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Short-term and long-term effects of tibolone in postmenopausal women (Review)

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[Intervention Review]

Short-term and long-term effects of tibolone in postmenopausal women

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ABSTRACT

Background

Tibolone is a synthetic steroid used for the treatment of menopausal symptoms, on the basis of short-term data suggesting its efficacy. We considered the balance between the benefits and risks of tibolone.

Objectives

To evaluate the effectiveness and safety of tibolone for treatment of postmenopausal and perimenopausal women.

Search methods

In October 2015, we searched the Gynaecology and Fertility Group (CGF) Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and PsycINFO (from inception), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and clinicaltrials.gov. We checked the reference lists in articles retrieved.

Selection criteria

We included randomised controlled trials (RCTs) comparing tibolone versus placebo, oestrogens and/or combined hormone therapy (HT) in postmenopausal and perimenopausal women.

Data collection and analysis

We used standard methodological procedures of The Cochrane Collaboration. Primary outcomes were vasomotor symptoms, unscheduled vaginal bleeding and long-term adverse events. We evaluated safety outcomes and bleeding in studies including women either with or without menopausal symptoms.

Main results

We included 46 RCTs (19,976 women). Most RCTs evaluated tibolone for treating menopausal vasomotor symptoms. Some had other objectives, such as assessment of bleeding patterns, endometrial safety, bone health, sexuality and safety in women with a history of breast cancer. Two included women with uterine leiomyoma or lupus erythematosus.

Tibolone versus placebo

Vasomotor symptoms

Tibolone was more effective than placebo (standard mean difference (SMD) -0.99, 95% confidence interval (CI) -1.10 to -0.89; seven RCTs; 1657 women; moderate-quality evidence), but removing trials at high risk of attrition bias attenuated this effect (SMD -0.61, 95% CI -0.73 to -0.49; odds ratio (OR) 0.33, 85% CI 0.27 to 0.41). This suggests that if 67% of women taking placebo experience vasomotor symptoms, between 35% and 45% of women taking tibolone will do so.

Unscheduled bleeding

Tibolone was associated with greater likelihood of bleeding (OR 2.79, 95% CI 2.10 to 3.70; nine RCTs; 7814 women; I^2 = 43%; moderate-quality evidence). This suggests that if 18% of women taking placebo experience unscheduled bleeding, between 31% and 44% of women taking tibolone will do so.

Long-term adverse events

Most of the studies reporting these outcomes provided follow-up of two to three years (range three months to three years).

Breast cancer

We found no evidence of differences between groups among women with no history of breast cancer (OR 0.52, 95% CI 0.21 to 1.25; four RCTs; 5500 women; I^2= 17%; very low-quality evidence). Among women with a history of breast cancer, tibolone was associated with increased risk (OR 1.5, 95% CI 1.21 to 1.85; two RCTs; 3165 women; moderate-quality evidence).

Cerebrovascular events

We found no conclusive evidence of differences between groups in cerebrovascular events (OR 1.74, 95% CI 0.99 to 3.04; four RCTs; 7930 women; I^2 = 0%; very low-quality evidence). We obtained most data from a single RCT (n = 4506) of osteoporotic women aged 60 to 85 years, which was stopped prematurely for increased risk of stroke.

Other outcomes

Evidence on other outcomes was of low or very low quality, with no clear evidence of any differences between the groups. Effect estimates were as follows:

• *Endometrial cancer:* OR 2.04, 95% CI 0.79 to 5.24; nine RCTs; 8504 women; I^2 = 0%.

• *Cardiovascular events:* OR 1.38, 95% CI 0.84 to 2.27; four RCTs; 8401 women; I^2 = 0%.

• *Venous thromboembolic events:* OR 0.85, 95% CI 0.37 to 1.97; 9176 women; I^2 = 0%.

• *Mortality from any cause:* OR 1.06, 95% CI 0.79 to 1.41; four RCTs; 8242 women; I^2 = 0%.

Tibolone versus combined HT

Vasomotor symptoms

Combined HT was more effective than tibolone (SMD 0.17, 95% CI 0.06 to 0.28; OR 1.36, 95% CI 1.11 to 1.66; nine studies; 1336 women; moderate-quality evidence). This result was robust to a sensitivity analysis that excluded trials with high risk of attrition bias, suggesting a slightly greater disadvantage of tibolone (SMD 0.25, 95% CI 0.09 to 0.41; OR 1.57, 95% CI 1.18 to 2.10). This suggests that if 7% of women taking combined HT experience vasomotor symptoms, between 8% and 14% of women taking tibolone will do so.

Unscheduled bleeding

Tibolone was associated with a lower rate of bleeding (OR 0.32, 95% CI 0.24 to 0.41; 16 RCTs; 6438 women; I^2 = 72%; moderate-quality evidence). This suggests that if 47% of women taking combined HT experience unscheduled bleeding, between 18% and 27% of women taking tibolone will do so.

Long-term adverse events

Most studies reporting these outcomes provided follow-up of two to three years (range three months to three years). Evidence was of very low quality, with no clear evidence of any differences between the groups. Effect estimates were as follows:

• *Endometrial cancer:* OR 1.47, 95% CI 0.23 to 9.33; five RCTs; 3689 women; I^2 = 0%.

• *Breast cancer:* OR 1.69, 95% CI 0.78 to 3.67; five RCTs; 4835 women; I^2 = 0%.

• *Venous thromboembolic events:* OR 0.44, 95% CI 0.09 to 2.14; four RCTs; 4529 women; I^2 = 0%.

• *Cardiovascular events:* OR 0.63, 95% CI 0.24 to 1.66; two RCTs; 3794 women; I^2 = 0%.

• *Cerebrovascular events:* OR 0.76, 95% CI 0.16 to 3.66; four RCTs; 4562 women; I^2 = 0%.

• *Mortality from any cause:* only one event reported (two RCTs; 970 women).

Authors' conclusions

Moderate-quality evidence suggests that tibolone is more effective than placebo but less effective than HT in reducing menopausal vasomotor symptoms, and that tibolone is associated with a higher rate of unscheduled bleeding than placebo but with a lower rate than HT.

Compared with placebo, tibolone increases recurrent breast cancer rates in women with a history of breast cancer, and may increase stroke rates in women over 60 years of age. No evidence indicates that tibolone increases the risk of other long-term adverse events, or that it differs from HT with respect to long-term safety.

Much of the evidence was of low or very low quality. Limitations included high risk of bias and imprecision. Most studies were financed by drug manufacturers or failed to disclose their funding source.

PLAIN LANGUAGE SUMMARY

Short-term and long-term effects of tibolone in postmenopausal women

Review question

Cochrane review authors aimed to evaluate the effectiveness and safety of tibolone for treatment of postmenopausal and perimenopausal women.

Background

Tibolone is an available option for the treatment of menopausal symptoms, and short-term data suggest its efficacy. However, healthcare providers must consider the balance between benefits and risks of tibolone, as concerns have arisen about breast and endometrial cancer and stroke.

Study characteristics

We included 46 randomised controlled trials (RCTs), which included 19,976 postmenopausal women. Most studies evaluated tibolone for treatment of menopausal vasomotor symptoms. Some studies reported other objectives: Four RCTs aimed to assess endometrial safety, four bleeding patterns, five bone loss or fracture prevention, one sexual outcomes and three safety in women with a history of breast cancer; two studies examined use of tibolone in women with fibroids or lupus erythematosus. The evidence is current to October 2015.

Key results

Moderate-quality evidence suggests that tibolone is more effective than placebo and less effective than combined hormone therapy (HT) in reducing vasomotor symptoms in postmenopausal women. Data suggest that if 67% of women taking placebo experience vasomotor symptoms, then between 35% and 45% of women taking tibolone will do so; and if 7% of women taking combined HT experience vasomotor symptoms, then between 8% and 14% of women taking tibolone will do so. Moderate-quality evidence also suggests that tibolone is associated with a higher rate of unscheduled bleeding than placebo, but a lower rate than HT.

Compared with placebo, tibolone increases the risk of recurrent breast cancer in women with a history of breast cancer, and may increase the risk of stroke in women over 60 years of age. No evidence suggests that tibolone increases the risk of other serious adverse events, and no evidence shows differences between tibolone and HT with respect to long-term adverse events. Nearly all evidence on adverse events was of very low quality, and reported events were scarce.

Quality of the evidence

Much of the evidence obtained was of low or very low quality. Limitations included high risk of bias in the included trials, very low event rates and potential conflicts of interest. Twenty-six of the studies were financed by drug manufacturers, and another 14 studies failed to disclose their source of funding.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Tibolone compared with placebo for treatment of vasomotor symptoms in postmenopausal women

Tibolone compared with placebo: vasomotor symptoms

Population: postmenopausal women with vasomotor symptoms
Settings: outpatient or community
Intervention: tibolone
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Tibolone				
Vasomotor symptoms (all doses) Follow-up: 12 weeks to 1 year	670 per 1000	400 per 1000 (350 to 450)	**OR 0.33** (0.27 to 0.41)	842 (5 RCTs)	⊕⊕⊖⊖ **moderate** [a]	Three studies at high risk of attrition bias were excluded from this analysis. Inclusion of these studies was associated with stronger effect of tibolone but with extreme heterogeneity (I^2= 97%)

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]Downgraded one level for serious risk of bias: poor reporting of study methods and potential conflict of interest (pharmaceutical funding) in most studies; standard deviations imputed for some studies. Effect estimate robust to a sensitivity analysis excluding studies at high risk of attrition bias

Summary of findings 2. Tibolone compared with placebo for postmenopausal women: adverse events

Tibolone compared with placebo: adverse events

Population: postmenopausal women with or without vasomotor symptoms
Settings: outpatient or community
Intervention: tibolone
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Tibolone				
Endometrial cancer (all doses) Follow-up: 1 to 3 years (median 1)	See comment		**OR 2.04** (0.79 to 5.24)	8504 (9 studies)	⊕⊖⊖⊖ **very low** a,b,c	Events very rare in both groups. Total of 21 events: 16/4486 in tibolone group, 5/4018 in placebo group
Breast cancer; women without previous breast cancer (all doses) Follow-up: 12 weeks to 3 years	4 per 1000	1 per 1000 (1 to 5)	**OR 0.52** (0.21 to 1.25)	5500 (4 studies)	⊕⊖⊖⊖ **very low** a,b	In women with a history of breast cancer, risk increased in the tibolone group at 1 to 2.75 years' follow up: OR 1.50 (1.21 to 1.85, 2 RCTs, 3165 women, moderate-quality evidence)
Unscheduled bleeding (all doses) Follow-up: 1 to 3 years (median 2)	177 per 1000	374 per 1000 (310 to 442)	**OR 2.79** (2.1 to 3.7)	7814 (9 studies)	⊕⊕⊖⊖ **moderate** *d*	
Venous thromboembolic events (clinical evaluation) all doses Follow-up: 1 to 2.75 years (median 1.5)	See comment		**OR 0.85** (0.37 to 1.97)	9176 (5 studies)	⊕⊖⊖⊖ **very low** a,b,c	Events very rare in both groups. Total of 24 events: 12/5054 in tibolone group, 12/4122 in placebo group
Cardiovascular events (all doses) Follow-up: 2 to 3 years (median 2.75)	10 per 1000	13 per 1000 (8 to 22)	1.38 (0.84 to 2.27)	8401 (4 studies)	⊕⊖⊖⊖ **very low** a,b,c	
Cerebrovascular events (all doses) Follow-up: 14 days to 2.8 years	5 per 1000	8 per 1000	**OR 1.74** (0.99 to 3.04)	7930 (4 studies)	⊕⊖⊖⊖ **very low** a,b	

		(4 to 14)			
Mortality from any cause (all doses) Follow-up: 1 to 3 years (median 2.77)	10 per 1000	10 per 1000 (8 to 14)	**OR 1.06** (0.79 to 1.41)	8242 (4 studies)	⊕⊕⊖⊖ **low** [b,e]

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]Downgraded two levels for very serious risk of bias: poor reporting of study methods, high attrition and/or potential conflict of interest in most studies
[b]Downgraded one level for serious imprecision: low event rate. Findings compatible with meaningful benefit in one or both arms, or with no effect
[c]Downgraded one level for serious risk of low applicability: Some studies compare doses of tibolone that have not been marketed (although downgrading has no effect on rating, as study already rated very low)
[d]Downgraded one level for serious risk of bias: poor reporting of study methods and potential conflict of interest in most studies
[e]Downgraded one level for potential conflict of interest (funding by pharmaceutical companies)

Summary of findings 3. Tibolone compared with combined HT for treatment of vasomotor symptoms in postmenopausal women

Tibolone compared with combined HT for postmenopausal women: vasomotor symptoms

Population: postmenopausal women with vasomotor symptoms
Settings: outpatient or community
Intervention: tibolone
Comparison: combined HT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Combined HT	Tibolone				
Vasomotor symptoms (ti-	70 per 1000	110 per 1000 (80 to 140)	**OR 1.57** (1.18 to 2.1)	646 (4 studies)	⊕⊖⊖⊖ **moderate** [a]	From a sensitivity analysis excluding studies with high risk of attrition bias. An inclusive analysis (9 studies, 1336 participants) suggests a similar but slightly re-

bolone 2.5 mg/d) Follow-up: 3 to 12 months						duced disadvantage of tibolone (OR (95% CI) 1.36 (1.11 to 1.66))

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]Downgraded one level for serious risk of bias: poor reporting of study methods and potential conflict of interest in all studies. Effect estimate robust to a sensitivity analysis excluding studies at high risk of attrition bias

Summary of findings 4. Tibolone compared with combined HT for postmenopausal women: adverse events

Tibolone compared with combined HT for postmenopausal women: adverse events

Population: postmenopausal women with or without vasomotor symptoms
Settings: outpatient or community
Intervention: tibolone
Comparison: combined HT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Combined HT	Tibolone				
Unscheduled bleeding (all doses) Follow-up: 3 to 36 months (median 12)	**474 per 1000**	**224 per 1000** (178 to 270)	**OR 0.32** (0.24 to 0.41)	6438 (16 studies)	⊕⊕⊖⊖ **moderate** [a]	
Endometrial cancer (all doses) Follow-up: 6.8 to 36 months (median 12)	See comments		**OR 1.47** (0.23 to 9.33)	3689 (5 studies)	⊕⊖⊖⊖ **very low** [b,c]	Events very rare in both groups. Total of 3 events: 2/1826 in ti-

						bolone group, 1/1863 in combined HT group
Breast cancer; women without previous breast cancer (all doses) Follow-up: 6.8 to 36 months (median 24)	3 per 1000	6 per 1000 (3 to 13)	**OR 1.69** (0.78 to 3.67)	4835 (5 studies)	⊕⊖⊖⊖ **very low** [b,c]	
Venous thromboembolic events (clinical evaluation; all doses) Follow-up: 6.8 to 24 months (median 12)	3 per 1000	1 per 1000 (0 to 6)	**OR 0.44** (0.09 to 2.14)	4529 (4 studies)	⊕⊖⊖⊖ **very low** [b,c]	
Cardiovascular events (all doses) Follow-up: 2 to 3 years	17 per 1000	10 per 1000 (4 to 27)	**OR 0.63** (0.24 to 1.66)	3794 (2 studies)	⊕⊖⊖⊖ **very low** [b,c]	
Cerebrovascular event (all doses) Follow-up: 3.4 to 24 (median 9.4) months	1 per 1000	1 per 1000 (0 to 3)	**OR 0.76** (0.16 to 3.66)	4562 (4 studies)	⊕⊖⊖⊖ **very low** [b,c]	
Mortality from any cause (tibolone 2.5 mg/d) Follow-up: 3.4 to 24 (median 9.4) months	See comments		**OR 3.05** (0.12 to 75.2)	970 (2 studies)	⊕⊖⊖⊖ **very low** [b,c]	Only 1 event (in tibolone group): 1/485 vs 0/485

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]Downgraded one level for serious risk of bias: poor reporting of study methods and potential conflict of interest in some studies
[b]Downgraded two levels for very serious risk of bias: poor reporting of study methods and potential conflict of interest in some studies
[c]Downgraded one level for serious imprecision: low event rate. Findings compatible with meaningful benefit in one or both arms, or with no effect

BACKGROUND

Description of the condition

Hot flushes are among the most characteristic clinical symptoms of menopause (Politi 2008); they are probably caused by lability in the hypothalamic thermoregulatory centre induced by reduction of oestrogen and progesterone levels (Freedman 1995). Hot flushes and sweats of increasing severity can occur during the night, leading to sleep problems (Porter 1996). Hot flushes and sweats are described as vasomotor symptoms.

Many postmenopausal women report a variety of symptoms such as vaginal dryness (Suckling 2006), sexual discomfort, urinary incontinence (Cody 2012) and frequent urinary infection, probably resulting from the natural decline of oestrogen levels (Speroff 2004).

All symptoms tend to fluctuate, and their perceived severity varies greatly among individuals, with some reporting intense discomfort and a substantial reduction in quality of life.

Researchers have successfully used oestrogens and progestogens to ameliorate vasomotor (MacLennan 2004) and vaginal symptoms (Suckling 2006), anxiety and low mood (NCC-WCH 2015). Urinary tract infections are less clearly influenced by combined hormone therapy (HT) (Soc Obstetr Gynaecol Canada 2014).

Description of the intervention

Tibolone (Livial®, ORG OD 14) is a synthetic steroid widely prescribed to postmenopausal women in Europe.

How the intervention might work

After its commercialisation, tibolone gained some popularity for combining oestrogenic and progestogen actions. Its mechanism of action is not well known, although many studies, most sponsored by the drug manufacturer, indicate that the drug undergoes different tissue-selective metabolic transformations and may exert weak oestrogen, progestogen and/or androgen activities (Modelska 2002). The oestrogenic effects, exerted mainly in brain, bone and vaginal tissues, are weaker on the endometrium, where the drug is transformed into progestogen metabolites. In breast tissue, limited conversion of oestrone to oestradiol may reduce the oestrogenic effects. In brain and liver, tibolone seems to have androgenic effects. Some randomised controlled clinical trials (RCTs) have suggested that tibolone decreases vasomotor symptoms and ameliorates vaginal dryness and discomfort, but results are not consistent. An RCT published in 2009 (Kenemans 2009) highlighted that tibolone increases recurrence of breast cancer, revealing a contraindication for women with a history of breast cancer. Although the drug is thought to have a possible role in preserving bone mineral density, control of osteoporosis is not a recommended indication.

Why it is important to do this review

The safety profile of tibolone has not been well defined, and trials evaluating its use to treat patients with vasomotor symptoms usually provide follow-up periods that are too short for assessment of potential long-term adverse events such as increased risk of endometrial (Beral 2005) and breast (Kenemans 2009; Beral 2003) cancer and of cardiovascular events (Cummings 2008). For this reason, safety has been evaluated in a wider population, and RCTs including women who did not take tibolone for symptomatic relief have been considered.

OBJECTIVES

To evaluate the effectiveness and safety of tibolone for treatment of postmenopausal and perimenopausal women.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). We did not include quasi-randomised and cross-over trials.

Types of participants

Menopausal and perimenopausal women with or without vasomotor and/or genital symptoms, defined as women with surgical menopause or with spontaneous menopause, or women who had menstruated irregularly over the past 12 months.

Types of interventions

- Tibolone use versus placebo
- Tibolone use versus oestrogens
- Tibolone use versus combined HT (referring to two different formulations: sequential combined and continuous combined)

This review did not consider tibolone use versus no treatment.

Types of outcome measures

Primary outcomes

- Vasomotor symptoms measured as occurrences or through scales, defined as any otherwise unexplained sensation of flushing/sweating experienced by the participant. We included studies that measured hot flushes (with or without night sweats), provided that they measured hot flushes as an outcome of efficacy in populations including symptomatic women
- Unscheduled bleeding (vaginal bleeding and/or spotting)
- Long-term adverse events: endometrial cancer, breast cancer, venous thromboembolic events, cardiovascular events, cerebrovascular events, mortality from any cause

Secondary outcomes

- Insomnia (frequency or continuous outcome)
- Genital symptoms: vaginal dryness and painful sexual intercourse (measured as frequency or severity), vaginal infection (inflammation of the vagina usually related to one of three infectious conditions: bacterial vaginosis, vulvovaginal candidiasis, trichomoniasis), urinary tract infection
- Endometrial hyperplasia

We measured all outcomes other than vasomotor symptoms in women with or without vasomotor symptoms.

We included studies assessing at least one of these specific outcomes, even if they did not report useable data. We excluded studies not assessing such outcomes.

Search methods for identification of studies

Electronic searches

We searched for all relevant published and unpublished RCTs, without language restriction, and in consultation with the Cochrane Gynaecology and Fertility Group (CGF) Information Specialist.

We searched the CGF Specialised Register (formerly known as the Menstrual Disorders and Subfertility Group Specialised Register), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), from inception until 15 October 2015, using the strategies shown in Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5 and Appendix 6. For the search of clinicaltrials.gov, we used "tibolone" as a keyword. We contacted individual researchers and the current manufacturer of tibolone to ask them to identify unpublished and ongoing trials.

Searching other resources

We contacted individual researchers working in relevant fields (gynaecology, endocrinology) and the current manufacturer of tibolone (Merck Sharp & Dome) to check for additional relevant references and unpublished and ongoing trials. We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

Four review authors (GF, EP, SM, SB) independently screened the titles and abstracts of articles found in the search for inclusion. We searched for outcomes of interest in the full texts, even if they had not been reported in the abstracts. We resolved disagreements by discussion and by consultation with two additional review authors (VB, a gynaecologist; and EM, an endocrinologist). We sought further information from study authors who published papers containing insufficient information to permit a decision about eligibility. We recorded reasons for excluding studies after debate and agreement.

Data extraction and management

Five review authors (GF, EP, SM, SB, JW) independently extracted details of study design, participants, interventions, follow-up, quality components, efficacy outcomes and adverse events.

Three other review authors (VB, a gynaecologist; EM, an endocrinologist; and AMM, a cardiologist) resolved discrepancies regarding extraction of quantitative data or risk of bias assessment of RCTs. When a trial was presented in abstract form, we sought further information by searching the Internet, by contacting study authors and by checking for the next best available resource or publication. We contacted study authors for further insight on study design and results, when we considered this necessary. For studies with more than one publication, we extracted data from all publications, but we considered the final or updated version of each trial to be the primary reference.

We extracted the following information from the studies included in the review (see also Characteristics of included studies table).

Trial characteristics

- Randomisation
- Allocation concealment
- Trial design: multi-centre or single-centre
- Number of women randomised, excluded and analysed
- Duration, timing and location of the trial
- Source of funding and conflicts of interest

Baseline characteristics of studied groups

- Definition and duration of preexisting menopausal condition
- Age of the women
- Previously administered treatment(s)

Interventions

- Type of intervention and control
- Dose regimen
- Treatment duration

Outcomes

- Outcomes reported
- Definitions of outcomes
- The way outcomes were measured
- Timing of outcome measurement

If data were reported only in figures, we used Microsoft PowerPoint to extract data from the figures. We opened the figure in the software and overlaid a grid. We drew horizontal or vertical lines as needed, and we 'snapped' (aligned) them to this grid, to ensure that they were parallel/perpendicular to the plot axes, as required. We could move lines drawn in the software vertically and horizontally, so we could read off the value corresponding to a given data point in a scatterplot or the height of a bar in a bar chart against the appropriate axis. A single review author (JW) extracted data from figures.

Assessment of risk of bias in included studies

We assessed risk of bias of included trials by taking six components into account: generation of the allocation sequence (participant randomisation), allocation concealment, blinding (or masking) of participants and personnel, blinding of outcome assessment, completeness of follow-up (attrition bias) and selective reporting. We used the following definitions when assessing risk of bias.

Generation of the allocation sequence

- Adequate: if the allocation sequence was generated by a computer or by a random number table. We considered drawing of lots, tossing of a coin, shuffling of cards or throwing of die as adequate if a person not otherwise involved in recruitment of participants performed the procedure
- Unclear: if the trial was described as randomised, but the method used for generation of the allocation sequence was not described
- Inadequate: if a system involving dates, names or admittance numbers was used for allocation of women. We excluded these studies, known as quasi-randomised, from the present review

We also excluded trials with alternating allocation.

Allocation concealment

- Adequate: if allocation of women involved a central, independent unit; an on-site locked computer; identical appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator; or sealed, opaque envelopes
- Unclear: if the trial was described as randomised but the method used to conceal the allocation was not described
- Inadequate: if the allocation sequence was known to investigators who assigned participants, envelopes were unsealed or transparent or the study was quasi-randomised

Blinding (or masking) of participants and personnel

- Adequate: if the trial was described as double-blind and the method of blinding involved identical placebo or active drugs, particularly:
  - double-blind (method described and use of a placebo(s) or dummy technique meant neither the participant nor the care provider or assessor knew which treatment was given)
  - single-blind (participant, care provider or assessor was aware of the treatment given)
- Unclear: if the trial was described as double-blind or single-blind but the method of blinding was not described
- Not performed: if the trial was open-label (all parties aware of treatment)

Blinding of outcome assessment

- Adequate: if in the absence of blinding of outcome assessment, review authors judged that outcome measurement was not likely to be influenced by lack of blinding; or if blinding of outcome assessment was ensured and it was unlikely that blinding could have been broken
- Unclear: if information was insufficient to permit judgement of 'low risk' or 'high risk', or if the study did not address this outcome
- Inadequate: if no blinding of outcome assessment occurred and outcome measurement was likely to be influenced by lack of blinding; or if blinding of outcome assessment was present but blinding could have been broken, and if outcome measurement was likely to be influenced by lack of blinding

Completeness of follow-up (attrition bias)

- Adequate: if numbers and reasons for dropouts and withdrawals in all intervention groups were described and 90% or more of randomised participants were included in the analysis; or if it was specified that no dropouts or withdrawals occurred
- Unclear: if the report gave the impression that no dropouts or withdrawals occurred but this was not specifically stated
- Inadequate: if less than 90% of randomised participants were included in the analysis; or numbers or reasons for dropouts and withdrawals were not provided

We contacted the authors of primary trial reports when necessary to request clarification of data and to obtain missing information.

Selective reporting

- Adequate: if the study protocol was available and all of the study's prespecified (primary and secondary) outcomes of interest in the review were reported in the prespecified way
- Unclear: if information was insufficient to permit judgement of 'low risk' or 'high risk'
- Inadequate: if not all of the study's prespecified primary outcomes were reported; if one or more primary outcomes were reported via measurements, analysis methods or subsets of data (e.g. subscales) that were not prespecified; if one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); if one or more outcomes of interest in the review were reported incompletely and could not be included in a meta-analysis; or if the study report failed to include results for a key outcome that would have been expected to be reported for such a study

Measures of treatment effect

We evaluated efficacy and safety outcomes by considering the number of women in the control and intervention groups of each study experiencing at least one event (dichotomous outcomes) to calculate Mantel-Haenszel odds ratios (DerSimonian 1986) with 95% confidence intervals (CIs), or (for continuous outcomes) mean scores, standard deviations and the number of women in each group, using the inverse variance method. The primary outcome 'vasomotor symptoms' and the secondary outcomes vaginal dryness and sleep were exceptions; we reported these outcomes as binary or continuous variables - the first two using several scales. Accordingly, we converted all treatment effect estimates from binary or continuous variables to standardised mean differences (SMDs), as this permitted pooling of these variants in a meta-analysis. Pooled SMDs computed in this manner can be transformed and interpreted as odds ratios, at the cost of information related to symptom severity (Higgins 2011).

Unit of analysis issues

This systematic review considered only RCTs. The unit of analysis in each RCT was the women who were randomised to one of the treatment arms. For vaginal bleeding, we considered endometrial hyperplasia and endometrial cancer only in women with a uterus.

Dealing with missing data

We analysed data on an intention-to-treat basis as far as possible by including all randomised participants in the groups to which they were allocated. Missing data in included studies compromised realisation of this strategy. Moreover, options to rectify the matter were limited in the absence of individual participant data. Accordingly, we took the approach of penalising trials with notable rates of attrition in the risk of bias assessment and conducting sensitivity analyses that were restricted to trials with low risk of bias in this domain. We incorporated these sensitivity analyses into our conclusions.

Assessment of heterogeneity

We included in the meta-analysis all outcomes reported by individual studies, noting heterogeneity by using Chi^2 and I^2 statistics (Higgins 2002). We stated that the Chi^2 statistic was statistically significant if $P < 0.10$. The I^2statistic indicated

the percent of variability due to between-study (or interstudy) variability, as opposed to within-study (or intrastudy) variability. We considered an I^2value greater than 50% to be large (Higgins 2002). When statistically significant heterogeneity existed, we conducted a careful clinical review of the data to seek the source of such heterogeneity and to decide whether statistical combining of trials was warranted.

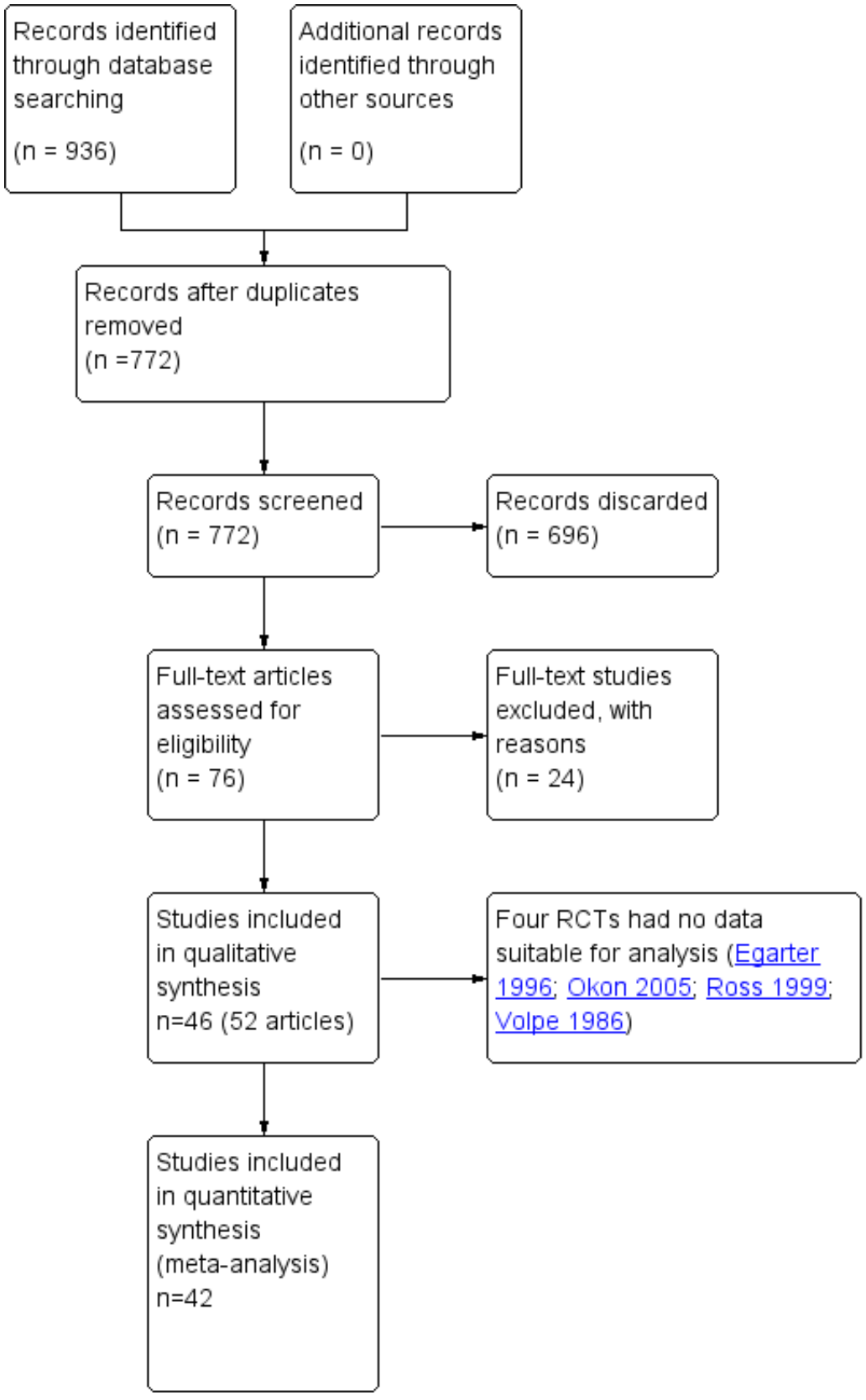
Assessment of reporting biases

We graphically assessed publication bias by using contour-enhanced funnel plots.

