Testosterone for peri and postmenopausal women (Review)

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[Intervention Review]

Testosterone for peri and postmenopausal women

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ABSTRACT

Background

The question of whether adding testosterone therapy to conventional postmenopausal hormone therapy (HT) is effective or safe is unresolved. Therefore, we aimed to determine the efficacy and safety of testosterone therapy for postmenopausal women using HT.

Objectives

To determine the benefits and risks of testosterone therapy for postmenopausal women taking HT.

Search strategy

We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (searched 21 July, November 2008), *The Cochrane Library* (2008, Issue 3), MEDLINE (1966 to July 2008), EMBASE (1980 to July 2008), Biological Abstracts (1969 to 2008), PsycINFO (1972 to July 2008), CINAHL (1982 to July 2008), and reference lists of articles. We also contacted pharmaceutical companies and researchers in the field.

Selection criteria

Studies included randomised comparisons of testosterone plus HT versus HT alone in peri or postmenopausal women.

Data collection and analysis

Two review authors independently assessed the quality of the trials and extracted data. For dichotomous outcomes, a Peto odds ratio (OR) and its 95% confidence interval (CI) were calculated. For continuous outcomes, non-skewed data from valid scales were synthesized using a weighted mean difference or standardized mean difference. If statistical heterogeneity was found, a random-effects model was used and reasons for the heterogeneity were explored and discussed.

Main results

Thirty-five trials with a total of 4768 participants were included in the review. The median study duration was six months (range 1.5 to 24 months). Most of the trials were of adequate quality with regard to randomisation and concealment of allocation sequence. The major methodological limitations were attrition bias and lack of a washout period in the crossover studies. The pooled estimate suggested that the addition of testosterone to HT regimens improved sexual function scores and number of satisfying sexual episodes for

postmenopausal women. Significant adverse effects were decreased high-density lipoprotein (HDL) cholesterol levels and an increased incidence of hair growth and acne. The discontinuation rate was not significantly greater with the addition of testosterone therapy (OR 0.99, 95% CI 0.83 to 1.19).

Authors' conclusions

There is good evidence that adding testosterone to HT has a beneficial effect on sexual function in post-menopausal women. However, the combined therapy is associated with a higher incidence of hair growth and acne and a reduction in HDL cholesterol. These adverse events may differ by the different doses and route of testosterone administration. There is insufficient evidence to determine the effect of testosterone in long term use.

PLAIN LANGUAGE SUMMARY

Testosterone for perimenopausal and postmenopausal women

There is good evidence that adding testosterone to hormone therapy (HT) has a beneficial effect on sexual function in postmenopausal women. However, the combined therapy is associated with a higher incidence of hair growth and acne and a reduction in high-density lipoprotein (HDL) cholesterol. These adverse events may vary with different doses and routes of administration of testosterone. Adding testosterone to HT did not increase the number of women who stopped HT therapy.

BACKGROUND

Description of the condition

The role of testosterone in women

Biological data support important physiological effects of testosterone in women. Testosterone acts directly via androgen receptors throughout the body, including in areas such as the brain, particularly the hypothalamus and amygdala; and at peripheral sites including bone, breast, skin, skeletal muscle, and adipose, vascular, and genital tissues (Davis 1995). The effects of testosterone are also mediated by aromatization to oestrogens as androgens are the essential precursor hormones for oestrogen biosynthesis in the ovaries and extra-gonadal tissues (Simpson 2000). Imbalance in androgen biosynthesis or metabolism in women may have undesirable effects on any or all of these systems. Exogenous testosterone may influence sexual desire, bone mineral density, muscle mass, adipose tissue distribution, mood, energy, and psychological well being (Burger 1984; Burger 1987; Davis 1995; Sherwin 1988; Sherwin 1988). Recognised causes of low testosterone production include hypopituitarism, adrenal insufficiency, premature ovarian failure, bilateral oophorectomy, oral glucocorticosteroid therapy, and oral oestrogen therapy (Davis 1995; Bachmann 2002; Burger 2002).

Effects of menopause on testosterone levels

Most studies addressing the changes in androgen levels with age have been limited by: the inclusion of small numbers of women with limited age ranges (Labrie 1997; Zumoff 1995), reproductive status (Pfeilschifter 1996; Randolph 2003), insensitivity of assays for the measurement of total and free testosterone levels in the female range (Burger 2000) and, for blood sampling, failure to take into account the cyclical variations in androgen levels (Overlie 1999; Rannevik 1995). In the late reproductive years there is a loss of the midcycle rise in free testosterone that characterizes the menstrual cycle in young ovulating women (Mushayandebvu 1996). To establish whether testosterone levels decline during the menopause transition, it is necessary to measure testosterone at times other than during the early follicular phase nadir that is evident in premenopausal women. A large cross-sectional study of 1423 women aged 18 to 75 years, randomly recruited from the community, and not seeking health care was undertaken to document androgen levels by decade of age (Davison 2005). Total testosterone was measured by a direct, manual radioimmunoassay method which is a clinically useful assay for the study of the 'low' testosterone levels within the female population. Free testosterone was calculated using the Sodergard equation (Sodergard 1982). This free testosterone estimate has been demonstrated to have a strong correlation with levels measured by equilibrium dialysis, which is generally considered the most accurate method of measuring free testosterone. The results of the study showed a decline in total and free testosterone, dehydroepiandrosterone sulphate (DHEAS), and androstenedione with age, commencing in the mid 30s (Davison 2005). An effect of natural menopause on circulating androgen levels was not found, which contrasts with the sharp decline in estradiol that occurs at this time (Davison 2005). These findings provide suggestive data that testosterone levels do not change across the menopause transition. In the same study

postmenopausal oophorectomised women had lower total and free testosterone levels than non-oophorectomised women, suggesting that the postmenopausal ovary remains a source of testosterone production.

Proposed female androgen insufficiency syndrome

It has been proposed that insufficient testosterone production in women may result in lowered sexual desire and arousal, and diminished well being (Bachmann 2002). However, there are no substantial data to support this hypothesis and no 'cut-off' level of testosterone has been demonstrated as a diagnostic indicator of female androgen insufficiency. In contrast, in women younger than 45 years low domain scores for desire, arousal, and responsiveness were associated with higher odds of having DHEAS levels in the lowest 10th centile. In women over 45 years of age a low domain score for responsiveness was associated with higher odds of having DHEAS levels in the lowest 10th centile (Davis 2003). The concept of female androgen insufficiency is primarily supported by results from therapeutic trials. However, demonstration of the clinical efficacy of testosterone therapy is only surrogate evidence for a female androgen insufficiency syndrome, which still remains to be appropriately researched.

Description of the intervention

Testosterone therapy for postmenopausal women

Results from several randomised controlled trials suggest that testosterone therapy has additional benefits for the health of postmenopausal women when compared with the use of HT alone. Proposed benefits include effects on sexual function, mood, bone density, and increased lean body mass (Burger 1984; Burger 1987; Davis 1995; Sherwin 1987a; Shifren 2000). These studies have not been systematically reviewed. Based on clinical data, potential risks of testosterone therapy include acne, excess facial and body hair, deepening of the voice, weight gain, emotional changes, and adverse effects on lipid profiles (Bachmann 2002). Lower high-density lipoprotein (HDL) cholesterol, increased hematocrit, and abnormal liver function tests have been reported with higher doses of oral methyltestosterone (Bachmann 2002). Cases of hepatotoxicity were associated with oral administration of methyltestosterone in men treated with dosages of 10 to 100 mg/day (Foss 1959). The incidence of toxic hepatitis in a study that involved 572,794 women who were exposed to oral esterified oestrogen plus methyltestosterone was 3 per 100,000 person-years (Ettinger 1998). The long-term effects of testosterone on breast and other cancers, cardiovascular disease, and stroke is unknown. As androgens are converted to oestrogens in vivo oestrogenic side effects are also potential consequences of androgen therapy, such as effects on the breast and endometrium.

How the intervention might work

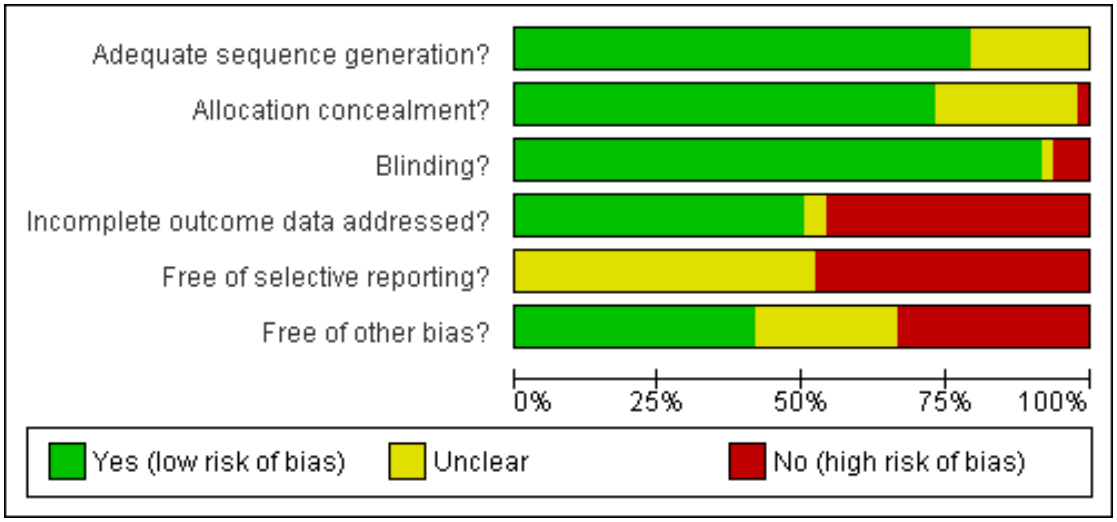
Mechanism of action of testosterone

Testosterone may act in a variety of ways in the different tissues but this is an area that requires further investigation. Primarily the testosterone action is likely to be directly via the androgen receptor (AR). However, testosterone is an important precursor for oestradiol production in target tissues. Thus the testosterone action may be as a consequence of conversion to oestradiol and then genomically via alpha or beta oestrogen receptors (ER), or non-genomically via other oestrogenic mechanisms. Grohe et al reported a series of elegant experiments in which they demonstrated local oestrogen biosynthesis from testosterone in cardiac myocytes and the subsequent activation of ER alpha and beta and downstream target genes, in a gender-based fashion. In a mechanistic randomised controlled trial of oestrogen replete postmenopausal women, aromatase inhibition did not alter the effects of testosterone therapy on improved sexual function, mood, and well being. Testosterone levels were restored to within the normal premenopausal range.

Why it is important to do this review

In our first version of this Cochrane review, a meta-analysis of two (and for some outcomes three) fair quality, randomised, controlled trials (Figure 1) comparing hormone therapy (HT) alone and with testosterone (T+HT) indicated that the latter improved libido by 0.42 points (95% CI 0.18 to 0.66), the mean composite score for sexual function by 0.41 points (95% CI 0.15 to 0.67), and the mean score for sexual activity by 1.00 point (95% CI 0.4 to 1.58). Thus, the evidence supported the beneficial effect of testosterone therapy on sexual health among postmenopausal women. A decrease in HDL cholesterol levels was a significant adverse effect. The discontinuation rate was not significantly greater with testosterone therapy than with HT alone. There was insufficient evidence of a treatment effect for other outcomes.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



For the Cochrane Review the results from this small number of studies were pooled so that the power of the meta-analysis to provide conclusions about efficacy and safety was limited. In addition, the meta-analysis combined studies using different testosterone regimens. It was thus difficult to estimate the effect of testosterone on sexual function in association with any individual HT formulation. Moreover, the subgroup analysis according to type of menopause, natural versus surgical, was not performed due to the limited number of studies. Therefore, it was uncertain as to whether the benefits and risks would differ according to type of menopause.

Since the cut-off date for publications in the initial Cochrane review, several clinical trials of testosterone therapy in postmenopausal women have been published (Braunstein 2005; Buster 2005; Chiuve 2004; Davis 2006; Floter 2002b;Floter 2004 Floter 2005; Leao 2006; Matthews 2005; Nathrost-Boos 2006;Nathorst-Böös 2005; Shifren 2006; Simon 2005; Warnock 2005; Zang 2006). Inclusion of these recent trials in this review increases the power of the meta-analyses to provide precise conclusions about efficacy and safety and so provide valuable evidence for clinical practice.

OBJECTIVES

To determine the benefits and risks of testosterone therapy for peri and postmenopausal women taking HT.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were considered for inclusion in the review. We excluded quasi-randomised controlled trials.

Types of participants

Study participants included perimenopausal women and women who had either a natural or surgically-induced menopause, regardless of ethnicity and duration of HT before randomisation.

Diagnostic criteria were as follows.

1) A naturally menopausal woman was defined as:

- a woman with an intact uterus who had had spontaneous amenorrhoea for at least 12 months, with a low serum oestradiol level or an elevated serum level of follicle stimulating hormone (FSH) in the postmenopausal range, or both;
- a woman who had had a hysterectomy and who had one or both ovaries conserved at hysterectomy with a low serum oestradiol level or an elevated serum level of FSH in the postmenopausal range, or both.

2) A surgically menopausal woman was defined as a woman who had undergone a bilateral oophorectomy.

3) A perimenopausal woman was defined as a woman who had experienced any symptom of approaching menopause and had an elevated serum level of FSH in the postmenopausal range and the final menstrual period was in a period less than 12 months prior to participating in the study.

We included all studies irrespective of prerequisite signs and symptoms of menopause before randomisation.

Types of interventions

Testosterone plus HT in all formulations versus HT alone in peri or postmenopausal women.

HT was defined as unopposed oestrogen therapy or oestrogen therapy with combined cyclic or continuous progestin therapy.

Studies that combined those interventions with other complementary therapies, such as vitamin or mineral supplements, diet, or exercise were considered for inclusion. The minimum period of acceptable treatment was four weeks.

Types of outcome measures

The following outcomes were recorded, if the information was available.

1. Major outcomes:

1.1 sense of well being, measured and scored by validated questionnaires for example the psychological general well-being index (PGWB);

1.2 unexplained fatigue, measured and scored by validated questionnaires;

1.3 sexual function, measured and scored by validated questionnaires in all aspects including libido, activity, satisfaction, pleasure, fantasy, and orgasm.

2. Minor outcomes.

2.1. Benefits:

2.1.1. bone health,

2.1.1.1. incidence of osteoporotic fracture,

2.1.1.2. bone mineral density;

2.1.2. body composition, measured in various aspects including body weight, body mass index, hip and waist circumferences;

2.1.3. cognition measured and scored by validated questionnaires;

2.1.4. menopausal symptoms measured and scored by validated questionnaires in the dimensions of psychological, somatic, vasomotor symptoms, and urogenital symptoms.

2.2. Adverse events:

2.2.1. increased facial and body hair growth, measured and scored by validated scales;

2.2.2. acne, measured and scored by known scales;

2.2.3. mood change, specifically aggression as measured and scored by validated questionnaires;

2.2.4. breast cancer,

2.2.4.1. mammographic findings,

2.2.4.2. incidence of breast cancer;
2.2.5. coronary heart disease, defined as acute myocardial infarction and silent myocardial infarction;
2.2.6. discontinuation rate;
2.2.7. lipid profile, measured as total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides;
2.2.8. coagulation parameters.

Search methods for identification of studies

The search strategy of the Menstrual Disorders and Subfertility Group (MDSG) (see Review Group details for more information) was used for the identification of randomised controlled trials (RCTs). All trials conducted from 1966 onwards were examined for eligibility regardless of language.

