo) **Adverse effects:** The RCT found that the soy diet increased the vaginal maturation index by more than placebo or linseed diet but did not report the significance of the difference (103% with soy diet *v* 6% with linseed diet *v* 11% with placebo)
99 postmenopausal women, mean age 53 years results from one RCT	**Menoquol vasomotor symptom severity score; Number of flushes/day; Flushing severity (from 1, none, to 7, severe), 16 weeks** soy flour muffins (42 mg isoflavones/day) flaxseed muffins (50 mg lignans/day) placebo	Reported as not significant Unclear which comparison significance was assessed for; P value not reported	**Comment:** This RCT is also reported above (see soy dietary supplements versus placebo)
Phyto-oestrogens versus oestrogen either alone or in combination with phyto-oestrogen			

Population	Outcome, Interventions and Absolute results	Statistical analysis	Comments
79 postmenopausal women, mean age 54 years results from single RCT	**Proportion of women reporting reduced symptoms, 24 weeks** soy extract capsules (120 mg isoflavones/day) oestrogen plus placebo capsules	Reported no significant difference; P value not reported	**Comment:** Absolute values not reported **Adverse effects:** The RCT found that soy extract was associated with a significantly reduced endometrial thickness compared with oestrogen (5.9 mm with oestrogen *v* 3.0 mm with soy extract; reported as significant, P value not reported)
136 postmenopausal women, mean ages 56−57 years results from single RCT 3-arm trial, the remaining arm received no treatment	**Vasomotor symptom scores (from symptom severity questionnaire), 12 weeks** pueraria lobata oestrogen plus cyclical medroxyprogesterone acetate	Reported no significant difference; P value not reported	**Comment:** Absolute values not reported **Adverse effects:** No information given

TABLE **GRADE evaluation of interventions for menopausal symptoms**

Important outcomes		Vasomotor symptoms; urogenital symptoms; psychological, cognitive, and sleep symptoms; quality of life; adverse effects							
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of medical treatments for menopausal symptoms?									
3 (1253) [3] [4] [5]	Vasomotor symptoms	Tibolone *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (38) [6]	Urogenital symptoms	Tibolone *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, no reporting of pre-crossover results, and lack of washout period
1 (3148) [14]	Adverse effects (breast cancer recurrence)	Tibolone *v* placebo	4	0	0	0	0	High	
2 (672) [7] [8]	Vasomotor symptoms	Tibolone *v* oestrogens plus progestogen	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
2 (487) [7] [10] [9]	Urogenital symptoms	Tibolone *v* oestrogens plus progestogen	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
9 (at least 5367) [15] [16] [17] [18] [19] [20] [21]	Vasomotor symptoms	Oestrogens *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
At least 7 (at least 1566) [22] [23] [17] [24]	Urogenital symptoms	Oestrogens *v* placebo	4	0	0	0	0	High	
5 (at least 3430) [25] [26] [32]	Psychological, cognitive, and sleep symptoms	Oestrogens *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, inclusion of cohort studies, and weak methods
2 (324) [28] [29]	Quality of life	Oestrogens *v* placebo	4	0	0	0	0	High	
at least 31 (at least 41,113) [32] [33] [38] [34] [35] [36] [37]	Adverse effects	Oestrogens *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for inclusion of combined HRT preparations in the analysis
4 (615) [23]	Urogenital symptoms	Different oestrogen preparations versus each other	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for small number of events in some analyses
1 (43) [30]	Vasomotor symptoms	Oestrogens versus progestins	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
At least 4 (20,328) [15] [16] [39]	Vasomotor symptoms	Oestrogens plus progestogens *v* placebo	4	–1	0	0	+1	High	Quality point deducted for incomplete reporting of results. Effect size point added for OR greater than 2
3 (16,834) [39] [41] [40]	Urogenital symptoms	Oestrogens plus progestogens *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (20,952) [27] [42] [43]	Psychological, cognitive, and sleep symptoms	Oestrogens plus progestogens *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for inconsistent results depending on outcome measure used. Directness point deducted for large RCT in atypical age group

Important outcomes		Vasomotor symptoms; urogenital symptoms; psychological, cognitive, and sleep symptoms; quality of life; adverse effects							
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (16,882) [42]	Quality of life	Oestrogens plus progestogens *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for inconsistent results depending on outcome measure used. Directness point deducted for RCT in atypical age group
at least 28 (at least 39,769) [39] [45] [46] [32] [48] [36] [37] [38] [49]	Adverse effects	Oestrogens plus progestogens *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for single agents included in analysis
1 (74) [44]	Quality of life	Different preparations of oestrogens plus progestogens versus each other	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
5 (327) [50] [51] [52] [53] [54]	Vasomotor symptoms	Progestogens *v* placebo	4	–2	0	0	0	Low	Quality points deducted for post-crossover analysis and low follow-up in one RCT
11 (1456) [55] [56]	Vasomotor symptoms	Antidepressants *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for inclusion of a co-intervention
4 (446) [55]	Vasomotor symptoms	Clonidine *v* placebo	4	–1	0	–2	0	Very low	Quality point deducted for short follow-up. Directness points deducted for co-intervention, and results sensitive to analysis undertaken
6 (1115) [57] [58]	Urogenital symptoms	Testosterone plus oestrogen-containing HRT *v* oestrogen-containing HRT alone	4	–1	–1	0	0	Low	Quality point deducted for weak methods. Consistency point deducted for different results for different outcomes
1 (40) [57]	Psychological, cognitive, and sleep symptoms	Testosterone plus oestrogen-containing HRT *v* oestrogen-containing HRT alone	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of non-prescribed treatments for menopausal symptoms?									
40 (at least 2730) [60] [55] [66]	Vasomotor symptoms	Phyto-oestrogens *v* placebo	4	–3	–1	–1	0	Very low	Quality points deducted for weak methods, incomplete reporting of results, unclear comparisons, and lack of standardisation of interventions. Consistency point deducted for conflicting results. Directness point deducted for lack of standard dosing
2 (154) [62] [63]	Urogenital symptoms	Phyto-oestrogens *v* placebo	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and crossover design. Directness points deducted for use of non-clinical assessment and lack of standardised dosing
2 (172) [62] [64]	Psychological, cognitive, and sleep symptoms	Phyto-oestrogens *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for lack of standardised dosing
1 (376) [65]	Adverse effects	Phyto-oestrogens *v* placebo	4	0	0	–2	0	Low	Directness points deducted for non-standard dose and small number of events

Important outcomes		Vasomotor symptoms; urogenital symptoms; psychological, cognitive, and sleep symptoms; quality of life; adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (79) [60]	Vasomotor symptoms	Phyto-oestrogens *v* oestrogen	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for lack of standard preparations and dosing
1 (136) [60]	Vasomotor symptoms	Phyto-oestrogens *v* oestrogen plus progestogen	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for lack of standard preparations and dosing

Type of evidence: 4 = RCT
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.