Data synthesis

We used a random-effects model, except for vasomotor symptoms, vaginal dryness and sleep, for which we combined data from dichotomous and continuous outcomes in a fixed-effect model by converting all treatment effect estimates to standardised mean differences (SMDs). We deemed this necessary because the key assumption of random-effects meta-analysis - that all observed treatment effects represent realisations from a common underlying distribution - did not appear to be warranted, given the diversity of outcome reporting scales used. Poor reporting standards required that we impute standard deviations for several studies reporting on menopausal symptoms to combine their results; we calculated all effect sizes and corresponding standard errors by using the metaphor package (Viechtbauer 2010) in R (R Core Team 2015). If results for this outcome were available at several time points, we used results corresponding to the longest period of use. Table 1 and Table 2 provide details of methods used in analyses of menopausal symptoms and vaginal dryness, as well as reasons for exclusion of several RCTs from these meta-analyses.

Figure 1. Study flow diagram.



We sought the following comparisons.

- Tibolone use, stratified by dose, versus placebo.

- Tibolone use, stratified by dose, versus oestrogens.
- Tibolone use, stratified by dose, versus combined HT.

To avoid multiple-counting of a control group in RevMan, we split the numbers of events and of exposed participants in studies with multiple arms, depending on the number of comparisons, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; see paragraph 16.5.4). We did not perform this procedure in cases of rare events (e.g. when one or three cases should have been split) or when estimated odds ratios differed by more than 0.05 from the non-stratified analysis. In the latter case, we combined intervention groups (e.g. different doses of tibolone) to create a single pair-wise comparison versus the control group.

Subgroup analysis and investigation of heterogeneity

We stratified results according to tibolone dose. Two of the largest RCTs, which assessed the occurrence of breast cancer and cardio-cerebrovascular events, selected very specific and heterogeneous populations; therefore, we considered that it would be informative to present results on breast cancer separately for women who had a history of breast cancer and those who had no such history, and results on cardiovascular and cerebrovascular events that distinguished women younger than and over 60 years of age. We did not prespecify these subgroup analyses.

Sensitivity analysis

We conducted sensitivity analyses of the primary outcome to determine whether conclusions were robust to arbitrary decisions regarding eligibility and analysis. In performing these analyses, we considered whether conclusions would have differed if:

- eligibility had been restricted to studies without high risk of attrition bias; and
- eligibility had been further restricted to studies that used validated scales to measure vasomotor symptoms.

Overall quality of the body of evidence - Summary of findings table

We used GRADEPRO software and methods of The Cochrane Collaboration to prepare a Summary of findings table (Higgins 2011). This table portrayed the overall quality of the body of evidence for main review outcomes (occurrence of vasomotor symptoms, vaginal bleeding, breast cancer, endometrial cancer, venous thromboembolic events, cardiovascular events, cerebrovascular events and mortality from any cause) and main comparisons (tibolone vs placebo, tibolone vs HT) on the basis of GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). We justified, documented and incorporated Judgements about evidence quality (high, moderate, low or very low) into the reporting of results for each outcome.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The original systematic search performed in 2011 through seven databases produced 540 records (after duplicates were removed). After selecting 57 papers of potential interest from their titles and abstracts, we eventually included 33 RCTs. Two of these articles (Ziaei 2010; Ziaei 2010b) appeared to report different outcomes for the same study; we have amalgamated these and counted them as a single study in the 2016 update.

We performed additional searches in 2015: we initially selected 62 additional abstracts and found 14 additional RCTs, plus another publication (Bots 2006) for one of the studies already included (Langer 2006). (See Figure 1 for study flow.) We have included in this update six studies that were excluded in the previous version of the review (see Differences between protocol and review). Therefore this review update includes a total of 46 studies (32 studies from the previous version of the review, six that were excluded from the previous version of the review and eight new studies).

Of these newly included reports, five (Bouchard 2012; Gupta 2013; Jacobsen 2012; Morais-Socorro 2012; Polisseni 2013) were published since 2012, and three (Baracat 2002; Doren 1999; Wender 2004) were cited among references provided in other studies. We asked drug manufacturers, as well as authors of conference proceedings, about possibly unpublished studies but obtained no information on this.

Included studies

Study design and setting

We included 46 RCTs of parallel design; 18 were multi-centre studies.

Participants

All selected RCTs included postmenopausal or perimenopausal women (n = 19,976), and in most of these RCTs, all or some participants had menopausal symptoms. A few studies did not clearly specify whether women were symptomatic, or whether investigators had other reasons to test the effectiveness of tibolone. Among these, five RCTs (Archer 2007; Hänggi 1997; Doren 1999; Okon 2005; Wender 2004) were carried out with the main objective to assess endometrial safety associated with the use of tibolone, and four RCTs (Elfituri 2005; Huber 2002; Winkler 2000; Ziaei 2010) had as their main objective assessment of bleeding patterns.

Five of the included RCTs (Cummings 2008; Gallagher 2001; Jacobsen 2012; Langer 2006; Roux 2002) assessed effects of tibolone on bone loss in postmenopausal women, in addition to its safety profile and its effects on menopausal symptoms. One study (Cummings 2008) also evaluated the reduction in fractures among women with osteoporosis.

Three RCTs (Kenemans 2009; Kroiss 2005; Kubista 2007) specifically studied individuals with breast cancer: Kenemans 2009 assessed the recurrence of breast cancer in women with vasomotor symptoms who were previously treated surgically; Kroiss 2005 evaluated the safety profile of tibolone administered to postmenopausal women after breast cancer surgery to prevent, relieve or delay the occurrence of menopausal symptoms; Kubista 2007 assessed the safety of 14-day tibolone treatment of breast tissue in patients with invasive cancer without metastatic spread, and we included this study because an ischaemic stroke occurred.

Among populations with specific characteristics other than menopausal symptoms, one RCT (de Aloysio 1998) selected patients with uterine leiomyomas to assess the effects of tibolone on bleeding patterns. Another RCT (Vieira 2009) assessed the frequency of flares in patients with lupus erythematosus.

Most of the included RCTs studied women in natural menopause only, although a few studies also included women without a uterus. In these cases, investigators evaluated endometrial outcomes (bleeding, hyperplasia, cancer) only in women with an intact uterus.

The mean age of women in most of the selected studies was between 52 and 55 years. In two trials (Cummings 2008; Jacobsen 2012) that selected women older than 60 years of age, researchers observed much higher means, whereas in one trial (Elfituri 2005) on Lybian women with natural or surgical menopause, the mean age of participants was lower (44 years). Mean time since menopause ranged from 1.5 to 17 years.

All but three of the selected RCTs included fewer than 1000 participants. Each of the three largest RCTs (Archer 2007; Cummings 2008; Kenemans 2009) actually included more than 3000 participants. Follow-up periods ranged from two weeks to four years.

Interventions

The included studies administered oral tibolone (usually 2.5 mg daily: range 0.625 mg to 5 mg daily) compared with placebo, unopposed oestrogen or combined HT, as detailed below. Unless otherwise stated, doses were daily and progesterone was continuous. Several studies included more than one comparator.

- Placebo (17 RCTs): Benedek-Jaszmann 1987, Berning 2000, Bouchard 2012, Cummings 2008, Gallagher 2001, Hudita 2003, Jacobsen 2012, Kenemans 2009, Kroiss 2005, Kubista 2007, Landgren 2002, Meeuwsen 2002, Morais-Socorro 2012, Swanson 2006, Vieira 2009, Volpe 1986, Wender 2004
- Unopposed oestrogen (three RCTs)
  - Conjugated equine oestrogen (CEE) 0.0625 (Gupta 2013)
  - Oestriol 2 to 4 mg (Volpe 1986)
  - 17β-Oestradiol patch 50 µg (Mendoza 2000)
- Combined HT (28 RCTs)
  - CEE 0.625 mg plus medroxyprogesterone acetate 2.5 to 5 mg (Archer 2007;Baracat 2002;de Aloysio 1998;Huber 2002;Kökçü 2000;Langer 2006;Uygur 2005;Wu 2001;Ziaei 2010)
  - Oestradiol valerate 2 mg and norethisterone 0.7 to 2mg (Al-Azzawi 1999;Okon 2005)
  - Oestradiol 50 µg + norethisterone acetate (140 microgr) in the form of a transdermal patch (Nijland 2009)
  - Oestradiol valerate 2 mg plus dienogest 2 mg (Osmanağaoğlu 2006)
  - Oestradiol 2 mg + oestriol 1 mg/d + norethindrone acetate 1 mg/d (Winkler 2000)
  - Oestradiol 1 to 2 mg plus norethindrone 0.5 to 1 mg (Polisseni 2013;Roux 2002)
  - 17β-Oestradiol 1 to 2 mg + norethisterone 0.5 to 1 mg (Doren 1999;Hammar 1998;Hammar 2007;Nappi 2006a;Nathorst-Böös 1997)
  - Oestradiol 2 mg + medrogestone 10 mg (Egarter 1996)
  - CEE 0.625 mg plus sequential 150 µg norgestrel (Ross 1999)
  - CEE 0.625 mg plus sequential medroxyprogesterone 5 mg (Siseles 1995)
  - CEE 0.625 mg plus sequential norethisterone 5 mg (Siseles 1995;Volpe 1986)
  - CEE 0.625 mg + sequential cyproterone acetate 12.5 mg/d (Volpe 1986)
  - Oestradiol valerate 2 mg plus sequential cyproterone acetate 12.5 mg (Volpe 1986)
  - Oestradiol valerate 2 mg plus sequential norethisterone 5 mg (Volpe 1986)
  - 17β-Oestradiol oral 2 mg or patch 50 µg plus sequential oral dydrogesterone 10 mg (Elfituri 2005;Hänggi 1997)
  - 17β-Oestradiol patch 50 µg plus sequential norethisterone 0.25 mg (Mendoza 2002)
  - Transdermal β-oestradiol patch 50 µg plus micronised natural progesterone 200 mg twice a week (Mendoza 2002)

Outcomes

Of 46 RCTs, 23 evaluated the effectiveness of tibolone for treatment of vasomotor symptoms in symptomatic women, measured as occurrence (Kökçü 2000; Meeuwsen 2002), as frequency (Bouchard 2012; Hammar 2007; Landgren 2002; Swanson 2006) or with the use of scales (Benedek-Jaszmann 1987; Elfituri 2005; Hammar 1998; Huber 2002; Hudita 2003; Morais-Socorro 2012; Polisseni 2013; Wu 2001; Ziaei 2010). Data from eight other RCTs (Al-Azzawi 1999; Baracat 2002; Egarter 1996; Ross 1999; Siseles 1995; Vieira 2009; Volpe 1986; Wender 2004) that evaluated vasomotor symptoms were unsuitable for analysis (see Table 1 for detailed explanations).

- Twenty-eight of 46 RCTs evaluated unscheduled bleeding (24 could be considered for meta-analyses).
- Ten of 46 RCTs evaluated breast cancer.
- Thirteen of 46 RCTs evaluated endometrial cancer.
- Nine of 46 RCTs evaluated venous thromboembolic events.
- Five of 46 RCTs evaluated cardiovascular events.
- Eight of 46 RCTs evaluated cerebrovascular events.
- Six of 46 RCTs evaluated mortality from any cause.
- Nine of 46 RCTs evaluated endometrial hyperplasia (extra one is Volpe 1986).
- Sixteen of 46 RCTs evaluated vaginal dryness and painful sexual intercourse (seven could be considered for meta-analyses) (extra ones are Mendoza 2000 and Uygur 2005).
- Four of 46 RCTs evaluated insomnia.
- Two of 46 RCTs evaluated vaginal infection.
- One of 46 RCTs evaluated urinary tract infection.

Excluded studies

We excluded 24 studies from the review. Following are the most common reasons for exclusion (occurring in more than one RCT).

- Three of 24 were not randomised.
- Fifteen of 24 did not assess outcomes of interest.
- Four of 24 did not include a comparator of interest.

Risk of bias in included studies

See also Characteristics of included studies, Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

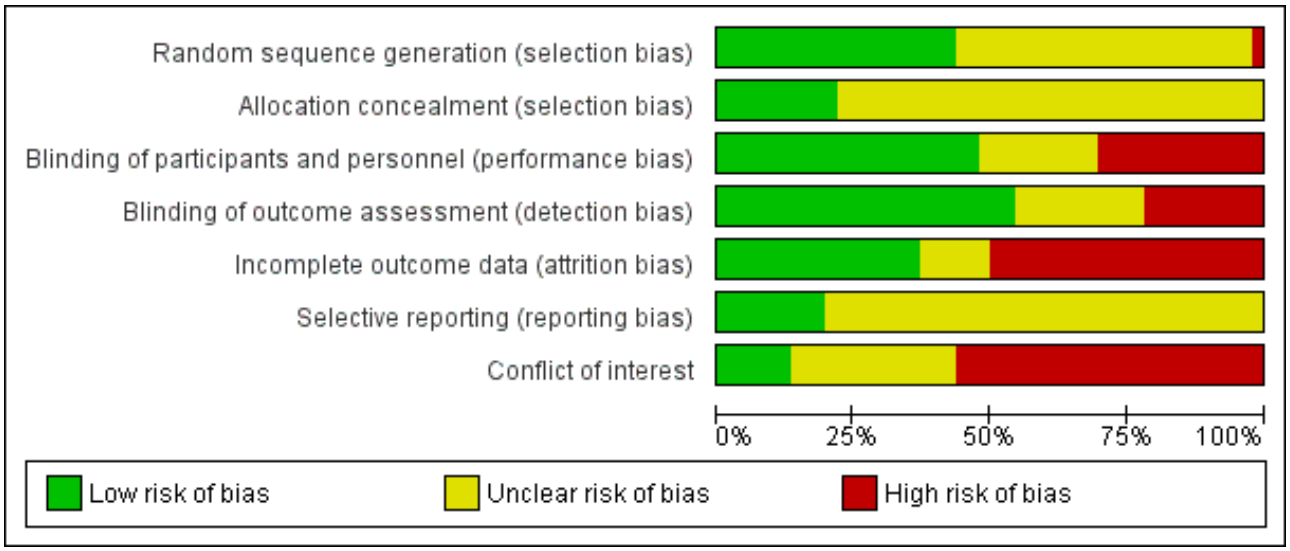


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

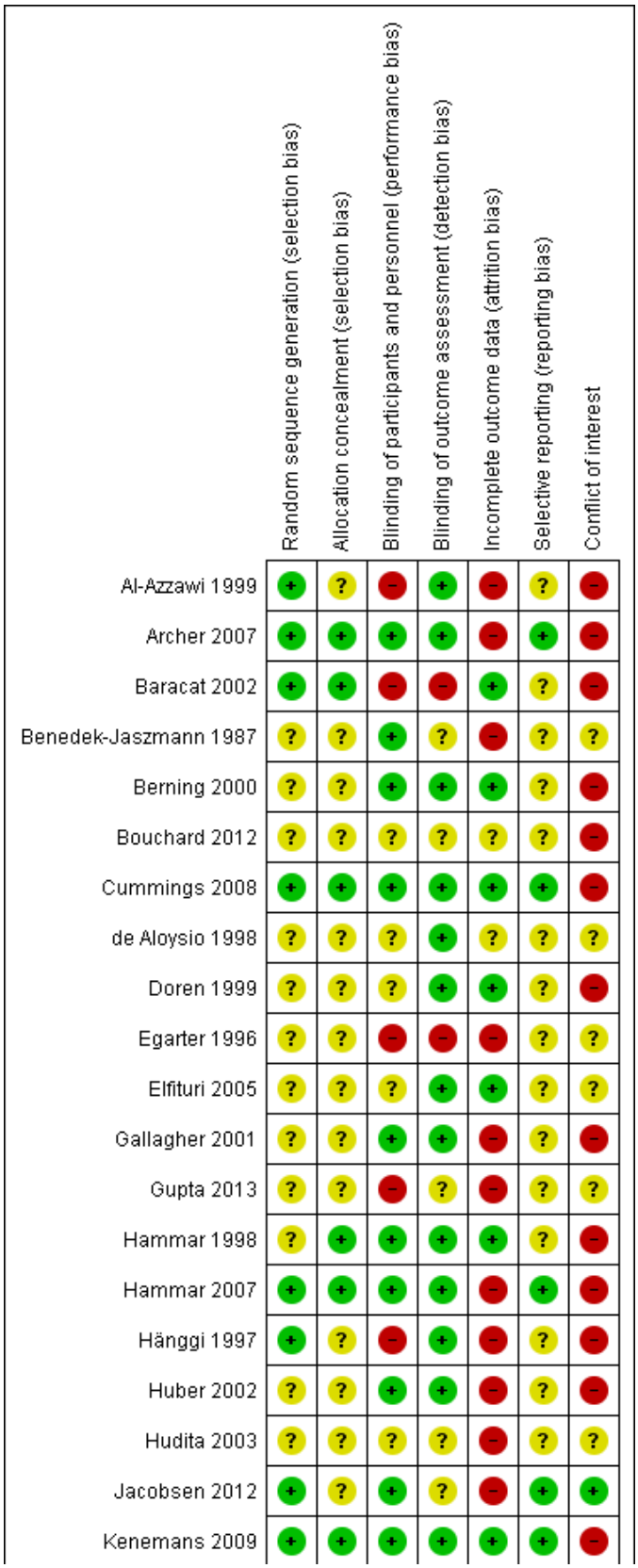
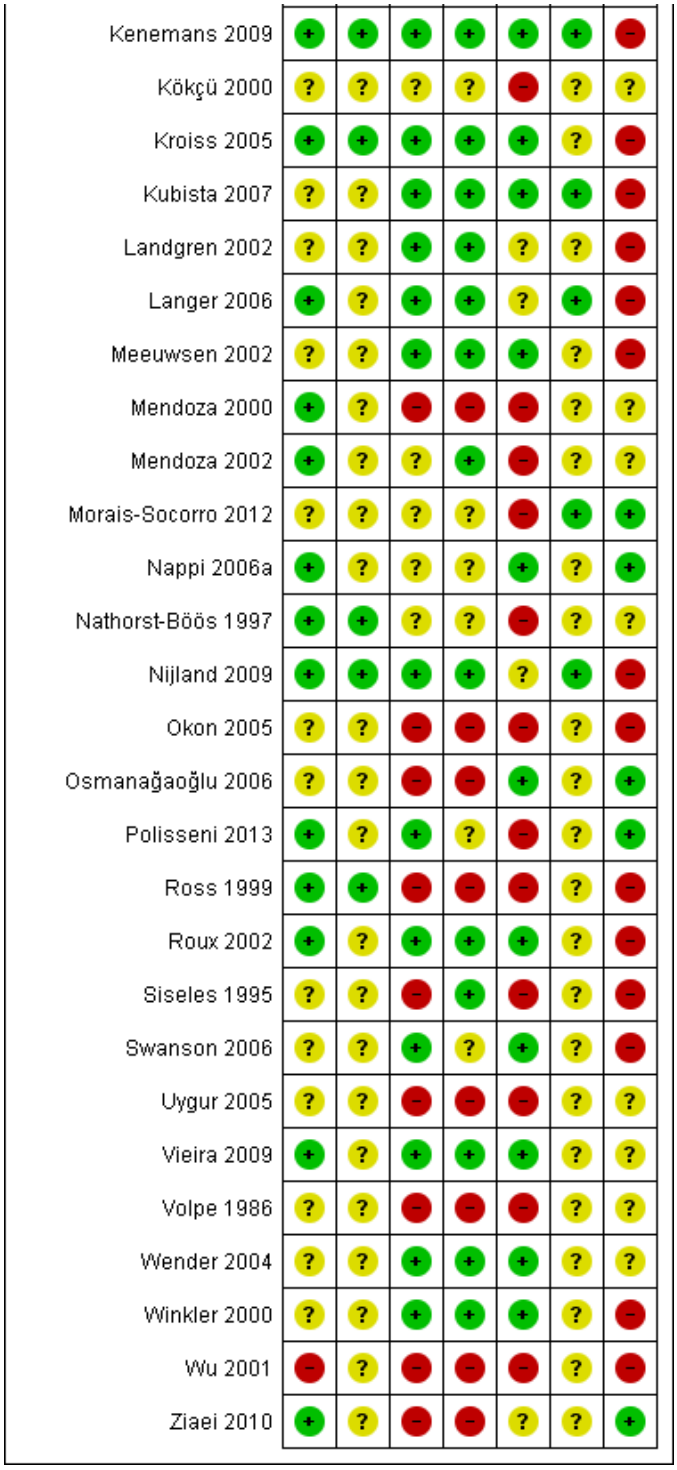


Figure 3. (Continued)



Allocation

Sequence generation

Twenty RCTs described adequate methods of sequence generation; we rated them as having low risk of bias in this domain. We rated 25 studies as having unclear risk. We rated one study (Wu 2001) as having high risk of bias; investigators stated they allocated to treatment groups randomly selected pairs of two women.

Allocation concealment

Most of the selected RCTs provided no information regarding allocation concealment. Only 10 of 46 RCTs specified that researchers used a system for concealing allocation (low risk of bias): an interactive voice response system in five RCTs, another computerised system (the Almedica Drug Labelling System; Almedica, Parsippany, NJ, USA) in one RCT and opaque envelopes

in four RCTs. We rated remaining studies as having unclear risk of bias.

Blinding

Performance bias

In 22 out of 46 RCTs, participants and/or personnel were blinded (low risk of bias). Fourteen RCTs were open trials or blinding appeared unlikely (high risk of bias), and 10 provided insufficient or no information by which this domain could be assessed (unclear risk).

Detection bias

We considered risk of bias as low in 25 of 46 RCTs, whereas 10 RCTs did not provide enough information for assessment, and we rated 13 studies as having high risk of bias in this domain.

Incomplete outcome data

We considered 17 of 46 RCTs to have low risk of attrition bias. Several RCTs reported some reasons for concern (lack of intention-to-treat analysis, loss to follow-up with no reasons specified). In particular, investigators gave no clear reasons for excluding participants from treatment and/or evaluation in six RCTs (rated as having unclear risk), and more than 10% of participants were lost to follow-up in 23 RCTs (rated as having high risk).

Selective reporting

Only nine of 46 study protocols were available; we judged risk of selective reporting bias as low in all of these studies, as they reported expected outcomes of interest for this review, or they reported data on adverse events that were not indicated in the study protocol but could be expected in the study report. We rated all other studies as having unclear risk.

Other potential sources of bias

The drug producer sponsored most of the RCTs, and its employees often authored the articles. We rated 26 as having high risk of bias and 10 unclear risk. Just six of 46 RCTs appeared truly independent, and we rated them as having low risk of bias in this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Tibolone compared with placebo for treatment of vasomotor symptoms in postmenopausal women; **Summary of findings 2** Tibolone compared with placebo for postmenopausal women: adverse events; **Summary of findings 3** Tibolone compared with combined HT for treatment of vasomotor symptoms in postmenopausal women; **Summary of findings 4** Tibolone compared with combined HT for postmenopausal women: adverse events

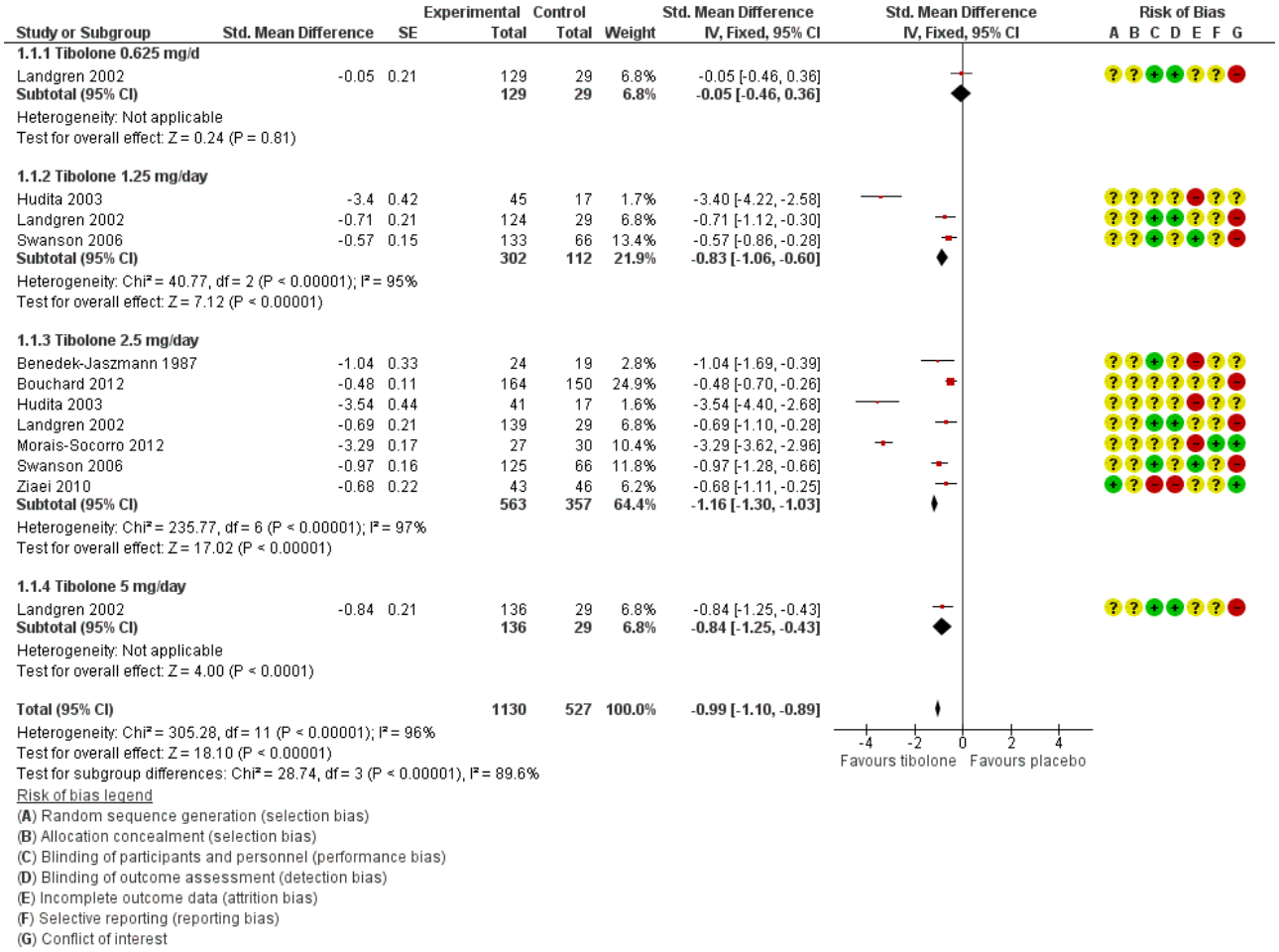
Tibolone versus placebo

Primary outcomes

Vasomotor symptoms

Eight RCTs reported useable data on this outcome; three other RCTs reported data that could not be used (see Table 1). A substantial effect of tibolone on vasomotor symptoms compared with placebo is suggested (see Analysis 1.1 and Figure 4), with a pooled estimate of the SMD of -0.99 (95% CI -1.10 to -0.89; n = 1657; I^2 = 96%; moderate-quality evidence). Multiplying this by the pooled standard deviation from Hammar 1998 (0.76) suggests that tibolone could improve vasomotor symptoms by around 0.75 (0.7 to 0.8) points on a 5-point severity scale. A sensitivity analysis (see Analysis 1.15) excluding three RCTs with attrition bias (Benedek-Jaszmann 1987; Hudita 2003; Morais-Socorro 2012 - the latter two also have very large estimates) still shows an effect of tibolone, with reduced heterogeneity and effect size (SMD -0.61, 95% CI -0.73 to -0.49; I^2 = 54%). The corresponding odds ratio (OR) is 0.33 (95% CI 0.27 to 0.41). These estimates can be translated to meaningful scales; multiplying the SMD by the pooled standard deviation from Hammar 1998 (0.76) suggests that tibolone could improve vasomotor symptoms by around 0.5 (0.4 to 0.6) points on a 5-point severity scale; this probably would not constitute a clinically meaningful effect.

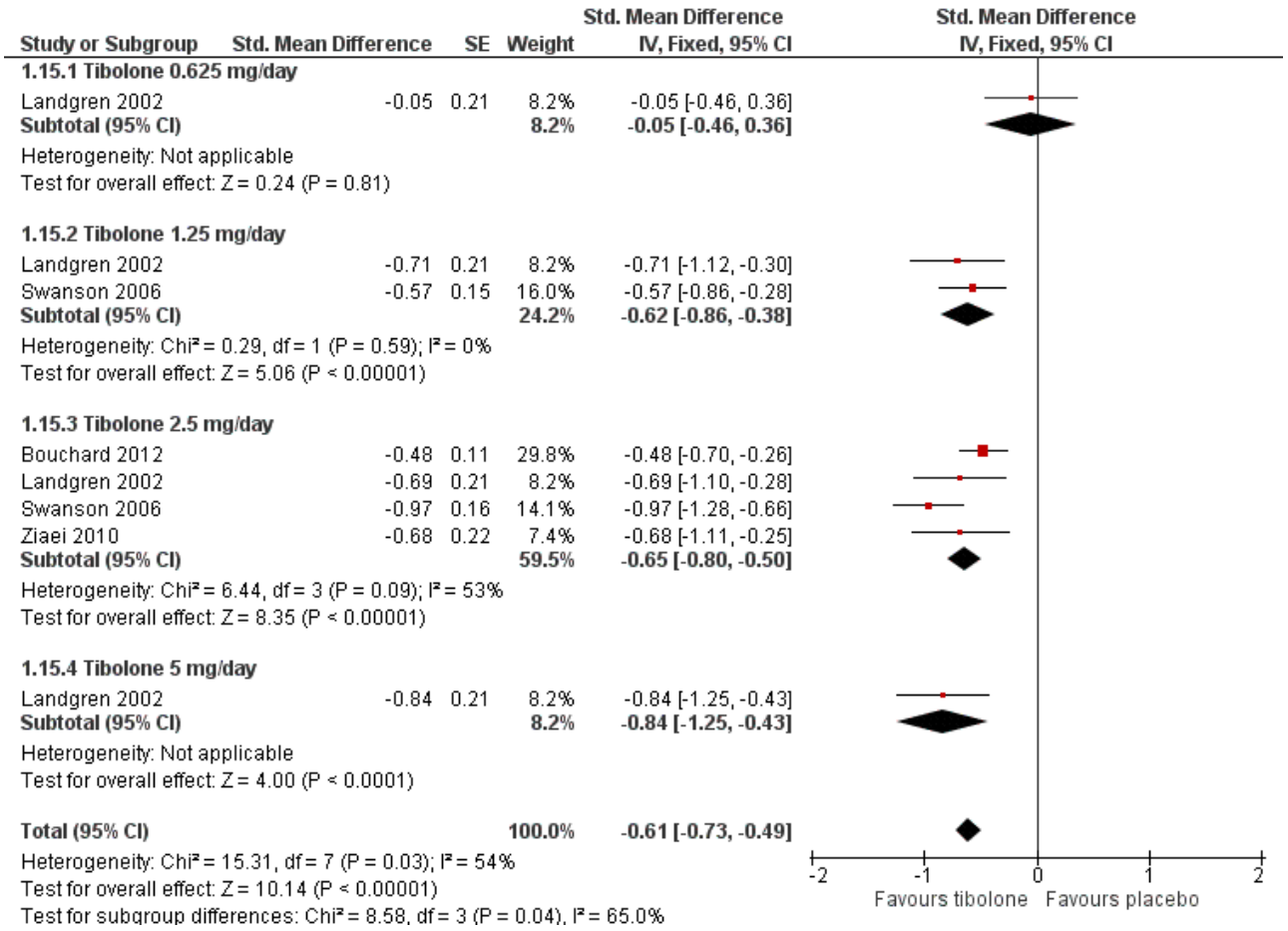
Figure 4. Forest plot of comparison: 1 Tibolone versus placebo, outcome: 1.1 Vasomotor symptoms.