1) The MDSG Trials Register was searched for any trials using a combination of terms (menopause, post menopause, testosterone, androgens, and oestrogen) present in the title, abstract, or keywords section. See the Review Group for more details on the make-up of the Specialised Register.
2) The following electronic databases were searched using Ovid software:
MEDLINE (1966 to 21st July 2008);
EMBASE (1980 to 21st July 2008);
Bio Abstracts (1980 to 21st July 2008);
CINAHL (1982 to 21st July 2008);
PsycINFO (1974 to 21st July 2008).
See Appendix 1; Appendix 2; Appendix 3; Appendix 4.
3) The MetaRegister of Controlled Trials (mRCT), which contains a number of databases of recent or ongoing trials, was searched for any trials with the following words: postmenopause, androgen, testosterone, oestrogen. This meta-database includes the National Research Register (NRR), entries from the Medical Research Council's Clinical Trials Register, and details on reviews in progress collected by the NHS Centre for Reviews and Dissemination.
4) Additional unpublished trials were identified from citation lists of relevant articles, communication with the corresponding authors of relevant articles, experts, and pharmaceutical companies.
5) The MDSG Specialised Register also included results from handsearching the following relevant journals for RCTs. We searched for any trials on androgen or testosterone that involved peri and postmenopausal women in:

Acta Europaea Fertilitatis (1969 to 1989 infertility RCTs only, 1990 on);
American Journal of Reproductive Immunology and Microbiology (1980 to 1990);
Andrologia (1980 to 1990 searched for infertility RCTs only, 1991 on);
Archives of Andrology (1978 to 1992 searched for infertility RCTs only, 1993 on);
Climacteric (1998 on);
Epidemiology (1990 to 1995);
Fertility and Sterility (1950 on);
Gynecological Endocrinology (1987 on);
Gynaecological Endoscopy (1991 on);
Human Reproduction (1986 on);
International Journal of Andrology (1978 to 1992 searched for infertility RCTs only, 1993 on);
International Journal of Fertility and Women's Medicine (previously International Journal of Fertility Menopausal Studies and International Journal of Fertility) 1968 - ongoing
Journal of Andrology (1980 to 1990 searched for infertility RCTs only, 1991 on);
Journal of Assisted Reproduction and Genetics (formerly Journal of In Vitro Fertility and Embryo Transfer, 1984 to 1991), 1984 to 1992 searched for infertility RCTs only, 1993 on);
Journal of Reproduction and Fertility (1966 to 1990 searched for infertility RCTs only, 1992 on);
Maturitas (1978 on);
Molecular Reproduction and Development (Formerly Gamete Research, 1978 to 1990) (1978 to 1992 infertility RCTs only, 1993 on);
Pediatric Perinatal Epidemiology (1987 to 1995);
Reproduction, Fertility, and Development (Clinical Reproduction and Fertility, 1982 to 1990) (1982 to 1993 searched for infertility RCTs only, 1982 on).

Data collection and analysis

1) Study selection
Selection of trials was performed by one of the review authors (WS) after employing the search strategy described above. WS obtained copies of the full text articles and made copies in which details of the authors and institutions had been struck out and the results section removed for RB. Each study identified by the search strategy was independently assessed against the inclusion criteria by two of the review authors (RB and WS). If necessary, SD sought additional information from the principal investigators of the study. If there was any study that did not contain enough detail to be examined, that study was listed in the awaiting assessment section of the review.
2) Assessment of methodological quality
Included trials were independently assessed by two of the review authors (RB and WS) for the following quality criteria and methodological details, using the standard checklist developed by the MDSG. Any disagreement in eligibility or quality assessment was discussed in detail. Major quality criteria were established to enable future sensitivity analyses.

Trial characteristics

1. Internal validity

1.1. Was the assigned treatment adequately concealed prior to allocation (scored according to the categories used by The Cochrane Collaboration)?
A. Adequate
B. Unclear
C. Inadequate
D. Not used
1.2. Were the outcomes of participants who withdrew or were excluded after allocation described and included in an intention-to-treat analysis?
A. Intention-to-treat
B. No intention-to-treat
C. Unclear
1.3. Were the outcome assessors blind to assignment status?
A. Yes
B. No
C. Unclear
1.4. Were the treatment and control groups comparable at entry?
A. Yes
B. No
C. Unclear
1.5. Were the participants blind to assignment status following allocation?
A. Yes
B. No
C. Unclear
1.6. Were the treatment providers blind to assignment status?
A. Yes
B. No
C. Unclear
1.7. Were the care programs, other than the trial options, identical?
A. Yes
B. No
C. Unclear
1.8. Were the withdrawals < 10% of the study population
A. Losses and withdrawals of less than 10%
B. Losses and withdrawals of 10% or more
C. Not reported or unclear
1.9. Method of randomisation
A. Truly randomised: centralised randomization scheme or on-site computer system with concealment of allocation or sequentially numbered, sealed opaque envelopes.
B. Pseudo randomised: alternating record numbers or dates of birth, or open list of random numbers or open envelopes or tables.
C. Not stated
2. External Validity
2.1. Were the inclusion and exclusion criteria for entry clearly defined?
A. Yes
B. No
C. Unclear
2.2. Were the outcome measures used clearly defined?
A. Yes
B. No
C. Unclear
2.3. Were the accuracy, precision, and observer variation of the outcome measures adequate?
A. Yes
B. No
C. Unclear
2.4. Was the timing of the outcome measures appropriate?
A. Yes
B. No
C. Unclear
2.5. Was a power calculation done?
2.6. Source of funding, if stated
This information was presented in the table 'Characteristics of included studies' and provided a context for discussing the reliability of the results.
3) Data collection
WS then provided RB with the results sections of the included studies and both review authors independently extracted information using the pro forma's designed by the Review Group. Discrepancies were resolved by discussion and a third review author (SD), if necessary. For each included trial, information was collected regarding the location of the study, methods of the study (as per the quality assessment checklist), the participants (age range, eligibility criteria), the nature of the interventions, and data relating to the outcomes, as follows.

Characteristics of the study participants
1. Age and menopausal status
2. Criteria for confirming menopausal status
3. Natural versus surgically induced menopause
4. The location of the study, and source of recruitment of participants
5. Ethnicity
6. Inclusion criteria
7. Exclusion criteria
8. Baseline quality of treatment groups
A. Groups balanced in terms of age and other variables(dependent on outcome of interest), e.g. baseline sexual function score, well-being score, bone mineral density, lipid profile, body composition, menopausal symptoms, cognition, and hormonal profile
B. Groups not balanced
C. Balance not reported
Intervention used
1. Types of therapies used
2. Mode of administration
3. Doses administered
4. Duration of treatment
Outcomes relevant to this analysis were as follows.
Benefits: sense of well being, improvement of unexplained fatigue, sexual functioning, bone health, body composition, cognition,

and menopausal symptoms.
Risks: hirsutism, acne, mood alteration, breast cancer, coronary heart disease, haematocrit, lipid profile, coagulation profile, and discontinuation rate.
Where possible, missing data were sought from the authors by SD.

4) Analysis
Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by the Menstrual Disorders and Subfertility Group. Heterogeneity (variation) between the results of different studies was examined by inspecting the scatter in the data points on the graphs and the overlap in their confidence intervals and, more formally, by checking the results of the chi square tests. Where possible, the outcomes were pooled statistically.
The following outcomes were presented as follows, if the information was available.
1. Primary outcomes
1.1. Sense of well being (as the percentage of women who improved or did not improve, mean or median of per cent change)
1.2. Unexplained fatigue (as the percentage of women who improved or did not improve, mean or median of per cent change)
1.3. Sexual function (as percentage of women who improved or did not improve, mean or median of per cent change)
2. Secondary outcomes
2.1. Benefits
2.1.1. bone health:
2.1.1.1. incidence of osteoporotic fracture (the number of osteoporotic fractures per year in each treatment group),
2.1.1.2. biochemical markers (as the percentage of women for whom there was an increase, no change, or a decrease in each marker; mean or median of per cent change in each marker),
2.1.1.3. bone mineral density (as percentage of women for whom there was an increase, no change, or decrease at each site (femur, lumbar spines, wrist); mean or median of per cent change at each site);
2.1.2. body composition (percentage of women for whom there was an increase, no change, or decrease; mean or median of percentage change in each value);
2.1.3. cognition (percentage of women who improved or did not improve; mean or median of percentage change);
2.1.4. menopausal symptoms (percentage of women who improved or did not improve; mean or median of percentage change).
2.2. Adverse events:
2.2.1. increased facial and body hair growth (percentage of women who did or did not have a change in score or who reported this side effect);
2.2.2. acne (percentage of women who have or do not have the side effect);
2.2.3. mood alteration, specifically aggression (percentage of women who experienced an increase, no change, or decrease);
2.2.4. breast cancer,
2.2.4.1. breast cell proliferation (percentage of women with decreased, stable, or increased breast cell proliferation),
2.2.4.2. mammographic finding (percentage of women with decreased, stable, or increased mammographic density or difference in mean dense area),
2.2.4.3. incidence of breast cancer (as percentage of women who did or did not develop breast cancer);
2.2.5. coronary heart disease (as the number of events per year);
2.2.6. discontinuation rate (percentage of women who discontinued treatment);
2.2.7. haematocrit (percentage of women for whom there was an increase, no change, or decrease; mean or median of percentage change);
2.2.8. lipid profile (percentage of women for whom there was an increase, no change, or decrease; mean or median of per cent change in each value);
2.2.9. coagulation profile (mean or median of percentage change).
The criteria for improvement in the particular outcomes were as defined by the trialist's.

For dichotomous data, results for each study were expressed as an odds ratio (OR) with 95% confidence intervals (95% CI) and combined for meta-analysis with RevMan software using the Peto method and a fixed-effect model.
For continuous data, results from each study were expressed as a weighted mean difference (WMD) with 95% CI and combined for meta-analysis. The fixed-effect model was used to calculate a simple weighted average of the study results. However if there was statistical heterogeneity (the test for heterogeneity results in a P-value of 0.05 or less), the random-effects model was used and reasons for the heterogeneity were explored and discussed. However, standardized mean differences were used if it was necessary to summarize results across studies with continuous data outcomes that were conceptually the same but were measured in different ways. Meta-analytic methods for continuous data assumed that the underlying distribution of the measurements was normal. Where data were skewed and results were reported in the publication as median and range using non-parametric tests of significance, the results were also reported in the 'Other data' section of the review (Table 1).

Table 1. Trial outcomes not included in the meta-analysis

Outcome	Study ID	N	Reason	Conclusion
Acne	Barrett-Connor 1999	291	The data was not available	Acne of mild or moderate severity was reported by 5 (3%) estrogen-testosterone treated participants, whereas no participants receiving oestrogen reported acne
Biochemical Markers of bone metabolism	Floter 2002b (Floter 2005)	50	A crossover study with no washout period	Both treatments had similar effects, with a significant decrease in bone resorption (ICTP) and bone turnover (osteocalcin) after 24 weeks. A 12% reduction in PICP during HT treatment was reversed by the addition of testosterone, and no significant decline was recorded during T-HT treatment
Biochemical markers of bone metabolism	Miller 2000	57	The data was likely to be skewed because the means were smaller than twice the SDs	There were no between group differences noted in baseline Dpd levels(p=0.111), Dpd% change (P=0.338), baseline NTx levels (P=0.112), or NTx % change (P=0.271)
Biochemical markers of bone metabolism	Raisz 1996	28	The data was not available	The effects of oestrogen-testosterone and oestrogen alone on markers of bone resorption were generally similar. The increase in bone formation markers after oestrogen-testosterone treatment was significantly different from the effect of oestrogen for all bone formation parameters.
Bone mineral density of lumbar spine and femur	Barrett-Connor 1999	199	The data was not available	BMD increased in the estrogen-testosterone(low dose) were comparable to those in the oestrogen(low dose) group, while the BMD changes at 24 months in the estrogen-testosterone(high dose) group significantly exceeded those in oestrogen(high dose) group(P=0.014 for lumbar spine,

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

				BMD and P=0.009 for total hip BMD)
Bone mineral density	Floter 2002b (Floter 2005)	50	A crossover study with no washout period.	No changes in BMD were noted in the total body, hip, or lumbar spine with either regimen
Bone mineral density	Garnett 1992	50	The data was not available.	There was no significant differences in bone density at any of the sites measured between women receiving oestrogen alone and those receiving estrogen-testosterone. No treated subjects had a significant bone loss(more than twice the measurement precision) at either spine or femoral neck at 1 year, but three in each treated group showed a small but non significant decrease at both sites
Bone mineral density of L1-L4, femur and forearm	Watts 1995	48	The data was not available	The estrogen-testosterone showed significant increases in spinal BMD at 12 and 24 months(P<0.01). The estrogen group demonstrated a non significant increase in spinal BMD. The difference between groups was not significant at 12 or 24 months. There were no significant changes in BMD from baseline in either group at the radius, femoral neck, Ward triangle, or greater trochanter
Body composition	Dobs 2002	40	It was unclear with regard to the standard deviation (SD) of the data	- When compared with oestrogen alone, estrogen-testosterone treatment significantly increased lean body mass in the arms, legs, and trunk. Body fat percentage decreased significantly from baseline in the same arms, legs, and trunk in the oestrogen-testosterone group but not the oestrogen alone group. When changes in arms, legs, and trunk in each participant were analysed simultaneously, the difference between treatments was significant

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

				for lean body mass(P=0.007) and percentage of fat tissue(P=0.077)
Body composition	Floter 2002b (Floter 2005)	50	A crossover study with no washout period	There was no significant differences in total body fat, total lean body mass, trunk fat, and trunk lean mass between the two treatments
Body composition	Leao 2006	37	The data was likely to be skewed	When compared to HT alone, T-HT treatment significantly increased visceral fat area (P = 0.009). However there was no significant difference in subcutaneous fat area between the two groups
Cognition and psychological well being	Regestein 2001	42	A crossover study with no washout period	Switching Attention Test that mean reaction time in the switching condition was faster in the estrogen-testosterone group than in the estrogen group(t=3.25, df=37, P<0.002, effect size = 0.53 SD). For other conditions of the same test, such as side condition and direction condition, they did not differ between two groups. There were no other effects of added methyltestosterone found on psychological, sleep, and exercise measures
Cognition	Sherwin 1988	49	The data was not available	There was no comparative effects between oestrogen-testosterone and oestrogen alone group. The women treated with all hormone preparations were higher during both treatment phases compared to scores of women who received placebo (P<0.01)
Cognition	Shepanek 1999	30	The data was likely to be skewed	No significant interactions were found showing an advantage for oestrogen-testosterone treated group as contrasted to oestrogen-treated group

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

Cognition (Cube Comparisons and Building Memory)	Dobs 2002(Wisniewski 2002)	26	The data was likely to be skewed	Differences in task performance between women receiving E or E-T treatment were assessed with a 2-factor(treatment group x test session), mixed analysis of variance for each cognitive task. Post hoc comparisons were conducted using Tukey's method of multiple comparisons. With regard to Cube Comparisons, performance improved for both groups across test sessions, however this improvement only approached statistical significance (P=0.09). No other effects were significant. Regarding Building Memory, a main effect of test session was observed, with performance declining across sessions for both groups(P<0.01). A treatment x test session interaction was observed(P<0.05). Post hoc comparison revealed that this effect was due to a decrease in the E group(P<0.05) but not The E-T group(P>0.1) across sessions.
Hematocrit	Barrett-Connor 1999	199	The data was not available.	There was no clinically significant difference in haematology
Hematocrit	Floter 2002b	50	A cross-over study with no washout period	They reported that there was no change in blood counts during the study
Hematocrit	Hickok 1993	26	The data was not available.	- At 6 months, statistically significant between-group differences were seen for hematocrit. The difference was small in magnitude, remained within the normal ranges, and was not considered clinically significant.
Hematocrit	Shifren 2000	67	A cross-over study with no washout period	Transdermal testosterone treatment had no significant effects on blood counts

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

Hematocrit	Watts 1995	48	The data were not available	No clinically significant changes in hematologic indices
Hirsutism	Barrett-Connor 1999	199	The data was not available	Changes in hair growth in the oestro- gen-testosterone(low dose) group were similar to those in the oestrogen(low dose) group, and there were no statistically significant differences in the hirsutism scores between the treatment groups. In the high-dose groups only four participants treated with oestrogen-testosterone and two treated with oestrogen reported hirsutism as an adverse event at month 12. At 24 months, 10 oestrogen-testosterone-treated and 3 oestrogen-treated participants reported hirsutism as an adverse event
Hirsutism and acne	Floter 2002b	50	A crossover study with no washout period	Incidences of hirsutism and acne were similar in two treatment groups
Hirsutism and acne	Shifren 2000	67	A crossover study with no washout period	The hirsutism and acne scores did not change significantly during treatment. The mean facial depilation rate increased slightly during treatment with estrogen-testosterone 300 microgram
Lipid profile	Dobs 2002	40	The data was not available.	After 16 weeks of treatment, significant decreases in total cholesterol, HDL, and triglycerides occurred in the estrogen-testosterone group. LDL values were virtually unchanged. The oestrogen group demonstrated the opposite effect on lipids, with a significant decrease in LDL and no meaningful change in the other lipid parameters

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

Lipid profile	Dobs 2002 (Floter 2005)	50	A crossover study with no washout period	Serum levels of total testosterone increased markedly from a baseline mean of 0.8-4.9 mmol/l during testosterone addition. Total and LDL-cholesterol levels were significantly reduced by both treatments as also were those of Lp-(a) although the difference was not significant. A 13% reduction in HDL-cholesterol levels was found when testosterone was added, but no change with oestrogen alone. Triglyceride levels were increased by oestrogen treatment, but not affected by the combination of oestrogen plus testosterone
Lipid profile	Miller 2000 (Luciano 1998a)	56	The data was not available	There were significant reductions in total cholesterol and LDL cholesterol in all groups. In estrogen-testosterone-treated group triglyceride levels increased 26.0% and HDL cholesterol levels decreased 9.0%. In contrast, with oestrogen therapy triglyceride levels decreased 9.0% and HDL cholesterol levels increased 9.0%
Lipid profile	Miller 2000	57	The data was likely to be skewed because the means were smaller than twice the SDs	The study found significant reductions in total cholesterol and LDL cholesterol in all groups. Triglyceride levels increased 26.0% and HDL cholesterol levels decreased 9.0% in estrogen-testosterone-treated group. In contrast, with oestrogens therapy triglyceride levels decreased 9.0% and HDL cholesterol levels increased 9.0%
Lipid profile	Nathrost-Boos 2006	60	A crossover study with no washout period	Total cholesterol, triglycerides, HDL and LDL revealed no significant differences between any of the periods or groups

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

Menopausal symptoms, sense of well being and sexual function	Barrett-Connor 1999	199	The data were not available	Women in all treatment groups reported an improvement in menopausal symptoms and quality of life measures at 24 months. There was a non significant trend toward greater improvement in well being and sexual interest and higher scores on the modified menopausal rating scale in the oestrogen-testosterone groups
Menopausal symptoms and sexual function	Dow 1983	40	The data were non-normal distribution	There were no significant differences between treatments on any variable at either 2 months or 6 months after treatment
Menopausal symptoms	Hickok 1993	26	The data were non-normal distribution	There was no statistically significant difference between two treatments in menopausal symptoms
Menopausal symptoms	Miller 2000 (Luciano 1999)	51	The data were not available	Vasomotor symptoms were reduced by at least 75% after treatment in all groups
Menopausal symptoms	Raisz 1996	28	The data was likely to be skewed	Both treatments significantly decreased somatic symptom scores, but only estrogen-testosterone treatment provided significant relief of psychosomatic and psychological symptoms
Menopausal symptoms	Sarrel 1998	20	The data was not available	There was no statistical difference between the estrogen-testosterone groups versus the oestrogen group
Menopausal symptoms	Sherwin 1988 (Sherwin 1984)	49	The data was not available	There was no result for the comparative effect on hot flushes between estrogen-testosterone and oestrogen alone
Menopausal symptoms	Sherwin 1988 (Sherwin 1985a)	43	The data were not available	Menopausal index: 1. Somatic symptoms: The scores of the oestrogen-testosterone, androgen alone groups were lower

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

				than those of the oestrogen alone and placebo groups (P<0.01). 2. Psychosomatic symptoms: There were no significant changes in any of the groups across time. 3. Psychological symptoms: The scores of the estrogen-alone and placebo groups were significantly higher than those of the oestrogen-testosterone, androgen-alone groups during both treatment phases (p<0.01). 4. Total scores: The E-T, androgen-alone groups attained lower total scores during treatment phases than the E-alone and P groups
Menopausal symptoms	Simon 1999	92	The data was not available	In general, estrogen-testosterone therapy provided greater relief from these symptoms than oestrogen therapy. This was most apparent in the finding that the degree of vasomotor symptom relief with low dose estrogen-testosterone preparation was similar to relief experienced with higher dose estrogen therapy alone.
Menopausal symptoms	Watts 1995	66	The data were not available	There were no significant differences in somatic symptoms between the oestrogen and estrogen-testosterone groups at baseline or after treatment. Psychosomatic and psychologic symptom values are not presented because of the small number of evaluable symptomatic participants
Mood (hostility)	Sherwin 1988 (Sherwin 1985c)	36	The data were not available	Hostility scores did not differ significantly in the two groups (testosterone-oestrogen or oestrogen alone)

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

Sense of well being	Dobs 2002	40	The data were not available.	With regard to QUALMS questionnaire, the oestrogen-testosterone group showed significant improvement from baseline in somatic symptoms(week 10, P=0.003; week 16, P=0.073). The oestrogen group showed significant improvement from baseline in well being (week 16, P= 0.049) and cognition (week 10, P=0.054)
Sense of well being	Floter 2002b	50	A crossover study with no washout period	There were no significant differences between the treatments in any of the sub scores or total PGWB index
Sense of well being	Montgomery 1987	84	The data were likely to be skewed	There was no difference in SRD 30 scores between the two active treatment groups at either 2 or 4 months
Sense of well being	Penotti 2001	40	The data were not available.	No conclusion on psycho-physical well being.
Sense of well being	Regestein 2001	35	A cross-over study with no washout period	No significant effects of adding testosterone into hormone therapy
Sense of well being	Sherwin 1988 (Sherwin 1985c)	43	The data was not available.	Anxiety: There was no differences among any of the groups across time. Depression: Mean group scores fell within the normal range. Depression scores in the placebo group were significantly higher than those in oestrogen-testosterone(P<0.05), A(P<0.01), E(P<0.05) groups during both treatment phases. Hostility: hostility scores did not differ significantly in the two groups (testosterone-oestrogen versus oestrogen alone)
Sense of well being	Shifren 2000	65	A crossover study with no washout period	Adding 300 microgram patch into oral oestrogen has a significant improvement in general well being by means of PGWB (P=0.04). There

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

				also were significant increases with oestrogen-testosterone 300 microgram treatment for sub scales of positive well being and depressed mood.
Sexual function	Burger 1987	20	The data was not available.	After six weeks the loss of libido in the single implant group remained, while the combined group showed significant symptomatic relief(P<0.01). Eight in the single implant group chose to have a testosterone implant at the first follow up visit at 6 weeks; the other two stopped coming because of dissatisfaction with the treatment
Sexual function	Dobs 2002	40	The data was not available.	The sample size was not powered, nor was entry criteria designed to assess sexual dysfunction parameters; however, there were significant results. In the oestrogen-testosterone group, BISF-W mean increases at each visit were statistically significant for frequency/psychosexual(P=0.05) and pleasure/orgasm(P=0.041) domains. The mean composite BISF-W score increased in the oestrogen-testosterone group, whereas the mean score in the estrogen group decreased. Although it appeared that the two treatment groups were not well balanced at baseline(the estrogen group seemed to have healthier sexual function at baseline than the estrogen-testosterone group), the estrogen-testosterone group showed significant improvement in sexual function compared with the estrogen group. The SRS total score in the estrogen-testosterone group improved significantly at each visit, whereas scores in the estrogen group did not

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

				change significantly. The SIQ score for the estrogen-testosterone group also increased significantly for interest in sex at weeks 10(P=0.031) and 16(P=0.014) when compared with before menopause. The oestrogen group showed no significant change from baseline
Sexual function (total McCoy score)	Floter 2002b	44	A crossover study with no washout period	After 24 weeks of treatment, the addition of testosterone had a significantly better effect on the variables 'enjoyment of sex', 'satisfaction with frequency of sexual activity' and 'interest in sex'. The total McCoy score was significantly increased by both treatments, but the addition of testosterone exerted a stronger effect (P<0.05)
Sexual function	Miller 2000 (Luciano 1999)	51	The data was not available	Improvement (P<0.05) in sexual interest, sexual satisfaction, frequency of sexual intercourse and intensity and frequency of orgasm during sexual intercourse were reported in all groups except the estrogen alone group
Sexual function	Nathrost-Boos 2006	60	A cross-over study with no washout period	The scores concerning frequency of sexual activity, orgasm and intercourse, sexual arousal, fantasies and enjoyment, satisfaction with orgasms, and interest in sex were all significantly improved for testosterone addition as compared to placebo both before and after crossover
Sexual function(desire and satisfaction)	Penotti 2001	33	The data was not available	No difference between two groups was observed at any of the considered time points.

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

Sexual function	Shepanek 1999	30	The data was likely to be skewed	Oestrogen-testosterone-treated participants reported significantly less lack of sexual desire or interest to engage in sexual activity, compared to participants receiving oestrogen alone
Sexual function	Sherwin 1988 (Sherwin 1985b)	43	The data was not available	Women who received either of the androgen-containing preparations had significantly higher scores than women in the estrogen and placebo groups(P<0.01) in association with their higher levels of plasma testosterone. Women in the estrogen-testosterone and testosterone-only group experienced a greater number of fantasies during every treatment than did women in the oestrogen and placebo group (P<0.01). During treatment phases, both androgen groups attained higher levels of sexual arousal than did the estrogen and placebo groups(P<0.01)
Sexual function (scores)	Shifren 2000	65	A cross-over study with no washout period	The mean composite score expressed as a percentage of the mean value for normal women, increased from 52(27) percent at baseline to 72(38) percent during estrogen treatment, 74(37) percent during treatment with estrogen plus 150 microgram of testosterone per day, and 81(37) percent during treatment with estrogen plus 300 microgram of testosterone per day(P=0.05 for the comparison with estrogen-alone). The scores for thoughts-desire, frequency of sexual activity, and pleasure-orgasm were lowest at baseline and increased in a dose-dependent fashion. With the estrogen plus testosterone 300 microgram, the increases in scores for frequency of sexual activity and pleasure-

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

				orgasm were significantly greater than those with estrogen-alone (P=0.03 for both comparisons). The score for problems affecting sexual function was 116%(48) of the normative mean at baseline and decreased to 98%(49) during treatment with estrogen plus 300 microgram of testosterone(P=0.07 for the comparison with oestrogen-alone)
Sexual function (the prevalence of particular types of sexual behavior)	Shifren 2000	65	A crossover study with no washout period	The percentage of women who reported having sexual fantasies at least once a week was 12% at baseline, 10% during oestrogen treatment, 18 percent during estrogen plus testosterone 150 microgram, and 24% during treatment with estrogen plus 300 microgram of testosterone. The percentage of women who reported masturbating at least once a week was 3%, 5% and 10% at baseline, estrogen treatment and estrogen plus testosterone treatment, respectively. Finally, the percentage of women who engaged in sexual intercourse at least once a week was 23% at baseline, 35% during treatment with either oestrogen-alone or oestrogen plus 150 microgram of testosterone, and 41% during treatment with oestrogen plus 300 microgram of testosterone
Unexplained fatigue (vitality)	Floter 2002b	50	A crossover study with no washout period	There was no significant difference between the treatments in vitality
Unexplained fatigue (vitality)	Shifren 2000	67	A crossover study with no washout period	Vitality improved in women treated with testosterone patch combined with oral conjugated equine oestrogen

Table 1. Trial outcomes not included in the meta-analysis (*Continued*)

Unexplained fatigue and sense of well being	Sherwin 1988 (Sherwin 1985a)	43	The data was not available	Women in estrogen alone and placebo groups reported significantly lower ratings of energy level and well being than did those who received either of the androgen-containing preparations (P<0.01)

Despite the lack of statistical heterogeneity, differences in clinical parameters were considerable (clinical heterogeneity). These differences were taken into account when analysing and interpreting the pooled results.

Sensitivity analysis was performed to look at the possible contribution of unpublished studies (if there were any), differences in methodological quality of trials, very large studies, length of the treatment follow-up period, and different dosages. We suspected results might differ significantly between groups in these sensitivity analyses, which were only performed if there were at least five trials in each group. With event rate data, the analysis was repeated using the risk difference and relative risk.

Subgroup analyses were performed according to surgical or natural menopause; perimenopause and postmenopause; oral and non-oral HT; methyltestosterone or testosterone; trial duration of less than three months or three to < six months, six to 12 months, or 12 months to 24 months; placebo-controlled trials or non placebo-controlled trials; and adequacy of symptom control.

Where there was an adequate number of studies, a funnel plot was drawn to examine the possibility of publication bias. The review will be updated every two years.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

1. Study inclusion

Ninety articles were assessed for inclusion in the review. Six of these did not contain sufficient information in their published format and were classified as awaiting assessment. We attempted to contact the authors in each case. Thirty-six articles were excluded and 49 were included. Among the 49 included references, there were 35 separate trials. The articles that were from the same trials were as follows: (1) Davis 1995 and Davis 2000b; (2) Dobs 2002, Basaria 2002, Nguyen 1999, and Wisniewski 2002; (3) Miller 2000, Luciano 1998a, and Luciano 1999; (4) Barrett-Connor 1999 and Barrett-Connor 1996; (5) Sherwin 1988, Sherwin 1984, Sherwin 1985a; Sherwin 1985b; Sherwin 1985c; (6) Floter 2002b, Floter 2004, Floter 2005; and (7) Hofling 2007a and Hofling 2007b. The results from different articles about the same trial were included in the review only if the different articles were reporting different outcomes.

Of the 36 excluded articles, the reasons for exclusion were: non randomization(13 studies), no HT group serving as a control group (10 studies), ineligible outcomes (9 studies), ineligible intervention (2 studies), and ineligible participants (2 studies).

2. Participants

For all the included trials there was a total of 4768 participants randomised. Five of 35 trials did not report the number of participants who completed the study (Chiuve 2004; Dow 1983; Garnett 1992; Hofling 2007; Regestein 2001; Watts 1995). Therefore, of 4445 randomised participants from the remaining 31 trials there were 3904 participants who completed the trials. Not all trials reported on all outcomes, and not all trials reported outcomes in a form suitable for inclusion in the meta-analysis. Therefore, there were different numbers of trials and participants analysed for each outcome.

2.1 Setting

Twenty trials were hospital-based or clinic-based studies. In 11 trials recruitment was from the general community (Braunstein 2005; Buster 2005; Davis 2006; El-Hage 2007; Floter 2002b; Matthews 2005; Nathrost-Boos 2006; Regestein 2001; Shepanek 1999; Shifren 2006; Simon 2005; Zang 2006). The setting was not stated in five trials (Chiuve 2004; Hofling 2007; Leao 2006; Montgomery 1987; Warnock 2005).

2.2 Location

The trials were located in seven countries, specifically United States of America (16 trials) (Barrett-Connor 1999; Chiuve 2004; Dobs 2002; Braunstein 2005; Hickok 1993; Lobo 2003; Matthews 2005; Miller 2000; Raisz 1996; Regestein 2001; Sarrel 1998; Shepanek 1999; Shifren 2000; Simon 1999; Warnock 2005; Watts 1995), United Kingdom (three trials) (Dow 1983; Farish 1984; Montgomery 1987), Australia (three trials) (Burger 1987; Davis 1995; El-Hage 2007), Italy (one trial) (Penotti 2001), Canada (one trial) (Sherwin 1988), Sweden (four trials) (Floter 2002b; Hofling

2007; Nathrost-Boos 2006; Zang 2006), and Brazil (three trials) (de Paula 2007; Leao 2006; Penteado 2008). Four trials were multinational studies (Buster 2005; Davis 2006; Shifren 2006; Simon 2005).

2.3 Ethnicity

There were 18 trials that specified ethnicity (Barrett-Connor 1999; Buster 2005; de Paula 2007; Dobs 2002; El-Hage 2007; Hickok 1993; Hofling 2007; Leao 2006; Lobo 2003; Matthews 2005; Penteado 2008; Sarrel 1998; Shepanek 1999; Shifren 2000; Shifren 2006; Simon 2005; Warnock 2005; Watts 1995). Of these trials the most common ethnicity was Caucasian.