Subgroup analysis by dose

We found strong evidence (P < 0.00001) of differences between subgroups defined by tibolone dose, although this was diminished when we removed trials with high risk of attrition bias, which were likely to provide overestimates (P = 0.04). Furthermore, once we removed these trials, we noted the suggestion of a dose-response relationship (Analysis 1.15; Figure 5), although trials were too few to allow formal investigation of this through meta-regression.

Figure 5. Forest plot of comparison: 1 Tibolone versus placebo, outcome: 1.15 Sensitivity analysis - Vasomotor symptoms without trials with high risk of attrition bias.



Subgroup analysis by duration

We noted some scope, albeit limited, for review authors to consider the impact of treatment duration on the effect; estimates from four of the included studies (Bouchard 2012; Landgren 2002; Morais-Socorro 2012; Swanson 2006) corresponded to 12 weeks, from one (Hudita 2003) to 24 weeks, from one (Ziaei 2010) to six months and from one (Benedek-Jaszmann 1987) to 12 months. All seven studies appeared in the stratum corresponding to a dose of 2.5 mg/d. Accordingly, we were able to look at estimates in this stratum to see whether duration modified the treatment effect when dose was held constant. As we recalled the high risk of attrition bias in Hudita 2003 and Morais-Socorro 2012, we noted that no such relationship was evident; neither the estimate from Benedek-Jaszmann 1987 (12 months) nor that from Ziaei 2010 (six months) was notably different from the 12 week estimates.

Unscheduled bleeding

Nine RCTs reported this outcome (Analysis 1.2). Unscheduled bleeding was more likely to occur in the tibolone group (OR 2.79, 95% CI 2.10 to 3.70; nine RCTs; n = 7814; I^2 = 43%; moderate-quality evidence). This suggests that if 18% of women taking placebo experience unscheduled bleeding, then between 31% and 44% of women taking tibolone will do so. Statistical significance persisted if we excluded the two largest RCTs (Cummings 2008; Kenemans 2009), which provided 47% of the total weight and about 85% of the population of interest.

Subgroup analysis by dose

Results were stratified by dose (2.5 and 1.25 mg daily). Effect estimates were similar in the two groups.

Long-term adverse events

Endometrial cancer

Eight RCTs reported this outcome (Analysis 1.3). We found no evidence of a difference between groups, although the event rate was low, with 16 cases reported in the tibolone arms and five in the placebo arms (OR 2.04, 95% CI 0.79 to 5.24; eight RCTs; 8504 women; I^2 = 0%; very low-quality evidence).

Evidence suggests that if one woman in a thousand taking placebo develops endometrial cancer, then between one and six women in a thousand who take tibolone may do so. Seven and four cases, respectively, occurred in Kenemans 2009 (with 2.5 mg/d; n = 3133), and four versus zero cases in Cummings 2008 (with 1.25 mg; n = 3519). Fifteen cases (11 in tibolone arms vs four in placebo arms) occurred in studies recruiting younger postmenopausal women (average age < 55 years).

Breast cancer

Six RCTs assessed this outcome: four in women without a history of breast cancer (Analysis 1.4) and two in women with a history of breast cancer (Analysis 1.5).

Among women without a history of breast cancer, we found no evidence of a difference between groups (OR 0.52, 95% CI 0.21 to 1.25; four RCTs; 5500 women; I^2 = 17%; very low-quality evidence).

Among women with a history of breast cancer, we noted increased risk in the tibolone group (OR 1.5, 95% CI 1.21 to 1.85; two RCTs; 3165 women; moderate-quality evidence). All events occurred in the largest of the studies (Kenemans 2009), which administered 2.5 mg/d of tibolone and was stopped prematurely owing to increased risk in the intervention group.

Venous thromboembolic events

Five RCTs assessed this outcome; three of them (Cummings 2008; Kenemans 2009; Landgren 2002) reported the occurrence of events (Analysis 1.6). We found no evidence of a difference between groups (OR 0.85, 95% CI 0.37 to 1.97; n = 9176; I^2 = 0%; very low-quality evidence).

Ten cases (seven in tibolone arms vs three in placebo arms) of a total of 24 occurred in studies recruiting younger postmenopausal women (average age < 55).

Cardiovascular events

We found no evidence of a difference between groups (OR 1.38, 95% CI 0.84 to 2.27; four RCTs; n = 8401; I^2 = 0%; very low-quality evidence; Analysis 1.7).

The four RCTs assessing this outcome involved women of very different age groups (Cummings 2008, mean age 68; Jacobsen 2012, mean age 74; Kenemans 2009, mean age 53 years; Langer 2006, mean age 59), but we observed no statistical heterogeneity between these studies.

Cerebrovascular events

Four RCTs assessed this outcome (Analysis 1.8) and provided no conclusive evidence of a difference between groups (OR 1.74, 95% CI 0.99 to 3.04; four RCTs; n = 7930; I^2 = 0%).

One RCT (Cummings 2008; n = 4506), which selected osteoporotic women aged 60 to 85 years, provided most of the data; this trial was stopped prematurely for increased risk of stroke with 1.25 mg/d of tibolone (28 vs 13 cases; OR 2.18, 95% CI 1.12 to 4.21). Among women younger than 60 years old (Kenemans 2009), five cases occurred in each group (OR 0.99, 95% CI 0.29 to 3.42; n = 3133).

Mortality from any cause

Four RCTs assessed this outcome, and three reported events (Analysis 1.9), providing no evidence of a difference between groups (OR 1.06, 95% CI 0.79 to 1.41; five RCTs; n = 8242; I^2 = 0%; low-quality evidence).

Secondary outcomes

Insomnia

Three RCTs reported insomnia or "sleep" (Analysis 1.10).

Results suggested an advantage of tibolone over placebo related to insomnia or quality of sleep (SMD -0.19, 95% CI -0.38 to 0.00; three RCTs; n = 3432; I^2 = 0%).

Genital symptoms

Vaginal dryness

Three RCTs (Hudita 2003; Kenemans 2009; Ziaei 2010) reported useable data on this outcome (see Analysis 1.11 and Table 2), suggesting an advantage of tibolone over placebo for vaginal dryness, although this would barely be evident if the two arms from Hudita 2003, which had a high dropout rate, were excluded. The SMD (95% CI) including Hudita 2003 was -0.66 (-0.90 to -0.43), which corresponds to improvement on a 0 to 3 severity score of 0.6 (0.4 to 0.8) points with a standard deviation (SD) of 0.89. This probably would not amount to a clinically meaningful difference.

Vaginal infection

Two RCTs reported this outcome (Analysis 1.12). The rate of vaginal infection was higher in the tibolone group (OR 2.50, 95% CI 1.24 to 5.06; two RCTs; n = 7639; I^2 = 88%). The direction of effect was consistent, but considerable statistical heterogeneity was probably due to differences in the population studied (osteoporotic women aged 60 to 85 years in Cummings 2008, and younger women who had experienced breast cancer in Kenemans 2009).

Urinary tract infection

One RCT (Kenemans 2009) reported this outcome (Analysis 1.13) and revealed no evidence of a difference between groups (OR 0.70, 95% CI 0.46 to 1.06; one RCT; n = 3133).

Endometrial hyperplasia

Four RCTs assessed this outcome, and two reported events (Analysis 1.14), providing no evidence of a difference between groups, although results revealed only seven events in total (OR 1.20, 95% CI 0.23 to 6.25; n = 4518; I^2 = 0%).

Tibolone versus oestrogens

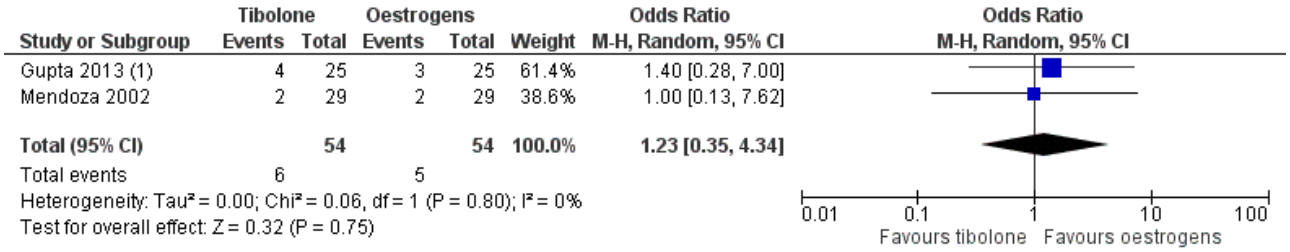
Primary outcomes

Two RCTs (Gupta 2013; Mendoza 2002) compared tibolone versus oestrogens and reported data on three outcomes (vasomotor symptoms, vaginal dryness and painful sexual intercourse, insomnia).

Vasomotor symptoms

We found no evidence of a difference between groups (OR 1.23, 95% CI 0.35 to 4.34; two RCTs; n = 108; I^2 = 0%; low-quality evidence), although the small number of events observed meant that large effects in either direction could not be ruled out. See Analysis 2.1 and Figure 6.

Figure 6. Forest plot of comparison: 2 Tibolone versus oestrogens, outcome: 2.1 Vasomotor symptoms.



Footnotes
(1) Symptomatic patients (no menopausal symptoms) with surgical menopause 3 days earlier

Secondary outcomes

Insomnia

No events occurred in either group (Analysis 2.2).

Genital symptoms

Vaginal dryness and painful sexual intercourse

We found no evidence of a difference between groups (OR 0.32, 95% CI 0.01 to 8.25; one RCT; n = 50), although the estimate was so imprecise as to be completely uninformative (Analysis 2.3).

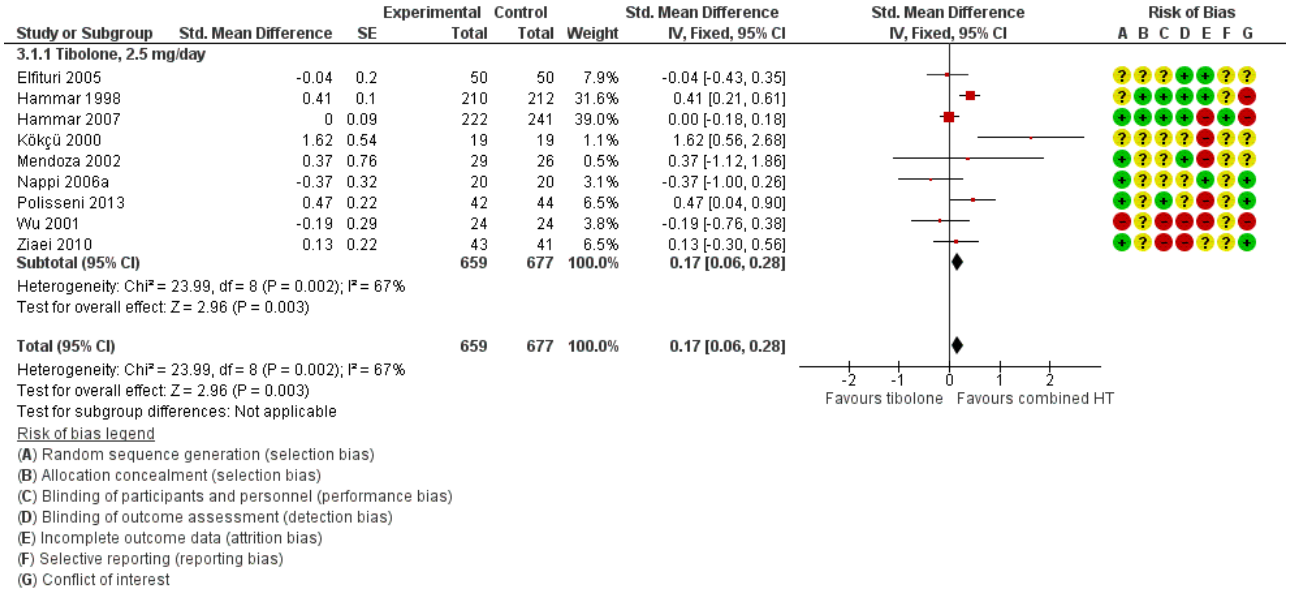
Tibolone versus combined HT

Primary outcomes

Vasomotor symptoms

Nine RCTs reported useable data on this outcome, and five other RCTs provided data that could not be used (see Table 1). Results suggested a small disadvantage of tibolone compared with combined HT (see Analysis 3.1 and Figure 7), with a pooled estimate of the SMD of 0.17 (95% CI 0.06 to 0.28; n = 1336; I^2 = 67%; moderate-quality evidence). Multiplying this estimate by the pooled standard deviation from Hammar 1998 (0.76) suggests that combined HT improves vasomotor symptoms by around 0.15 (0.08 to 0.23) compared with tibolone on a 5-point severity scale. The corresponding OR was 1.36 (95% CI 1.11 to 1.66). A sensitivity analysis (see Analysis 3.11) excluding five RCTs with high attrition bias provided slightly larger but similar estimates (SMD 0.25, 95% CI 0.09 to 0.41; I^2 = 0%). A further sensitivity analysis excluding the latter five RCTs plus Hammar 1998 (using a non-validated scale) revealed no evidence of a difference between treatments because the estimate lacked precision once other studies were excluded (see Analysis 3.12).

Figure 7. Forest plot of comparison: 3 Tibolone versus combined HT, outcome: 3.1 Vasomotor symptoms.



Subgroup analysis by duration

Duration of treatment in this comparison ranged from 12 weeks to 12 months, while dose was the same in all studies (2.5 mg/d); therefore, a tentative investigation of the impact of treatment duration on treatment effect could be undertaken. Although we identified too few studies to permit a formal analysis (e.g. using meta-regression), we were able to order the studies according to duration so as to inspect whether a trend in the size of the SMDs was

suggested (Analysis 3.13). However, we observed no clear trend, and consequently found no evidence that the difference between tibolone and HT varies according to the duration of treatment.

Unscheduled bleeding

Seventeen RCTs reported this outcome: 15 compared tibolone with continuous combined HT, two with continuous sequential HT (Analysis 3.2). The latter studies included cases of bleeding if they had been reported as side effects by study authors.

Tibolone was associated with fewer breakthrough events than combined HT (OR 0.32, 95% CI 0.24 to 0.41; 16 RCTs; n = 6438; I^2 = 72%; low-quality evidence), suggesting that if 47% of women taking combined HT experience unscheduled bleeding, then between 18% and 27% of those taking tibolone will do so. High heterogeneity was attributable in part to an RCT (Nijland 2009) in which HT was delivered in patch form, and also to a difference between dose subgroups, as noted below.

Statistical significance persisted if we excluded the largest RCT (Archer 2007, which provided about half of the population of interest).

One RCT (Okon 2005) reported this outcome as days of bleeding over one year of follow-up. Study authors reported no significant differences between groups.

Subgroup analysis by dose

We stratified results by dose, revealing a statistically significant difference between 2.5 mg and 1.25 mg subgroups (test for subgroup differences: Chi^2 = 7.28; df = 1 (P = 0.007); I^2 = 86.3%), which suggested that the lower dose of tibolone was associated with a more beneficial effect when compared with HT (OR 0.21, 95% CI 0.16 to 0.26; two RCTs; n = 1718; I^2 = 0%).

Long-term adverse events

Endometrial cancer

Five RCTs reported this outcome (Analysis 3.3). Few events occurred (two cases in tibolone arms vs one in combined HT arms in three trials), and investigators provided no evidence of a difference between groups (OR 1.47, 95% CI 0.23 to 9.33; five RCTs; n = 3689; I^2 = 0%; very low-quality evidence).

Breast cancer

Five RCTs assessed this outcome (Analysis 3.4). All included women without a history of breast cancer. Few events occurred (17 cases in tibolone arms vs 10 in combined HT arms), and researchers provided no evidence of a difference between groups (OR 1.69, 95% CI 0.78 to 3.67; n = 4835; I^2 = 0%; very low-quality evidence).

Twenty-two cases (13 in tibolone arms vs nine in placebo arms) occurred in studies recruiting younger postmenopausal women (average age < 55).

Venous thromboembolic events

Four RCTs assessed this outcome (Analysis 3.5). Few events occurred (one case of pulmonary embolism in tibolone arms vs two cases of pulmonary embolism and three of deep venous thrombosis in combined HT arms), and researchers provided no evidence of a difference between groups (OR 0.44, 95% CI 0.09 to 2.14; four RCTs; n = 4529; I^2 = 0%; very low-quality evidence).

Cardiovascular events

Two RCTs assessed this outcome (Archer 2007; Langer 2006). Few events occurred (seven in tibolone arms vs 11 in combined HT arms), and results showed no evidence of a difference between groups (OR 0.63, 95% CI 0.24 to 1.66; two RCTs; n = 3794; I^2 = 0%; very low-quality evidence; Analysis 3.6). The mean age of women in these RCTs was less than 60 years.

Cerebrovascular events

Four RCTs assessed this outcome (Analysis 3.7). Few events occurred (two cases in tibolone arms vs four cases in combined HT arms), and data show no evidence of a difference between groups (pooled OR 0.76, 95% CI 0.16 to 3.66; four RCTs; n = 4562; I^2 = 0%; very low-quality evidence). The mean age of women in these RCTs was less than 60 years.

Mortality from any cause

Two RCTs (Langer 2006; Nijland 2009; n = 970) reported this outcome, with only one case noted in the tibolone arm (Analysis 3.8).

Secondary outcomes

Insomnia

Just one RCT (Egarter 1996) used a validated scale (a domain of the Kupperman Index) to assess this outcome but provided no data suitable for analysis (SD was not reported and could not be calculated sensibly via the information provided). The publication reported no evidence of a difference between tibolone and combined HT.

Genital symptoms

Vaginal dryness and painful sexual intercourse

Evidence at face value suggested little or no difference between tibolone and combined HT in relation to vaginal dryness (SMD 0.02, 95% CI -0.12 to 0.17; seven RCTs; n = 1098; moderate-quality evidence; Analysis 3.10).

Mendoza 2000 (n = 76) also measured painful sexual intercourse as an outcome but provided no data suitable for analysis; study authors reported no significant difference between groups.

Similarly, Nathorst-Böös 1997 evaluated dyspareunia but provided no data suitable for analysis, and study authors reported that they found no evidence of a difference between groups.

Vaginal infection

None of the selected RCTs reported useable data on this outcome

Urinary tract infection

None of the selected RCTs reported useable data on this outcome.

Endometrial hyperplasia

Five RCTs assessed this outcome (Analysis 3.9), reporting few events (zero cases in tibolone arms vs three cases in the combined HT arm) and no evidence of a difference between groups (OR 0.35, 95% CI 0.05 to 2.21; five RCTs; n = 2846; I^2 = 0%).

Sensitivity analyses

Aside from sensitivity analyses performed for evaluation of vasomotor symptoms, as described above (see Results 1.1 and 3.1), review authors performed sensitivity analyses for primary outcomes, considering alternative scenarios in participants lost to follow-up. We performed three analyses on placebo-controlled RCTs (specifically on venous thromboembolic events and breast cancer in women who had or had no history of breast cancer) and two on combined HT controlled RCTs (specifically on unscheduled bleeding and vasomotor symptoms). None of these analyses showed differences in terms of direction of effect and statistical significance.

Assessment of review-wide reporting bias

Funnel plot analyses were not helpful to review authors in assessing the presence of publication bias, given the relative scarcity of studies and data. Vasomotor symptoms and unscheduled bleeding were the only outcomes with sufficient RCTs to permit such an assessment, which revealed no evidence of bias for this outcome. As for the other outcomes, we cannot exclude the occurrence of publication bias because the drug manufacturer, who sponsored almost all of the published RCTs, was asked for possibly unpublished data but provided no written response.

DISCUSSION

Summary of main results

For this review, we retrieved randomised controlled trials (RCTs) comparing tibolone versus placebo and versus combined hormone therapy (HT). We identified only three RCTs comparing tibolone versus oestrogens without progestogens (Gupta 2013; Mendoza 2000; Volpe 1986), and only two of these were suitable for analysis. The addition of progestogens is considered important for lowering the risk of endometrial carcinoma in women with a uterus.

Effectiveness *in* treatment of menopausal symptoms

Our findings suggest that tibolone reduces vasomotor symptoms compared with placebo and is less effective than combined HT. The clinical relevance of observed differences is disputable - especially for comparison versus combined HT - as their magnitude is limited. It should be noted that the quality of evidence for this outcome was moderate. In particular, attrition bias and use of non-validated scales were frequently observed, as was statistical heterogeneity, although sensitivity analyses excluding RCTs with high risk of attrition bias confirmed both statistical significance and direction of effects. Available evidence suggests at most a modest effect of tibolone on insomnia and vaginal dryness compared with placebo. No clinically relevant differences are apparent between tibolone and combined HT in relation to vaginal dryness outcomes.

Short-term safety

This review suggests that tibolone has a better bleeding profile than combined HT and is associated with more numerous breakthrough bleeding events than placebo.

Evidence is scarce and unclear on vaginal and urinary tract infections. Only two RCTs (Cummings 2008; Kenemans 2009) provided data on vaginal infection. Cummings 2008 performed cervical cytological smears annually in women with a cervix, whereas Kenemans 2009 provided no information on diagnostic technique. Both RCTs suggested that tibolone increases vaginal infection and provided no information on specific aetiologic agents. Only one study reported urinary tract infections.

Long-term safety

For this systematic review, we found few RCTs providing data that could be used to assess the long-term safety of tibolone. Nearly all of the evidence on adverse events was of very low quality, and events were scarce.

Available evidence indicates that compared with placebo, tibolone increases the risk of recurrent breast cancer in women with a history of breast cancer, and may increase the risk of stroke among women over 60 years of age. No evidence suggests that tibolone increases the risk of other long-term adverse events, and no evidence reveals a difference between tibolone and HT with respect to long-term adverse events.

In particular, the LIBERATE study (Kenemans 2009) confirmed that tibolone could significantly increase breast cancer among high-risk women who were surgically treated within five years for breast cancer (for whom usual oestrogen and combined HT therapies were contraindicated) and who were using adjuvant therapy and/or chemotherapy in about seven cases out of 10. A daily dose of 2.5 mg led to an average of 15 extra recurrences each year for every 1000 women. It is a matter of concern that more than 70% of recurrence events were distant metastases, ultimately leading to death. This study failed to confirm the initial hypothesis of non-inferiority of tibolone versus placebo for breast cancer risk, and was stopped after 3.1 years.

The latter findings sharply contrast with results from the LIFT study (Cummings 2008), in which 1.25 mg of tibolone, administered to osteoporotic women to reduce the risk of vertebral fracture, slightly but significantly reduced new-onset breast cancer (about two fewer cases for every 1000 women each year). However, the absolute number of events in this study was low (six for tibolone vs 19 for placebo, for a total population of about 4500 women between 60 and 85 years of age). We should also note that LIFT researchers used half of the recommended dose for menopausal symptoms in women over 60 years of age (mean age 68). The Million Women Study (Beral 2011) suggested that breast cancer risk may be greater in women starting hormonal therapies within five years of menopause.

Populations for the LIBERATE and LIFT studies were too different for results to be combined meaningfully, and populations in both studies are not a typical target for HT addressing menopausal symptoms, so transferability of their results is a matter of concern. Other RCTs have not added useful data for better assessment of the breast cancer hypothesis. We should consider that follow-up in available RCTs was between 12 weeks and three years, which may be too short a period for a drug therapy to induce cancer, except for the LIBERATE study, in which high-risk women were treated and the study was powered for assessment of breast cancer recurrence.

We found 13 RCTs reporting on endometrial cancer, which occurred in only seven of these trials. Its incidence was low (most cases occurred in placebo-controlled trials - 15 cases in tibolone arms vs five cases in placebo arms - most in Kenemans 2009), so that the hypothesis emerging from observational studies of greater risk with tibolone could not be confirmed. In this case, we should also

consider that study follow-up ranged between 12 weeks and three years - an inadequate duration for a drug therapy to induce cancer.

Data on cerebrovascular events provide some suggestion of higher risk of stroke with tibolone versus placebo. This result was driven by the LIFT study (Cummings 2008), which recruited women over 60 years of age and stopped after 33 months for such an unexpected difference of 2.3 more events every 1000 women per year, which was even greater during the first year of treatment. These data are consistent with data from systematic reviews of RCTs testing combined HT therapies versus placebo; among those, a Cochrane review (Sanchez 2005) including 10 RCTs with a total of 24,283 women randomised to hormone therapy (HT) or placebo for an average of five years (risk ratio (RR) for stroke 1.25, 95% confidence interval (CI) 1.07 to 1.45). As for RCTs directly comparing tibolone versus combined HT, our review did not show differences between treatments, but data were scant. Unpublished data from the Million Women Study (available as rapid response; Beral 2007) had suggested higher risk of fatal stroke with tibolone versus other hormonal therapies (RR 1.58, 95% CI 1.06 to 2.37).

Our review provides no evidence of an increase in cardiovascular events with tibolone versus placebo, whereas data on thromboembolic events are very scant and unhelpful. As for combined HT, Sanchez 2005 found no increase in cardiovascular events and total mortality with HT but reported an increase in thromboembolic events. Randomised controlled trials directly comparing tibolone versus combined HT have provided few data and have revealed no statistically significant differences.

Last, two large RCTs (Cummings 2008; Kenemans 2009), which included higher-risk women than were included in other studies (for previous cancer or more advanced age), provided most of the data on mortality, revealing no statistically significant differences or trends.

Summary of benefits and harms

Moderate-quality evidence suggests that tibolone is more effective than placebo and less effective overall than combined HT in reducing postmenopausal symptoms, although the magnitude of observed differences is low. Tibolone provides a clear advantage in terms of less vaginal bleeding, but available data from RCTs on its long-term safety compared with other hormonal therapies are insufficient.

We found no evidence that tibolone increases the risk of serious adverse events for women taking it over a short term to treat vasomotor symptoms, provided they have had no history of breast cancer, but data are scarce and more evidence is required. Evidence indicates that tibolone is associated with increased risk of serious adverse events when used in other contexts. Tibolone leads to increased risk of breast cancer among women with a history of breast cancer and appears to increase the risk of stroke in older women. Data on endometrial cancer are inconclusive.

Overall completeness and applicability of evidence

Moderate-quality evidence on symptomatic relief may limit its applicability and clinical relevance. Very little evidence is available on the risks of breast and endometrial cancer in women typically treated for menopausal symptoms. In addition to this, we found no unpublished studies and did not obtain such information from the drug manufacturer. It should be highlighted that absence of publication bias is unusual in therapeutic areas with strong commercial interests, especially as almost all of the published RCTs were sponsored by the drug manufacturer (Bekelman 2003; Lexchin 2003).

Most of the included RCTs assessed effects of tibolone 2.5 mg - the most frequently used dose. Therapeutic schemes and doses of active controls (combined HT) also reflect those normally used. Most of the selected RCTs included postmenopausal women with menopausal symptoms. Two of the largest RCTs, which strongly influenced results on several outcomes, included very specific populations (patients with breast cancer and those with osteoporosis, respectively), and findings of these studies are of limited applicability to women taking tibolone for menopausal symptoms.

Quality of the evidence

We rated the quality of the evidence for the primary outcome of our review 'vasomotor symptoms' as moderate for comparisons of tibolone versus placebo and combined HT, and very low for the comparison against oestrogens. We consider the quality to be very low for the comparison versus oestrogen because we identified only two small studies, both of which were compromised by attrition bias. Given that dropout in these studies is very likely to be informative (women with poorer responses will be more likely to drop out), attrition could be fatal to the validity of a trial. In relation to comparisons against combined HT and placebo, we have identified weaknesses in many of the individual studies. However, on the basis of our sensitivity analyses, we believe we can be reasonably confident in our conclusions related to vasomotor symptoms, for the following reasons.

First, many of the relevant studies in these comparisons are subject to attrition bias, which, as noted above, could undermine the validity of a trial. However, we have shown that our conclusions are quite robust if we include only studies without high risk of attrition bias. Another concern is the matter of poor reporting in these studies. This is a matter of concern because we had to make some assumptions about variance in some studies, and we had to pool outcomes measured on different scales. However, although this may have had some impact on the exact size (and precision) of the estimate, it is probably unlikely that we arrived at estimates in the wrong direction (i.e. it is unlikely that placebo is actually better than tibolone, or that HT is worse than tibolone, with respect to vasomotor symptoms). Heterogeneity among studies is notable, but for the comparison versus placebo, we appear to explain much of it as the result of dose effects and artificially large estimates due to attrition bias in several studies. Substantial heterogeneity remains for the comparison versus HT, which we cannot explain; we see no evidence of a difference in treatment effectiveness according to treatment duration, and considerable variation remains after studies with high risk of attrition bias were excluded. One study (Hammar 1998) dominates this comparison: It is reasonably sized and appears to be of fair quality (given its use of a non-validated measurement scale). This study has a conflict of interest, as the manufacturer of tibolone is involved. However, the estimate from this trial actually suggests a disadvantage of tibolone, so the conflict of interest is not really a concern. Many of the other included studies have similar conflicts of interest. However, specific concerns in relation to this would involve selective reporting and publication bias, and we would expect these to manifest as artificial exaggeration of the benefits of tibolone. We have ended up

concluding that tibolone is inferior to HT in relation to vasomotor symptoms; it seems unlikely that companies would be hiding studies or analyses that showed tibolone as superior to HT, so it is unlikely that our conclusion would change if we discovered new studies. These biases may have affected our estimate of the effect of tibolone compared with placebo, although we tentatively note that trials with no apparent conflict of interest also demonstrated benefit in relation to vasomotor symptoms (tentatively, because these studies are themselves subject to other sources of bias). In summary, although the individual studies have weaknesses, we believe we can be fairly confident in our conclusions related to vasomotor symptoms, given the collective evidence. Although the exact size and precision of our estimates could change in light of further research, we believe that our clinical conclusions are reasonably unlikely to do so. In our view, this warrants a GRADE assessment of moderate quality.

We would similarly assess the quality of the evidence for the outcome unscheduled bleeding. We found no evidence for the comparison against oestrogens, but we would consider the evidence to be of moderate quality when taken collectively for the comparisons against placebo and combined HT, because estimates from studies with conflicts of interest and showing attrition bias appear to be generally similar to those from studies not revealing these weaknesses. We have rated the quality of evidence related to other adverse events as very low, as the result of low or very low event rates, leading to imprecision in our estimates and a corresponding inability to comment on the effects of tibolone on these endpoints.

Potential biases in the review process

As stated above, we asked the drug manufacturer, which sponsored almost all of the published RCTs, to provide possibly unpublished data but received no written response. Funnel plot analyses did not help review authors in assessing the presence of publication bias, given the relative scarcity of studies and data, although we were able to produce such plots for both unscheduled bleeding and vasomotor symptoms, and these suggested no obvious bias.