2.4 Disease status

Disease status was classified by considering the participant characteristic requirements at enrolment. Three categories were created for this review: no symptom requirement, particular symptom requirement, and the prerequisite of impaired sexual function with low serum testosterone levels. The majority of the studies recruited only healthy postmenopausal women, regardless of symptoms (Barrett-Connor 1999; Dobs 2002; Floter 2002b; Hickok 1993; Hofling 2007; Matthews 2005; Miller 2000; Leao 2006; Penotti 2001; Raisz 1996; Regestein 2001; Shepanek 1999; Sherwin 1988; Simon 1999; Watts 1995; Zang 2006). Ten trials enrolled postmenopausal women with a particular condition; such as having an indication for implant therapy (Davis 1995), menopausal symptoms despite being on standard HT (Farish 1984; Montgomery 1987), impaired sexual function (Burger 1987; Buster 2005; de Paula 2007; Dow 1983; El-Hage 2007; Lobo 2003; Penteado 2008; Shifren 2006; Warnock 2005), dissatisfaction with HT alone (Sarrel 1998). Four studies included only postmenopausal women with low serum testosterone levels who had impaired sexual function (Braunstein 2005; Davis 2006; Chiuve 2004; Nathrost-Boos 2006).

2.5 Type of menopause

Thirteen trials included both surgically and naturally menopausal women (Burger 1987; Davis 1995; Dobs 2002; Dow 1983; El-Hage 2007; Leao 2006; Lobo 2003; Matthews 2005; Montgomery 1987; Raisz 1996; Regestein 2001; Sarrel 1998; Sherwin 1988). Thirteen trials included only surgically menopausal women (Barrett-Connor 1999; Braunstein 2005; Buster 2005; Chiuve 2004; Davis 2006; Farish 1984; Floter 2002b; Shepanek 1999; Sherwin 1988; Shifren 2000; Simon 1999; Watts 1995; Warnock 2005), and eight trials were conducted in naturally menopausal women only (de Paula 2007; Hofling 2007; Nathrost-Boos 2006; Penotti 2001; Penteado 2008; Shifren 2006; Simon 1999; Zang 2006). For one trial the type of menopause was unclear (Hickok 1993).

2.6 Menopausal status

Most trials included only postmenopausal women. Only three trials recruited both peri and postmenopausal women (Montgomery 1987; Sarrel 1998; Simon 1999).

3. Study design

3.1 Blinding and placebo

All of the trials were randomised clinical trials. Most trials were double-blind, placebo-controlled studies. There were three open randomised trials (Penotti 2001; Raisz 1996; Zang 2006) and three single-blind trials (Burger 1987; Davis 1995; Dow 1983).

To ensure double blinding (participants and assessors), one trial used an identical form of medication (Miller 2000) where oestrogen and testosterone were combined in a tablet that was identical to the oestrogen tablet; 15 trials used placebo therapy (Braunstein 2005; Buster 2005; Davis 2006; de Paula 2007; El-Hage 2007; Hofling 2007; Leao 2006; Matthews 2005; Nathrost-Boos 2006; Penteado 2008; Sherwin 1988; Shifren 2000; Shifren 2006; Simon 2005; Warnock 2005); six trials used double-dummy placebo tablets (Floter 2002b; Hickok 1993; Lobo 2003; Regestein 2001; Sarrel 1998; Watts 1995); and two used an independent doctor, who did not assess the outcome, to provide medication (Farish 1984; Montgomery 1987). Five trials did not report the blinding method (Barrett-Connor 1999; Chiuve 2004; Dobs 2002; Shepanek 1999; Simon 1999).

3.2 Crossover studies

Seven trials were crossover studies (de Paula 2007; El-Hage 2007; Floter 2002b; Nathrost-Boos 2006; Regestein 2001; Sherwin 1988; Shifren 2000). The principal problem with this kind of study is an effect or carry over after the treatment crossover. Therefore, a period between treatments, known as a washout period, is needed as a means of minimizing carry over effects. In addition, the statistical techniques to demonstrate absence of carry over may not be satisfactory. Thus only a crossover study that had a washout period was considered as an appropriate trial. Accordingly, for this review, two trials conducted by El-Hage et al and Sherwin et al were recognized as suitable crossover studies (El-Hage 2007; Sherwin 1988). Because of the possibility of a carry-over effect, it was decided that only the first half of the remaining studies would be considered for inclusion. However, after contacting corresponding authors of these studies it was established that the data from the first treatment periods were no longer available.

3.3 Centres

There were 18 single-centre trials (Dobs 2002; Davis 1995; de Paula 2007; Dow 1983; El-Hage 2007; Floter 2002b; Hickok 1993; Hofling 2007; Matthews 2005; Miller 2000; Montgomery 1987; Nathrost-Boos 2006; Penotti 2001; Penteado 2008; Regestein 2001; Sarrel 1998; Sherwin 1988; Zang 2006) and the remaining trials were multicentre (more than two centres) studies.

3.4 Source of funding

There were 17 trials that were sponsored by pharmaceutical companies (Barrett-Connor 1999; Braunstein 2005; Buster 2005; Chiuve 2004; Davis 1995; Davis 2006; de Paula 2007; El-Hage 2007; Hofling 2007; Penteado 2008; Regestein 2001; Sarrel 1998; Shepanek 1999; Shifren 2000; Simon 2005; Warnock 2005; Watts 1995), 10 trials partly funded by pharmaceutical companies (Dobs 2002; Burger 1987; Floter 2002b; Hickok 1993; Leao 2006;

Matthews 2005; Miller 2000; Nathrost-Boos 2006; Raisz 1996; Zang 2006), and eight trials did not state their funding source (Dow 1983; Farish 1984; Leao 2006; Lobo 2003; Montgomery 1987; Penotti 2001; Sherwin 1988; Simon 1999).

3.5 Duration of study

There were five trials with a study duration of less than three months (Chiuve 2004; Matthews 2005; Raisz 1996; Sarrel 1998; Warnock 2005), 12 trials lasting three to less than six months (de Paula 2007; Dobs 2002; Dow 1983; Lobo 2003; Montgomery 1987; Nathrost-Boos 2006; Regestein 2001; Shepanek 1999; Sherwin 1988; Shifren 2000; Simon 1999; Zang 2006), 12 trials lasting six to less than 12 months (Braunstein 2005; Burger 1987; Buster 2005; Davis 2006; El-Hage 2007; Farish 1984; Floter 2002b; Hickok 1993; Hofling 2007; Penotti 2001; Shifren 2006; Simon 2005), and six studies of 12-months duration or more (Barrett-Connor 1999; Davis 1995; Leao 2006; Miller 2000; Penteado 2008; Watts 1995).

4. Intervention

4.1 Route

4.1.1 HT: the majority of trials involved oral HT. The non-oral forms included sublingual tablets (Miller 2000), implants (Burger 1987; Davis 1995; Dow 1983; Farish 1984; Montgomery 1987), transdermal therapy (Davis 2006; El-Hage 2007; Penotti 2001; Shifren 2000), percutaneous gel (Leao 2006), and intramuscular injection (Sherwin 1988). Three studies included women who were receiving a stable dose of oral or transdermal oestrogen therapy (Buster 2005; Nathrost-Boos 2006; Simon 2005).

4.1.2 Testosterone therapy: testosterone was most commonly administered orally. Non-oral administration included implants (Burger 1987; Davis 1995; Dow 1983; Farish 1984; Montgomery 1987), transdermal patches (Braunstein 2005; Buster 2005; Davis 2006; Hofling 2007; Shifren 2000; Shifren 2006; Simon 2005), sublingual tablets (Miller 2000), percutaneous gel (Nathrost-Boos 2006), percutaneous cream (El-Hage 2007), and intramuscular injection (Sherwin 1988). For orally administered testosterone, 15 trials used methyltestosterone (Barrett-Connor 1999; Chiuve 2004; de Paula 2007; Dobs 2002; Hickok 1993; Leao 2006; Lobo 2003; Penteado 2008; Raisz 1996; Regestein 2001; Sarrel 1998; Shepanek 1999; Simon 1999; Warnock 2005; Watts 1995), and the remaining trials used testosterone undecanoate (Floter 2002b; Penotti 2001; Zang 2006).

4.2 Progestin use

In women with an intact uterus, eight trials did not include any kind of progestin during the study period (Dobs 2002; Hickok 1993; Lobo 2003; Raisz 1996; Regestein 2001; Sarrel 1998; Simon 1999; Zang 2006) while 12 trials used a progestin to oppose the oestrogenic effects on the endometrium (Burger 1987; Davis 1995; de Paula 2007; Dow 1983; Hofling 2007; Matthews 2005; Miller 2000; Montgomery 1987; Nathrost-Boos 2006; Penotti 2001; Penteado 2008; Shifren 2006).

4.3 Dosages of testosterone

4.3.1 Methyltestosterone: there were three dosages of methyltestosterone used in the included studies. These were 1.25, 2 and 2.5 mg. The 1.25 mg dose was commonly used together with 0.625 mg of esterified oestrogen or another equivalent dose of oestrogen (Barrett-Connor 1999; Hickok 1993; Leao 2006; Lobo 2003; Regestein 2001; Shepanek 1999; Simon 1999). The 2 mg dose was used together with 0.625 mg of conjugated equine oestrogen (Penteado 2008). The 2.5 mg dose was used with 1.25 mg of esterified oestrogen or another equivalent dose of oestrogen (Barrett-Connor 1999; Chiuve 2004; de Paula 2007; Dobs 2002; Matthews 2005; Raisz 1996; Sarrel 1998; Simon 1999; Warnock 2005; Watts 1995).

4.3.2 Non-methyltestosterone: the testosterone undecanoate dose was 40 mg once a day; the micronized testosterone dose was 1.25 mg twice a day; testosterone patches were 150, 300, and 450 µg twice a week; and testosterone implant doses were 50 mg and 100 mg.

5. Outcomes

This review had a broad range of outcomes of interest. Data synthesis in each outcome was from meta-analysis, descriptive analysis, or both depending on the availability and appropriateness of data. The availability of data is presented in this section. For construct outcomes only the available data that were measured by validated questionnaires were subsequently included for data synthesis and considered for meta-analysis. Construct outcomes were sense of well being, unexplained fatigue, sexual function, mood, menopausal symptoms, increased facial and body hair growth, and acne. The available data from parallel studies and the one crossover study with a washout period where the data were non-skewed were included for meta-analysis. Information about data that were not included in the meta-analysis was presented in an additional table of trial outcomes not included in the meta-analysis.

5.1 **Primary outcomes**

5.1.1. Sense of well being: there were 11 trials that reported data pertaining to this outcome (Barrett-Connor 1999; Dobs 2002; Floter 2002b; Matthews 2005; Montgomery 1987; Nathrost-Boos 2006; Penotti 2001; Regestein 2001; Sherwin 1988; Shifren 2000; Warnock 2005). Two of these did not provide comparative results (Dobs 2002; Penotti 2001). Therefore, only nine trials were considered for data synthesis and only two trials were suitable for meta-analysis (Matthews 2005; Warnock 2005).

5.1.2. Unexplained fatigue: this outcome was most commonly presented in the analysis of sense of well being or menopausal symptoms. Of trials that included either of these two outcomes, there were three crossover trials that provided data pertaining to unexplained fatigue for descriptive data synthesis (Floter 2002b; Sherwin 1988; Shifren 2000). No data were suitable for meta-analysis.

5.1.3. Sexual function: 23 trials reported the effects of testosterone on sexual function (Barrett-Connor 1999; Braunstein 2005; Burger 1987; Buster 2005; Davis 1995; Davis 2006; Dobs 2002; Dow 1983; El-Hage 2007; Floter 2002b; Lobo 2003;

Miller 2000; Nathrost-Boos 2006; Penotti 2001; Penteado 2008; Regestein 2001; Sarrel 1998; Shepanek 1999; Sherwin 1988; Shifren 2000; Shifren 2006; Simon 2005; Warnock 2005). One study did not report any data for this outcome that was suitable for descriptive data synthesis (Regestein 2001). Only nine trials provided suitable data for meta-analysis (Braunstein 2005; Buster 2005; Davis 1995; Davis 2006; Lobo 2003; Sarrel 1998; Shifren 2006; Simon 2005; Warnock 2005).

5.2 **Secondary outcomes**

5.2.1. *Benefits*

5.2.1.1. Bone health

5.2.1.1.1. Incidence of osteoporotic fracture: there was no trial that reported this outcome.

5.2.1.1.2. Bone mineral density: six trials described this result (Barrett-Connor 1999; Davis 1995; Floter 2002b; Miller 2000; Watts 1995; Zang 2006). There were three double-blind, parallel-group studies (Barrett-Connor 1999; Miller 2000; Watts 1995), one crossover study (Floter 2005), one single-blind study (Davis 1995), and one open study (Zang 2006). Only three trials provided appropriate data for meta-analysis (Davis 1995; Miller 2000; Zang 2006). The remaining trials were included in descriptive data synthesis.

5.2.1.2. Body composition: five studies provided the data pertaining to this outcome (Davis 1995; Dobs 2002; Floter 2005; Leao 2006; Zang 2006). The weight gain data from four studies was suitable for meta-analysis (Davis 1995; Dobs 2002; Leao 2006; Zang 2006).

5.2.1.3. Cognition: of the five randomised trials (Dobs 2002; Regestein 2001; Shepanek 1999; Sherwin 1988; Warnock 2005) that reported effects of testosterone on cognition only two were eligible for meta-analysis (Dobs 2002; Warnock 2005). The remaining trials were considered for descriptive data synthesis.

5.2.1.4. Menopausal symptoms: this outcome was stated in 11 trials (Barrett-Connor 1999; Dow 1983; Hickok 1993; Miller 2000; Raisz 1996; Regestein 2001; Sarrel 1998; Sherwin 1988; Simon 1999; Warnock 2005; Watts 1995) but only one trial provided data suitable for meta-analysis (Warnock 2005). The remaining trials were considered for descriptive data synthesis.

5.2.2. *Adverse events*

5.2.2.1. Increased facial or body hair: only the results of trials that used a standard method of assessment were included in the data synthesis. Accordingly there were 12 eligible trials (Barrett-Connor 1999; Braunstein 2005; Buster 2005; Chiuve 2004; Davis 2006; El-Hage 2007; Floter 2002b; Lobo 2003; Shifren 2000; Shifren 2006; Simon 2005; Warnock 2005). Eight trials provided suitable results for meta-analysis (Braunstein 2005; Buster 2005; Chiuve 2004; Davis 2006; Shifren 2006; Simon 2005; Warnock 2005; Lobo 2003).

5.2.2.2. Acne: only the results of trials that used a standard method of assessment were included in the data synthesis. Accordingly there were 12 eligible trials (Barrett-Connor 1999; Braunstein 2005; Buster 2005; Chiuve 2004; Davis 2006; El-Hage 2007; Floter 2002b; Lobo 2003; Shifren 2000; Shifren 2006; Simon 2005; Warnock 2005). Eight trials provided suitable results for meta-analysis (Braunstein 2005; Buster 2005; Chiuve 2004; Davis 2006; Lobo 2003; Shifren 2006; Simon 2005; Warnock 2005).

5.2.2.3. Mood alteration, specifically aggression: only two trials reported the effects of testosterone on aggression; the data were not appropriate for meta-analysis (El-Hage 2007; Sherwin 1988). Therefore, only descriptive data synthesis was performed.

5.2.2.4. Breast cancer

5.2.2.4.1. Mammographic findings: only two trials reported the effects of testosterone on breast cell proliferation; the data were not appropriate for meta-analysis.

5.2.2.4.2 Incidence of breast cancer: no trial reported this outcome.

5.2.2.5. Coronary heart disease: no trial reported this outcome.

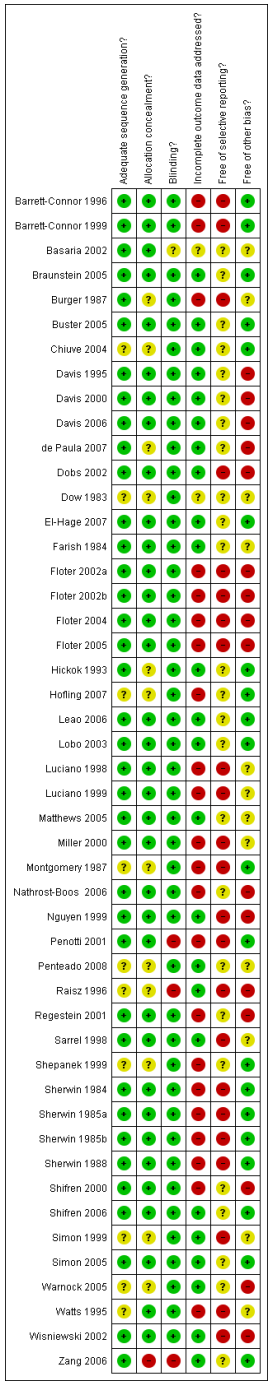
5.2.2.6. Lipid profile: there were 17 trials that were appropriate for inclusion in the meta-analysis (Barrett-Connor 1999; Braunstein 2005; Buster 2005; Chiuve 2004; Dobs 2002; Davis 1995; Davis 2006; Farish 1984; Hickok 1993; Leao 2006; Lobo 2003; Penotti 2001; Raisz 1996; Shifren 2006; Simon 2005; Watts 1995; Warnock 2005). Five trials did not provide suitable data for the meta-analysis but they were included in the descriptive data synthesis (Dobs 2002; El-Hage 2007; Floter 2002b; Miller 2000; Nathrost-Boos 2006).

5.2.2.7. Discontinuation rate: of 35 included trials, data from 14 trials were incomplete for meta-analysis (Chiuve 2004; de Paula 2007; El-Hage 2007; Dow 1983; Floter 2002b; Hofling 2007; Miller 2000; Nathrost-Boos 2006; Raisz 1996; Regestein 2001; Shepanek 1999; Sherwin 1988; Shifren 2000; Watts 1995). Therefore, 21 trials were included in the meta-analysis.

Risk of bias in included studies

The methodological risks of bias for the included studies are presented in Figure 1 and Figure 2.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



1. Randomisation and concealment of allocation sequences

Randomisation and concealment of allocation sequences were adequate in 21 trials (Barrett-Connor 1999; Braunstein 2005; Buster 2005; Davis 2006; Davis 1995; Dobs 2002; El-Hage 2007; Farish 1984; Floter 2002b; Leao 2006; Lobo 2003; Matthews 2005; Miller 2000; Nathrost-Boos 2006; Penotti 2001; Regestein 2001; Sarrel 1998; Sherwin 1988; Shifren 2000; Shifren 2006; Simon 2005) while in nine trials these were unclear (Chiuve 2004; Dow 1983; Hofling 2007; Montgomery 1987; Penteado 2008; Raisz 1996; Shepanek 1999; Simon 1999; Warnock 2005). In one study randomisation was adequate but concealment was inadequate (Zang 2006). In three trials randomisation was adequate but concealment was unclear (Burger 1987; de Paula 2007; Hickok 1993). In one study concealment was adequate but randomisation was unclear (Watts 1995).

2. Baseline equality

This issue applied to parallel studies only. Of the included parallel studies five publications did not comment on baseline equality (Burger 1987; Dow 1983; Farish 1984; Sarrel 1998; Simon 1999). Seven publications stated that baseline characteristics were similar in terms of age and menopausal status but did not comment on the baseline values of the main outcomes (Barrett-Connor 1999; Buster 2005; Hofling 2007; Matthews 2005; Miller 2000 (two publications); Penteado 2008; Watts 1995). Baseline equality in terms for age, menopausal status, and baseline values of the outcomes were reported in 14 publications (Braunstein 2005; Chiuve 2004; Davis 2006; Dobs 2002; Hickok 1993; Leao 2006; Lobo 2003; Miller 2000; Penotti 2001; Shepanek 1999; Shifren 2006; Simon 2005; Warnock 2005; Zang 2006). However, baseline inequality was documented in two trials for sexual function score (Davis 2006; Dobs 2002), one for menopausal symptom scores (Raisz 1996), and three for age (Davis 1995; Raisz 1996; Warnock 2005).

3. Non-compliers and intention-to-treat analysis

Only five studies reported no withdrawals (El-Hage 2007; Farish 1984; Hickok 1993; Leao 2006; Zang 2006) and eight reported a discontinuation rate of less than 10% (Chiuve 2004; Davis 1995; de Paula 2007; Dobs 2002; Matthews 2005; Penteado 2008; Sarrel 1998; Simon 1999). The majority of trials reported a non-compliance rate of at least 10% (Barrett-Connor 1999; Braunstein 2005; Burger 1987; Buster 2005; Davis 2006; Floter 2002b; Hofling 2007; Lobo 2003; Miller 2000; Montgomery 1987; Nathrost-Boos 2006; Penotti 2001; Regestein 2001; Shepanek 1999; Sherwin 1988; Shifren 2000; Shifren 2006; Simon 2005; Warnock 2005). The remaining two studies did not report on discontinuation rate.

Ten trials stated that analyses were performed on an intention-to-treat basis (Barrett-Connor 1999; Braunstein 2005; Buster 2005; Davis 2006; El-Hage 2007; Lobo 2003; Shifren 2000; Shifren 2006; Simon 2005; Warnock 2005). Seven trials clearly described the method of intention-to-treat analysis. The 'last observation carried forward' approach was used for the intention-to-treat analysis (Braunstein 2005; Buster 2005; Davis 2006; Shifren 2006; Simon 2005; Lobo 2003; Warnock 2005) however the number of participants analysed was still less than the number of participants randomised. For the other two of the nine trials the number of participants analysed was obviously less than that at randomisation (Barrett-Connor 1999; Shifren 2000). There were two criteria for an intention-to-treat analysis. Firstly, trial participants should be analysed in the groups to which they were randomised regardless of which (or how much) treatment they actually received and regardless of other protocol irregularities, such as ineligibility. In addition, all participants should be included regardless of whether their outcomes were actually collected. According to these criteria none of the studies were analysed by a genuine intention-to-treat analysis.

4. Standardized outcome measurement

Standardized outcome measurement was considered for the construct variables in term of validated scales or questionnaire use.

4.1 Sense of well being: of all the relevant trials one study used a self-rating scale (Penotti 2001); eight used validated questionnaires (Dobs 2002; Floter 2002b; Matthews 2005; Montgomery 1987; Regestein 2001; Sherwin 1988; Shifren 2000; Warnock 2005), and one did not describe the questionnaire used (Barrett-Connor 1999). The names of the validated questionnaires were: the Quality of Life at Menopause Scale (QUALMS), The Menopausal Quality of Life Questionnaire, the Psychological General Well Being Index (PGWB), the short version of Kellner and Sheffield's self rating scale of distress (SRD 30), the Trait Anxiety Inventory, the Zung Self-Rated Depression Inventory, the symptom Check List-90 Revised, the Adult Playfulness Scale, and the Multiple Adjective Affect Checklist (MAACL).

4.2 Unexplained fatigue: all relevant trials used validated questionnaires (Floter 2002b; Sherwin 1988; Shifren 2000). As stated above, this outcome was most commonly presented in the analysis of sense of well being. Names of the validated questionnaires were: the Psychological General Well Being Index (PGWB), and Daily Menopausal Rating Scale (DMRS).

4.3 Sexual function: of 21 trials that reported this outcome four studies used self-rating scales (Burger 1987; Miller 2000; Penotti 2001; Regestein 2001) and 17 studies used validated questionnaires (Braunstein 2005; Buster 2005; Davis 1995; Davis 2006; Dobs 2002; El-Hage 2007; Floter 2002b; Lobo 2003; Nathrost-Boos 2006; Penteado 2008; Sarrel 1998; Shepanek 1999; Sherwin 1988; Shifren 2000; Shifren 2006; Simon 2005; Warnock 2005). In two studies the assessment method was not stated (Barrett-Connor 1999; Dow 1983). The names of the validated questionnaires were: the Brief Index of Sexual Functioning for Women (BISF-W), Changes in Sexual Functioning Questionnaire (CSFQ-F-C), Sabbatsberg Revised Sexual Self-Rating Scale (SRS), Sexual Interest Questionnaire (SIQ), Sexual Activity Log (SAL), Menopausal Sexual Interest Questionnaire (MSIQ), the Profile of Female Sexual Function (PFSF), Sabbatsberg self-rating scale,

McCoy's sex scale questionnaire, the 10-item Sexual Activity and Libido Scale, and DMRS.

4.4 Mood: validated questionnaires were used in the relevant trials (El-Hage 2007; Sherwin 1988).

4.5 Cognition: all five studies used validated questionnaires (Dobs 2002; Regestein 2001; Shepanek 1999; Sherwin 1988; Warnock 2005).

4.6 Menopausal symptoms: of the 12 relevant trials five trials used validated questionnaires (Dow 1983; Montgomery 1987; Regestein 2001; Sherwin 1988; Warnock 2005). Five trials used a modified version of an original questionnaire (Barrett-Connor 1999; Raisz 1996; Sarrel 1998; Simon 1999; Watts 1995), one used a self-rating scale (Miller 2000), and one trial did not report the source of the questionnaire used (Hickok 1993). The validated questionnaires included the Greene scale and the Menopause Specific Quality of Life Questionnaire.

4.7 Increased facial and body hair growth: of the 13 relevant trials eight trials used standard scales for hirsutism evaluation (Braunstein 2005; Buster 2005; Davis 2006; El-Hage 2007; Lobo 2003; Shifren 2000; Shifren 2006; Simon 2005), one trial used a modified scale (Barrett-Connor 1999), and five trials did not state the scale used (Braunstein 2005; Chiuve 2004; Floter 2002b; Nathrost-Boos 2006; Warnock 2005).

4.8 Acne: eight trials used original scales for acne evaluation (Braunstein 2005; Buster 2005; Davis 2006; El-Hage 2007; Lobo 2003; Shifren 2000; Shifren 2006; Simon 2005), one trial used a modified scale (Barrett-Connor 1999), and four trials did not state the scale used (Chiuve 2004; Floter 2002b; Nathrost-Boos 2006; Warnock 2005).

Effects of interventions

Outcomes

1. **Primary outcomes**

1.1. Sense of well being

1.1.1. Meta-analysis (comparison 1): two studies were eligible for this analysis (Matthews 2005; Warnock 2005). There were 10 domains of well being. Of these domains only sexual function was improved by testosterone addition. We reported the improvement with testosterone in terms of the standardized mean difference (SMD). The improvement with testosterone was 0.47 (95% CI 0.15 to 0.80).

1.1.2. Descriptive data synthesis: of the five available trials that used validated questionnaires there was one crossover study with no washout period that reported a significant benefit to general well being of adding a testosterone patch to an hormone (HT) regimen (Shifren 2000). In contrast, there was no evidence of a significant difference in another crossover study, with no washout period, which examined the effect of adding testosterone undecanoate to HT (Floter 2002b). These two trials measured sense of well being by the Psychological General Well Being Index. For other trials that used other types of questionnaires, one crossover study reported no effect on anxiety with the addition of a testosterone injection (Sherwin 1988) and there was no evidence of a significant difference for sense of well being from two parallel trials (Montgomery 1987; Regestein 2001).

1.2. Unexplained fatigue

1.2.1. Meta-analysis: no appropriate data were available

1.2.2. Descriptive data synthesis: data were available from three crossover studies in surgically menopausal women (Floter 2002b; Sherwin 1988; Shifren 2000). One crossover study with a washout period found that women treated with oestrogen alone reported significantly lower ratings of energy levels than those who received either of the androgen-containing preparations ($P < 0.01$) (Sherwin 1988). Two other studies with no washout period found no significant difference between the treatments in term of vitality (Floter 2002b; Shifren 2000). It is possible that lack of a washout period in these studies contributed to underestimation of a treatment effect for this outcome.

1.3. Sexual function

1.3.1. Meta-analysis (comparison 2): there was an improved outcome with testosterone for a number of domains of sexual function. For one of the domains, the parameters sexual activity and coital frequency were considered together. We reported the improvement with testosterone in terms of the standardized mean difference (SMD). The mean scores were greater in the T-HT group than in the HT alone group. The improvement was 0.29 (95% CI 0.20 to 0.38) for the number of satisfying sexual events, 0.25 (95% CI 0.17 to 0.34) for the total number of sexual events, 0.30 (95% CI 0.21 to 0.39) for the total number of orgasms, 0.35 (95% CI 0.26 to 0.43) for desire, 0.28 (95% CI 0.19 to 0.37) for orgasm, 0.36 (95% CI 0.27 to 0.45) for arousal, 0.33 (95% CI 0.22 to 0.43) for pleasure, 0.32 (95% CI 0.22 to 0.41) for sexual concerns, 0.32 (95% CI 0.23 to 0.40) for responsiveness, 0.26 (95% CI 0.16 to 0.35) for sexual self-image, and 0.41 (95% CI 0.15 to 0.67) for the composite sexual function score. The decrease in mean personal distress scores in the T-HT group was significantly greater than the decrease in the HT group. The difference was -8.13 (95% CI -10.59 to -5.67). One study provided data that showed that use of testosterone was associated with an improved outcome: SMD of 0.98 (95% CI 0.24 to 1.72) for satisfaction, 1.37 (95% CI 0.59 to 2.15) for fantasy, and 0.29 (95% CI 0.20 to 0.38) for frequency of desire.

Subgroup analysis was not practical due to the limited number of studies.

1.3.2. Descriptive data synthesis: of 14 available studies there were nine trials that used validated questionnaires for assessing sexual function. All of these trials reported positive effects of testosterone on sexual functioning (Braunstein 2005; Davis 2006; Dobs 2002; El-Hage 2007; Floter 2002b; Penteado 2008; Shepanek 1999; Sherwin 1988; Shifren 2000). Descriptive data synthesis using other studies that measured sexual function by other scores or scales found inconsistent results.

The majority of trials did not have progestin use as a co-intervention to oppose oestrogenic effects on the endometrium during the

study period. However, beneficial effects of testosterone on sexual function were reported when progestin was added (Burger 1987; Davis 1995; Penteado 2008).

2. **Secondary outcomes**

2.1. *Benefits*

2.1.1. Bone health: for bone health the best outcome measure is the incidence of osteoporotic fracture; however, no study provided this outcome. The most commonly used outcome to measure bone health was bone mineral density (BMD).

2.1.1.1. Meta-analysis (comparison 3): meta-analyses using either the mean endpoint or change values from the three eligible trials showed no significant difference between treatment groups for lumbar BMD after 12 and 24 months of treatment. For femoral BMD, there were inconsistent results between analyses using mean endpoint and change values, after 12 months of treatment. By using the mean endpoint, WMD was -0.05 g/cm^2 (95% CI -0.09 to -0.01) while for change in value the difference in means was 1.40 g/cm^2 (95% CI 0.14 to 2.66). This inconsistency was likely to be due to the effect of the baseline BMD values. The oestrogen plus testosterone group had noticeably lower BMD values at baseline at both sites in two studies, even though in the Miller study the difference in baseline values was not statistically significant (Davis 1995; Miller 2000).

2.1.1.2. Descriptive data synthesis: three studies showed inconsistent results. One study showed that there was no significant difference between treatment groups for BMD of either the lumbar spine or femur (Watts 1995). In contrast, another study demonstrated a significantly greater improvement in both lumbar and femoral BMD at 24 months in the testosterone plus hormone therapy (T-HT) group than in the HT group (Barrett-Connor 1999). In a study over six months, there were no changes in BMD of the total body, hip, or lumbar spine with either regimen (Floter 2002b).

2.1.2. Body composition

2.1.2.1. Meta-analysis (comparison 4): data were derived from one or two studies for each parameter. Using mean or mean change, results did not achieve a significant difference for any parameter.

2.1.2.2. Descriptive data synthesis: results from three studies for other parameters of body composition were not included in the meta-analysis (Dobs 2002; Floter 2002b; Leao 2006). Standard deviations were unclear in one study (Dobs 2002). This study reported that T-HT treatment, when compared with HT alone, significantly increased lean body mass in the arms, legs, and trunk. When the changes in arms, legs, and trunk in each participant were analysed together, the difference between treatments was significant for lean body mass ($P < 0.05$) and percentage of fat tissue ($P < 0.05$) but not significant for fat tissue ($P < 0.05$). In a crossover study, there were no significant differences in total body fat, total lean body mass, trunk fat, and trunk lean mass between the two treatments (Floter 2002b). The addition of testosterone to HT was associated with a significant increase in visceral fat area ($P = 0.009$) in one study (Leao 2006). However, there was no significant difference in subcutaneous fat area between the two groups (Leao 2006).

2.1.3. Cognition

2.1.3.1. Meta-analysis (comparison 5): one trial was eligible for meta-analysis for each domain of cognition. These domains were: cognition difficulty (Warnock 2005), identical pictures, and shape memory (Dobs 2002). The results showed no statistically significant difference in the means between treatments (difference in means 0.0, 95% CI -0.21 to 0.21; 2.4, 95% CI -6.67 to 1.87; and 0.10, 95% CI -2.19 to 2.39 for cognition difficulty, identical pictures, and shape memory, respectively) (Dobs 2002; Warnock 2005).