Agreements and disagreements with other studies or reviews

Use of tibolone for the treatment of menopausal symptoms has never been supported by demonstrated advantages over oestrogens and combined HT therapies, such as lower risks of breast and endometrial cancer. On the contrary, observational data from the Million Women Study (Beral 2003; Beral 2005) suggested greater risk of breast cancer (RR 1.45, 95% CI 1.25 to 1.68) and endometrial cancer (RR 1.79, 95% CI 1.43 to 2.25) versus non-users of HT, and two more recent RCTs included in this review (Cummings 2008; Kenemans 2009) have raised concerns about the benefit/risk profile of this drug. The latter two trials targeted very specific populations (women over 60 years of age and women who had already had breast cancer), and their results are not easily generalisable, although it may be wise to apply a precautionary principle and not exclude the possibility of safety problems for other groups. It should be noted that the Food and Drug Administration rejected the application for the registration of tibolone in the United States, although the reason for this is unknown.

With regard to the effectiveness of tibolone for treating menopausal symptoms, the effectiveness of combined HT over placebo has been shown more convincingly (MacLennan 2004).

AUTHORS' CONCLUSIONS

Implications for practice

Moderate-quality evidence suggests that tibolone is more effective than placebo and is less effective than combined hormone therapy (HT) in treating vasomotor symptoms. Tibolone is associated with a higher rate of unscheduled bleeding than placebo but a lower rate than combined HT.

Compared with placebo, tibolone increases the risk of recurrent breast cancer in women with a history of breast cancer, and may increase the risk of stroke in women over 60 years of age. No evidence indicates that tibolone increases the risk of other long-term adverse events, and no evidence has revealed a difference between tibolone and HT with respect to long-term adverse events.

Many of the included randomised controlled trials (RCTs) were of low or very low quality. Limitations included high risk of bias in the included trials, very low event rates and potential conflicts of interest. Twenty-four studies were financed by drug manufacturers, and another 10 failed to disclose their source of funding.

Implications for research

This review may reveal a systematic misunderstanding of RCT methods in this field, with study authors routinely misinterpreting their own trials. In particular, trial authors frequently interpret change from baseline in a study arm as evidence of a treatment effect. Change from baseline within a treatment group, even if statistically significant, can never be interpreted in this way; even in the absence of any effect of treatment at all, the appearance of improvement would be due to the twin spectres of variation in repeated responses of any given individual and so-called *regression to the mean,* whereby subsequent measurements will tend to be closer to the population average compared with relatively severe baseline measurements introduced by a study's inclusion criteria. Patient-reported outcome measures, such as those commonly used in this field, are particularly susceptible to these phenomena. It may help researchers to consider the fact that, were it possible to make a conclusion of treatment effectiveness based on the evolution of a single group, no comparator group, and therefore no RCT, would be required. Researchers should keep this in mind before making erroneous inferences that may be used as the basis for clinical decision making.

Other areas of statistical weakness in these trials include poor methods for handling missing outcome data due to dropout and for analysing longitudinal outcomes. In relation to the former, we found that it was common to ignore participants who had dropped out or to carry their last observation forward for analysis. These approaches may introduce serious bias if a patient is more or less likely to drop out depending on her symptoms. Researchers should instead employ such appropriate methods as multiple imputation (Sterne 2009). In relation to longitudinal analysis, researchers generally analysed separately mean responses at each of several time points. This is problematic because it both ignores the variation in patterns of response over time and increases the possibility of false-positive results due to multiple testing. Researchers instead should employ linear mixed models for which

statistical expertise is available (Diggle 1994), or should perform analyses based on summary measures of longitudinal responses when it is not (Matthews 1990).

Finally, we would appeal to researchers to adhere to CONSORT guidelines when reporting RCTs. Reporting was poor in the included studies, representing a considerable obstacle to meta-analysis in this review.

In this specific clinical area, well-designed comparative RCTs are needed to better assess whether, in women with troublesome menopausal symptoms who use short-term therapies, tibolone is as effective as combined HT in relieving symptoms. Although no evidence indicates that use of tibolone for up to three years increases the risk of serious adverse events in younger postmenopausal women without a history of breast cancer, observational studies and RCTs in other populations have raised serious doubts on the risks of long-term use of both tibolone and combined HT. Therefore, RCTs realised to better clarify the comparative safety of these drugs would be unethical. A systematic review of observational studies may be warranted to improve our understanding in this regard.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Al-Azzawi 1999

Methods	Randomised open-label controlled trial
Participants	235 healthy women with intact uteri, ≥ 12 months postmenopausal (mean 61 months), with serum FSH exceeding 20 IU/L. None of the women enrolled in the study had received hormone therapy during the 3 months before enrolment. Mean age: 54 years
Interventions	• Tibolone 2.5 mg/d • Micronised oestradiol valerate 2 mg/d + norethisterone 0.7 mg/d Administered for 1 year
Outcomes	Vaginal bleeding (0 to 3 months), menopausal symptoms, pulmonary embolism
Notes	Commented on menopausal symptoms that were assessed according to the Greene menopausal symptoms scale but provided no data on women who completed ≥ 3 months of treatment 12-Month data on vaginal bleeding not available. Cumulative data available only for the first 3 months Timing: unclear Location: unclear (UK?) Multi-centre: 15 sites

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified but, given the nature of the outcomes assessed, evaluation likely to be "objective". Open design may affect evaluation of climacteric symptoms, but these were not taken into consideration (score)

Al-Azzawi 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants analysed was variable for different outcomes and throughout the study, depending on the number of completed diaries. Cumulative 12-month incidence of vaginal bleeding not available
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Financed by the drug manufacturer. Study authors have conflicts of interest

Archer 2007

Methods	Randomised controlled trial
Participants	3240 postmenopausal healthy women, with an intact uterus and with a screening biopsy classified as atrophic or inactive endometrium and a double-layer endometrial thickness ≤ 6 mm as assessed by transvaginal ultrasonography (TVUS). Mean time since menopause: 4.5 years. Mean age: 54.4 years
Interventions	• Tibolone 2.5 mg/d • Tibolone 1.25 mg/d • Continuous combined conjugated equine oestrogen 0.625 mg/d plus medroxyprogesterone acetate 2.5 mg/d Administered for 2 years
Outcomes	Unscheduled bleeding, breast cancer, endometrial cancer, endometrial hyperplasia, ovarian cancer, cardiovascular events, cerebrovascular events, thromboembolic events
Notes	Timing: not reported Location: USA, Europe, Chile Multi-centre:146 centres

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No details on random generation of the allocation sequence, but use of an interactive voice response system should keep risk of selection bias very low
Allocation concealment (selection bias)	Low risk	Interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified but, given the nature of outcomes assessed, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	High risk	No information on withdrawals/dropouts

Archer 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	No difference between study protocol and assessed outcomes
Conflict of interest	High risk	Financed by the drug manufacturer; some study authors are employees of the drug manufacturer

Baracat 2002

Methods	Randomised controlled trial; open label, multi-centre
Participants	85 generally healthy postmenopausal women, with an intact uterus, in menopause for ≥ 4 years, absence of endometrial hyperplasia, mean age 52 years
Interventions	• Tibolone 2.5 mg/d • CEE/MPA 0.625 mg/5.0 mg/d For 13 treatment cycles, each of 28 days
Outcomes	Hot flushes, unscheduled bleeding, vaginal dryness, painful intercourse, endometrial hyperplasia
Notes	Timing: not available Location: Brasil Multi-centre: number of sites not specified Hot flushes not measured with a validated score (frequency and intensity of hot flushes for each participant in each cycle were calculated as the sum of the mean # of hot flushes per day multiplied by the respective score (1 = mild, 2 = moderate, 3 = severe)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Describe: “the randomization was performed in balanced blocks of ten subjects using the table of aleatory numbers; each study center received 20 envelopes with the number of the subject and respective code (treatment group)” (p 62)
Allocation concealment (selection bias)	Low risk	Describe: “the randomization was performed in balanced blocks of ten subjects using the table of aleatory numbers; each study center received 20 envelopes with the number of the subject and respective code (treatment group)” (p 62)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Describe: open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Describe: participants unblinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Describe: similar rates of discontinuation, reasons given

Baracat 2002 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Describe: sponsored by manufacturer of CEE/MPA

Benedek-Jaszmann 1987

Methods	Parallel-group RCT
Participants	60 healthy postmenopausal women 44 to 61 years old, with hot flushes, who had undergone natural or surgical menopause and were experiencing hot flushes and associated symptoms
Interventions	• Tibolone 2.5 mg/d • Placebo 1 tablet/d Administered for 1 year
Outcomes	Hot flushes, insomnia Following scoring system used for clinical parameters: absent = 0, mild = 1, moderate = 2, strong = 3
Notes	Menopausal symptoms measured on a non-validated scale Timing: unclear Trial location: Netherlands Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study authors state that the trial is double-blind and that identical-looking placebo tablets have been used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes evaluated through a questionnaire with insufficient information to judge whether outcome measurement could have been influenced
Incomplete outcome data (attrition bias) All outcomes	High risk	17/60 participants dropped out. Unclear how many were randomised to each group
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	No information provided

Berning 2000

Methods	Randomised placebo-controlled trial
Participants	94 healthy non-smoking women, 1 to 3 years following spontaneous menopause (mean 22 months), with body mass index < 27 kg/m^2, free of diseases or medication known to influence calcium metabolism or to contraindicate the trial medication. Mean age: 53 years
Interventions	• Tibolone 2.5 mg/d • Tibolone 1.25 mg/d • Placebo Administered for 2 years
Outcomes	Vaginal bleeding
Notes	Timing: unclear Location: Netherlands Multi-centre: number of sites not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear what "random medication number" means
Allocation concealment (selection bias)	Unclear risk	Method not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Although study authors do not state whether trial is double-blind or single-blind, they used identical looking interventions and a placebo control
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of the outcome assessed, evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Bleeding: all randomised participants assessed
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Financed by the drug manufacturer. Study authors have conflicts of interest

Bouchard 2012

Methods	Randomised double-blind placebo-controlled trial
Participants	485 postmenopausal women 40 to 65 years of age, seeking treatment for hot flushes, who had completed their last natural menstrual period 12 months before screening (or had a follicle-stimulating hor-

Bouchard 2012 *(Continued)*

	mone (FSH) level 40 mIU/mL). Women had intact uterus, BMI ≤ 34 and minimum of 7 moderate and severe hot flushes per day, or 50 moderate and severe hot flushes per week, recorded for 7 consecutive days during screening. Mean age: 53.6 years
Interventions	Tibolone 2.5 mg/d, placebo, desvenlafaxine 100 mg/d (not considered in meta-analyses)
Outcomes	Hot flushes (frequency), hot flushes (severity, through the Greene climacteric scale), uterine bleeding, endometrial cancer
Notes	Multi-centre trial (35 sites in Europe, 2 sites in South Africa, 1 site in Mexico) Timing: unclear Follow-up: 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study authors declare that this is a double-blind trial but do not provide information on blinding methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants in each of tibolone and placebo groups not assessed for taking study medications for less than 5 days
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Study sponsored by Wyeth; 4 study authors are former Wyeth or current Pfizer employees

Cummings 2008

Methods	Randomised placebo-controlled trial
Participants	4538 women between 60 and 85 years of age (mean 68) who had bone mineral density T score ≤ −2.5 at the hip or lumbar spine or T score ≤ −2.0 with radiological evidence of vertebral fracture
Interventions	• Tibolone 1.25 mg/d • Placebo Administered for 34 months (median)

Cummings 2008 *(Continued)*

Outcomes	Vaginal bleeding, vaginal infection, endometrial cancer and endometrial hyperplasia, breast cancer, stroke, coronary heart disease, venous thromboembolism, mortality from any cause
Notes	Timing: July 2001 to Feb 2006, when trial was stopped because increased risk of stroke was identified Location: Europe, the Americas Multi-centre: 80 sites in 22 countries All participants received 2 to 4 tablets of calcium + vit D daily

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No details on random generation of the allocation sequence, but use of an interactive voice response system should keep risk of selection bias very low
Allocation concealment (selection bias)	Low risk	Centralised interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled and identical looking interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of outcomes assessed, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 of 4538 participants not evaluated for not receiving any dose of the interventions under study
Selective reporting (reporting bias)	Low risk	Study reported data on outcomes as indicated in the protocol. Additional data on vaginal bleeding, vaginal infection, endometrial cancer and endometrial hyperplasia, breast cancer, stroke, coronary heart disease, venous thromboembolism and mortality from any cause were available in the study publication and were included in this review
Conflict of interest	High risk	Financed by the drug manufacturer. Study authors have conflicts of interest

de Aloysio 1998

Methods	Randomised controlled trial
Participants	50 women, 13 to 30 months since menopause (mean 20 months); 1 to 4 submucous or intramural asymptomatic uterine leiomyomas (with longest diameter ranging from 3 to 8 cm); body mass index (BMI) < 28; without blood coagulation disease; without endometrial pathology. Mean age: 51 years
Interventions	• Tibolone 2.5 mg/d • Conjugated equine oestrogens (CEE), 0.625 mg/d plus medroxyprogesterone acetate (MPA), 5 mg/d Administered for twelve 28-day cycles
Outcomes	Irregular bleeding, endometrial hyperplasia

de Aloysio 1998 *(Continued)*

Notes	Bleeding measured as incidence of bleeding cycles/number of cycles Timing and trial location unclear Multi-centre: no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of the outcome assessed (endometrial hyperplasia), its evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants excluded from analysis for non-compliance (reasons not related to the study but not better specified)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	Not financed by drug manufacturer; other conflicts of interest not stated

Doren 1999

Methods	Randomised double-blind placebo-controlled study
Participants	98 healthy postmenopausal women, with intact uterus (mean age 56 years), mean BMI 25 kg/m^2, mean time since menopause 6 years
Interventions	• Tibolone 2.5 mg/d • 17beta-oestradiol + NETA (2 + 1 mg/d) For 12 months
Outcomes	Unscheduled bleeding
Notes	Timing: unclear Location: Netherlands; single centre Hot flashes and sleeplessness reported as adverse events, each by 1 participant

Risk of bias

Doren 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Describe: no details on randomisation
Allocation concealment (selection bias)	Unclear risk	Describe: no details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Describe: participants blinded but no details on personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Describe: participants recorded bleeding episodes in a diary
Incomplete outcome data (attrition bias) All outcomes	Low risk	Describe: reasons for withdrawal explained
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Describe: study sponsored by manufacturer of tibolone; employer among study authors

Egarter 1996

Methods	Randomised controlled trial
Participants	129 women with physiological menopause (for ≥ 12 months), mean age 53 years
Interventions	• Tibolone 2.5 mg/d • Oestradiol 2 mg + medrogestone 2 × 5 mg/d for 12 days/mo For 6 months
Outcomes	Unscheduled bleeding, severity of menopausal symptoms (hot flashes, insomnia, vaginal dryness)
Notes	Data on unscheduled bleeding reported in a graph but number of events unclear Timing: not reported Location: Austria Multi-centre: 5 sites To register severity of climacteric symptoms, a modified Kupperman Index was used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided

Egarter 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants lost to follow-up: 19.4% in tibolone group, 34.6% in combined HT group
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	Not reported

Elfituri 2005

Methods	Randomised controlled trial
Participants	100 healthy Lybian women with a uterus, with natural or surgical menopause, with menopausal symptoms. All had received no previous oestrogen and/or progestogen in preceding 12 months. 1 to 9 years since menopause (mean 2 years). Mean age 44.3 years
Interventions	• Tibolone 2.5 mg/d • 17beta-oestradiol 2 mg sequentially combined with dydrogesterone 10 mg For 1 year
Outcomes	Unscheduled bleeding, endometrial cancer, vasomotor symptoms quantified as none (0), mild (1), moderate (2) and severe (3)
Notes	Timing: not reported Location: Lybia Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Unclear risk	No information provided

Elfituri 2005 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of outcomes assessed, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for withdrawals/dropouts (2 women)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	Not reported

Gallagher 2001

Methods	Pooled data from 1 randomised placebo-controlled trials
Participants	770 healthy postmenopausal Caucasian or Asian women, mean duration of menopause 2.5 years, without osteoporosis (BMD of lumbar vertebrae within 2 standard deviations of age-matched mean). Mean age: 52.4 years
Interventions	• Tibolone 0.3 mg/d • Tibolone 0.625 mg/d • Tibolone 1.25 mg/d • Tibolone 2.5 mg/d • Placebo For 2 years. All groups also received 500 mg/d of calcium
Outcomes	Hot flashes, endometrial hyperplasia, endometrial cancer, thromboembolic events
Notes	Timing: not reported Location: USA Multi-centre: more than 20 centres per study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Defined by study authors as randomised but no details given on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical appearing tibolone and placebo tablets
Blinding of outcome assessment (detection bias)	Low risk	Not specified, but given the nature of outcomes assessed, their evaluation is likely to be "objective"

Gallagher 2001 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	85% of randomised participants analysed
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Financed by drug manufacturer, no declaration of conflicts of interest

Gupta 2013

Methods	Randomised controlled trial
Participants	100 asymptomatic patients (no menopausal symptoms) with surgical menopause 3 days earlier (total abdominal hysterectomy with bilateral salpingo-oophorectomy)
Interventions	Tibolone 2.5 mg/d; CEE 0.625 mg; DHEA 25 mg/d (all administered orally); no treatment. Latter 2 arms not considered in the meta-analysis
Outcomes	Vasomotor symptoms (occurrence of hot flushes and night sweats), insomnia (occurrence), vaginal dryness
Notes	Trial location: India (single centre) Follow-up: 12 months Timing: 2005

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	This RCT is presumably an open trial - includes a "no treatment" arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Study authors acknowledged losses to follow-up, but total number of lost participants is unclear
Selective reporting (reporting bias)	Unclear risk	Study protocol not available

Gupta 2013 *(Continued)*

Conflict of interest	Unclear risk	No information provided

Hammar 1998

Methods	Randomised double-blind controlled trial
Participants	437 women with menopausal symptoms, in good physical and mental health, ≥ 1 year since last menstrual bleeding, menopausal symptoms, intact uterus, body mass index (BMI) < 30 kg/m^2. Mean age 55 years
Interventions	• Tibolone 2.5 mg/d • 17β-Oestradiol 2 mg plus norethisterone acetate 1 mg (E2/NETA) Administered for 48 weeks
Outcomes	Vaginal bleeding (more than 1 sanitary napkin per day)/spotting (just 1 sanitary napkin per day), hot flushes (1 = none, 2 = light, 3 = moderate, 4 = severe, 5 = very severe), sweating, vaginal dryness, endometrial cancer, breast cancer, cerebrovascular events
Notes	Timing: June 1992 to Feb 1995 Location: Denmark, Norway, Sweden Multi-centre: 44 sites

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of outcomes eventually assessed, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	14/437 participants not assessed for lack of post-baseline assessment
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Financed by drug manufacturer. Study authors have conflicts of interest

Hammar 2007

Methods	Randomised controlled trial
Participants	572 postmenopausal healthy women with an intact uterus, with or without vasomotor symptoms. Mean age 55 years. Time since menopause 5 years. Mean number of hot flashes at baseline 5.8
Interventions	• Tibolone 2.5 mg/d • 17-beta-oestradiol 1 mg + norethisterone acetate 0.5 mg/d Administered for 48 weeks
Outcomes	Unscheduled vaginal bleeding or spotting, hot flashes, thromboembolic events, breast cancer
Notes	Hot flashes measured as median number per treatment period and reported as graph Timing: from November 2002 to March 2005 Location: 7 Northern European countries Multi-centre: 32 centres

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Restricted block-wise randomisation (1:1 ratio within each specific site). No details on random generation of the allocation sequence, but use of an interactive voice response system should keep risk of selection bias very low
Allocation concealment (selection bias)	Low risk	Automatic interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators, study site personnel and participants remained blinded until after database was locked
Incomplete outcome data (attrition bias) All outcomes	High risk	87% of randomised participants analysed but reasons for withdrawals/dropouts not given
Selective reporting (reporting bias)	Low risk	Outcomes assessed in the study and of specific interest for the review had been indicated in the protocol
Conflict of interest	High risk	Financed by the drug producer. One study author was an employee of the drug producer

Huber 2002

Methods	Randomised controlled trial
Participants	502 postmenopausal women, with last menstrual period ≥ 12 months previously, younger than 65 years of age (mean age 55). If the date of natural menopause could not be established because of hormonal

Huber 2002 *(Continued)*

	treatment, participants had to be ≥ 53 years of age and must have been receiving hormonal therapy for ≥ 2 years; if applicable, hormone therapy had to end with a progestogen phase. All participants were required to have an intact uterus and a body mass index (BMI) of 18 to 29 kg/m^2
Interventions	• Tibolone 2.5 mg/d • Conjugated equine oestrogens 0.625 mg continuously combined with medroxyprogesterone acetate 5 mg (CEE–MPA)/d Administered for 12 months
Outcomes	Vaginal bleeding/spotting (defined as requiring sanitary protection with more than 1 sanitary pad per day vs just 1 or none), dyspareunia, severity of VM symptoms, stroke, pulmonary embolism
Notes	Severity of VM symptoms quantified as none = 0, light = 1, moderate = 2, severe = 3, very severe = 4 Timing: Feb 1996 to June 1998 Location: Austria, Denmark, Spain, Sweden, Switzerland, UK Multi-centre: 37 sites

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of outcomes assessed and/or self-evaluation by blind patients, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	High risk	Several participants (about 80, depending on different outcomes) were excluded from final analyses for adverse events and insufficient compliance/efficacy
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Financed by the drug producer. One study author was the employee of a drug producer

Hudita 2003

Methods	Randomised placebo-controlled trial

Hudita 2003 *(Continued)*

Participants	162 healthy, non-obese, postmenopausal women (with evidence of ≥ 12 months of amenorrhoea with levels of FSH > 30 mIU/mL and of 17β-oestradiol < 50 pg/mL), between 40 and 65 years of age (mean age 55), with an intact uterus
Interventions	• Tibolone 2.5 mg/d • Tibolone 1.25 mg/d • Placebo Administered for 24 weeks
Outcomes	Vaginal bleeding and spotting, hot flushes, sweating, vaginal dryness
Notes	Used a non-validated scale to assess menopausal symptoms; they were reported also as frequency reduction from baseline Timing: unclear Location: Romania Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Defined as "double-blind" but no other specific information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about assessment of vaginal bleeding; unclear if trial is truly "double-blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	42/162 participants not analysed because of adverse events, loss to follow-up, lack of efficacy, etc
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	Not reported

Hänggi 1997

Methods	Randomised controlled trial
Participants	140 healthy early postmenopausal women between 45 and 55 years of age (mean age 52) with an amenorrhoeic interval >12 months or serum FSH > 30 IU/L. In addition, women > 55 years of age were included if they had a menopausal age < 5 years

Hänggi 1997 *(Continued)*

Interventions	• Tibolone 2.5 mg/d • Micronised 17β-oestradiol, orally 2 mg/d continuously plus sequential dydrogesterone orally 10 mg/d for 14 days every 4 weeks • 17β-oestradiol patch releasing 50 micrograms/d continuously plus sequential dydrogesterone orally 10 mg/d for 14 days every 4 weeks Administered for 24 months
Outcomes	Endometrial hyperplasia, endometrial cancer, breast cancer
Notes	No-treatment arm with 35 women not considered (as stated in our protocol; moreover they were not randomised) Timing: unclear Location: Switzerland Multi-centre: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial because women in 1 study arm were treated with an oestrogen patch
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of outcomes assessed, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	High risk	55/105 (after 12 months) and 46/105 (after 24 months) participants were evaluated through endometrial biopsy. Reasons why remaining women were not assessed were not specified
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Sponsored by the drug manufacturer. Study authors' conflicts of interest not reported

Jacobsen 2012

Methods	Randomised double-blind double-dummy placebo-controlled trial
Participants	318 community-living women > 70 years of age
Interventions	Tibolone 1.25 mg/d, placebo, raloxifene 60 mg/d (not considered in the meta-analysis) for 24 months

Jacobsen 2012 *(Continued)*

Outcomes	Cardiovascular events (TIA; cerebrovascular events; myocardial infarction)
Notes	Trial location: Netherlands (single centre) Timing: July 2003 to Jan 2008

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial; study authors declared that use of double dummy blinded participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial losses to follow-up (already > 20% at 3 months)
Selective reporting (reporting bias)	Low risk	Study reported data on outcomes as indicated in the protocol. Additional data on cardiovascular and cerebrovascular events available in the study publication and included in this review
Conflict of interest	Low risk	Sponsored by the Dutch Organization for Health Research and Development. Study authors declare that they have no conflicts of interest

Kenemans 2009

Methods	Randomised placebo-controlled non-inferiority trial
Participants	3148 postmenopausal women with vasomotor symptoms, in menopause for ≥ 12 months, who were surgically treated for breast cancer (T1-3, N0-2, M0) within the previous 5 years; excluded women with endometrial abnormalities at transvaginal ultrasonography. Mean time since menopause 6.2 years. Mean age 52.7 years. At study entry, 67% of participants were using tamoxifen
Interventions	• Tibolone 2.5 mg/d • Placebo Administered for 2.75 years
Outcomes	Unscheduled bleeding, vulvovaginal dryness, vaginal infection, urinary tract infection, insomnia, recurrence of breast cancer, endometrial cancer, venous thromboembolic events, cardiovascular and cerebrovascular events, mortality
Notes	Women who did not have adequate relief of their vasomotor symptoms were allowed to use concomitant non-hormonal medication, such as soy products, clonidine and antidepressants

Kenemans 2009 *(Continued)*

Timing: from June 2002 to July 2007 (study prematurely interrupted for safety reasons)

Location: USA, Europe, Asia, Australia

Multi-centre: 245 centres

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done by use of a centralised interactive voice response system, stratified by centre, with a block size of 4
Allocation concealment (selection bias)	Low risk	Centralised interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind fashion
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of outcomes assessed, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	98% of randomised participants were analysed; reasons given for withdrawals/dropouts
Selective reporting (reporting bias)	Low risk	Data on all outcomes indicated in the protocol were eventually available in the study publication
Conflict of interest	High risk	Financed by the drug producer. Some study authors with conflicts of interest

Kroiss 2005

Methods	Randomised placebo-controlled trial
Participants	70 postmenopausal women (hospital outpatients; < 75 years old; body mass index 18 to 30 kg/m^2) with newly diagnosed and histologically confirmed invasive or non-invasive early-stage breast cancer (< stage IIb), for which they were to receive surgical treatment (conservation therapy or modified radical mastectomy) followed by tamoxifen (20 mg/d). The women were required to have had their last natural menstrual period > 1 year before diagnosis of breast cancer (mean time since menopause 107 months) and to have a serum oestradiol concentration < 30 pg/mL. Mean age 58 years
Interventions	• Tibolone 2.5 mg • Placebo Administered for 12 months
Outcomes	Vaginal bleeding/spotting, endometrial hyperplasia, endometrial cancer, recurrence of breast cancer, hot flushes, sweating, vaginal dryness
Notes	Menopausal symptoms were evaluated as frequency reduction from baseline (for participants who could be evaluated) and as mean change in number and severity from baseline. No data available on vaginal dryness

Kroiss 2005 *(Continued)*

	Timing: July 1996 to July 2000 Location: unclear Multi-centre: described as multi-centre trial but unclear number and locations of sites

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automated random assignment using ADLS system
Allocation concealment (selection bias)	Low risk	Automated random assignment using ADLS system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled, double-blind (identical medication)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of outcomes assessed, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/35 participants in the placebo group did not receive study treatment
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Two study authors were employees of the drug manufacturer

Kubista 2007

Methods	Randomised placebo-controlled trial
Participants	102 postmenopausal women with initially stage I or II, oestrogen receptor–positive (ER+), previously untreated, core-biopsy proven, invasive breast cancer without evidence of metastatic spread; any endocrine or enzyme modulator therapy was stopped ≥ 3 months before randomisation. Mean age 65 years. Mean time since menopause 17 years
Interventions	• Tibolone 2.5 mg • Placebo Administered for 14 days
Outcomes	Ischaemic stroke, breast tumoural markers
Notes	Tumoural markers (surrogate outcome) measured as median/mean Timing: March 2003 to April 2005 Location: unclear Multi-centre: 14 sites in 5 countries (not provided)

Kubista 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled and defined as "double-blind" (1 pill administered per day)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of the outcome assessed (stroke), its evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Stroke evaluated referring to the "all subject treated group"
Selective reporting (reporting bias)	Low risk	Some of the outcomes indicated in the protocol were assessed and reported in the study publication. Those not reported were of no interest for the review. Additional data on ischaemic stroke were available in the study publication and were included in this review
Conflict of interest	High risk	Financed by the drug manufacturer. Two study authors were employees of the drug manufacturer

Kökçü 2000

Methods	Randomised controlled trial
Participants	50 women in spontaneous menopause ≥ 1 year (mean 25 months), still sexually active with a partner with no sexual problems, did not have any gynaecological surgery and had no absolute contraindication for HRT. Mean age 52 years
Interventions	• Tibolone 2.5 mg/d • Conjugated oestrogens (CE) 0.625 mg/d plus medroxyprogesterone acetate (MPA) 2.5 mg/d Administered for 1 year
Outcomes	Vaginal dryness/dyspareunia, vasomotor symptoms, irregular spotting/bleeding
Notes	Timing: unclear Location: Turkey Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement

Kökçü 2000 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study authors did not specify whether study drugs were identical looking. They stated that (1) the trial was single-blind; and (2) the women did not have any previous knowledge and did not receive any information on the possible effects on sexual function of the study drugs. It is then unclear whether they were intended as "blind" just because they were not provided any information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified (and not clear whether the women were blind)
Incomplete outcome data (attrition bias) All outcomes	High risk	6/50 women were not evaluated for not attending visits
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	No information about funding or study authors' conflicts of interest

Landgren 2002

Methods	Randomised placebo-controlled trial
Participants	775 women with a uterus between 40 and 60 years (mean 52 years), with absence of spontaneous vaginal bleeding for ≥ 10 months and presence of menopausal symptoms (≥ 1 moderate to severe hot flush per day). Body weight had to be between 80% and 130% of ideal body weight. Mean time since menopause 35 months
Interventions	• Tibolone 5 mg/d • Tibolone 2.5 mg/d • Tibolone 1.25 mg/d • Tibolone 0.625 mg/d • Placebo Administered for 12 weeks
Outcomes	Hot flashes, sweats, vaginal bleeding, thromboembolic events
Notes	Menopausal symptoms were evaluated as intensity and as frequency for participants with a decrease from baseline of 3 or more hot flushes and sweats per day; vaginal bleeding reported only on a graph Timing: March 1994 to July 1995 Location: Sweden, Netherlands, Finland, Norway Multi-centre: 28 sites (9 in Sweden; 8 in Netherlands; 7 in Finland; 4 in Norway)

Risk of bias

Bias	Authors' judgement	Support for judgement

Landgren 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not explained how the randomisation list was generated
Allocation concealment (selection bias)	Unclear risk	Not specified whether assignment of the corresponding number on the randomisation list was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled, double-blind (use of identical tablets)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of the outcome assessed (thromboembolism), its evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	30 of 770 participants who started treatment were not evaluable (reasons not specified)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	3 out of 4 study authors were employees of the drug producer

Langer 2006

Methods	Randomised placebo-controlled trial
Participants	866 healthy postmenopausal women (45 to 79 years of age with a body mass index > 19 and < 32 kg/m^2) who had been amenorrhoeic for ≥ 1 year (mean time since menopause 11 years), with or without intact uterus. If the date of final menstruation was unclear, the woman was to have used hormone therapy (HT) for > 2 years and had to be > 53 years old or fulfil the US Food and Drug Administration (FDA) criteria for menopause (serum oestradiol ≤ 20pg/mL [or 73 pmol/L] and follicle-stimulating hormone ≥ 40 mIU/mL). Mean age 59 years
Interventions	• Tibolone 2.5mg/d • 0.625 mg continuous combined conjugated equine oestrogen and 2.5 mg medroxyprogesterone acetate (CEE/MPA) • Placebo Administered for 3 years (39 cycles of 28 days) CF336 study numbers
Outcomes	Vaginal bleeding (requiring more than 1 sanitary napkin or tampon per day), vaginal spotting (requiring just 1 sanitary napkin or tampon per day), breast cancer, cardiovascular events, mortality from any cause, endometrial cancer • For bleeding outcomes: reported in 97% (689/707) of women with a uterus • For endometrial cancer: only 50% (351/707) of randomised women with a uterus had baseline biopsy, and only 33% had endpoint biopsy • For other outcomes: 70% completed 3 years of follow-up with treatment, but total proportion of women followed up for other adverse events unclear
Notes	Data on endometrial cancer considered in separate publication