2.1.3.2. Descriptive data synthesis: this same study showed that performance on building memory was significantly different between the two groups (Dobs 2002). Women receiving oestrogen and methyltestosterone maintained a steady level of performance on the building memory task, whereas those receiving oestrogen alone showed a decrease in performance. A double-blind, crossover study reported a significant benefit of testosterone on the Switching Attention Test (Regestein 2001). Reaction time in the switching condition was faster in the oestrogen plus testosterone group than in the oestrogen group ($t = 3.25$, $df = 37$, $P < 0.002$, effect size = 0.53 SD) (Regestein 2001). For other conditions of the same test, such as side condition and direction condition, there were no differences between the two groups (Regestein 2001). Results from another double-blind study showed no significant advantage of adding testosterone to oestrogen therapy on tasks involving spatial transformation or orientation, mathematics, or non-verbal reasoning (Shepanek 1999). Another crossover study did not report an effect on cognitive function of oestrogen alone versus oestrogen plus testosterone (Sherwin 1988). No studies involved co-administered progestin during the study period.

2.1.4. Menopausal symptoms

2.1.4.1. Meta-analysis (comparison 6): only one trial was eligible for meta-analysis, looking at vasomotor symptoms (Warnock 2005). The results showed no statistically significant difference between the treatment means (difference in means 0.10, 95% CI -2.19 to 2.39).

2.1.4.2. Descriptive data synthesis: menopausal symptoms were measured by validated questionnaires in three trials (Dow 1983; Regestein 2001; Sherwin 1988). Dow et al measured menopausal symptoms using a menopausal symptom scale developed by Greene 1976 and reported no significant difference between treatments in any domain. In a crossover trial with no washout period, menopausal symptoms were measured by the Menopause-Specific Quality of Life Questionnaire (MENQOL) and the study found that the mean overall outcome change score between treatments was not different from zero (Regestein 2001). Sherwin et al measured the symptoms using a menopausal index and reported a significantly greater improvement in somatic and psychological symptoms in the combined testosterone-oestrogen treated group than in the oestrogen alone group (Sherwin 1988). No compar-

ative effects on hot flushes were provided in another report of the same trial (Sherwin 1988). Descriptive data synthesis from other studies that measured menopausal symptoms using modified scores and scales also found inconsistent results.

2.2. Adverse events

2.2.1. Increased facial and body hair

2.2.1.1. Meta-analysis (comparison 7): hirsutism and facial hair growth were considered together. Seven studies that were eligible for meta-analysis (Braunstein 2005; Buster 2005; Chiuve 2004; Davis 2006; Shifren 2006; Simon 2005; Warnock 2005) showed that the incidence of increased facial or body hair growth was significantly higher in the T-HT group than that in the HT group (Peto OR 1.52, 95% CI 1.07 to 2.17). By using a mean hirsutism score, one study eligible for meta-analysis (Lobo 2003) showed that the mean score was not significantly different between the two treatments (difference in means 0.4, 95% CI -0.15 to 0.95).

2.2.1.2. Descriptive data synthesis: a parallel study reported no differences in the hirsutism scores between the low-dose groups (conjugated equine oestrogen 0.625 mg versus conjugated equine oestrogen 0.625 mg and methyltestosterone 1.25 mg) (Barrett-Connor 1999). In the high-dose groups (conjugated equine oestrogen 1.25 mg versus conjugated equine oestrogen 1.25 mg and methyltestosterone 2.5 mg) in the same study, 10 HT-T treated participants and three HT treated participants reported hirsutism as an adverse event. Three crossover studies with no washout period reported no difference in increased hair growth between treatment groups (El-Hage 2007; Floter 2002b; Shifren 2000).

2.2.2. Acne

2.2.2.1. Meta-analysis (comparison 8): seven studies that were eligible for meta-analysis (Braunstein 2005; Buster 2005; Chiuve 2004; Davis 2006; Shifren 2006; Simon 2005; Warnock 2005) showed that the incidence of acne was significantly higher in the T-HT group than that in the HT group (Peto OR 1.51, 95% CI 1.07 to 2.14). Using the mean acne score, one study that was eligible for meta-analysis (Lobo 2003) showed that the score was not significantly different between the two treatments (difference in means 0.1, 95% CI -0.03 to 0.23).

2.2.2.2. Descriptive data synthesis: the incidence of acne was not different between groups as reported in three crossover studies with no washout period (El-Hage 2007; Floter 2002b; Shifren 2000). In the interim analysis of a two-year study (Barrett-Connor 1999), acne of mild or moderate severity was reported by 5 (3%) in the oestrogen plus methyltestosterone treated participants whereas no participants receiving oestrogen alone reported acne (Barrett-Connor 1999).

2.2.3. Mood alteration, specifically aggression

2.2.3.1. Meta-analysis: no appropriate data were available.

2.2.3.2. Descriptive data synthesis: the data synthesis found no significant differences between treatments for hostility (El-Hage 2007; Sherwin 1988).

2.2.4. Breast cancer

2.2.4.1. Mammographic density (comparison 9): only one trial was eligible for meta-analysis (Hofling 2007). The results showed no statistically significant difference in the mean increase in area of dense breast between the two treatment groups.

2.2.4.2. Incidence of breast cancer: no trial reported an outcome for incidence of breast cancer.

2.2.5. Coronary heart disease: no trial reported this as an outcome.

2.2.6. Lipid profile

2.2.6.1. Meta-analysis (comparison 10 and 11): four lipid parameters were analysed according to route of testosterone administration. As significant heterogeneity was found in the meta-analyses of all lipid parameters, we used the random-effects model to analyse the outcomes. When we combined the results for all routes of testosterone there were significant reductions in total cholesterol and HDL-cholesterol levels while there were significant increases in LDL cholesterol and triglyceride levels. For subgroup analyses according to route of testosterone administration not only did oral testosterone significantly increase LDL cholesterol but it also significantly decreased total cholesterol, HDL cholesterol, and triglyceride levels. When compared with conventional hormone therapy, the addition of a testosterone patch did not significantly alter the levels of total cholesterol, LDL cholesterol, and triglyceride but it significantly decreased the HDL level by -1.09 mg/dl (95% CI -1.98 to - 0.91). Possible sources of heterogeneity were clinical and methodological diversities. Baseline inequality was documented in the study conducted by Chiuve et al in terms of triglyceride levels (Chiuve 2004) and Raisz et al. in terms of age and total cholesterol (Raisz 1996). Baseline triglyceride levels were noticeably lower in the T-HT group than those in the HT group (Chiuve 2004). Participants in the T-HT group were younger than those in the HT group and baseline total cholesterol levels in the T-HT group were significantly higher than in the HT only group ($P < 0.05$) (Raisz 1996). Baseline equality was not mentioned in the study conducted by Farish et al (Farish 1984). However, baseline lipid levels as shown in a table were similar in both groups (Farish 1984).

Five parameters were analysed at five time periods: less than three months, three to < six months, six to < 12 months, at 12 months, and at 24 months. The parameters were: total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, and the total cholesterol to HDL cholesterol ratio.

2.2.6.1.1. Studies of less than three-month duration: there were four eligible studies. The direction of the results was different between studies for total cholesterol, triglyceride, and LDL cholesterol. Furthermore, there was statistically significant heterogeneity for triglyceride, HDL cholesterol, and LDL cholesterol ($P < 0.05$). Therefore these trials were not pooled for triglyceride and LDL cholesterol; a random-effects model was used for the meta-analysis of total cholesterol and HDL cholesterol. Possible sources of heterogeneity were clinical and methodological diversities. Baseline inequality was documented in the study conducted by Chiuve

et al in terms of triglyceride levels (Chiuve 2004) and Raisz et al in terms of age and baseline total cholesterol levels (Raisz 1996). Baseline triglyceride levels were noticeably lower in the T-HT group than in the HT group (Chiuve 2004). Participants in the T-HT group were younger than those in the HT group and total cholesterol levels in the T-HT group were significantly higher than in the HT-only group (P < 0.05) (Raisz 1996). Baseline equality was not mentioned in the study conducted by Farish et al (Farish 1984). However, baseline lipid levels shown in a table were similar in both treatment groups (Farish 1984). Another possible source of heterogeneity was the route of hormone administration. In two studies both hormones were administered orally (Chiuve 2004; Raisz 1996) and in the other study by implant (Farish 1984).
In the meta-analysis: total cholesterol and HDL cholesterol were significantly lower after treatment in the T-HT group than in the HT group. The weighted mean differences (WMD) were -14.92 mg/dl (95% CI -27.81 to -2.03) and -17.11 mg/dl (95% CI -23.47 to -10.75), respectively.

2.2.6.1.2. Studies over three to < six months: two studies were eligible for this analysis (Dobs 2002; Lobo 2003). Because statistically significant heterogeneity was found using the Chi^2 test the random-effects model was used to estimate the treatment effects. A possible source of heterogeneity was the dose of methyltestosterone. In the study conducted by Lobo et al, the dose of methyltestosterone was 1.25 mg (Lobo 2003) while 2.5 mg of methyltestosterone was administered in the study conducted by Dobs et al (Dobs 2002). When we combined the mean scores and the change in scores, triglyceride and HDL cholesterol levels were significantly lower in the T-HT group than in the HT group (total WMD -25.62 mg/dl, 95% CI -38.53 to -12.72; -18.72 mg/dl, 95% CI -26.04 to -11.39 respectively) while total cholesterol and LDL cholesterol levels were not significantly different between treatment groups.
2.2.6.1.3. Studies at six to < 12 months: 10 studies were eligible for this analysis. By using mean scores or change in scores, HDL cholesterol was consistently significantly lower in the T-HT group than in the HT group (WMD -9.38 mg/dl, 95% CI -13.64 to -5.12; -4.74 mg/dl, 95% CI -8.42 to -1.07 respectively) while total cholesterol, triglyceride, and LDL cholesterol levels were not significantly different between treatment groups. Subgroup analysis according to oral or non-oral testosterone (comparison 21) showed that HDL levels consistently decreased in both subgroups; however, the decrease was less in the non-oral subgroup. Only one study was eligible for the meta-analysis of the total cholesterol to HDL cholesterol ratio. For this the decrease in the ratio was greater in the T-HT group than in the HT group (difference in means 20.60, 95% CI 12.76 to 28.44).
2.2.6.1.4. Studies at 12 months: using mean scores or change in scores, only HDL cholesterol was consistently significantly lower in the T-HT group than in the HT group (WMD -7.22 mg/dl, 95% CI -13.99 to -0.45; -23.64 mg/dl, 95% CI -28.95 to -18.33 respectively). However, using change in scores the increase in LDL cholesterol was significantly greater in the T-HT group than in the HT group (WMD 9.5 mg/dl, 95% CI 2.1 to 16.9) whereas the decrease in triglycerides was significantly greater in the T-HT group than in the HT group (WMD -45.29, 95% CI -80.17 to-10.40).
2.2.6.1.5. Studies at 24 months: using mean scores there were no differences between the two treatment groups. However, using change in scores the increase in LDL cholesterol was significantly greater in the T-HT group than in the HT group (WMD 9.8 mg/dl, 95%CI 1.3 to 18.3). Triglyceride and HDL cholesterol levels were significantly lower in the T-HT group than in the HT group (WMD -58.1 mg/dl, 95% CI -76.1 to -40.1; -26.3 mg/dl, 95% CI -30.0 to -22.7 respectively). The total cholesterol to HDL cholesterol ratio was significantly higher in the T-HT group at both 12 and 24 months (WMD 20.8 mg/dl, 95% CI 11.0 to 30.6).
For changes in scores, the meta-analyses at both 12 and 24 months were limited to esterified oestrogen 1.25 mg versus esterified oestrogen 1.25 mg plus methyltestosterone 2.5 mg.
2.2.6.2. Descriptive data synthesis: results from a study of esterified oestrogen 1.25 mg versus esterified oestrogen 1.25 mg plus methyltestosterone 2.5 mg showed that after 16 weeks of treatment significant decreases in the levels of total cholesterol, HDL cholesterol, and triglycerides occurred in the oestrogen plus testosterone group; LDL cholesterol values were virtually unchanged (Dobs 2002). The oestrogen group demonstrated the opposite effect on lipids with a significant decrease in LDL cholesterol levels and no meaningful change in the other lipid parameters (Dobs 2002). Results from a study of micronized oestrogen (with or without micronized progesterone) versus micronized oestrogen plus micronized testosterone (with or without micronized progesterone) found significant reductions in total cholesterol and LDL cholesterol in all groups (Miller 2000). Triglyceride levels increased 26.0% and HDL cholesterol levels decreased 9.0% in the oestrogen plus testosterone group. In contrast, with oestrogen therapy the triglyceride levels decreased 9.0% and HDL cholesterol levels increased 9.0%.
2.2.7. Discontinuation rate
2.2.7.1. Meta-analysis (comparisons 12, 13, and 14): meta-analyses involving 20 trials showed that there was no statistically significant difference in discontinuation rates between treatments. For the overall discontinuation rate and the discontinuation rate due to adverse events, Peto ORs were 0.99 (95% CI 0.83 to 1.19) and 1.24 (95% CI 0.95 to 1.62), respectively. Sensitivity analyses (comparison 23) based on quality of randomization and concealment of allocation sequences, study size (taking out three large studies with more than 100 participants), blinding, crossover studies, doses of testosterone, and doses of oestrogen did not affect the result. Subgroup analyses on the basis of symptoms at recruitment, menopausal status, type of menopause, duration of treatment, blinding, and disease status did not affect results.

Sensitivity analysis

Sensitivity analysis was performed only for the discontinuation rate due to limitations in the number of trials for each outcome. There was no substantial effect of methodological quality of trials, very large studies, length of treatment follow up, and different doses on the discontinuation rate.

Publication bias

Funnel plots were created to examine any possibility of publication bias. For the discontinuation rate, the funnel plot had a symmetrical shape around the overall effect with a wide base and a narrow peak. It indicated the absence of bias. However, visual examination of funnel plots for other outcomes had limited power because the numbers of studies were small.

DISCUSSION

Summary of main results

Based on the results of this review, adding testosterone to an HT regimen has significant beneficial effects on sexual function for several domains, specifically number of satisfying sexual events (SMD 0.29, 95% CI 0.20 to 0.38), the total number of sexual events (SMD 0.25, 95% CI 0.17 to 0.34), number of orgasms (SMD 0.30, 95% CI 0.21 to 0.39), degree of libido or desire (SMD 0.35, 95% CI 0.26 to 0.43), level of orgasm (SMD 0.28, 95% CI 0.19 to 0.37), arousal (SMD 0.36, 95% CI 0.27 to 0.45), pleasure or enjoyment of sex (SMD 0.33, 95% CI 0.22 to 0.43), sexual concerns (SMD 0.32, 95% CI 0.22 to 0.41), responsiveness (SMD 0.32, 95% CI 0.23 to 0.40), sexual self-image (SMD 0.26, 95% CI 0.16 to 0.35), and for the composite sexual function score (SMD 0.41, 95% CI 0.19 to 0.63). The decrease in personal distress scores in the testosterone group at 24 weeks was significantly greater for the placebo group (-8.13, 95% CI -10.59 to -5.67). The clearly documented adverse effects of therapy were a reduction in HDL cholesterol, an increased incidence of facial hair growth (Peto OR 1.52, 95% CI 1.07 to 2.17) and acne (Peto OR 1.52, 95% CI 1.07 to 2.14). A reduction in HDL cholesterol was consistently seen for all testosterone regimens over all study durations that were evaluated. However, the magnitude and precision of this effect varied with the study duration and route of administration. In a subgroup analysis, HDL levels were markedly decreased in postmenopausal women who were treated with oral testosterone (WMD -18.63, 95% CI -22.18 to -15.08) while the effect size was smaller in the women who were treated with a testosterone patch (WMD -1.09, 95% CI -1.98 to -0.91). The discontinuation rate was not significantly greater with testosterone therapy (Peto OR 0.98, 95% CI 0.83 to1.17). There was no convincing evidence for effects on sense of well being, unexplained fatigue, bone health, body composition, menopausal symptoms, cognition, or hostility. However, conclusions are limited by the paucity of studies that have included these outcomes. Evidence for long-term effects on breast cancer and coronary heart disease is lacking.

Overall completeness and applicability of evidence

For applicability of the evidence the following factors should be considered.