Langer 2006 *(Continued)*

	Timing: unclear Location: United States and Europe Multi-centre: 11 sites (6 in the United States, 5 in Europe) All participants also received oral calcium (500 mg/d) 707/857 women taking ≥ 1 dose of study medication had intact uterus

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No information provided in the published article. In a private communication, the main study author assured that study treatments were allocated through random codes generated by a central co-ordinating group
Allocation concealment (selection bias)	Unclear risk	In another published article describing the study methods (Bots ML; Cont Clin Trials 2003;24:752-75), it is stated: "code numbers were assigned to subjects in the order of their randomisation in the trial, that is, the first subject received the first number (the lowest), the second subject received the next number in sequence, and so on". This specification made the allocation concealment issue unclear, but in a private communication, the main study author assured that such process was concealed to investigators but provided no further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled with double-dummy technique
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of outcomes assessed, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of women not completing the trial and with no assessment of outcomes of interest is unclear
Selective reporting (reporting bias)	Low risk	Study reported data on outcomes as indicated in the protocol. Additional data on breast and endometrial cancer, cardiovascular events and mortality from any cause available in the study publication and included in this review
Conflict of interest	High risk	Financed by the drug manufacturer. One study author was an employee of the drug manufacturer

Meeuwsen 2002

Methods	Randomised placebo-controlled trial
Participants	85 healthy postmenopausal women, who were ≥ 1 year and at maximum 15 years after natural menopause. Mean age 54.2 years
Interventions	• Tibolone 2.5mg/d • Placebo

Meeuwsen 2002 *(Continued)*

	Administered for 1 year
Outcomes	Vasomotor symptoms, unscheduled bleeding and sleep
Notes	Timing: not reported Location: Netherlands Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not explained how the randomisation list was generated
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Tablets of identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of the outcome assessed, its evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for withdrawals (4 women)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Drug manufacturer was involved in the trial (random sequence generation was performed by the drug manufacturer)

Mendoza 2000

Methods	Parallel-group RCT
Participants	76 hysterectomised women < 50 years old. Excluded if had had any previous malignant gynaecological process, oestrogen-producing tumour, endocrinological or metabolic problems, cardiovascular disease, uncontrolled hypertension, active hepatic disease, serious skin illness, intestinal sickness or chronic obstructive respiratory disease. Patients with psychiatric problems or receiving anxiolytic or antidepressive drugs were also excluded Unclear whether all women were symptomatic
Interventions	• Tibolone 2.5 mg per day (n = 38) • Transdermic 17β-oestradiol 50 micrograms per day (n = 38) Administered for 1 year
Outcomes	Climacteric symptoms through a modified version of the Kupperman Index

Mendoza 2000 *(Continued)*

	Vasomotor symptoms measured as frequently (2), occasionally (1) or never (0) Reports binary measure of "reduction in vasomotor symptoms" Dyspareunia reported as part of a composite outcome of sexual symptoms (“behavioural changes”), which included libido
Notes	Timing: Feb 1, 1995, to January 31, 1996 Trial location: Nicaragua Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers with simple blind randomisation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of participants and personnel not stated and therefore unlikely
Incomplete outcome data (attrition bias) All outcomes	High risk	14/76 participants interrupted or changed therapy, or were lost to follow-up; 6/76 did not start therapy
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	No information provided

Mendoza 2002

Methods	Randomised controlled trial
Participants	165 women with intact uterus younger than 60 years (mean 50 years), who had been amenorrhoeic for 1 to 5 years (mean 22.3 months). Women who had had a hysterectomy or had received hormone treatment in the 3 months before the trial were excluded, as were those with a history of a malignant gynaecological process, oestrogen-producing tumour or obesity (body mass index > 32)
Interventions	• Tibolone 2.5 mg/d • Cyclical combined regimen of transdermal oestrogen and progestogen: transdermal patch of 17β-oestradiol 50 µg/d during 14 days and transdermal patch of 17β-oestradiol 50 µg/d plus 0.25 mg/d of norethisterone acetate during the following 14 days • Intermittent progesterone regimen: transdermal 17β-oestradiol 50 µg/d and oral micronised natural progesterone 200 mg twice a week

Mendoza 2002 *(Continued)*

	For 1 year
Outcomes	Irregular bleeding, vasomotor symptoms frequency 0 = never, 1 = occasionally, 2 = frequently
Notes	Data on vasomotor symptoms expressed as number of women with reduced symptoms Timing: September 1996 to April 1998 Location: Spain Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done following a table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Defined as "simple-blind", but no details given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of outcomes assessed, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	High risk	32/165 women did not start HRT, no reasons given
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	Not reported

Morais-Socorro 2012

Methods	Randomised double-blind placebo-controlled trial
Participants	65 women between 40 and 55 years of age, with menstrual irregularity during the previous 6 months but fewer than 12 months of amenorrhoea, presence of a uterus without anomalies in an initial vaginal ultrasonography evaluation and an endometrial thickness measurement ≤ 10 mm; Kupperman Menopausal Index (KMI) score ≥ 14 points. Mean age 48.5 years
Interventions	Tibolone 2.5 mg/d, placebo for 12 weeks
Outcomes	Greene scale (vasomotor symptoms), Kupperman Index, vaginal bleeding-spotting (based on number of days of uninterrupted bleeding and number of pads or tampons/d required)
Notes	Trial location: Brazil (unclear if multi-centre) Timing: unclear

Morais-Socorro 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study authors declare that this is a double-blind trial but do not provide information on blinding methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	10% and 14% dropout in tibolone and placebo arms, respectively
Selective reporting (reporting bias)	Low risk	Some of the outcomes indicated in the protocol (Kupperman Index, Greene scale) were assessed and reported in the study publication. Those not reported were of no interest for this review. Additional information on vaginal bleeding-spotting was available in the study publication and was considered for this review
Conflict of interest	Low risk	Supported by grant from the CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico - "National Counsel of Technological and Scientific Development")

Nappi 2006a

Methods	Randomised controlled trial
Participants	40 women with menopausal symptoms and primary headache (migraine without aura [MwA] and ETTH) of premenopausal onset (history ≥ 10 years), spontaneous menopausal status ≥ 12 months (mean 18 months) with follicle-stimulating hormone levels > 30 IU/L, age between 51 and 55 years (mean age 53 years), body mass index > 19 and < 30 kg/m^2
Interventions	• Tibolone 2.5 mg/d • 1 mg 17β-oestradiol + 0.5 mg norethisterone acetate Administered for 6 months
Outcomes	Vaginal bleeding/spotting, vasomotor symptoms, vaginal dryness
Notes	Women had been using symptomatic medications and headache drug prophylaxis ≥ 3 months before entering the study Results on vasomotor symptoms and vaginal dryness (evaluated using Greene scale) available only as a graph Timing: unclear

Nappi 2006a *(Continued)*

	Location: Italy Multi-centre: no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of numbers
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is stated that outcome measures were evaluated by a blind study author, although it is not clear whether this referred to the database level or to the clinical assessment of outcomes, which was not likely to be conducted in a blind fashion
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study authors state that all women completed the study following appropriate evaluation
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Low risk	Supported by a grant from the Italian Ministry of Health. No conflicts of interest reported

Nathorst-Böös 1997

Methods	Randomised controlled trial
Participants	437 healthy women, ≥ 1 year postmenopausal or had been using hormone replacement therapy (HRT) > 2 years. Women were older than 53 years at entry and had been without HRT for longer than 1 month. All had had hot flushes and sweating, had a body mass index < 30 and had an intact uterus
Interventions	• Tibolone 2.5 mg/d • 17β-oestradiol 2 mg/d and norethisterone acetate 1 mg/d Administered for 12 months
Outcomes	Vaginal dryness and pain during sexual intercourse as score at baseline and as differences between pretreatment and post-treatment
Notes	Timing: unclear Location : Denmark, Norway, Sweden Unclear number of sites, but locations in 3 Scandinavian countries

Nathorst-Böös 1997 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list and codes
Allocation concealment (selection bias)	Low risk	Sealed envelope containing the code
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, double-dummy not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Subjective outcomes (McCoy's Sex Scale Questionnaire) that may be subject to bias in the absence of double-blind (double-dummy not specified).
Incomplete outcome data (attrition bias) All outcomes	High risk	264/437 (60.4%) completed all assessments (baseline, at 24 and 48 weeks)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	Unclear risk: not specified

Nijland 2009

Methods	Randomised controlled trial
Participants	403 healthy women who had undergone natural menopause, with an intact uterus and with female sexual dysfunction associated with sexuality-related personal distress. Mean age 55.8 years
Interventions	• Tibolone 2.5 mg/d • Estradiol (50 microgr) + norethisterone acetate (140 microgr) in the form of a transdermal patch Administered for 24 weeks
Outcomes	Unscheduled bleeding, cerebrovascular events, mortality from any cause
Notes	Timing: June 2004 to November 2005 Location: Europa, USA, Australia Multi-centre: 29 centres

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised automatic interactive voice response system was used

Nijland 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	Computerised automatic interactive voice response system was used, and treatment assignment was stored electronically
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy fashion
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6% to 10% were not analysed for unspecified protocol violations
Selective reporting (reporting bias)	Low risk	Some outcomes indicated in the protocol (vaginal bleeding and spotting rate) were assessed and reported in the study publication. Those not reported were of no interest for this review. Additional information on cerebrovascular events and mortality from any cause was available in the study publication and was considered for this review
Conflict of interest	High risk	Study sponsored by the drug manufacturer, and some study authors were employees of the drug firm

Okon 2005

Methods	Parallel RCT
Participants	30 postmenopausal women with an intact uterus, requesting HT, who had had ≥ 12 months of amenorrhoea with plasma follicle-stimulating hormone (FSH) > 20 IU/L; < 65 years old
Interventions	Tibolone 2.5 mg daily 2 mg micronised oestradiol valerate and norethisterone acetate 0.7 mg daily for 12 months
Outcomes	Irregular bleeding - reported as days of bleeding over 1 year
Notes	Timing: unclear Single centre UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of sequence allocation concealment not described

Okon 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 19/30 women included in analysis (5 in tibolone group and 6 in HT group withdrew; 1 was excluded from analysis)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Funded by pharmaceutical company

Osmanağaoğlu 2006

Methods	Randomised controlled trial
Participants	165 naturally postmenopausal women; absence of menstruation > 1 year; FSH ≥ 30 IU/L; not undergone any gynaecological operation; no absolute contraindication for HT. Mean age 50 years
Interventions	• Tibolone 2.5 mg/d • Oestradiol valerate 2 mg plus dienogest 2 mg/d Administered for 6 months
Outcomes	Lubrication and pain during sexual intercourse as score at baseline and at post treatment
Notes	Only 107 women were considered in the analyses (excluding women assigned to "no treatment") Even if not specified in the protocol, lubrication has been evaluated as a measure of vaginal dryness Timing: unclear Location: Turkey? Multi-centre: not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study authors declare that the study is single-blind (participant), but in some cases, women were given doctor samples from drug companies

Osmanağaoğlu 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were evaluated through a self-administered questionnaire, but it is unclear whether participating women were blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/165 participants without follow-up data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Low risk	Study authors declare that they did not receive external funding and that they do not have conflicts of interest

Polisseni 2013

Methods	Randomised double-blind controlled trial
Participants	174 postmenopausal women between 45 and 60 years of age with moderate or pronounced vasomotor symptoms and a Blatt–Kupperman menopausal index (BKMI) ≥ 20 points, with no treatment for menopausal symptoms in the past 6 months
Interventions	Tibolone 2.5 mg/d; 1 mg oestradiol + 0.5 mg norethindrone acetate; 50 mg calcium carbonate and 200 UI vitamin D3 (not considered in the meta-analysis)
Outcomes	Vasomotor symptoms, insomnia (measured through the Women's Health Questionnaire)
Notes	Trial location: Brazil (single centre) Follow-up: 12 weeks Timing: June 2009 to June 2011

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial; study authors declared that all capsules appeared identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	47 participants lost to follow-up (with differential attrition among groups); only treated women appear to have been assessed

Polisseni 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Low risk	Study authors declare that they have no conflicts of interest

Ross 1999

Methods	Parallel-group RCT
Participants	36 perimenopausal women (amenorrhoea ≥ 3 months), > 45 years old, with no past psychotic history nor current use of antidepressants or psychotherapeutic agents. All participants "suffering from menopausal symptoms and requesting HRT"
Interventions	• Tibolone 2.5 mg/d • 0.625 mg conjugated oestrogens daily for 28 days, plus 150 µg norgestrel daily on days 17 to 28 Administered for 12 weeks
Outcomes	Women's Health Questionnaire (subscales on vasomotor symptoms, sleep) Greene's Climacteric Scale (subscale on vasomotor symptoms)
Notes	Timing: unclear Trial location: Scotland Multi-centre: no; single site

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by pre-generated, sequential randomisation lists
Allocation concealment (selection bias)	Low risk	Used a block size of 10, and each packet was given a code number. Copies of the code were kept in opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study authors state that some of the women knew which drug they were on. Therefore, it is likely that clinicians/researchers had been unblinded too
Blinding of outcome assessment (detection bias) All outcomes	High risk	Incomplete blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	22% of participants withdrew (2 in tibolone group and 6 in HT group)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Study funded by Organon

Roux 2002

Methods	Randomised controlled trial
Participants	225 healthy women with physiological menopause (time since menopause 3.9 years, mean age 53.3 years)
Interventions	• Tibolone 1.25 mg/d • Tibolone 2.5 mg/d • Estradiol 2 mg/d + norethindrone acetate 1 mg/d Administered for 24 months
Outcomes	Menopausal vaginal bleeding
Notes	Each participant also received 1 tablet of 500 mg calcium supplement daily Timing: not specified Trial location: France Multi-centre: 66 participating centres

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation (block size of 6)
Allocation concealment (selection bias)	Unclear risk	Not clear if centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-reported outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Bleeding was evaluated for all randomised women
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Study sponsored by drug manufacturer

Siseles 1995

Methods	Randomised open-label controlled trial

Siseles 1995 *(Continued)*

Participants	30 postmenopausal women ≥ 1 year postmenopausal and reporting hot flushes and other menopausal symptoms (but otherwise healthy). Age range 48 to 62 years
Interventions	• Tibolone 2.5 mg/d • Conjugated oestrogens 0.625 mg/d continuously, medroxyprogesterone 5 mg/d sequentially for 12 days of each 28-day cycle Administered for six 28-day cycles
Outcomes	Hot flushes, sweating, sleeplessness, irregular bleeding, endometrial hyperplasia
Notes	Menopausal symptoms measured through Kupperman Index but results available only as a graph Bleeding not evaluable because insufficient information provided Timing: June to Dec 1990 Trial location: Argentina Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of the outcome of interest (endometrial hyperplasia), its evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	High risk	6/30 patients excluded from final analyses
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Financed by drug manufacturer. Study authors' conflicts of interest not stated

Swanson 2006

Methods	Randomised placebo-controlled trial
Participants	396 healthy postmenopausal women (≥ 40 years of age; mean age 52 years) who had been amenorrhoeic ≥ 6 months (women with a uterus only) and who were experiencing a minimum of 7 moderate to severe hot flashes per day (or 60 per week). In addition, women had to be within 70% to 140% of their ide-

Swanson 2006 *(Continued)*

	al body weight, smoke fewer than 15 cigarettes daily and have tested negative for pregnancy. Mean time since menopause 84 months
Interventions	• Tibolone 2.5 mg/d • Tibolone 1.25 mg/d • Placebo Administered for 12 weeks
Outcomes	Hot flashes, vaginal dryness, dyspareunia, endometrial hyperplasia, endometrial cancer, breast cancer
Notes	Menopausal symptoms evaluated as mean change from baseline using a non-validated scale: 1 = mild sensation of heat without perspiration; 2 = moderate sensation of heat with perspiration, able to continue activity; 3 = severe sensation of heat with sweating, causing the woman to stop activity Timing: unclear Location: United States Multi-centre: 31 sites

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled. Defined as "double-blind"; 3 daily interventions were compared
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Evaluation of endometrial hyperplasia and cancers should not suffer from detection bias. Methods for (and blinding when) diagnosing heart failure not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/396 excluded for not receiving any study treatment
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Financed by the drug manufacturer. Two study authors were employees of drug manufacturer

Uygur 2005

Methods	Parallel-group RCT

Uygur 2005 *(Continued)*

Participants	80 postmenopausal women (56 years old), married, with spontaneous menopausal status ≥ 1 year with follicle-stimulating hormone level > 30 mIU/L and no contraindication to use of HRT, without chronic disease. Participants were not selected on the basis of sexual function or dysfunction
Interventions	• Tibolone 2.5 mg/d (n = 40) • 0.625 mg continuous conjugated equine oestrogen and 5 mg medroxyprogesterone acetate (CEE/MPA)/d Administered for 6 months (n = 40)
Outcomes	Vaginal dryness, pain during sexual intercourse as score at baseline and at post treatment
Notes	Sexual function measured on a non-validated questionnaire Timing: unclear Trial location: Turkey Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants and providers. States "not double blind"
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding, with outcomes evaluated through a questionnaire
Incomplete outcome data (attrition bias) All outcomes	High risk	8/80 dropped out (2 from tibolone group because of bleeding, 6 from CEE/MPA group - 1 for mastalgia, 1 for menorrhagia, 2 for weight gain, 2 for loss to follow-up)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	No information provided

Vieira 2009

Methods	Randomised placebo-controlled trial
Participants	30 postmenopausal women with systemic lupus erythematosus, between 30 and 65 years of age (mean age 51.7 years), who had not menstruated for over a year (mean 7.1 years); had follicle-stimulating hormone (FSH) levels > 20 mIU/mL in 2 (chemiluminescence) tests performed 30 days apart; had not used any HRT for ≥ 6 months; and had presented with symptoms of hypoestrogenism (night sweats, hot flashes or symptoms of urogenital atrophy) at inclusion. Other than oral corticosteroids, use of oth-

Vieira 2009 *(Continued)*

	er medications for treatment of SLE was allowed if doses remained stable for ≥ 3 months before study outset
Interventions	• Tibolone 2.5 mg/d • Placebo For 1 year
Outcomes	Menopausal symptoms, breast cancer, endometrial cancer, venous thromboembolic events, mortality from any cause
Notes	Data on menopausal symptoms were assessed through Kupperman Index; it is not possible to derive results on those specific symptoms provided in the protocol Timing: enrolment between March 2002 and December 2004 Location: Brazil Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	GraphPad StatMate® (Graphpad Software, San Diego, CA) software programme was used to randomise participants into 2 groups
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given the nature of outcomes assessed, their evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/30 excluded owing to SLE reactivation
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	Not reported

Volpe 1986

Methods	Parallel-group RCT
Participants	113 postmenopausal women with menopausal symptoms: 81 were naturally menopausal (mean age 51 years); 32 were post hysterectomy and oophorectomy (mean age 41 years) Last menstrual period 1 to 5 years previously

Volpe 1986 *(Continued)*

	Excluded women who had received hormone preparations during preceding 8 weeks or in whom oestrogen therapy was contraindicated Dropouts: 11/15 in placebo group dropped out by 6 months

Interventions	Tibolone 2.5 mg daily (n = 27)
	
	vs
	
	• Placebo (n = 15)
	• Oestrogen: oestriol (E) 2 to 4 mg/d (n = 21)
	• HT (total n = 50)
	  • Conjugated oestrogens (CEE) 0.625 mg/d for 21 days + norethisterone (NET) 5 mg/d on days 12 to 21 (n = 15)
	  • CEE + cyproterone acetate (CPA) 12.5 mg/d from day 1 to day 10 (n = 15)
	  • Oestradiol valerate (EV) 2 mg/d for 21 days + sequential NET (n = 10)
	  • EV 2 mg/d for 21 days + CPA 12.5 mg/d from day 1 to day 10 (n = 10)
	
	All for 6 cycles

Outcomes	Hot flushes, scored as follows: 0 = absent, 3 = mild, 6 = moderate, 9 = severe No comparative data on AEs were reported. Endometrial hyperplasia was reported, but no histology was done in the placebo group
Notes	Menopausal symptoms measured on a non-validated questionnaire Timing: unclear Trial location: Italy Multi-centre: no; single site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States “randomly allocated". Baseline characteristics of groups not mentioned
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information about blinding provided. Blindness unlikely at least for providers/researchers (it is a placebo-controlled trial)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Histology assessment blinded, but symptoms evaluated through a questionnaire; unlikely that providers/researchers were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition in placebo group (11/15), numbers assessed for hot flushes in active groups not reported
Selective reporting (reporting bias)	Unclear risk	Study protocol not available

Volpe 1986 *(Continued)*

Conflict of interest	Unclear risk	No information provided about conflicts of interest. Non-validated measure used for VM symptoms

Wender 2004

Methods	Randomised double-blind placebo-controlled trial
Participants	40 healthy postmenopausal women, mean age 55 years, mean time since natural menopause 5 to 7.7 years, mean BMI 26 kg/m^2
Interventions	• Tibolone 2.5 mg/d • Placebo For 1 year
Outcomes	Endometrial thickness, endometrial cancer, uterine bleeding
Notes	Timing: not specified Location: Brasil Single centre

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	page 424: “the tibolone and the placebo tablets and bottles looked identical; the bottles were identified with numbers from 1 to 40. The correspondence between the numbers and the group to which the participant belonged was not disclosed until the end of the study”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	page 424: “all ultrasonographic exams were performed at the Hospital’s Gynecology and Obstetrics Service by the same operator, who was blinded to information concerning participant groups. […] “ The material was analysed twice by 2 pathologists who were also blinded to participant information”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for withdrawal given: 3 participants/group withdrew from the study • Placebo: 1 owing to dizziness, 2 owing to intense climacteric symptoms that did not improve • Tibolone: 1 moved to another city, 2 because of missing appointments
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Unclear risk	No details given

Winkler 2000

Methods	Randomised controlled trial
Participants	62 healthy postmenopausal women, between 45 and 70 years of age (mean age 54 years), spontaneous menopause with last menstrual period ≥ 36 months before enrolment or artificial menopause (hysterectomy and/or oophorectomy) with FSH level > 30 IU/L (mean time since menopause 8.5 years)
Interventions	• Tibolone 2.5 mg/d • Oestradiol 2 mg/d + oestriol 1 mg/d + norethindrone acetate 1 mg/d Administered for 24 weeks
Outcomes	Vaginal bleeding/spotting (defined as requiring > 1/just 1 tampon/d), hot flushes, sweating
Notes	Menopausal symptoms measured as frequency but number of participants evaluated is unclear Timing: Feb 1995 to 1996 Location: Germany Multi-centre: no; participants were selected from private practices of 2 specialists in Germany

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Concern because participants were selected from private practices of 2 specialists
Allocation concealment (selection bias)	Unclear risk	No information provided. Concern because participants were selected from private practices of 2 specialists
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but given self-assessment of the outcome of interest (vaginal bleeding/spotting), its evaluation is likely to be "objective"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women with a uterus were evaluated for vaginal bleeding/spotting
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Financed by the drug producer. One study author was an employee of the drug producer

Wu 2001

Methods	Randomised controlled trial

Wu 2001 *(Continued)*

Participants	48 healthy postmenopausal women (52 years old), postmenopausal for 12 to 36 months (confirmation by FSH > 40 mIU/mL and oestradiol < 20 pg/mL), with ≥ 1 climacteric symptom according to the Greene Climateric Scale
Interventions	• Tibolone 2.5 mg/d • 0.625 mg conjugated equine oestrogen and 5 mg medroxyprogesterone acetate (CEE/MPA)/d Administered for 3 months
Outcomes	Menopausal symptoms (assessed using Greene's Climateric Scale), attitudes of sexuality (assessed using McCoy Sex Scale), unscheduled bleeding
Notes	Timing: not clear Not clear if multi-centre or not

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomly selected pairs of 2 women were allocated to treatment groups
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	12/48 dropped out, but reasons given
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	High risk	Study sponsored by the manufacturer. Study authors declare that they have no conflicts of interest

Ziaei 2010

Methods	Randomised controlled trial
Participants	150 healthy postmenopausal women (mean age at menopause: 49 years), 45 to 60 years of age (mean age 52 years), whose last menstrual period was more than a year ago with plasma 17β-oestradiol < 35 pg/mL
Interventions	• Tibolone 2.5 mg plus a Cal + vit D tablet (500 mg/200 IU) • 0.625 mg conjugated equine oestrogen and 2.5 mg medroxyprogesterone acetate (CEE/MPA) plus 1 Cal+D tablet (500 mg/200 IU)

Ziaei 2010 *(Continued)*

	Administered for 6 months
Outcomes	Vaginal bleeding (requiring > 1 sanitary napkin per day), vaginal spotting (requiring just 1 sanitary napkin per day), vaginal dryness, vasomotor symptoms, lubrication and pain during sexual intercourse, as scored at baseline and at post treatment
Notes	An arm with 50 women who received only 1 Cal + D tablet (500 mg + 200 IU) was not considered Timing: unclear Location: Iran Multi-centre: only 2 sites (in Tehran)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not specified whether blind/double-blind trial. All women received Ca + vit D but 1 control group did not receive active treatments; no dummy placebo mentioned
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only blood samples stated to have been assessed in blinded fashion (corresponding outcome is not of interest for this review)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/150 lost to follow-up for bleeding outcomes; 20/150 (13%) for vasomotor symptoms
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Conflict of interest	Low risk	Publicly financed; study authors state no competing interests

ADLS: Almedica Drug Labeling System
AE: adverse event.
BKMI: Blatt-Kupperman menopausal index.
BMD: bone mineral density.
BMI: body mass index.
CE: conjugated oestrogen.
CEE: conjugated equine oestrogen.
ETTH: Episodic tension-type headache
EV: oestradiol valerate.
FDA: Food and Drug Administration.
FSH: follicle-stimulating hormone.
HRT: hormone replacement therapy.
HT: hormone therapy.
MPA: medroxyprogesterone acetate.
RCT: randomized controlled trial.
SLE: systemic lupus erythematosus.
TIA: transient ischaemic attack.

TVUS: transvaginal ultrasonography.
VM: vasomotor symptoms.

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

Study	Reason for exclusion
Argyroudis 1997	Not clear whether randomised or not; impossible to contact study author to ask for details on methods
Baksu 2005	Inclusion not apparently limited to women who were experiencing vasomotor symptoms at baseline. No other outcomes of interest measured
Beardsworth 1999	Study vs no treatment
Berlanga 2003	Inclusion not apparently limited to women who were experiencing vasomotor symptoms at baseline. No other outcomes of interest measured
Bhattacharya 2008	Results on somatovegetative and urogenital symptoms assessed through score but specific outcomes of interest to this review not measured
Bhattacharya 2010	Results on somatovegetative and urogenital symptoms assessed through score but specific outcomes of interest to this review not measured
Bukulmez 2001	Measured no outcomes of interest
Cagnacci 2004	Measured no outcomes of interest
Cayan 2008	No available data explicitly comparing tibolone vs combined hormone therapy
De Censi 2013	Participants not randomised to tibolone
Fedele 2000	No outcomes of interest measured
Gambacciani 2004	Study vs no treatment
Genazzani 2011	Wrote to study authors to ask for data but received no response
Inan 2005	No outcomes of interest measured
Lundstrom 2011	Ineligible outcomes (breast density)
Nappi 2006b	Sexual dysfunction as vaginal health index (not provided for in the protocol)
Onalan 2005	No outcomes of interest measured
Palacios 1995	Compared tibolone vs calcium tablets
Silva 2015	Conference proceeding with no data on outcomes of interest
Simsek 2002	Measured no outcomes of interest
Stefanos 2010	Included participants with regular menstruation
Stevenson 2011	Not an RCT; review with unretrievable full text
Tasic 2011	Measured no outcomes of interest

Study	Reason for exclusion
Yuk 2012	Ineligible outcomes (changes in body composition and body size), unretrievable full text

DATA AND ANALYSES

Comparison 1. Tibolone versus placebo

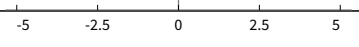
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vasomotor symptoms	7	1657	Std. Mean Difference (Fixed, 95% CI)	-0.99 [-1.10, -0.89]
1.1 Tibolone 0.625 mg/d	1	158	Std. Mean Difference (Fixed, 95% CI)	-0.05 [-0.46, 0.36]
1.2 Tibolone 1.25 mg/day	3	414	Std. Mean Difference (Fixed, 95% CI)	-0.83 [-1.06, -0.60]
1.3 Tibolone 2.5 mg/day	7	920	Std. Mean Difference (Fixed, 95% CI)	-1.16 [-1.30, -1.03]
1.4 Tibolone 5 mg/day	1	165	Std. Mean Difference (Fixed, 95% CI)	-0.84 [-1.25, -0.43]
2 Unscheduled bleeding	9	7814	Odds Ratio (M-H, Random, 95% CI)	2.79 [2.10, 3.70]
2.1 Tibolone, 2.5 mg/day	8	4186	Odds Ratio (M-H, Random, 95% CI)	2.58 [1.89, 3.52]
2.2 Tibolone, 1.25 mg/day	3	3628	Odds Ratio (M-H, Random, 95% CI)	3.63 [2.37, 5.55]
3 Endometrial cancer	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Tibolone, all doses	9	8504	Odds Ratio (M-H, Random, 95% CI)	2.04 [0.79, 5.24]
4 Breast cancer; women without previous breast cancer	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Tibolone, all doses	4	5500	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.21, 1.25]
5 Breast cancer; women with previous breast cancer	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Tibolone, 2.5 mg/day	2	3165	Odds Ratio (M-H, Random, 95% CI)	1.50 [1.21, 1.85]
6 Venous thromboembolic events (clinical evaluation)	5	9176	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.37, 1.97]
6.1 Tibolone (all doses)	5	9176	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.37, 1.97]
7 Cardiovascular events	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Tibolone, all doses	4	8401	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.84, 2.27]
8 Cerebrovascular events; women's mean age over 60 years	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Tibolone (all doses)	4	7930	Odds Ratio (M-H, Random, 95% CI)	1.74 [0.99, 3.04]
9 Mortality from any cause	4	8242	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.79, 1.41]
9.1 Tibolone, 2.5 mg/day	3	3736	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.32, 2.73]
9.2 Tibolone, 1.25 mg/day	1	4506	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.54, 1.59]
10 Insomnia	3	3432	Std. Mean Difference (Fixed, 95% CI)	-0.19 [-0.38, -0.00]
10.1 Tibolone, 2.5 mg/day	3	3432	Std. Mean Difference (Fixed, 95% CI)	-0.19 [-0.38, -0.00]
11 Vaginal dryness and painful sexual intercourse	3	3348	Std. Mean Difference (Fixed, 95% CI)	-0.66 [-0.90, -0.43]
11.1 Tibolone, 1.25mg/day	1	62	Std. Mean Difference (Fixed, 95% CI)	-1.78 [-2.43, -1.13]
11.2 Tibolone, 2.5 mg/day	3	3286	Std. Mean Difference (Fixed, 95% CI)	-0.49 [-0.75, -0.24]
12 Vaginal infections	2	7639	Odds Ratio (M-H, Random, 95% CI)	2.50 [1.24, 5.06]
12.1 Tibolone, 2.5 mg/day	1	3133	Odds Ratio (M-H, Random, 95% CI)	1.73 [1.17, 2.55]
12.2 Tibolone, 1.25 mg/day	1	4506	Odds Ratio (M-H, Random, 95% CI)	3.54 [2.61, 4.81]
13 Urinary tract infections	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Tibolone, 2.5 mg/day	1	3133	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.46, 1.06]
14 Endometrial hyperplasia	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Tibolone, all doses	4	4518	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.23, 6.25]
15 Sensitivity Analysis - Vasomotor symptoms without trials with high risk of attrition bias	4		Std. Mean Difference (Fixed, 95% CI)	-0.61 [-0.73, -0.49]
15.1 Tibolone 0.625 mg/day	1		Std. Mean Difference (Fixed, 95% CI)	-0.05 [-0.46, 0.36]
15.2 Tibolone 1.25 mg/day	2		Std. Mean Difference (Fixed, 95% CI)	-0.62 [-0.86, -0.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.3 Tibolone 2.5 mg/day	4		Std. Mean Difference (Fixed, 95% CI)	-0.65 [-0.80, -0.50]
15.4 Tibolone 5 mg/day	1		Std. Mean Difference (Fixed, 95% CI)	-0.84 [-1.25, -0.43]

Analysis 1.1. Comparison 1 Tibolone versus placebo, Outcome 1 Vasomotor symptoms.

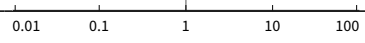
Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Fixed, 95% CI	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.1.1 Tibolone 0.625 mg/d						
Landgren 2002	129	29	-0 (0.21)		6.83%	-0.05[-0.46,0.36]
Subtotal (95% CI)					**6.83%**	**-0.05[-0.46,0.36]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.24(P=0.81)						
1.1.2 Tibolone 1.25 mg/day						
Hudita 2003	45	17	-3.4 (0.42)		1.71%	-3.4[-4.22,-2.58]
Landgren 2002	124	29	-0.7 (0.21)		6.83%	-0.71[-1.12,-0.3]
Swanson 2006	133	66	-0.6 (0.15)		13.38%	-0.57[-0.86,-0.28]
Subtotal (95% CI)					**21.92%**	**-0.83[-1.06,-0.6]**
Heterogeneity: Tau^2=0; Chi^2=40.77, df=2(P<0.0001); I^2=95.09%						
Test for overall effect: Z=7.12(P<0.0001)						
1.1.3 Tibolone 2.5 mg/day						
Benedek-Jaszmann 1987	24	19	-1 (0.33)		2.76%	-1.04[-1.69,-0.39]
Bouchard 2012	164	150	-0.5 (0.11)		24.88%	-0.48[-0.7,-0.26]
Hudita 2003	41	17	-3.5 (0.44)		1.56%	-3.54[-4.4,-2.68]
Landgren 2002	139	29	-0.7 (0.21)		6.83%	-0.69[-1.1,-0.28]
Morais-Socorro 2012	27	30	-3.3 (0.17)		10.42%	-3.29[-3.62,-2.96]
Swanson 2006	125	66	-1 (0.16)		11.76%	-0.97[-1.28,-0.66]
Ziaei 2010	43	46	-0.7 (0.22)		6.22%	-0.68[-1.11,-0.25]
Subtotal (95% CI)					**64.43%**	**-1.16[-1.3,-1.03]**
Heterogeneity: Tau^2=0; Chi^2=235.77, df=6(P<0.0001); I^2=97.46%						
Test for overall effect: Z=17.02(P<0.0001)						
1.1.4 Tibolone 5 mg/day						
Landgren 2002	136	29	-0.8 (0.21)		6.83%	-0.84[-1.25,-0.43]
Subtotal (95% CI)					**6.83%**	**-0.84[-1.25,-0.43]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=4(P<0.0001)						
Total (95% CI)					**100%**	**-0.99[-1.1,-0.89]**
Heterogeneity: Tau^2=0; Chi^2=305.28, df=11(P<0.0001); I^2=96.4%						
Test for overall effect: Z=18.1(P<0.0001)						
Test for subgroup differences: Chi^2=28.74, df=1 (P<0.0001), I^2=89.56%						



Favours tibolone Favours placebo

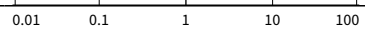
Analysis 1.2. Comparison 1 Tibolone versus placebo, Outcome 2 Unscheduled bleeding.

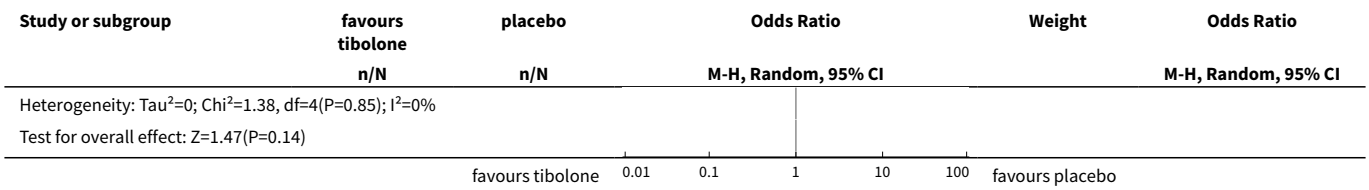
Study or subgroup	tibolone n/N	placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Tibolone, 2.5 mg/day					
Berning 2000	18/35	3/12		3.32%	3.18[0.73,13.75]
Bouchard 2012	38/166	14/152		11.53%	2.93[1.52,5.65]
Hudita 2003	7/41	4/17		3.67%	0.67[0.17,2.67]
Kenemans 2009	230/1575	107/1558		25.2%	2.32[1.82,2.95]
Kroiss 2005	10/35	7/32		5.32%	1.43[0.47,4.35]
Langer 2006	107/222	53/235		18.93%	3.2[2.13,4.78]
Meeuwsen 2002	16/35	4/37		4.49%	6.95[2.03,23.83]
Wender 2004	0/17	0/17			Not estimable
Subtotal (95% CI)	**2126**	**2060**		**72.46%**	**2.58[1.89,3.52]**
Total events: 426 (tibolone), 192 (placebo)					
Heterogeneity: Tau^2=0.05; Chi^2=9.2, df=6(P=0.16); I^2=34.79%					
Test for overall effect: Z=5.98(P<0.0001)					
1.2.2 Tibolone, 1.25 mg/day					
Berning 2000	16/36	2/11		2.63%	3.6[0.68,19.07]
Cummings 2008	165/1746	45/1773		21.46%	4.01[2.86,5.61]
Hudita 2003	10/45	3/17		3.46%	1.33[0.32,5.58]
Subtotal (95% CI)	**1827**	**1801**		**27.54%**	**3.63[2.37,5.55]**
Total events: 191 (tibolone), 50 (placebo)					
Heterogeneity: Tau^2=0.03; Chi^2=2.16, df=2(P=0.34); I^2=7.23%					
Test for overall effect: Z=5.94(P<0.0001)					
Total (95% CI)	**3953**	**3861**		**100%**	**2.79[2.1,3.7]**
Total events: 617 (tibolone), 242 (placebo)					
Heterogeneity: Tau^2=0.07; Chi^2=15.9, df=9(P=0.07); I^2=43.4%					
Test for overall effect: Z=7.12(P<0.0001)					
Test for subgroup differences: Chi^2=1.62, df=1 (P=0.2), I^2=38.3%					



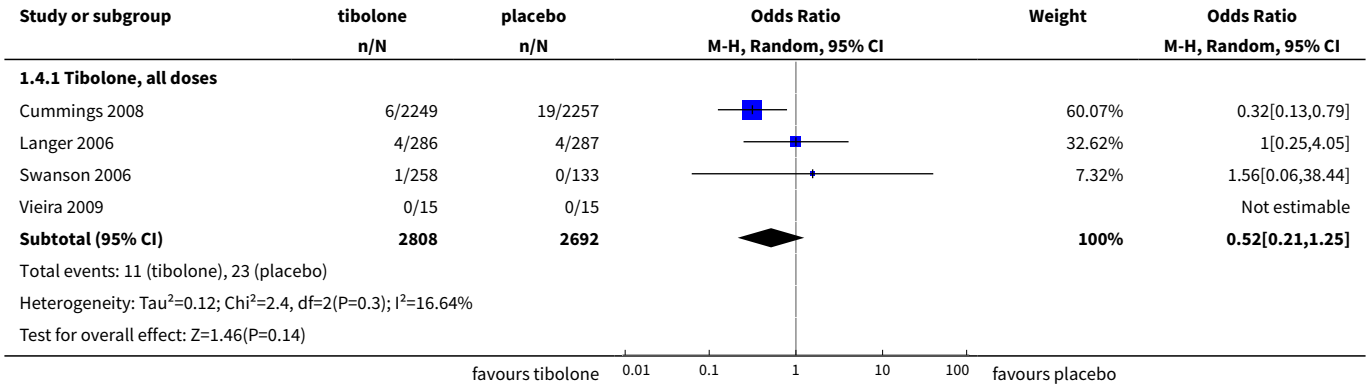
Analysis 1.3. Comparison 1 Tibolone versus placebo, Outcome 3 Endometrial cancer.

Study or subgroup	favours tibolone n/N	placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 Tibolone, all doses					
Bouchard 2012	1/166	0/152		8.69%	2.76[0.11,68.37]
Cummings 2008	4/1746	0/1773		10.48%	9.16[0.49,170.26]
Gallagher 2001	3/511	0/128		10.15%	1.77[0.09,34.46]
Kenemans 2009	7/1575	4/1558		59.09%	1.73[0.51,5.94]
Kroiss 2005	0/35	0/32			Not estimable
Langer 2006	1/228	1/243		11.6%	1.07[0.07,17.14]
Swanson 2006	0/193	0/100			Not estimable
Vieira 2009	0/15	0/15			Not estimable
Wender 2004	0/17	0/17			Not estimable
Subtotal (95% CI)	**4486**	**4018**		**100%**	**2.04[0.79,5.24]**
Total events: 16 (favours tibolone), 5 (placebo)					

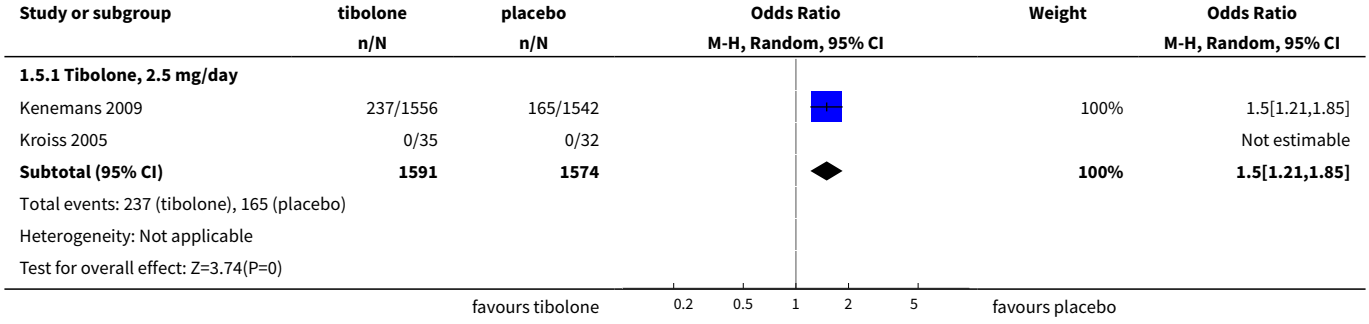




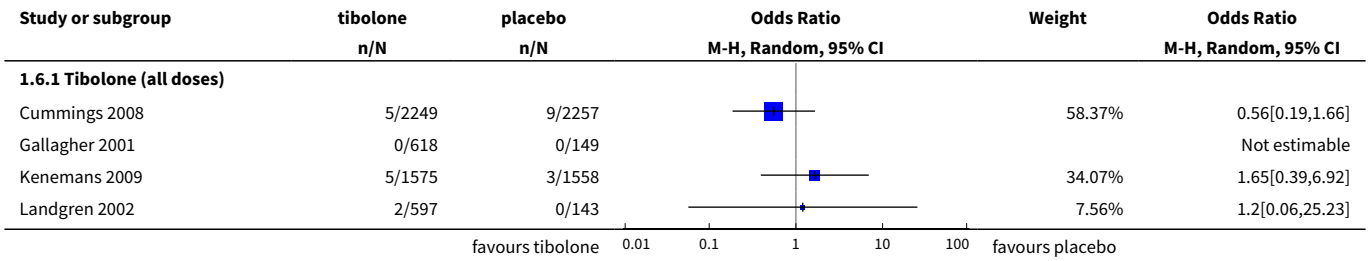
Analysis 1.4. Comparison 1 Tibolone versus placebo, Outcome 4 Breast cancer; women without previous breast cancer.

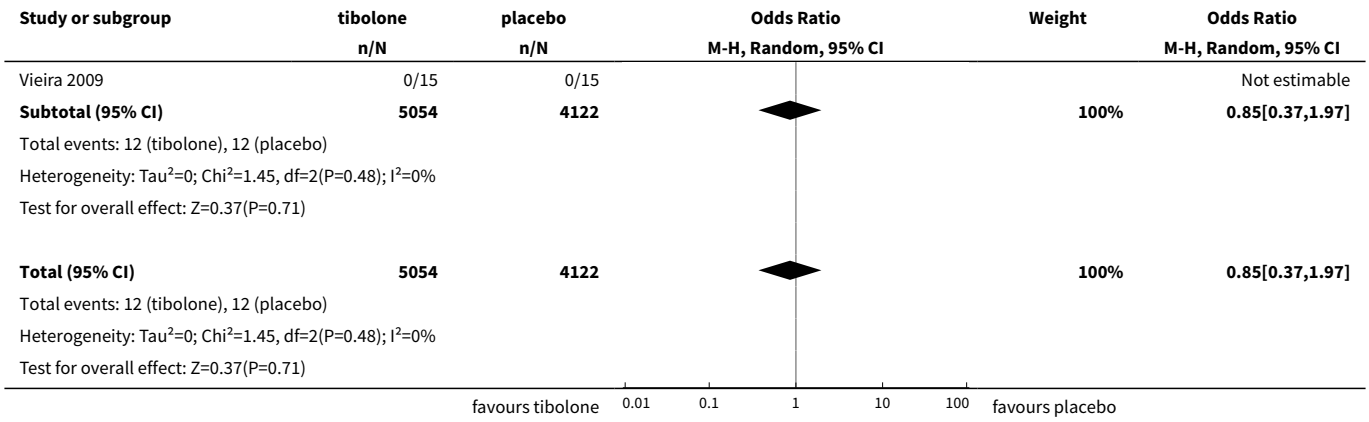


Analysis 1.5. Comparison 1 Tibolone versus placebo, Outcome 5 Breast cancer; women with previous breast cancer.

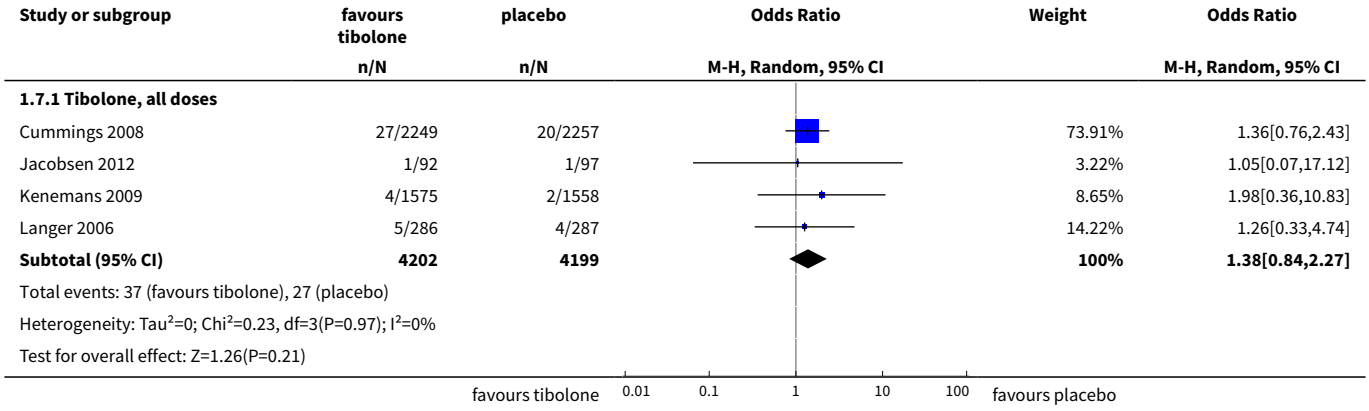


Analysis 1.6. Comparison 1 Tibolone versus placebo, Outcome 6 Venous thromboembolic events (clinical evaluation).

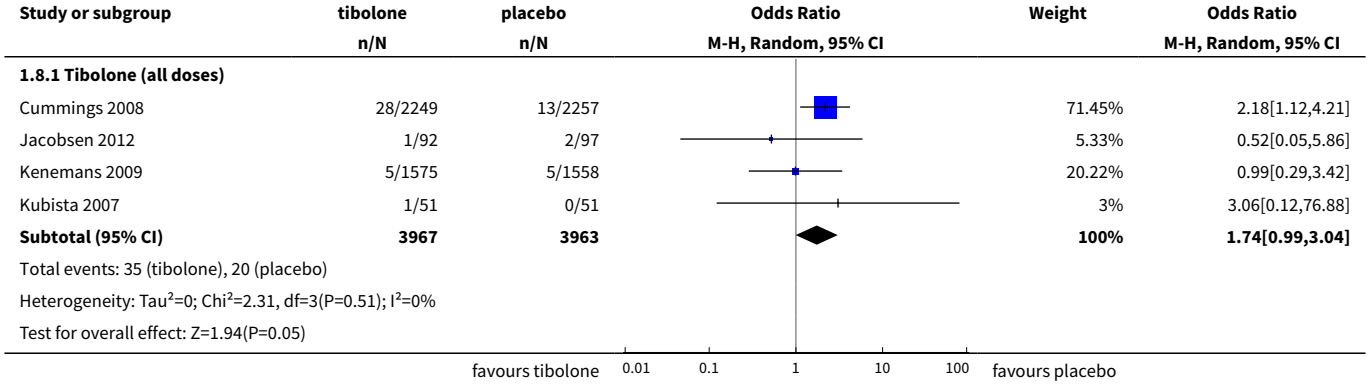




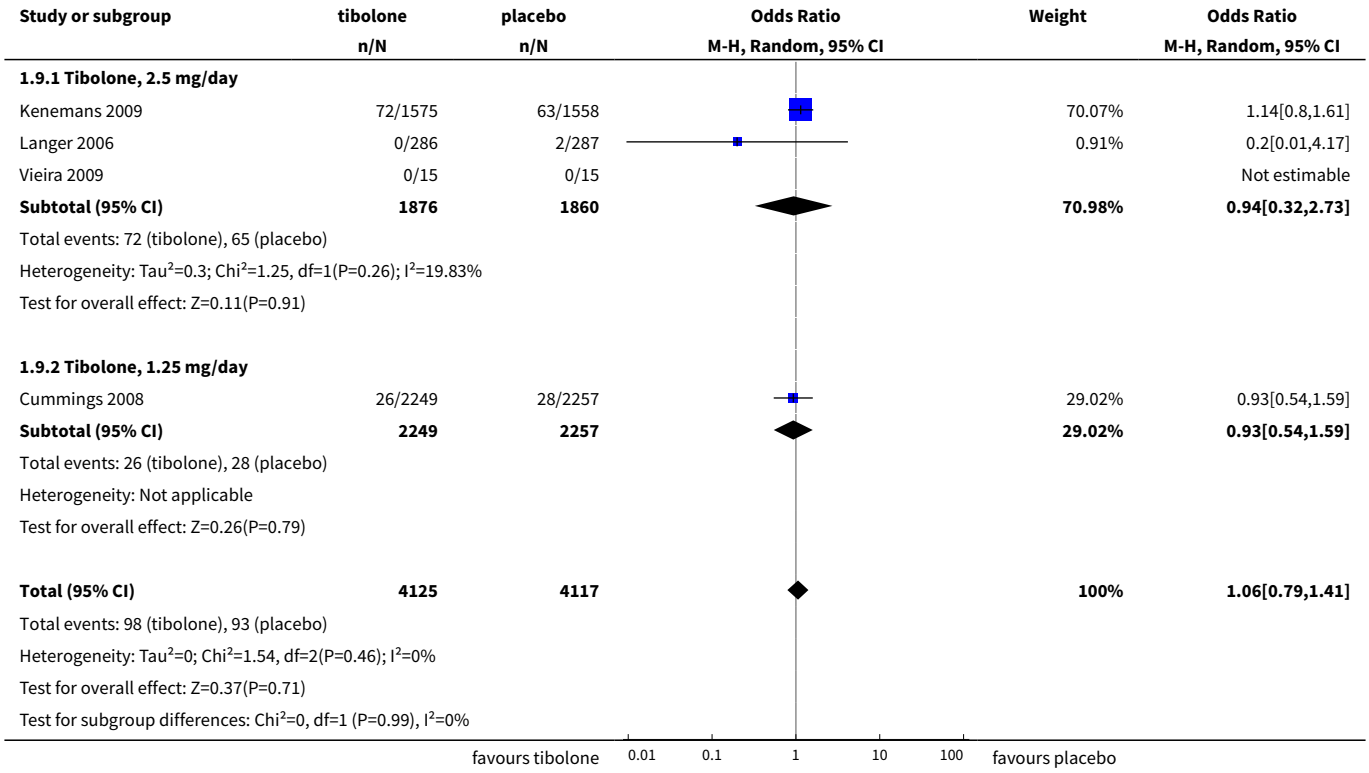
Analysis 1.7. Comparison 1 Tibolone versus placebo, Outcome 7 Cardiovascular events.



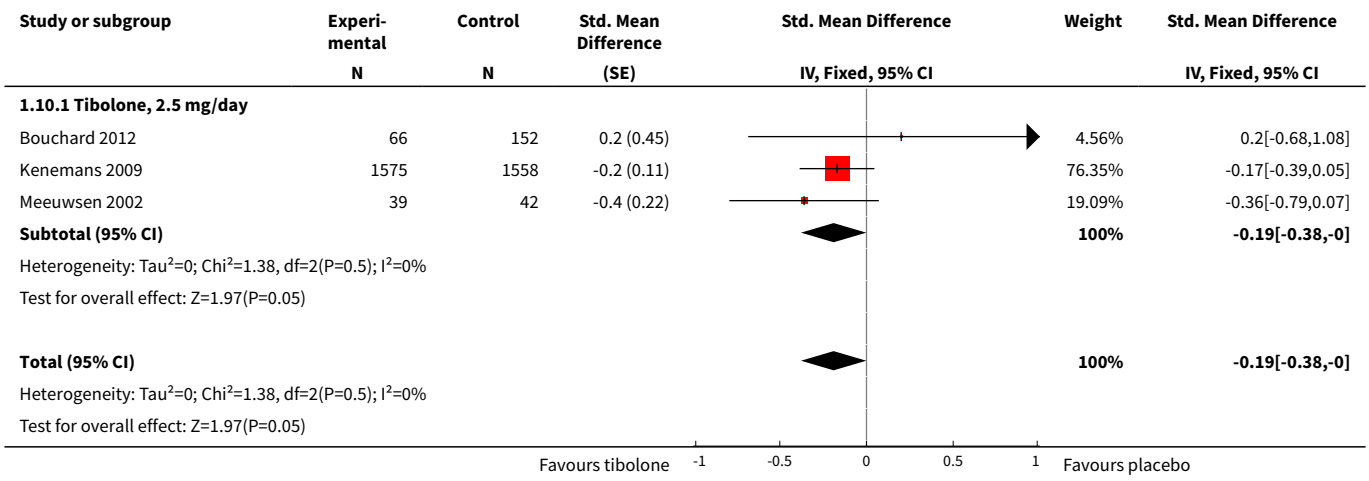
Analysis 1.8. Comparison 1 Tibolone versus placebo, Outcome 8 Cerebrovascular events; women's mean age over 60 years.



Analysis 1.9. Comparison 1 Tibolone versus placebo, Outcome 9 Mortality from any cause.

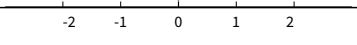


Analysis 1.10. Comparison 1 Tibolone versus placebo, Outcome 10 Insomnia.



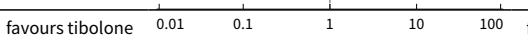
Analysis 1.11. Comparison 1 Tibolone versus placebo, Outcome 11 Vaginal dryness and painful sexual intercourse.

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Fixed, 95% CI	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.11.1 Tibolone, 1.25mg/day						
Hudita 2003	45	17	-1.8 (0.33)		13.24%	-1.78[-2.43,-1.13]
Subtotal (95% CI)					**13.24%**	**-1.78[-2.43,-1.13]**
Heterogeneity: Not applicable						
Test for overall effect: Z=5.39(P<0.0001)						
1.11.2 Tibolone, 2.5 mg/day						
Hudita 2003	41	17	-1.9 (0.34)		12.47%	-1.88[-2.55,-1.21]
Kenemans 2009	1575	1558	-0.3 (0.18)		44.5%	-0.35[-0.7,0]
Ziaei 2010	47	48	-0.1 (0.22)		29.79%	-0.13[-0.56,0.3]
Subtotal (95% CI)					**86.76%**	**-0.49[-0.75,-0.24]**
Heterogeneity: Tau^2=0; Chi^2=20, df=2(P<0.0001); I^2=90%						
Test for overall effect: Z=3.84(P=0)						
Total (95% CI)					**100%**	**-0.66[-0.9,-0.43]**
Heterogeneity: Tau^2=0; Chi^2=33.16, df=3(P<0.0001); I^2=90.95%						
Test for overall effect: Z=5.54(P<0.0001)						
Test for subgroup differences: Chi^2=13.17, df=1 (P=0), I^2=92.41%						



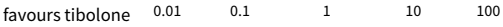
Analysis 1.12. Comparison 1 Tibolone versus placebo, Outcome 12 Vaginal infections.

Study or subgroup	tibolone n/N	placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.12.1 Tibolone, 2.5 mg/day					
Kenemans 2009	72/1575	42/1558		48.56%	1.73[1.17,2.55]
Subtotal (95% CI)	**1575**	**1558**		**48.56%**	**1.73[1.17,2.55]**
Total events: 72 (tibolone), 42 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.77(P=0.01)					
1.12.2 Tibolone, 1.25 mg/day					
Cummings 2008	186/2249	56/2257		51.44%	3.54[2.61,4.81]
Subtotal (95% CI)	**2249**	**2257**		**51.44%**	**3.54[2.61,4.81]**
Total events: 186 (tibolone), 56 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=8.14(P<0.0001)					
Total (95% CI)	**3824**	**3815**		**100%**	**2.5[1.24,5.06]**
Total events: 258 (tibolone), 98 (placebo)					
Heterogeneity: Tau^2=0.23; Chi^2=8.17, df=1(P=0); I^2=87.76%					
Test for overall effect: Z=2.55(P=0.01)					
Test for subgroup differences: Chi^2=8.15, df=1 (P=0), I^2=87.73%					



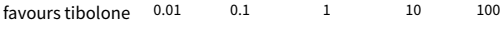
Analysis 1.13. Comparison 1 Tibolone versus placebo, Outcome 13 Urinary tract infections.

Study or subgroup	tibolone n/N	placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.13.1 Tibolone, 2.5 mg/day					
Kenemans 2009	40/1575	56/1558		100%	0.7[0.46,1.06]
Subtotal (95% CI)	**1575**	**1558**		**100%**	**0.7[0.46,1.06]**
Total events: 40 (tibolone), 56 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.7(P=0.09)					



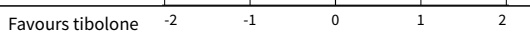
Analysis 1.14. Comparison 1 Tibolone versus placebo, Outcome 14 Endometrial hyperplasia.

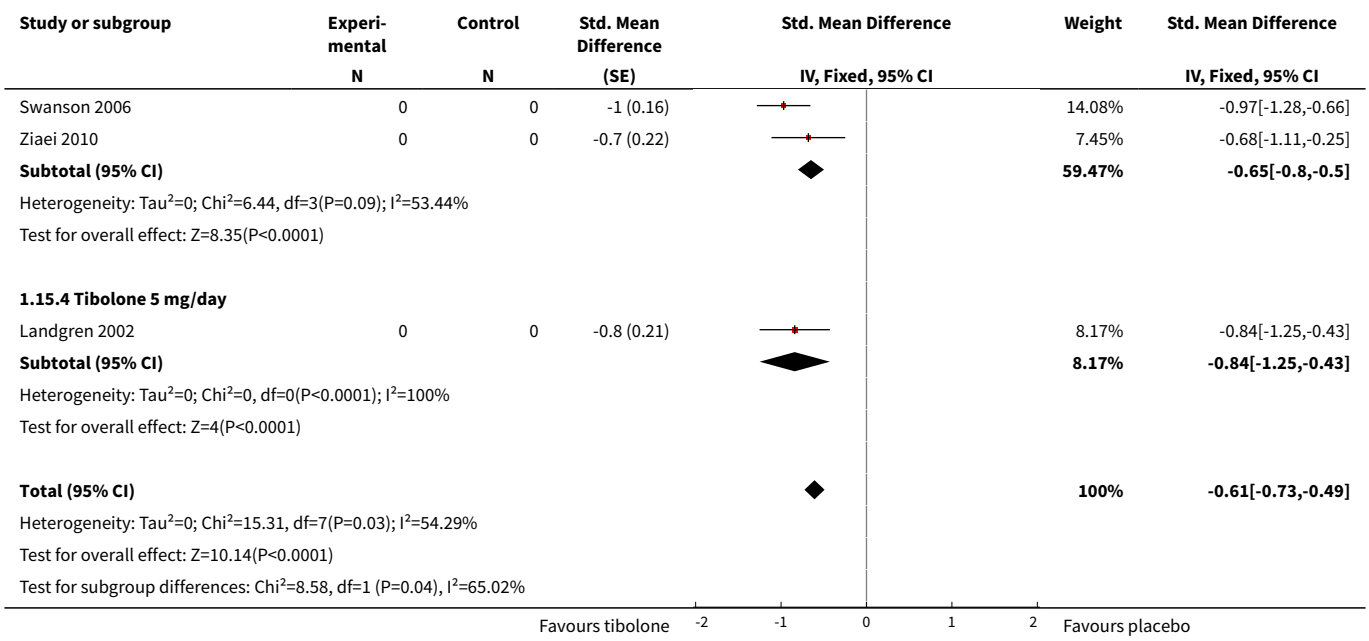
Study or subgroup	tibolone n/N	placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.14.1 Tibolone, all doses					
Cummings 2008	2/1746	1/1773		47.22%	2.03[0.18,22.43]
Gallagher 2001	3/511	1/128		52.78%	0.75[0.08,7.27]
Kroiss 2005	0/35	0/32			Not estimable
Swanson 2006	0/193	0/100			Not estimable
Subtotal (95% CI)	**2485**	**2033**		**100%**	**1.2[0.23,6.25]**
Total events: 5 (tibolone), 2 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.55); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					



Analysis 1.15. Comparison 1 Tibolone versus placebo, Outcome 15 Sensitivity Analysis - Vasomotor symptoms without trials with high risk of attrition bias.