1) Testosterone regimens: all types of testosterone therapy exhibit a beneficial effect on sexual function. An adverse effect on HDL cholesterol levels was seen for testosterone implants, methyltestosterone, and testosterone patches.

2) Characteristics of participants: the improvement in sexual function together with the adverse effect on HDL cholesterol were reported in women treated with HT plus testosterone regardless of the type of menopause, disease status, duration or location of the study. There was no evidence available for perimenopausal women as distinct from postmenopausal women.

3) Biologic and cultural aspects: the age of natural menopause and the experience of menopausal symptoms vary geographically and culturally (Gold 2000). Additional factors that influence sexual function after menopause include endocrine factors, socioeconomic status, various concurrent illnesses, as well as the availability and sexual vitality of an intimate partner (Bachmann 2000). The effects of exogenous testosterone therapy on sexual function will be superimposed on this complex background.

Because of the complex nature of female sexual dysfunction it is often difficult to establish the meaningful steps in treatment. Treatment options for sexual dysfunction include identification of correctable causes, education and counselling, and medical therapy. Evidence from this systematic review provides information to be considered within the overall management of female sexual dysfunction.

Quality of the evidence

The methodological strengths of the included studies are that most had adequate randomisation and concealment of allocation sequences, to prevent selection bias. Methodological limitations included attrition bias, baseline inequality, the possibility of detection bias, and lack of a washout period in crossover studies. Attrition bias, baseline inequality, and detection bias all may have caused inaccurate effect estimates in the meta-analyses. Attrition bias is evident by a significant number of non-compliers and the lack of an intention-to-treat analysis in most of the included studies. Baseline inequality was documented in the studies that were included in the meta-analysis for sexual function and lipid profile (Chiuve 2004; Davis 1995; Davis 2006; Raisz 1996). Detection bias may have occurred in the assessment of sexual function in a single-blind study (Davis 1995) and may have resulted in overestimation of the treatment effect. In addition, the baseline inequality that was documented in the studies by Raisz and Chiuve might provide an explanation for the heterogeneity found in the meta-

analysis for the lipid outcome with less than three months of treatment. The difference in baseline frequency for total satisfactory activity may have contributed to the inaccurate effect estimate in one of the studies (Davis 2006); however, the direction of treatment effect was the same as in the other studies. With respect to the crossover studies included in the descriptive data synthesis for the outcomes of sense of wellbeing, unexplained fatigue, cognition, excess facial and body hair, and acne the lack of a washout period is likely to have resulted in underestimation of a treatment effect. This may have led to inconclusive results in these studies. In addition, different types of questionnaires used for outcome measurements of the construct variables may also have contributed to an underestimation of treatment effect.

Nevertheless, descriptive data synthesis of other double-blind studies that were not included in the meta-analyses confirms a benefit of testosterone therapy on sexual function. The positive effect of testosterone on sexual function and the negative effect on HDL cholesterol levels are likely to be reliable as the direction of the effects is consistent across the relevant studies not included in the meta-analyses.

Potential biases in the review process

The strengths of this review are that we looked at a broad range of outcomes in relation to the addition of testosterone to HT regimens and thoroughly searched for all relevant studies, both published and unpublished, in electronic databases. We also made contact with the corresponding authors of relevant articles, experts, and pharmaceutical companies; and relevant journals were handsearched. In addition, there was a pre-determined strategy for study selection and quality assessment of included studies, conducted by two independent assessors. These procedures were used to optimize the validity of the results of this review. Last but not least, we have now included more data in our meta-analyses, specifically on sexual function, lipid profile, excess facial and body hair, and acne, resulting in more precise estimates of efficacy and safety than those in the previous review (Cochrane 2005).

Limitations of this review are the small number of studies and that no study was suitable for meta-analyses for some outcomes, specifically sense of well being, unexplained fatigue, bone health, body composition, cognition, menopausal symptoms, mood alteration, breast cancer, and cardiovascular disease. In addition we included different regimens in the same analysis. The former limitation contributed to the inconclusive results and limited the power of the meta-analysis to provide conclusions about some aspects of efficacy and safety. To address our question on whether there is evidence for the efficacy of testosterone therapy, we included all eligible studies in the meta-analyses regardless of the treatment regimen. The limitation of this approach is that the effect estimate cannot be interpreted for a single treatment regimen.

Progestin was a co-intervention in eight of the included trials. This could potentially obscure the treatment effects of testosterone on sexual function, body composition, BMD, biochemical markers of bone turnover, and lipid profiles. This review did not distinguish adverse events specific to the study medication from other adverse events since there was inconsistent reporting of the classification of adverse events among the studies. We did not review the effects of HT plus testosterone on liver function, endometrial histology, or hormonal profiles.

Agreements and disagreements with other studies or reviews

In support of the effects of testosterone on sexual function, a dose-response relationship between testosterone and sexual function was suggested by six studies (Braunstein 2005; Buster 2005; Davis 2006; Shifren 2000; Shifren 2006; Simon 2005). The test for a linear dose-response relationship for changes in sexual desire showed a positive trend although it did not reach statistical significance (P = 0.06) (Braunstein 2005). In the study by Shifren et al higher testosterone doses resulted in further increases in scores for thoughts-desire, frequency of sexual activity, and pleasure-orgasm determined using the Brief Index of Sexual Functioning for women (Shifren 2000). There was no formal statistical analysis for the dose-response relationship provided. Thus a dose-response relationship may exist but the limited number and size of available studies provided us with limited power to assess a dose-response effect. The correlation between testosterone levels and sexual function was supported by evidence from six therapeutic trials (Braunstein 2005; Buster 2005; Davis 2006; Lobo 2003; Shifren 2006; Simon 2005). Lobo et al reported a significant association between changes in female sexual interest or desire and responsiveness and bioavailable testosterone (Lobo 2003). However, the correlation coefficient was not reported. Braustein et al reported a significant association between testosterone (total, free, and bioavailable) and many domains of sexual function; specifically sexual desire, sexual arousal, orgasm, and pleasure (Braunstein 2005). Significant correlations were also consistently observed between changes in serum total, bioavailable, and free testosterone levels and changes in the frequency of satisfying activity (Spearman's rank correlation of 0.16 to 0.18; $P < 0.05$), sexual desire (0.20 to 0.25; $P<0.05$), and personal distress (-0.11 to -0.17, $P < 0.05$) (Buster 2005). These correlations were consistently reported by other studies using testosterone patches (Davis 2006; Shifren 2006; Simon 2005). The magnitude of the correlation coefficient varied across the studies. The highest coefficients were 0.61, 0.40, and 0.48 for the correlation between free testosterone and the frequency of satisfying activity, sexual desire, and personal distress, respectively. These figures showed a moderately strong relationship between serum levels of testosterone and sexual function.

Evidence from therapeutic trials regarding testosterone levels and the change of lipid profile is controversial. In a study of methyltestosterone in surgically postmenopausal women taking esterified oestrogens, changes in serum testosterone, total or free, were not

found to be significantly correlated with changes in any of the lipoproteins (Chiuve 2004). In a crossover study, during the phase of oestradiol valerate 2 mg plus testosterone undecanoate 40 mg the difference between baseline and 24 weeks showed a significant positive correlation between free testosterone and total cholesterol ($r = 0.33$, $P < 0.027$). However, no correlations were found between the levels of total testosterone, free testosterone, and serum levels of HDL cholesterol (Floter 2002b).

AUTHORS' CONCLUSIONS

Implications for practice

1) Based on the evidence provided by our review of published data, an indication for adding testosterone to HT is to enhance sexual function in postmenopausal women. Adding testosterone to HT improved the number of satisfying sexual events (SMD 0.29, 95% CI 0.20 to 0.38), total number of sexual events (SMD 0.25, 95% CI 0.17 to 0.34), number of orgasms (SMD 0.30, 95% CI 0.21 to 0.39), degree of libido or desire (SMD 0.35, 95% CI 0.26 to 0.43), level of orgasm (SMD 0.28, 95% CI 0.19 to 0.37), arousal (SMD 0.36, 95% CI 0.27 to 0.45), pleasure or enjoyment of sex (SMD 0.33, 95% CI 0.22 to 0.43), sexual concerns (SMD 0.32, 95% CI 0.22 to 0.41), responsiveness (SMD 0.32, 95% CI 0.23 to 0.40), sexual self image (SMD 0.26, 95% CI 0.16 to 0.35), and the composite sexual function score (SMD 0.41, 95% CI 0.19 to 0.63). The decrease in personal distress scores in the testosterone group at 24 weeks was significantly greater than the decrease in the placebo group (SMD -8.13, 95% CI 1-0.59 to -5.67). The overall reporting of side effects in the studies included in this review was inadequate. Hence testosterone therapy should be used with caution.

2) Close surveillance for hirsutism, acne, change in HDL cholesterol, and other side effects is necessary. The incidence of hirsutism or facial hair growth and acne are clearly increased by addition of testosterone to hormone therapy (Peto OR 1.52, 95% CI 1.07 to 2.17; Peto OR 1.52, 95% CI 1.07 to 2.14 respectively). Another documented adverse event of adding testosterone to hormone therapy is a significant decrease in HDL cholesterol levels. The changes ranged from -5.84 (95% CI -9.10.13 to -2.58) to -17.63 (95% CI -31.45 to -3.80) at 6 to less than 12 months and 24 months of study, respectively). At this time, testosterone therapy should be limited to short-term use, as long-term studies are not available.

Implications for research

1) Study design for further research into the use of testosterone in women: double-blind, randomised controlled studies will best estimate treatment effects. A crossover study with an adequate washout period to discard any carry-over effect is an alternative.

2) Type of outcome measurement: the most useful type of data is dichotomous or categorical data. These data convey the number of women who receive a benefit and the number of women who are put at increased risk. Therefore, if possible, further research should measure outcomes as dichotomous or categorical outcomes, such as improved, not improved, or worsened, in addition to continuous outcomes.

3) Outcome of interest: the following outcomes remain unclear and should be further investigated by appropriate studies.

3.1. Benefits of testosterone on well being, unexplained fatigue, bone health (bone mineral density and fracture rate), and cognition.

3.2. Adverse effects on deepening of voice, coagulation profile, haematocrit, and mood changes.

3.3. Long-term complications: breast cancer, stroke, and coronary heart disease.

4) Intervention: use of testosterone alone in postmenopausal women may increase with new product availability. However, this cannot be recommended until adequate safety data is available. More studies addressing the use of testosterone with oestrogen versus testosterone alone in postmenopausal women are required.

5) Co-intervention: the majority of studies in which methyltestosterone was administered did not include co-administration of a progestin, therefore the effects of methyltestosterone plus oestrogen and progestin in naturally menopausal women requires further study.

6) Target population: effects of testosterone therapy in perimenopausal women needs investigation.

7) Duration of treatment: although the available evidence suggests a benefit of testosterone on sexual function, the ideal duration of treatment is still unclear.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Barrett-Connor 1996

Methods	See Barrett-Connor 1999
Participants	See Barrett-Connor 1999
Interventions	See Barrett-Connor 1999
Outcomes	See Barrett-Connor 1999
Notes	See Barrett-Connor 1999

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Barrett-Connor 1999
Allocation concealment?	Yes	See Barrett-Connor 1999
Blinding? All outcomes	Yes	See Barrett-Connor 1999
Incomplete outcome data addressed? All outcomes	No	See Barrett-Connor 1999
Free of selective reporting?	No	See Barrett-Connor 1999
Free of other bias?	Yes	See Barrett-Connor 1999

Barrett-Connor 1999

Methods	-Design: double-blind randomised (A), parallel group -No of centres: multicentre -Duration: 2 years -Power calculation: not stated -Intention-to-treat analysis: no -No of participants randomised: 331; E group 79, E-T group 81, E(high dose) group 78, E-T(high dose) 73 -No of participants completed the study: 199 -No of participants analysed: depended on outcomes, 196 for lipid profile, unclear for other outcomes. -No of noncom pliers: 122/311= 39.2%; Reasons were adverse events(45), non-drug event(24), protocol violation(21), lost to follow up (22) -No of losses to follow up: 22/311=7.1% -Compliance assessment: not stated -Source of funding: drug company
Participants	-Location: US -Setting: hospital-based -Ethnicity: Caucasians -Run-in period: no -Characteristics: healthy surgically menopausal women -Age (SD): E(low dose) group 46.5 (7.5), E-T(low dose) group 44.8 (8.1), E(high dose) group 45.1 (7.1), E-T(high dose) group 46.3 (7.8) -Inclusion criteria: 1. Caucasian 2. Age 21-65 years 3. TAH with BSO at least 3 months but not more than 5 years 4. Body weight within 75-125% of ideal body weight 5. A stable personal relationship for at least 6 months -Exclusion criteria: 1. Use of estrogen or hormone therapy in the previous six weeks 2. Use of psychotropic drugs in the previous four weeks 3. History of pelvic or breast malignancy 4. Dependence on alcohol, tobacco or illicit drugs
Interventions	-CEE 0.625 mg once a day -CEE 1.25 mg once a day (high dose) -CEE 0.625 mg plus mT 1.25 mg once a day -CEE 1.25 mg plus mT 2.5 mg once a day (high dose) -Route:oral -Co-intervention: all participants received calcium supplement
Outcomes	-Relevant outcomes: 1. General well being 2. Sexual behavior and enjoyment 3. BMD of lumbar spines and hip: DEXA

Barrett-Connor 1999 (*Continued*)

	4. Menopausal symptoms: scales modified from those developed by Sherwin and Kupperman 5. Lipid profile 6. Haematocrit -Other outcomes: 1. Other safety outcomes
Notes	-Baseline equality: no differences in mean age, weight, height, body mass index and duration of menopause in four treatment groups. There was no report of the baseline equality of groups for the outcome of interest. -The author was contacted. The further supplied information was not allowed by drug company.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	No	Discontinuation >10%
Free of selective reporting?	No	Acne data reported incompletely
Free of other bias?	Yes	Possible free of other sources of bias

Basaria 2002

Methods	See Dobs 2002
Participants	See Dobs 2002
Interventions	See Dobs 2002
Outcomes	See Dobs 2002
Notes	See Dobs 2002

Risk of bias

Basaria 2002 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Dobs 2002
Allocation concealment?	Yes	See Dobs 2002
Blinding? All outcomes	Unclear	See Dobs 2002
Incomplete outcome data addressed? All outcomes	Unclear	See Dobs 2002
Free of selective reporting?	Unclear	See Dobs 2002
Free of other bias?	Unclear	See Dobs 2002

Braunstein 2005

Methods	-Design: double-blind randomised (C), parallel group -No. of centres: multicentre -Duration: 24 weeks -Power calculation: not stated -Intention-to-treat analysis: available case analysis -No. of participants randomised:447(119 in E group, 107 in E-T150, 110 in E-T300, 111 in E-T450) -No. of participants completed the study: E group 81/119(68%), E-T150 72/107(67%), E-T300 81/110(74%), E-T450 85/111(77%), overall 319/447(71%) -No. of participants analysed: not stated -No. of non compilers: E group 32%. Reasons were adverse event(12%), voluntary(10%), other(10%); E-T150 33%. Reasons were adverse event(13%), voluntary(8%), other(11%); E-T300 26%. Reasons were adverse event(7%), voluntary(10%), other(9%); E-T450 23%. Reasons were adverse event(10%), voluntary(7%), other(6%) -No of losses to follow up: E group10/119 (0.6%); E-T150 8/107 (0.7%) ; E-T300 7/110 (0.6%); E-; E-T450 7/111 (0.6%) -Compliance assessment: not stated -Source of funding: drug company
Participants	-Characteristics: surgically menopausal women with menopausal onset of low sexual desire with low serum T levels -Age: E group 49, E-T150 group 50, E-T300 group 50, E-T450 group 49 -Location: US -Setting: population-based -Ethnicity: Caucasian 89% -Run-in period: 8-week pretreatment baseline period -Inclusion criteria:

Braunstein 2005 (*Continued*)