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Fixed, 95% CI	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.15.1 Tibolone 0.625 mg/day						
Landgren 2002	0	0	-0 (0.21)		8.17%	-0.05[-0.46,0.36]
Subtotal (95% CI)					**8.17%**	**-0.05[-0.46,0.36]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.24(P=0.81)						
1.15.2 Tibolone 1.25 mg/day						
Landgren 2002	0	0	-0.7 (0.21)		8.17%	-0.71[-1.12,-0.3]
Swanson 2006	0	0	-0.6 (0.15)		16.02%	-0.57[-0.86,-0.28]
Subtotal (95% CI)					**24.19%**	**-0.62[-0.86,-0.38]**
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%						
Test for overall effect: Z=5.06(P<0.0001)						
1.15.3 Tibolone 2.5 mg/day						
Bouchard 2012	0	0	-0.5 (0.11)		29.78%	-0.48[-0.7,-0.26]
Landgren 2002	0	0	-0.7 (0.21)		8.17%	-0.69[-1.1,-0.28]

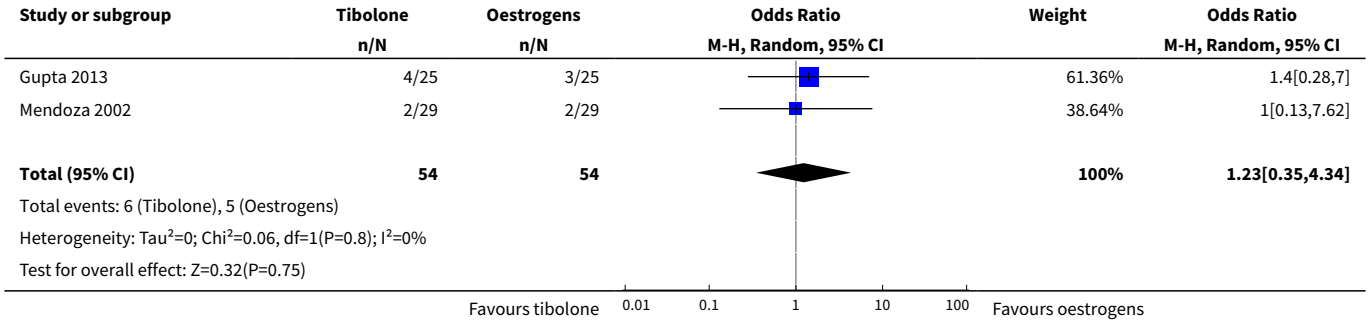




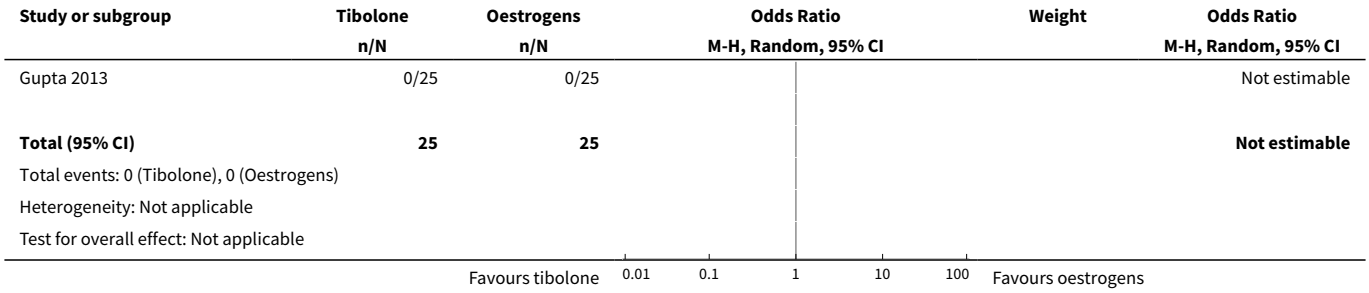
Comparison 2. Tibolone versus oestrogens

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vasomotor symptoms	2	108	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.35, 4.34]
2 Insomnia	1	50	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Vaginal dryness and painful sexual intercourse	1	50	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.25]

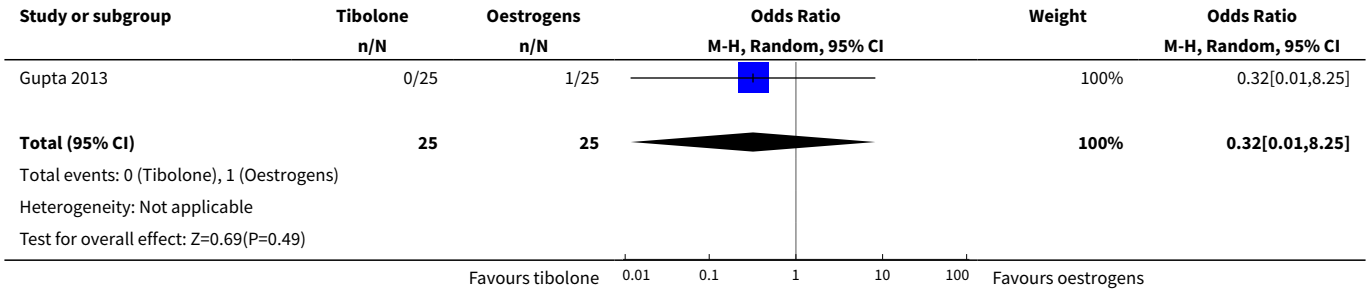
Analysis 2.1. Comparison 2 Tibolone versus oestrogens, Outcome 1 Vasomotor symptoms.



Analysis 2.2. Comparison 2 Tibolone versus oestrogens, Outcome 2 Insomnia.



Analysis 2.3. Comparison 2 Tibolone versus oestrogens, Outcome 3 Vaginal dryness and painful sexual intercourse.



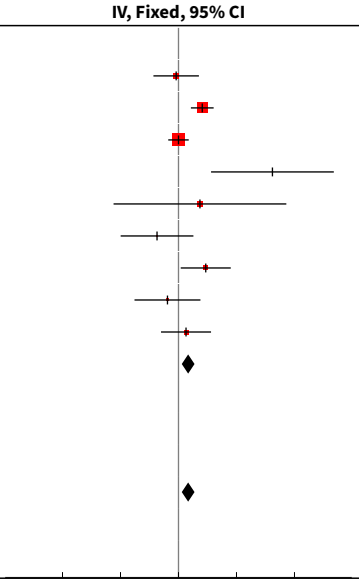
Comparison 3. Tibolone versus combined HT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vasomotor symptoms	9	1336	Std. Mean Difference (Fixed, 95% CI)	0.17 [0.06, 0.28]
1.1 Tibolone, 2.5 mg/day	9	1336	Std. Mean Difference (Fixed, 95% CI)	0.17 [0.06, 0.28]
2 Unscheduled bleeding	16	6438	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.24, 0.41]
2.1 Tibolone, 2.5 mg/day	16	4720	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.26, 0.45]
2.2 Tibolone, 1.25 mg/day	2	1718	Odds Ratio (M-H, Random, 95% CI)	0.21 [0.16, 0.26]
3 Endometrial cancer	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Tibolone, 2.5 mg/day	5	3689	Odds Ratio (M-H, Random, 95% CI)	1.47 [0.23, 9.33]
4 Breast cancer; women without previous breast cancer	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Tibolone (all doses)	5	4835	Odds Ratio (M-H, Random, 95% CI)	1.69 [0.78, 3.67]
5 Venous thromboembolic events (clinical evaluation)	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Tibolone (all doses)	4	4529	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.09, 2.14]
6 Cardiovascular events; all women's mean age below 60 years. No data available on different doses	2	3794	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.24, 1.66]
7 Cerebrovascular events; women's mean age below 60 years	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Tibolone (all doses)	4	4562	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.16, 3.66]
8 Mortality from any cause	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Tibolone, 2.5 mg/day	2	970	Odds Ratio (M-H, Random, 95% CI)	3.05 [0.12, 75.20]
9 Endometrial hyperplasia	5	2846	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.05, 2.21]
9.1 Tibolone, 2.5 mg/day	5	1549	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.04, 3.36]
9.2 Tibolone, 1.25 mg/day	1	1297	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.48]
10 Vaginal dryness and painful sexual intercourse	7	1098	Std. Mean Difference (Fixed, 95% CI)	0.02 [-0.12, 0.17]
10.1 Tibolone, 2.5 mg/day	7	1098	Std. Mean Difference (Fixed, 95% CI)	0.02 [-0.12, 0.17]
11 Sensitivity Analysis - Vasomotor symptoms without trials with high risk of attrition bias	4		Std. Mean Difference (Fixed, 95% CI)	0.25 [0.09, 0.41]
12 Sensitivity analysis - vasomotor symptoms - excluding studies with attrition bias and using nonvalidated scales	3		Std. Mean Difference (Fixed, 95% CI)	-0.03 [-0.30, 0.23]
13 Vasomotor symptoms - ordered by duration	9		Std. Mean Difference (Fixed, 95% CI)	0.17 [0.06, 0.28]
13.1 Tibolone, 2.5 mg/day	9		Std. Mean Difference (Fixed, 95% CI)	0.17 [0.06, 0.28]

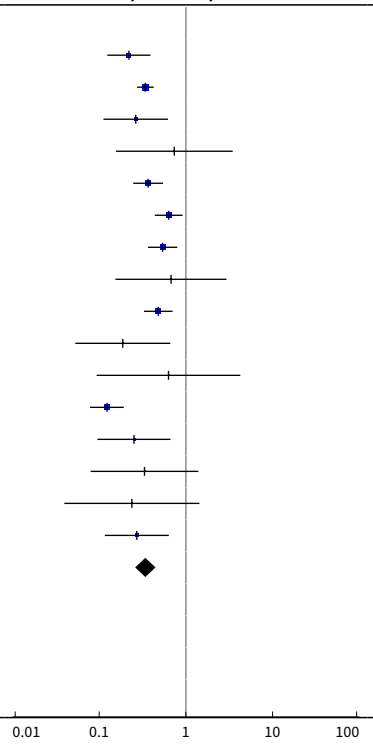
Analysis 3.1. Comparison 3 Tibolone versus combined HT, Outcome 1 Vasomotor symptoms.

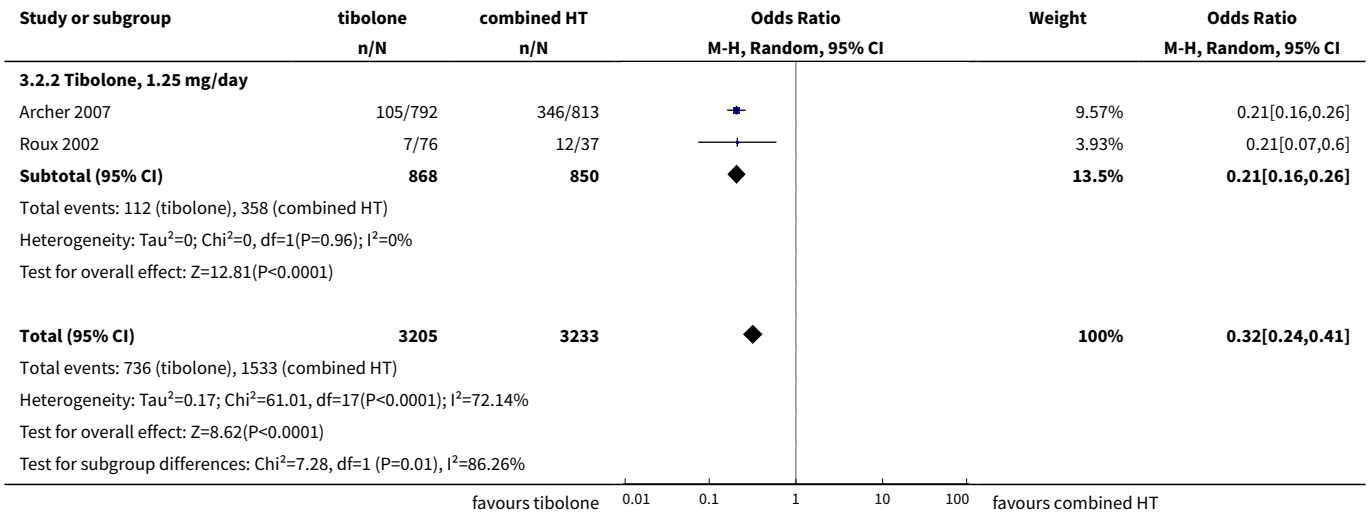
Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Fixed, 95% CI	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.1.1 Tibolone, 2.5 mg/day						
Elfituri 2005	50	50	-0 (0.2)		7.9%	-0.04[-0.43,0.35]
Hammar 1998	210	212	0.4 (0.1)		31.59%	0.41[0.21,0.61]
Hammar 2007	222	241	0 (0.09)		39%	0[-0.18,0.18]
Kökçü 2000	19	19	1.6 (0.54)		1.08%	1.62[0.56,2.68]
Mendoza 2002	29	26	0.4 (0.76)		0.55%	0.37[-1.12,1.86]
Nappi 2006a	20	20	-0.4 (0.32)		3.08%	-0.37[-1,0.26]
Polisseni 2013	42	44	0.5 (0.22)		6.53%	0.47[0.04,0.9]
Wu 2001	24	24	-0.2 (0.29)		3.76%	-0.19[-0.76,0.38]
Ziaei 2010	43	41	0.1 (0.22)		6.53%	0.13[-0.3,0.56]
Subtotal (95% CI)					**100%**	**0.17[0.06,0.28]**
Heterogeneity: Tau^2=0; Chi^2=23.99, df=8(P=0); I^2=66.65%						
Test for overall effect: Z=2.96(P=0)						
Total (95% CI)					**100%**	**0.17[0.06,0.28]**
Heterogeneity: Tau^2=0; Chi^2=23.99, df=8(P=0); I^2=66.65%						
Test for overall effect: Z=2.96(P=0)						



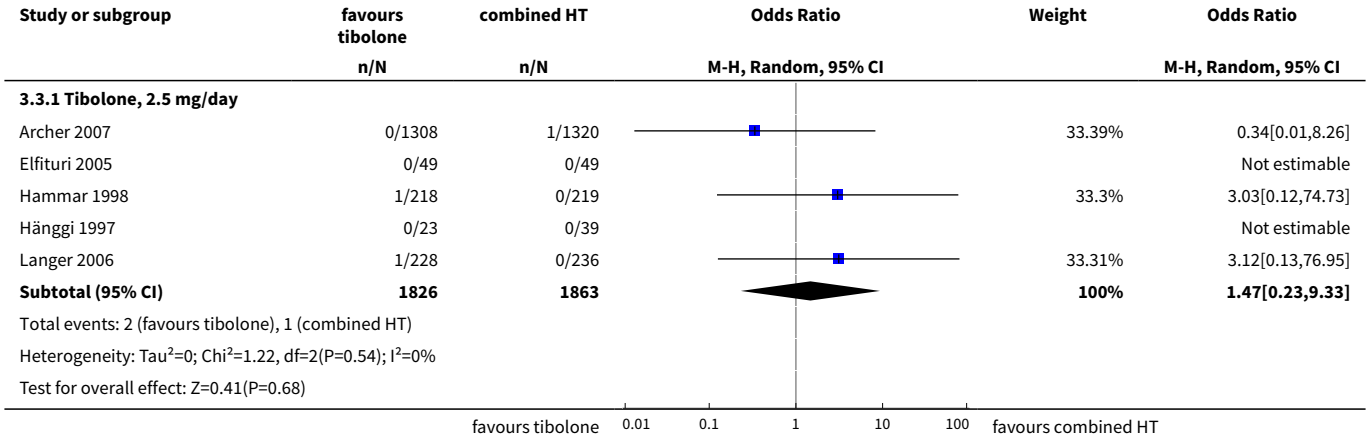
Analysis 3.2. Comparison 3 Tibolone versus combined HT, Outcome 2 Unscheduled bleeding.

Study or subgroup	tibolone n/N	combined HT n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
3.2.1 Tibolone, 2.5 mg/day					
Al-Azzawi 1999	31/111	67/105		6.94%	0.22[0.12,0.39]
Archer 2007	163/806	347/813		9.74%	0.34[0.27,0.42]
Doren 1999	13/47	29/49		4.92%	0.26[0.11,0.62]
Elfituri 2005	3/50	4/50		2.22%	0.73[0.16,3.46]
Hammar 1998	71/210	124/213		8.44%	0.37[0.25,0.54]
Hammar 2007	75/241	107/257		8.66%	0.63[0.44,0.92]
Huber 2002	75/208	109/213		8.48%	0.54[0.36,0.79]
Kökçü 2000	4/23	5/21		2.41%	0.67[0.15,2.94]
Langer 2006	107/222	153/232		8.58%	0.48[0.33,0.7]
Mendoza 2002	3/44	25/89		3.04%	0.19[0.05,0.66]
Nappi 2006a	2/20	3/20		1.58%	0.63[0.09,4.24]
Nijland 2009	48/199	145/201		8%	0.12[0.08,0.19]
Roux 2002	9/75	13/37		4.27%	0.25[0.1,0.66]
Winkler 2000	4/16	10/20		2.52%	0.33[0.08,1.39]
Wu 2001	2/16	6/16		1.76%	0.24[0.04,1.43]
Ziaei 2010	14/49	28/47		4.95%	0.27[0.12,0.64]
Subtotal (95% CI)	**2337**	**2383**		**86.5%**	**0.34[0.26,0.45]**
Total events: 624 (tibolone), 1175 (combined HT)					
Heterogeneity: Tau^2=0.15; Chi^2=45.13, df=15(P<0.0001); I^2=66.76%					
Test for overall effect: Z=7.82(P<0.0001)					

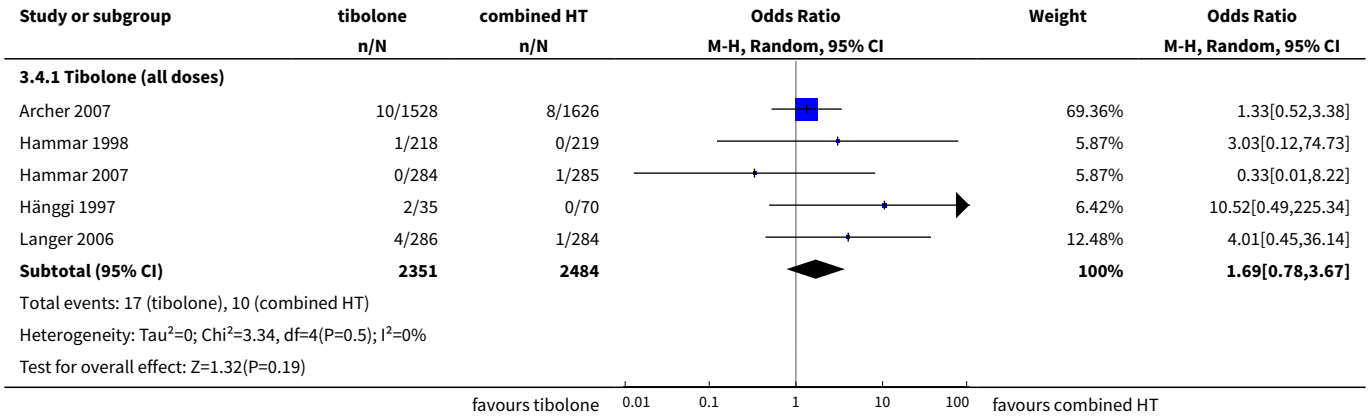




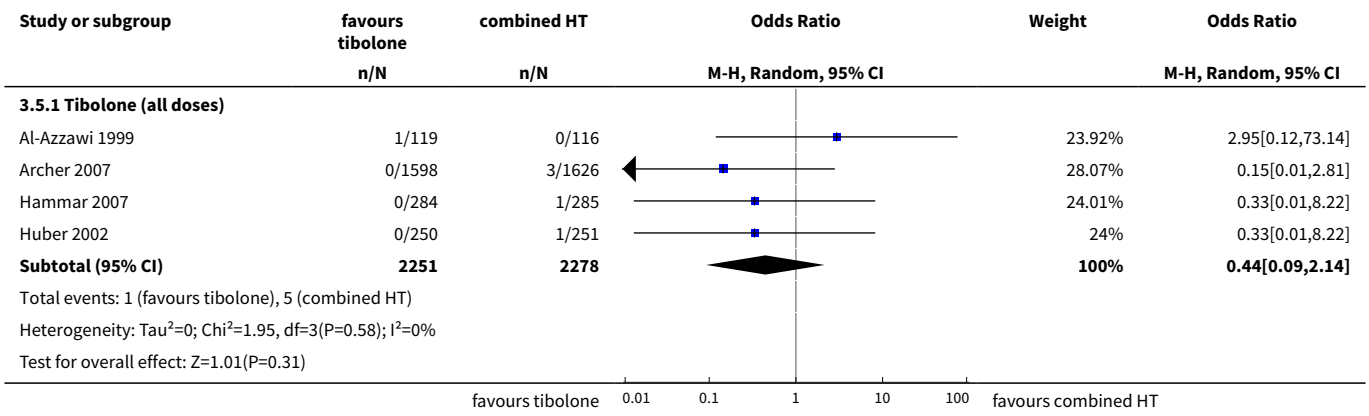
Analysis 3.3. Comparison 3 Tibolone versus combined HT, Outcome 3 Endometrial cancer.



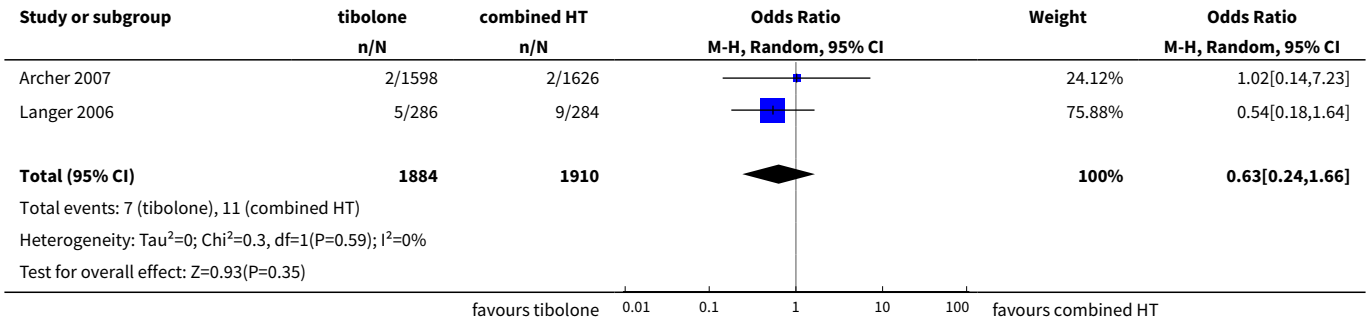
Analysis 3.4. Comparison 3 Tibolone versus combined HT, Outcome 4 Breast cancer; women without previous breast cancer.



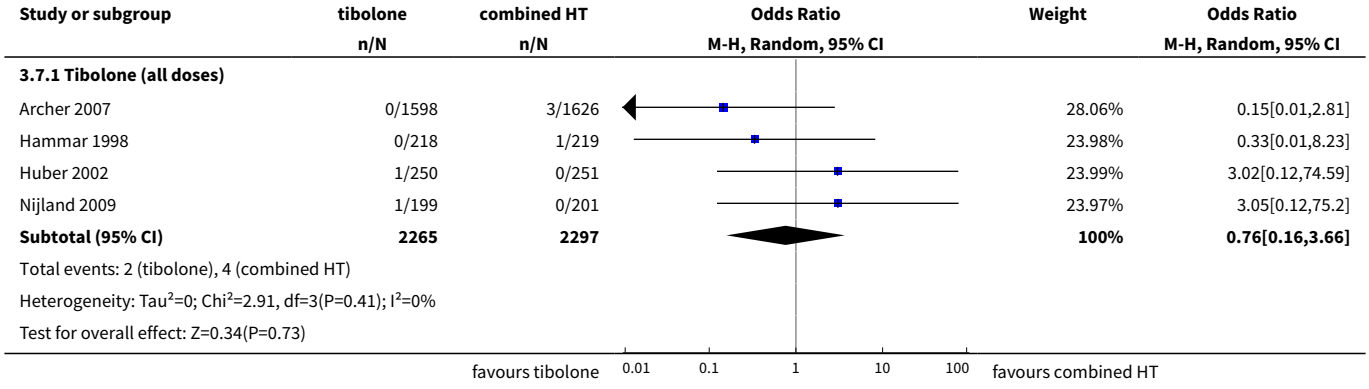
Analysis 3.5. Comparison 3 Tibolone versus combined HT, Outcome 5 Venous thromboembolic events (clinical evaluation).



Analysis 3.6. Comparison 3 Tibolone versus combined HT, Outcome 6 Cardiovascular events; all women's mean age below 60 years. No data available on different doses.

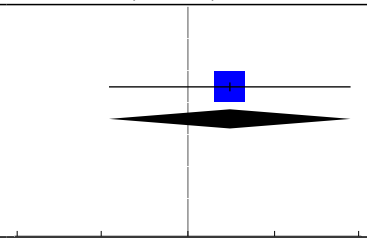


Analysis 3.7. Comparison 3 Tibolone versus combined HT, Outcome 7 Cerebrovascular events; women's mean age below 60 years.



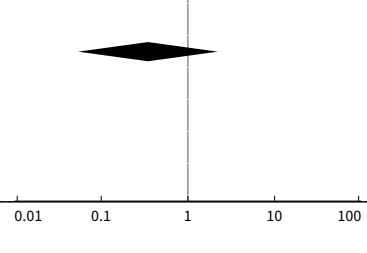
Analysis 3.8. Comparison 3 Tibolone versus combined HT, Outcome 8 Mortality from any cause.

Study or subgroup	tibolone n/N	combined HT n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
3.8.1 Tibolone, 2.5 mg/day					
Langer 2006	0/286	0/284			Not estimable
Nijland 2009	1/199	0/201		100%	3.05[0.12,75.2]
Subtotal (95% CI)	**485**	**485**		**100%**	**3.05[0.12,75.2]**
Total events: 1 (tibolone), 0 (combined HT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					



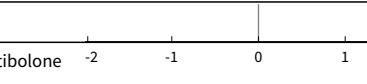
Analysis 3.9. Comparison 3 Tibolone versus combined HT, Outcome 9 Endometrial hyperplasia.

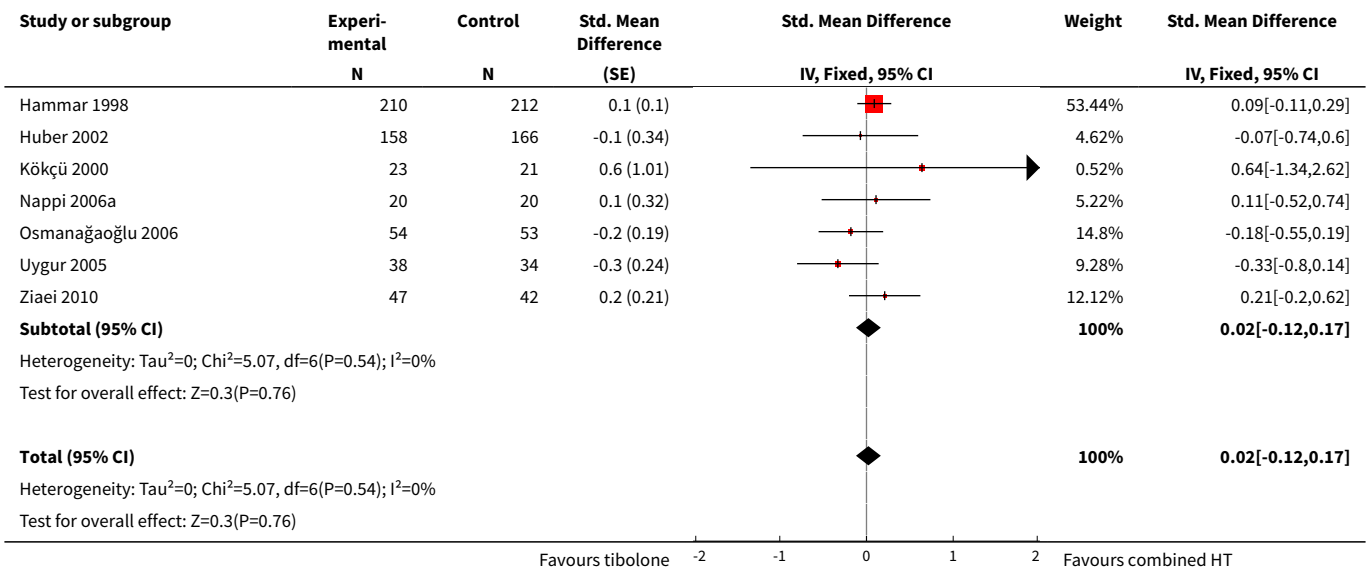
Study or subgroup	favours tibolone n/N	combined HT n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
3.9.1 Tibolone, 2.5 mg/day					
Archer 2007	0/671	1/660		33.52%	0.33[0.01,8.05]
Baracat 2002	0/40	1/45		32.97%	0.37[0.01,9.25]
de Aloysio 1998	0/24	0/23			Not estimable
Hänggi 1997	0/23	0/39			Not estimable
Siseles 1995	0/13	0/11			Not estimable
Subtotal (95% CI)	**771**	**778**		**66.49%**	**0.35[0.04,3.36]**
Total events: 0 (favours tibolone), 2 (combined HT)					
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=1(P=0.96); $I^2=0\%$					
Test for overall effect: Z=0.91(P=0.36)					
3.9.2 Tibolone, 1.25 mg/day					
Archer 2007	0/637	1/660		33.51%	0.34[0.01,8.48]
Subtotal (95% CI)	**637**	**660**		**33.51%**	**0.34[0.01,8.48]**
Total events: 0 (favours tibolone), 1 (combined HT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.51)					
Total (95% CI)	**1408**	**1438**		**100%**	**0.35[0.05,2.21]**
Total events: 0 (favours tibolone), 3 (combined HT)					
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=2(P=1); $I^2=0\%$					
Test for overall effect: Z=1.12(P=0.26)					
Test for subgroup differences: $Chi^2=0$, df=1 (P=1), $I^2=0\%$					



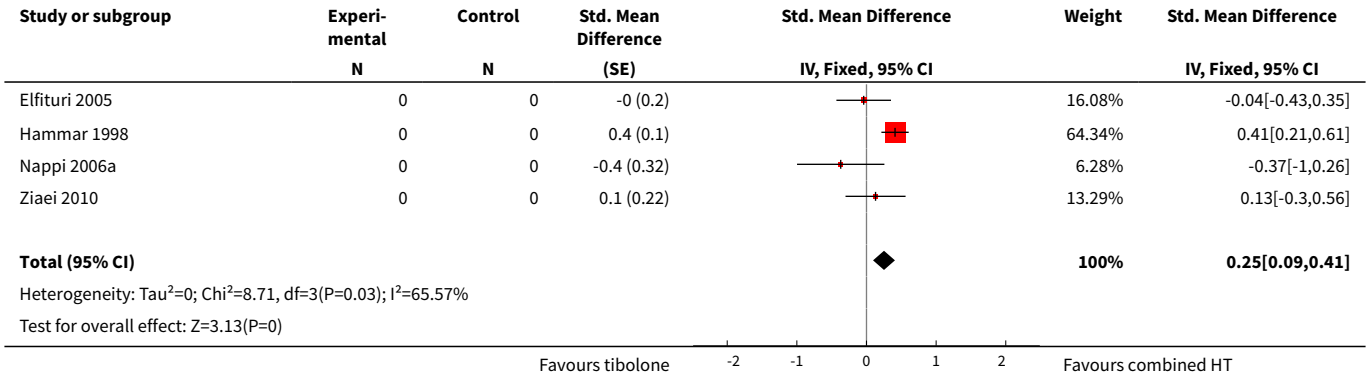
Analysis 3.10. Comparison 3 Tibolone versus combined HT, Outcome 10 Vaginal dryness and painful sexual intercourse.

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Fixed, 95% CI	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.10.1 Tibolone, 2.5 mg/day						

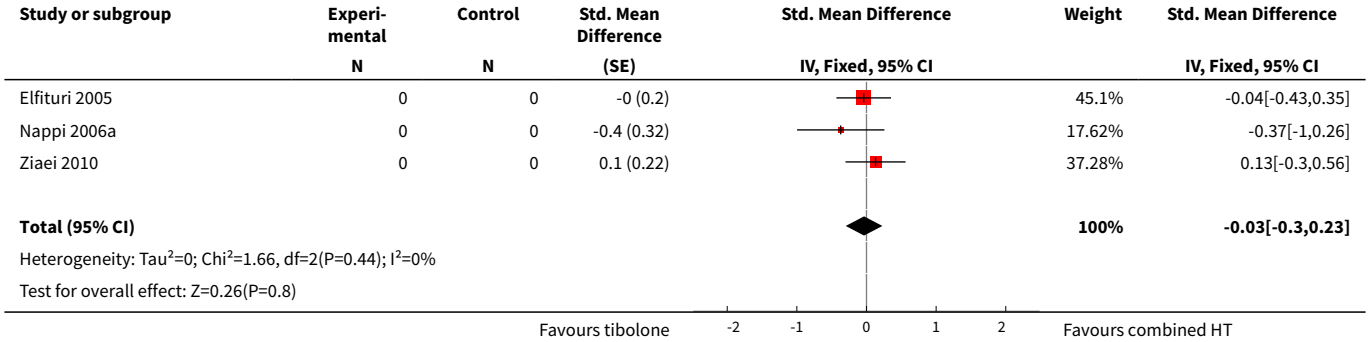




Analysis 3.11. Comparison 3 Tibolone versus combined HT, Outcome 11 Sensitivity Analysis - Vasomotor symptoms without trials with high risk of attrition bias.

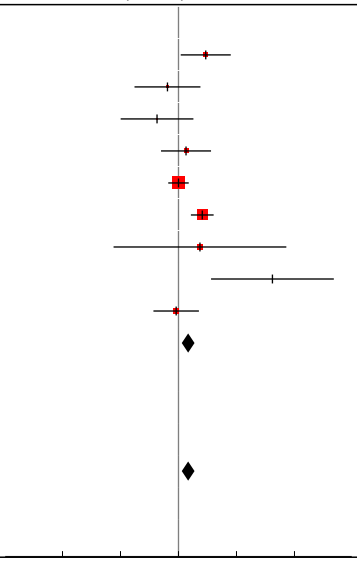


Analysis 3.12. Comparison 3 Tibolone versus combined HT, Outcome 12 Sensitivity analysis - vasomotor symptoms - excluding studies with attrition bias and using nonvalidated scales.



Analysis 3.13. Comparison 3 Tibolone versus combined HT, Outcome 13 Vasomotor symptoms - ordered by duration.

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Fixed, 95% CI	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.13.1 Tibolone, 2.5 mg/day						
Polisseni 2013	42	44	0.5 (0.22)		6.53%	0.47[0.04,0.9]
Wu 2001	24	24	-0.2 (0.29)		3.76%	-0.19[-0.76,0.38]
Nappi 2006a	20	20	-0.4 (0.32)		3.08%	-0.37[-1,0.26]
Ziaei 2010	43	41	0.1 (0.22)		6.53%	0.13[-0.3,0.56]
Hammar 2007	222	241	0 (0.09)		39%	0[-0.18,0.18]
Hammar 1998	210	212	0.4 (0.1)		31.59%	0.41[0.21,0.61]
Mendoza 2002	29	26	0.4 (0.76)		0.55%	0.37[-1.12,1.86]
Kökçü 2000	19	19	1.6 (0.54)		1.08%	1.62[0.56,2.68]
Elfituri 2005	50	50	-0 (0.2)		7.9%	-0.04[-0.43,0.35]
Subtotal (95% CI)					**100%**	**0.17[0.06,0.28]**
Heterogeneity: Tau^2=0; Chi^2=23.99, df=8(P=0); I^2=66.65%						
Test for overall effect: Z=2.96(P=0)						
Total (95% CI)					**100%**	**0.17[0.06,0.28]**
Heterogeneity: Tau^2=0; Chi^2=23.99, df=8(P=0); I^2=66.65%						
Test for overall effect: Z=2.96(P=0)						



ADDITIONAL TABLES

Table 1. Details on RCTs assessing vasomotor symptoms requiring additional data or analysis before data synthesis

Study	*Comparator*	*Outcome measure*	*Information available*	*Notes*	*Results for meta-analysis*	*SMD*
Al-Azzawi 1999	HT	Presence of vasomotor symptoms, severity measured by Greene menopausal symptoms scale	6 HRT and 9 tibolone patients were without symptoms at baseline. 67 HRT and 58 tibolone patients were free at month 3	Contacted study authors, no reply		
Baracat 2002	HT	Total score: mean number of hot flushes per day multiplied by severity score	Means plotted as bar chart in Figure 1. Baseline, 11 for tibolone (n = 40), 12 for control (n = 45). At 3 months, 1.8 for tibolone and 1.5 for control. At 13 months, 0.2 for both	Would have to impute SDs – 'no significant difference' Unclear how to do this, given the available info Unable to find contact details		

Table 1. Details on RCTs assessing vasomotor symptoms requiring additional data or analysis before data synthesis *(Continued)*

Benedeck-Jaszmann 1987	Placebo	0 to 3 severity score	12 months From Fig 1: Mean P: 1.6 T: 0.6 SD P: 1 T: 0.9 N P: 19 T: 24 (assuming 30 per arm to start, not explicitly stated)	Extracted from figure	Mean P: 1.6 T: 0.6 SD P: 1 T: 0.9 N P: 19 T: 24	SMD: -1.0384784 SE: 0.3268612
Bouchard 2012	Placebo	Severity score	Calculate 12 week values P: 1.59 T: 1.16 Sample sizes of 150 (P) and 164 (T) Wk 12	Use SD from sample size calc, which is in line with other studies	P: Mean 1.59 SD 0.9 N = 150 T: Mean 1.16 SD: 0.9 N = 164	SMD: -0.4766282 SE: 0.1145686
Egarter 1996	HT	Severity of hot flushes (modified Kupperman Index)	Baseline mean C: 2.1 T: 2.2 6 months C: 0.4 T: 0.4 'N/S' N = 34 (C) N = 62 (T)	Impute SD - unclear how to Contacted study authors: no reply		
Hammar 2007	HT	Number of hot flushes	Week 48, baseline mean of both groups 6, follow-up mean ≤ 1 Baseline SD C: 4.40 T: 4.37 N = 241 (C)	Use baseline SDs (these appear reasonable, given Landgren 2002)	C: mean 1, SD 4.40; N = 241 T: mean 1, SD 4.37 N = 222	SMD: 0.00 SE: 0.09302624

Table 1. Details on RCTs assessing vasomotor symptoms requiring additional data or analysis before data synthesis *(Continued)*

			N = 222 (T)			
Hudita 2003	Placebo (3 –arm study)	5-point severity scale for hot flushes	Week 24 P: 3 T: 1.25 mg: 0.2 T: 2.5mg: 0.1 N = 34 N = 45 N = 41 P < 0.01 for both compared with placebo	Split control group size between 2 arms Used P value to calculate SD Get implausible answers. Used known value instead (e.g. Hammar 1998)	Mean P: 3 T: 1.25 mg: 0.2 T: 2.5 mg: 0.1 N N = 34/2 = 17 N = 45 N = 41 SD P: 0.63 T: 1.25: 0.87 T: 2.5: 0.87	1.25 SMD: -3.4009511 SE: 0.4175209 2.5 SMD: -3.5375963 SE: 0.4371477
Kokcu 2000	HT	Occurrence of hot flushes		OR: 4.16 (0.75 to 22.9)	2/19 have symptoms in C 12/19 have symptoms in T	SMD: 1.6236743 SE: 0.5369759
Landgren 2002	Placebo (5-arm study)	Frequency of hot flushes	Read means and SEs at 12 weeks from Figure 1 Mean P = 5.2 T 0.625 = 5 T 1.25 = 2.1 T 2.5 = 1.8 T 5.0 = 1.6 Standard error P = 0.37 T 0.625 = 0.37 T 1.25 = 0.40 T 2.5 = 0.43 T 5.0 = 0.37 Ns (calculated as all evaluable – dropouts -this assumes dropout occurred after 1st measurement at week 4)	Read means and SEs from Figure 1 Calculated SDs using SEs and sample sizes Split placebo group size in 4 113/4 = 28.25	Mean P = 5.2 T 0.625 = 5 T 1.25 = 2.1 T 2.5 = 1.8 T 5.0 = 1.6 SD P = 3.93 T 0.625 = 4.20 T 1.25 = 4.45 T 2.5 = 5.07 T 5.0 = 4.31 N (calculated as all evaluable – dropouts – this assumes	0.625 SMD: -0.04792794 SE: 0.20552850 1.25 SMD: -0.7077526 SE: 0.2102005 2.5 SMD: -0.6912512 SE: 0.2076033 5.0 SMD: -0.8437215

Table 1. Details on RCTs assessing vasomotor symptoms requiring additional data or analysis before data synthesis *(Continued)*

			P = 113 T 0.625 = 129 T 1.25 = 124 T 2.5 = 139 T 5.0 = 136		dropout occurred after 1st measurement at week 4) P = 28.25 T 0.625 = 129 T 1.25 = 124 T 2.5 = 139 T 5.0 = 136	SE: 0.2097448
Mendoza 2002	HT	Flushes subscore of the Modified Kupperman Index, 0 to 2 score Number (%) reduced	Have number and percentage that improved in terms of vasomotor symptoms after 1 year Have 2 possible control groups – choose the best performing to give a conservative estimate 25/26 reduced in control group 27/29 reduced in T groups	Calculate odds ratio for reduced vasomotor symptoms. Turn this into an SMD for combination (27/2)/(25/1) = 0.54 SE log(OR) = Sqrt(1/27+1/2+1/25+1/1) = 1.26	OR for improvement: OR = 0.54 SE(log(OR)) = 1.26 (so T worse)	SMD: 0.3734461 SE: 0.7610917
Nappi 2006a	HT	Vasomotor symptoms (0 to 3 severity score)	At 6 months Means from Figure 4 C: 1.75 T: 1.5 P value for treatment term in ANOVA given as 'P < 0.4' N = 20 in both groups	Assume ANOVA P value is 0.4 and work out SDs as though this was a t-test Gives SD of 0.657, assuming same in both groups		SMD: -0.3729492 SE: 0.3189649
Ross 1999	HT	Greene Climacteric Scale subscore	Nothing usable. Only present 1 of 6 relevant comparisons because it is almost significant. Do not present 3 month score			
Siseles 1995	HT	Kupperman Index	No information given for vasomotor subscale	Have contacted study authors, no reply		
Swanson 2006	Placebo (3-arm study)	Number of hot flushes per day	Median change from baseline at week 12 -5.5 P -9.7 T 2.5 -8.3 T 1.25 P < 0.001 for T 2.5 vs P P < 0.003 for T 125 vs P	Use reported values and calculate as for t-tests. Split placebo group in half. Will have to impute SDs and final scores, as changes cannot be pooled with final scores if SMDs are used.	Mean P: 10 - 5.85 = 4.15 T 2.5: 10 - 10 = 0 T 1.25: 10 - 8.32 = 1.68 SD	1.25 SMD: -0.5741771133 SE: 0.1532927 2.5 SMD: -0.9661562

Table 1. Details on RCTs assessing vasomotor symptoms requiring additional data or analysis before data synthesis *(Continued)*

			N P: 133 T 2.5: 125 T 1.25: 133 Actually, mean changes at week 12 and P values given in abstract T 2.5 vs P -10.14 vs -5.85, P < 0.001 T 1.25 vs P, week12 -8.32 P < 0.003	For baseline, take median of values from Hammar 2007 and Landgren 2002 6,6,8,8,8,9,9.7 Mean 7.8. Too low – Figure 2 shows large changes. Say, 10 P: 10 - 5.85 = 4.15 T 2.5: 10 - 10 = 0 T 1.25: 10 - 8.32 = 1.68 SDs too large when calculated from t-test. Use values from Langren: P: 3.93 T 2.5: 5.07 T 1.25: 4.45	P: 3.93 T 2.5: 5.07 T 1.25: 4.45 N P: 66 T 2.5: 125 T 1.25: 133	SE: 0.1599848
Vieira 2009	Placebo	Kupperman Index	Only overall Kupperman Index shown	Have contacted study authors, no reply		
Volpe 1986	Placebo HT	0 to 9 score, with 0 = absent, 3 = mild, 6 = moderate, 9 = severe Unclear whether intermediate scores are possible	Can extract means for 24 weeks for tibolone arm, placebo arm and each of several HT arms, which have been partially combined, from Figure 1 in the paper	No real way to calculate SD from info in the paper, and the scale is different from those used in other studies (so not reasonable to use one from another study)		
Wender 2004	Placebo	Kupperman Index	Only overall Kupperman Index shown	Have contacted study authors, no reply		

Table 2. Details on RCTs assessing vaginal dryness requiring additional data or analysis before data synthesis

Study	*Comparator*	*Outcome measure*	*Information available*	*Method used*	*Results for meta-analysis*	*SMD*
Hudita 2003	Placebo (3-arm study)	0 to 4 scale	From figure Week 24 P: 2.6	Split control group size between 2 arms Use known value from other study for SD	Mean P: 2.6 T 1.25 mg: 1	1.25mg SMD: -1.7751711 SE: 0.3262804

Table 2. Details on RCTs assessing vaginal dryness requiring additional data or analysis before data synthesis *(Continued)*

			T 1.25 mg: 1 T 2.5 mg: 0.9 N = 34/2 = 17 N = 45 N = 41	Use those from Nappi 2006a SD T: 0.89 HT: 0.89	T 2.5 mg: 0.9 N N = 34/2 = 17 N = 45 N = 41 SD P: 0.89 T 1.25: 0.89 T 2.5: 0.89	2.5mg SMD: -1.8843965 SE: 0.3373802
Kenemans 2009	Placebo	Vaginal dryness as binary	P: 33/1558 T: 19/1575	Convert OR to SMD	P: 33/1558 T: 19/1575	
Swanson 2006	Placebo (3-arm study)	0 to 3 score	Mean change from baseline at week 12 P: -0.2 T 2.5: -0.26 T 1.25: -0.39 N P: 133 T 2.5: 125 T 1.25: 133	Split control group size between 2 arms Calculate final means using baseline and change – but no baseline values given Would also need to use SDs from another study	Cannot use	
Huber 2002	HT	Vaginal dryness as binary	HT: 7/166 T: 6/158	Convert OR to SMD	HT: 7/166 T: 6/158	SMD: -0.06613757 SE: 0.34411866
Kokcu 2000	HT	Vaginal dryness as binary	HT: 0/21 T: 1/23	Convert OR to SMD	HT: 0/21 T: 1/23	SMD: 0.6382727 SE: 1.0064298
Ziaei 2010	HT and placebo	Vaginal dryness as binary Also, lubrication scores 1 to 5, higher is better – can reverse signs of mean differences	HT: 20/42 T: 33/47 P: 37/48 Mean HT: 4.93 T: 4.58 P: 3.65 SD HT: 1.95	Use the continuous data Calculate and reverse sign, so that greater = increased vaginal dryness	HT: 20/42 T: 33/47 P: 37/48	Using OR to SMD vs HT SMD: 0.5774306 0.2691251 vs placebo SMD -0.5904427 SE: 0.2096301 Using lubrication scores vs HT:

Table 2. Details on RCTs assessing vaginal dryness requiring additional data or analysis before data synthesis *(Continued)*

			T: 1.26 P: 1.81			SMD after switching sign: 0.2138954 SE: 0.2129393 vs placebo: SMD after switching sign: -0.1313959 SE: 0.2185150
Nappi 2006a	HT	Vaginal dryness 0 to 3 score	From Figure 4, mean at 6 months Mean T: 0.7 HC: 0.6 SD: can read SE off Figure 4 and calculate SD N = 20 both groups	SD: can read SE off Figure 4 and calculate SD T: 0.89 HT: 0.89	Mean T: 0.7 HC: 0.6 SD T: 0.89 HT: 0.89 N = 20	SMD: 0.1101248 SE: 0.3164674
Uygur 2005	HT	7-point scale with -3 as worsened a lot and 3 as improved a lot	6 months Mean (higher is better) HT: 0 T: 0.56 N HT: 34 T: 38	P < 0.05 given. Assume P = 0.05 and calculate SD, assuming equal in 2 groups: Gives SD = 1.7	Mean (higher is better) HT: 0 T: 0.56 N HT: 34 T: 38 Sd=1.7 for both	SMD after sign change: -0.3258676 0.2376236

APPENDICES

Appendix 1. Gynaecology and Fertility (GF) Specialised Register search strategy

Formerly known as the Menstrual Disorders and Subfertility database (MDSG)

Inception until 14.10.15

Keywords CONTAINS "climacteric "or "menopausal" or "*Menopause" or "postmenopausal" or "postmenopause" or "perimenopausal" or "perimenopause" or "vasomotor" or "hot flashes" or "hot flushes" or "night sweats" or "night time awakenings" or Title CONTAINS "climacteric "or "menopausal" or "*Menopause" or "postmenopausal" or "postmenopause" or "perimenopausal" or "perimenopause" or "vasomotor" or "hot flashes" or "hot flushes" or "night sweats" or "night time awakenings"

AND

Keywords CONTAINS "tibolone" or "Livial" or Title CONTAINS "tibolone" or "Livial" (289 hits)

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials (Ovid platform)

From inception until 14.10.15

1 exp climacteric/ or exp menopause/ or exp menopause, premature/ or exp perimenopause/ or exp postmenopause/ (5805)
2 (climacteric or menopaus$).tw. (5145)
3 (postmenopaus$ or perimenopaus$).tw. (10135)
4 exp Hot Flashes/ (514)
5 (hot flush$ or hot flash$).tw. (1247)
6 vasomotor.tw. (1057)
7 or/1-6 (14853)
8 (tibolone or tibilone).tw. (430)
9 17 hydroxy.tw. (29)
10 17 alpha.tw. (149)
11 (boltin or livial).tw. (44)
12 (liviella or tibofem).tw. (0)
13 xyvion.tw. (0)
14 (org od 14 or org od 4).tw. (26)
15 17 beta hydroxy$.tw. (8)
16 or/8-15 (625)
17 7 and 16 (399)

Appendix 3. MEDLINE(R) search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

From inception to 14.10.15

1 exp climacteric/ or exp menopause/ or exp menopause, premature/ or exp perimenopause/ or exp postmenopause/ (52515)
2 (climacteric or menopaus$).tw. (41594)
3 (postmenopaus$ or perimenopaus$).tw. (47307)
4 exp Hot Flashes/ (2625)
5 (hot flush$ or hot flash$).tw. (3908)
6 vasomotor.tw. (11184)
7 or/1-6 (100994)
8 (tibolone or tibilone).tw. (912)
9 17 hydroxy.tw. (553)
10 17 alpha.tw. (5521)
11 (boltin or livial).tw. (66)
12 (liviella or tibofem).tw. (0)
13 xyvion.tw. (0)
14 (org od 14 or org od 4).tw. (44)
15 17 beta hydroxy$.tw. (1658)
16 or/8-15 (8186)
17 randomized controlled trial.pt. (414057)
18 controlled clinical trial.pt. (91918)
19 randomized.ab. (335509)
20 placebo.tw. (173417)
21 clinical trials as topic.sh. (179333)
22 randomly.ab. (242103)
23 trial.ti. (147798)
24 (crossover or cross-over or cross over).tw. (66140)
25 or/17-24 (1025496)
26 (animals not (humans and animals)).sh. (4035803)
27 25 not 26 (944593)
28 7 and 16 and 27 (391)

Appendix 4. Embase search strategy

Database: Ovid Embase

From inception until 14.10.15

1 exp "menopause and climacterium"/ or exp climacterium/ or exp early menopause/ or exp menopause/ or exp postmenopause/ (94150)
2 (climacteric or menopaus$).tw. (56667)
3 (postmenopaus$ or perimenopaus$).tw. (61730)
4 vasomotor.tw. (12794)
5 exp hot flush/ (12544)
6 (hot flush$ or hot flash$).tw. (5365)
7 or/1-6 (145116)
8 exp Tibolone/ (2591)
9 (tibilone or tibolone).tw. (1219)
10 (boltin or livial).tw. (425)
11 17 beta hydroxy$.tw. (488)
12 17 hydroxy.tw. (573)
13 17 alpha.tw. (2144)
14 (liviella or tibofem).tw. (25)
15 xyvion.tw. (7)
16 (org od 14 or org od 4).tw. (105)
17 or/8-16 (5728)
18 Clinical Trial/ (851552)
19 Randomized Controlled Trial/ (385597)
20 exp randomization/ (68366)
21 Single Blind Procedure/ (21090)
22 Double Blind Procedure/ (124054)
23 Crossover Procedure/ (44662)
24 Placebo/ (264312)
25 Randomi?ed controlled trial$.tw. (124841)
26 Rct.tw. (18429)
27 random allocation.tw. (1456)
28 randomly allocated.tw. (23397)
29 allocated randomly.tw. (2061)
30 (allocated adj2 random).tw. (738)
31 Single blind$.tw. (16431)
32 Double blind$.tw. (155332)
33 ((treble or triple) adj blind$).tw. (491)
34 placebo$.tw. (221733)
35 prospective study/ (309654)
36 or/18-35 (1510043)
37 case study/ (34071)
38 case report.tw. (292028)
39 abstract report/ or letter/ (940292)
40 or/37-39 (1259859)
41 36 not 40 (1470095)
42 7 and 17 and 41 (979)

Appendix 5. PsycINFO search strategy

Database: Ovid PsycINFO

From inception until 14.10.15

1 exp menopause/ (3151)
2 (climacteric or menopaus$).tw. (4257)
3 (postmenopaus$ or perimenopaus$).tw. (2524)
4 vasomotor.tw. (1224)
5 or/1-4 (6700)
6 (tibilone or tibolone).tw. (33)
7 (boltin or livial).tw. (3)
8 (liviella or tibofem).tw. (0)
9 xyvion.tw. (0)
10 (org od 14 or org od 4).tw. (0)
11 17 hydroxy.tw. (34)
12 17 alpha.tw. (27)
13 17 beta hydroxy$.tw. (6)
14 or/6-13 (99)

15 5 and 14 (30)

Appendix 6. CINAHL search strategy

Database: Ovid CINAHL

From inception until 13.12.07

S28 S9 AND S26 AND S27 (80)

S27 S10 OR S11 OR S12 OR S13 OR S14 (593)

S26 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 (921,449)

S25 TX allocat* random* (4,096)

S24 (MH "Quantitative Studies") (12,613)

S23 (MH "Placebos") (8,922)

S22 TX placebo* (32,488)

S21 TX random* allocat* (4,096)

S20 (MH "Random Assignment") (38,014)

S19 TX randomi* control* trial* (78,710)

S18 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*)) (739,304)

S17 TX clinic* n1 trial* (166,477)

S16 PT Clinical trial (76,624)

S15 (MH "Clinical Trials+") (179,629)

S14 TX 17 beta hydroxy (5)

S13 TX (boltin or livial) (16)

S12 TX 17 alpha (314)

S11 TX 17 hydroxy* (251)

S10 TX (tibilone or tibolone) (147)

S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 (21,930)

S8 TX climacteri* (1,622)

S7 TX (postmenopaus* or perimenopaus*) (13,847)

S6 TX menopaus* (11,430)

S5 TX hot flash* (1,998)

S4 TX hot flush* (465)

S3 TX vasomotor (1,060)

S2 (MM "Postmenopause") (3,318)

S1 (MM "Climacteric"# OR #MM "Perimenopause"# OR #MM "Perimenopausal Symptoms"# OR #MM "Menopause+"# OR #MM "Hot Flashes"# (8,921)

Database: Ebsco CINAHL

From inception until 14.10.15

#	Query	Results
S28	S9 AND S26 AND S27	82
S27	S10 OR S11 OR S12 OR S13 OR S14	645
S26	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25	990,143
S25	TX allocat* random*	4,464
S24	(MH "Quantitative Studies")	13,814
S23	(MH "Placebos")	9,427
S22	TX placebo*	34,772
S21	TX random* allocat*	4,464
S20	(MH "Random Assignment")	39,802
S19	TX randomi* control* trial*	93,467
S18	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	789,912
S17	TX clinic* n1 trial*	175,948
S16	PT Clinical trial	78,685
S15	(MH "Clinical Trials+")	192,364
S14	TX 17 beta hydroxy	5
S13	TX (boltin or livial)	18
S12	TX 17 alpha	338
S11	TX 17 hydroxy*	281
S10	TX (tibilone or tibolone)	153
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	23,371
S8	TX climacteri*	1,799
S7	TX (postmenopaus* or perimenopaus*)	14,679
S6	TX menopaus*	12,192
S5	TX hot flash*	2,163
S4	TX hot flush*	484

(Continued)

S3	TX vasomotor	1,147
S2	(MM "Postmenopause")	3,604
S1	(MM "Climacteric") OR (MM "Perimenopause") OR (MM "Perimenopausal Symptoms") OR (MM "Menopause+") OR (MM "Hot Flashes")	9,562

WHAT'S NEW

Date	Event	Description
23 November 2016	Review declared as stable	We have made this a stable review as further evidence is unlikely to change its conclusions.

HISTORY

Protocol first published: Issue 6, 2010
Review first published: Issue 2, 2012

Date	Event	Description
15 September 2016	New search has been performed	Updated version
15 September 2016	New citation required but conclusions have not changed	Thirteen new studies (Baracat 2002; Benedek-Jaszmann 1987; Bouchard 2012; Gupta 2013; Jacobsen 2012; Mendoza 2000; Morais-Socorro 2012; Okon 2005; Polisseni 2013; Ross 1999; Uygur 2005; Volpe 1986; Wender 2004) added and additional data included for one study (Langer 2006). Two reports of the same study (Ziaei 2010) amalgamated. Total of 46 studies in updated review
20 September 2010	New search has been performed	Contact details updated.
9 February 2010	Amended	made corrections according to Editorial Board's requests
23 March 2006	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Giulio Formoso: co-ordinated the review; contributed to study screening, quality appraisal, data extraction and interpretation; wrote the final texts.

Enrica Perrone: contributed to study screening, quality appraisal, data extraction and interpretation; provided relevant feedback on the final texts.

Susanna Maltoni: performed previous work that was the foundation of the current study; participated in conceiving the review and co-ordinated protocol development; contributed to study screening, quality appraisal, data extraction and interpretation.

Sara Balduzzi: contributed to study screening, quality appraisal, data extraction and interpretation; provided statistical support.

Jack Wilkinson: extracted, analysed and contributed to interpretation of data from RCTs assessing vasomotor symptoms and vaginal dryness; contributed to related portions of the text.

Vittorio Basevi: performed previous work that was the foundation of the current study; participated in conceiving the review and in protocol development; provided constant support in interpreting the clinical relevance of data; provided relevant feedback on the final texts.

Anna Maria Marata: performed previous work that was the foundation of the current study; participated in conceiving the review and in protocol development; provided support in interpreting the clinical relevance of data.

Nicola Magrini: provided relevant feedback in interpreting the clinical relevance of data and in reviewing the final texts.

Roberto D'Amico: participated in conceiving the statistical methods of the review and in protocol development; participated in study screening; provided statistical support.

Chiara Bassi: designed search strategies at the protocol stage.

Emilio Maestri: performed previous work that was the foundation of the current study; participated extensively in conceiving the review and in protocol development; provided support in interpreting the clinical relevance of data; provided relevant feedback on the final texts.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Emilia-Romagna Health and Social Policies Directorate, Italy.

  Emilia-Romagna Health and Social Policies Directorate, Italy, provided the salary for reviewers

External sources

- Cochrane Gynaecology and Fertility Group, New Zealand.

  Provided feedback and support during the whole review process; provided bibliographic support

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Title: We changed the protocol title ("Tibolone for menopausal symptoms") to "Short-term and long-term effects of tibolone in postmenopausal women", because the review is focused mostly on the long-term safety of tibolone (in particular for the incidence of breast and endometrial cancer and of cardiovascular events, which were included among the primary outcomes - see next paragraph), in addition to its efficacy for symptoms. Protocol criteria allowed the inclusion of RCTs testing tibolone also in women without menopausal symptoms, as far as safety data were reported; in fact, the largest trial in the review tested the effects of tibolone in osteoporotic women. Therefore, the title "Tibolone for menopausal symptoms" would have been misleading. The new title is consistent with Cochrane editorial policies, using the [Intervention] in OR for [participant group/location] structure, as proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Table 4.2.a: Structure for Cochrane review titles). Moreover, "short-term and long-term effects" helps to suggest that the goal is to review short-term and especially long-term safety, in addition to symptom improvement in the short term.

Outcomes: Given the importance of safety in the objectives of the review, we followed reviewers' suggestions to include major adverse events (breast cancer, endometrial cancer, venous thromboembolic events, cardiovascular events, cerebrovascular events and mortality from any cause) as primary outcomes, along with reduction in symptoms and shifting genital symptoms (excluding vaginal bleeding because it may also be a drug-related adverse event) as secondary outcomes. We evaluated cardiovascular and cerebrovascular events separately and added endometrial hyperplasia as a secondary outcome. We no longer considered irregular menstrual periods.

In previous versions of the review, we applied the criterion that *To be eligible for inclusion in the review, studies had to report useable data on one of more of the outcomes listed below* (in our list of included outcomes), although we did not explicitly state this. In line with current Cochrane methods, we now include all studies that measured our outcomes of interest, even if they were not reported in a useable format.

Statistical methods: We did not fully anticipate at the protocol stage the variation in reporting of the primary outcome, vasomotor symptoms, and so, some of the methods for combining these data in meta-analysis (explained in the Methods section) are necessarily post hoc and data driven in nature. Although we believe we have reached the most appropriate conclusion given the available information, another review team may have made different decisions in relation to the analysis and could plausibly have arrived at a different conclusion. We have attempted to make our methods transparent, so that the competent reader may determine their suitability for herself.

Aside from data on vasomotor symptoms, vaginal dryness and sleep (as explained in the Methods section), we did not combine outcomes by using the fixed-effect model (as stated in the protocol); we used the random-effects model instead, because it takes population heterogeneity into better account. We considered that two of the major RCTs (Cummings 2008; Kenemans 2009) studied very heterogeneous populations (women who had had breast cancer and osteoporotic women, respectively), whose characteristics differ widely from women taking hormonal therapies for postmenopausal symptoms. A recent textbook (Borenstein 2009) highlights (page 86): “The selection of a model must be based solely on the question of which model fits the distribution of effect sizes, and takes account of the relevant source(s) of error. When studies are gathered from the published literature, the random-effects model is generally a more plausible match”.

Subgroup analyses: As two of the largest RCTs selected very specific populations, it was considered informative to present, together with a full analysis set, results on breast cancer distinguishing patients who had already had breast cancer from those who had not, and distinguishing results on cardiovascular and cerebrovascular events for patients under and over 60 years of age. As stated in the protocol, we also considered subgroup analyses based on methodological risks of bias components and duration of treatment. We eventually did not perform these, given the lack of studies in most of the strata.

We took the "multi-centre" item out of the risk of bias tables because participation of more centres in an RCT should mainly increase its external rather than internal validity. However, we kept this information in the "Notes" items under Characteristics of included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Breast Neoplasms [chemically induced] [prevention & control]; Dyspareunia [drug therapy]; Estrogen Receptor Modulators [adverse effects] [*therapeutic use]; Estrogen Replacement Therapy [adverse effects] [*methods]; Hot Flashes [*drug therapy]; Neoplasm Recurrence, Local [chemically induced]; Norpregnenes [adverse effects] [*therapeutic use]; Postmenopause [*drug effects]; Randomized Controlled Trials as Topic; Stroke [chemically induced]; Sweating [drug effects]; Uterine Hemorrhage [chemically induced]

MeSH check words

Aged; Female; Humans; Middle Aged