	1. 20-70 year-old 2. Generally good health 3. BMI 18-30 kg/m^2 4. TAH with BSO at least 1 year 5. Stable relationship with partner present more than 50% of the time 6. Serum free-T < 3.5 pg/ml at baseline 7. Stable estrogen dose > 3 months 8. Menopause onset of low sexual desire -Exclusion criteria: 1. >15 moderate to severe hot flushes per week 2. Recent androgen use 3. Hirsutism, virilization, severe acne 4. Positive screening for depression or hypothyroidism 5. Ongoing medical, psychiatric or relationship disturbance 6. Medications known to affect sexual function 7. Severe hyperlipidaemia/metabolic disorders 8. Dyspareunia, physical limitations affecting sexual function
Interventions	- once a day -CEE once a day plus T 150 mg twice a week -CEE once a day plus T 300 mg twice a week -CEE plus T 450 mg -Route:oral oestrogen, transdermal T patch -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Sexual function: SAL and PFSF 2. Hirsutism 3. Acne -Other outcomes: 1. Safety outcomes(adverse events, clinical laboratory measurements, vital signs, and physical examinations.
Notes	-Baseline equality: no statistically significant differences across treatment groups with regard to age, ethnicity, percent married to partner, duration of relationship, age at oophorectomy and years since oophorectomy -The author was contacted. The further information was supplied.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate

Braunstein 2005 (*Continued*)

Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing data have been imputed using appropriate methods
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possibly free of other sources of bias

Burger 1987

Methods	-Design: single-blind randomised (A), parallel group -No of centres: two -Duration: 24 weeks -Power calculation: not stated -Intention-to-treat analysis: not stated -No of participants randomised: 20 (10 in each group) -No of participants completed: 18/20 = 90% -No of participants analysed: not stated -No of non compilers: 2/10=20% -No of losses to follow up: not stated -Compliance assessment: not stated -Source of funding: drug company provided medication
Participants	-Location:Australia -Setting:hospital-based -Ethnicity:unspecified -Run-in period:current treatment with oral estrogens was stopped for a duration of 2 weeks -Characteristics:surgically(9 in E-T, 10 in E group) and naturally (1 in E-T group) menopausal women with loss of libido despite treatment of oral estrogens-progestogens -Age(SD):E group 48.2(5.2), E-T group 43.5(7.6) -Inclusion criteria: as above -Exclusion criteria: not stated
Interventions	-oestradiol 40 mg -oestradiol 40 mg plus T 50 mg -Route: implant -Co-intervention: norethisterone 2.5 mg daily for 10 days every month was prescribed for women with intact uterus

Burger 1987 (*Continued*)

Outcomes	-Relevant outcomes: 1. Libido:self-rating analogue scales(0-100) 2. Sexual enjoyment: 0-3 rating scale -Other outcomes: 1. Plasma testosterone
Notes	-Baseline equality: the mean number of years since menopause of the single and combined implant were 5.6(3.9) and 7.8(4.8), respectively. Nine of the combined implant group and all 10 in the single implant group had had hysterectomies, and three from each group had had oophorectomies. -The author was contacted and kindly supplied further information.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Outcome assessment was blinded
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Free of selective reporting?	No	One or more outcomes of interest in the review (sexual function) are reported incompletely
Free of other bias?	Unclear	insufficient information

Buster 2005

Methods	-Design: double-blind randomised(A), parallel group -No of centres: multicentre -Duration: 24 weeks -Power calculation: yes -Intention-to-treat analysis: available case analysis -No of participants randomised: 533 (266 in E group, 267 in E-T) -No of participants completed the study: 417 (206 in E group, 211 in E-T) -No of participants analysed: 532 -No of non compilers: E group 49/266 (18.4%). Reasons were adverse event (22), voluntary (25), protocol violation (2); E-T 50/267 (18.7%). Reasons were adverse event (22), voluntary (22), protocol violation (6) -No of losses to follow up: 16/533 (3.0%); E group 11, E-T group 5 -Compliance assessment: not stated -Source of funding: drug company
Participants	-Characteristics: surgically menopausal women with menopausal onset of hypoactive sexual desire disorder -Age: E group 49.5+7.55, E-T group 48.3+7.45 yr -Location: US -Setting: population-based -Ethnicity: E group African American 14 (5%), White 244 (92%), Hispanic 7 (3%), other 1 (<1%); E-T group African American 13 (5%), White 237 (89%), Hispanic 11 (4%), other 5 (2%) -Run-in period: 8 week pretreatment baseline period -Inclusion criteria: 1. 20-70 year old 2. Generally good health 3. BMI 18-30 kg/m^2 4. TAH with BSO at least 1 year 5. Stable monogamous relationship for at least 1 year to a sexually (both psychologically and physically) functional partner who was available for sexual activity at least 50% of each month during the study 6. Stable oral or transdermal estrogen dose > 3 months 7. Hypoactive sexual desire disorder -Exclusion criteria: 1. Recent androgen use 2. Hirsutism, virilization, severe acne 3. Positive screening for depression or hypothyroidism 4. Ongoing medical, psychiatric or relationship disturbance 5. Medications known to affect sexual function 6. Severe hyperlipidaemia/metabolic disorders 7. Dyspareunia, physical limitations affecting sexual function
Interventions	- Oral or transdermal oestrogen plus T patch 300 microgram/d - Oral or transdermal oestrogen plus placebo patch - Co-intervention: no

Buster 2005 (*Continued*)

Outcomes	-Relevant outcomes: 1. Sexual function: SAL and PFSF 2. Lipid profile 3. Hirsutism 4. Acne -Other outcomes: 1. Safety outcomes
Notes	-Baseline equality: no statistically significant differences across treatment groups with regard to mean age, ethnicity, percent married to partner, duration of relationship, route of oestrogen, and body mass index -The author was contacted. The further information was supplied.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing data have been imputed using appropriate methods
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possible free of other sources of bias

Chiuve 2004

Methods	-Design: double-blind randomised (C), parallel group -No. of centres: multicentre -Duration: 10 weeks -Power calculation: no -Intention-to-treat analysis: available case analysis -No of participants randomised:84 -No of participants completed the study: Not stated -No of participants analysed: 79 -No of non compilers: not stated -No of losses to follow up: not stated -Compliance assessment: not stated -Source of funding: drug company
Participants	-Characteristics: surgically menopausal women with menopausal onset of low sexual desire with low serum T levels -Age:E group 49, E-T150 group 50, E-T300 group 50, E-T450 group 49 -Location:US -Setting:population-based -Ethnicity: Caucasian 89% -Run-in period: 8-week pretreatment baseline period -Inclusion criteria: 1. TAH with BSO >3 months 2. Stable relationship for > 2 years 3. Serum free-T < 2 pg/ml at baseline 4. Stable estrogen dose (oral, topical, transdermal) > 3 months -Exclusion criteria: 1. A medical history or current diagnosis of known sensitivity or contraindications to hormone therapy with estrogens or androgens 2. Major mental illness or an eating disorder within the past 2 yr 3. BMI of 35 kg/m^2 or more 4. Current or prior history of cardiovascular disease 5. Clinically significant haematological, autoimmune, endocrine, renal, gastrointestinal, or neurological disorder 6. Current history of breast cancer or breast cancer in an identical twin 7. Malignant melanoma or any cancer diagnosed < 5 yr 8. Uncontrolled hypertension or poorly controlled diabetes mellitus 9. Gall bladder disease or gallstones 10. Drug or alcohol abuse within the past 6 months before screening 11. Life-threatening illness 12. Undiagnosed abnormal vaginal bleeding 13. Malignancy of the genital organs. 14. Abnormal physical or laboratory findings included abnormal vaginal cytology, abnormal mammographic findings, abnormal TSH levels, haematocrit < 30%, fasting serum glucose > 140 mg/dl, fasting serum triglycerides > 300 mg/dl, and fasting creatinine > 2.0 mg/dl. 15. Taking any of the following medications: progestin; androgen; glucocorticoid therapy; alternative estrogen-like agents (such as phytoestrogens); selective oestrogen recep-

Chiuve 2004 (*Continued*)

	tor modulators; liver enzyme-inducing medications such as rifampicin, phenytoin, barbiturates, antidepressants, and anxiolytics; anticoagulants; or cholesterol-lowering medications.
Interventions	- Methyltestosterone (2.5 mg) plus esterified oestrogens (1.25 mg) compared with esterified oestrogens (1.25 mg) alone -Route:oral oestrogen and testosterone, transdermal T patch -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Lipid profile 2. Hirsutism 3. Acne 4. Discontinuation rate -Other outcomes: 1. Hormone levels
Notes	-Baseline equality: no significant differences across treatment groups with regard to age, BMI, race, years since surgical menopause, FSH and TSH. Baseline triglyceride levels were shown in a table. Triglyceride levels were somewhat lower in the T-HT group than those in the HT group. -The author was contacted. No additional information was supplied.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	C - Not stated
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Discontinuation rate <10%
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possibly free of other sources of bias

Davis 1995

Methods	-Design: single-blind randomised (A), parallel group -No of centres: single -Duration: 2 years -Power calculation:not stated -Intention-to-treat analysis: no -No of participants randomised:34(17 in each group) -No of participants completed: 32/34 = 94.1% -No of participants analysed: 33/34 = 97.1% at 12 months(17 in E group, 16 in E-T group), 32/34 = 94.1% at 24 months(17 in E group, 15 in E-T group). -No of noncom pliers: 2/34=5.9%. One woman discontinued for personal reasons early after commencement, and the other discontinued after 12 months because of weight gain. -Compliance assessment:- -Source of funding: not stated
Participants	-Location: Australia -Setting: hospital-based -Ethnicity: unspecified -Characteristics: surgically and naturally menopausal women with indication for implants -Age (SD): E group 51.3 (5.7), E-T group 57.0 (5.2) yr -Inclusion criteria: 1. Postmenopausal women who had been on oral estrogen therapy at least 6 weeks and had an indication for an implant -Exclusion criteria: 1. Serious endocrine disorders with systemic disease 2. Use of drugs which affect response to treatment 3. History of alcohol or drug abuse 4. A rapidly progressive fatal disease 5. Major contraindication to HT 6. Other abnormal findings which might affect the interpretation of the result.
Interventions	-oestradiol 50 mg every three month -oestradiol 50 mg plus T 50 mg every three months -Route: implant -Co-intervention: women with an intact uterus were treated with either cyclical MPA 5-10 mg or norethisterone 2.5 mg orally for 12 days per months
Outcomes	-Relevant outcomes: 1. Sexual function: Sabbatsberg self-rating scale 2. BMD of lumbar spines and hip: DEXA 3. Lipid profile -Other outcomes: 1. Implant accumulation

Davis 1995 (*Continued*)

Notes	-Baseline equality: no differences in smoking, alcohol habits, hysterectomy, oophorectomy, BMI, or baseline values of sexual function, lipid or hormone in two groups. However the mean age of the E group was less than that of the E-T group. The mean BMDs were significantly lower for the E-T group compared to the E group. -The author was contacted and kindly provided additional information.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Outcome assessment was blinded
Incomplete outcome data addressed? All outcomes	Yes	Discontinuation rate <10%
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	No	Baseline imbalance (age, bone mineral density)

Davis 2000

Methods	See Davis 2006
Participants	See Davis 2006
Interventions	See Davis 2006
Outcomes	See Davis 2006
Notes	See Davis 2006

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Davis 2006
Allocation concealment?	Yes	See Davis 2006

Davis 2000 (*Continued*)

Blinding? All outcomes	Yes	See Davis 2006
Incomplete outcome data addressed? All outcomes	Yes	See Davis 2006
Free of selective reporting?	Unclear	See Davis 2006
Free of other bias?	No	See Davis 2006

Davis 2006

Methods	-Design: double-blind randomised (A), parallel group -No of centres: multicentre -Duration: 24 weeks -Power calculation: yes -Intention-to-treat analysis: available case analysis -No of participants randomised: 77 (40 in E group, 37 in E-T group) -No of participants completed the study: 61; E group 31/40 (77.5%), E-T 30/37 (81.1%) -No of participants analysed: primary end point (total satisfying activity) 72, secondary end point (sexual desire) 69 -No of noncom pliers: E group 7/40 (32%). Reasons were adverse event 4 (10%), voluntary 2 (5%), protocol violation 1 (2.5%); E-T 6/37 (16.2%). Reasons were adverse event 3 (8.1%), voluntary 3 (8.1%) -No of losses to follow up: E group 1/40 (2.5%), E-T group 1/37 (2.7%) -Compliance assessment: not stated -Source of funding: drug company
Participants	-Characteristics: surgically menopausal women with menopausal onset of low sexual desire with low serum T levels -Age: E group 49.3(30-63), E-T 51.0(38-66) yr -Location: Australia, UK, France, Germany, Netherlands, Italy -Setting: population-based -Ethnicity: unclear -Run-in period: 8-week pretreatment baseline period -Inclusion criteria: 1. 20-70 year-old 2. Generally good health 3. BMI 18-30 kg/m^2 4. TAH with BSO at least 1 year 5. Stable relationship with partner present more than 50% of the time 6. Serum free-T < 3.5 pg/ml at baseline 7. Stable estrogen dose > 3 months 8. Menopause onset of hypoactive sexual desire disorder -Exclusion criteria:

Davis 2006 (*Continued*)

	1. >15 moderate to severe hot flushes per week 2. Recent androgen use 3. Hirsutism, virilization, severe acne 4. Positive screening for depression or hypothyroidism 5. Ongoing medical, psychiatric or relationship disturbance 6. Medications known to affect sexual function 7. Severe hyperlipidaemia/metabolic disorders 8. Dyspareunia, physical limitations affecting sexual function
Interventions	- Transdermal oestrogen plus T 150 microgram/d - Transdermal oestrogen - Route: transdermal oestrogen patch, transdermal T patch - Co-intervention: no
Outcomes	-Relevant outcomes: 1. Sexual function 2. Hirsutism 3. Acne -Other outcomes: 1. Safety outcomes(adverse events)
Notes	-Baseline equality: no significant differences across treatment groups with regard to age, BMI, duration of relationship, and years since oophorectomy. However, there is somewhat different in frequency of total satisfactory activity. -The author was contacted. The further information was supplied.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing data have been imputed using appropriate methods
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	No	Baseline imbalance (sexual function)

de Paula 2007

Methods	-Design: a randomised, double-blind, placebo-controlled and crossover trial -No. of centres: single -Duration: 16 weeks -Power calculation: yes -Intention-to-treat analysis: no -No. of participants randomised: 85 -No. of participants completed/analysed: 80 -No. of non compilers: Five participants ceased to participate in this study because of abnormal uterine bleeding (n = 1) and private reasons (n = 4) -Compliance assessment: not stated -Source of funding: not stated
Participants	-Location: Sao Paulo, Brazil -Setting: hospital-based -Ethnicity: Caucasian -Run-in period: no -Characteristics: naturally menopausal women with sexual dysfunction -Age: 49-63 yr -Inclusion criteria: 1.Women had to report complaints of sexual dysfunction acquired in the postmenopausal period and to regularly use HRT. 2. Sexually active and satisfied with the performance of their partners. -Exclusion criteria 1. Use of other medication 2. Having other health problems or post-menopausal symptoms that could interfere with their sexual life including hot flashes, insomnia and other psychosomatic symptoms.
Interventions	Methyltestosterone 2.5 mg/day combined with HRT (conjugated equine oestrogens 0.625 mg/day plus medroxyprogesterone acetate 5 mg/day) versus HRT (conjugated equine oestrogens 0.625 mg/day plus medroxyprogesterone acetate 5 mg/day)
Outcomes	Lipid profile, sexual function, acne, hair growth, nervousness, aggressiveness, and discontinuation rate
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Unclear	B- Unclear
Blinding? All outcomes	Yes	Participants and key personnel were blinded

de Paula 2007 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Discontinuation rate <10%
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	No	Crossover trial, no washout period

Dobs 2002

Methods	-Design: double-blind randomised (A), parallel group -No of centres: single -Duration: 16 weeks -Power calculation: not stated -Intention-to-treat analysis: no -No of participants randomised: 40(20 in each group) -No of participants completed/analysed: 37(92.5%); 19 in E group, 18 in E-T group -No of noncompliers: 3/40 = 7.5%. Reason was adverse events(two in the E-T group, one in E group) -Compliance assessment: not stated -Source of funding:partly funded by drug company
Participants	-Location: United States -Setting: hospital-based -Ethnicity: White (85%), Hispanic (5%), Black (2%) -Run-in period: no -Characteristics: healthy surgically and naturally menopausal women -Age(SD): E group 55.4(6.6), E-T group 58.3(9.1) -Inclusion criteria: 1. A postmenopausal woman being on a stable dose of estrogen at least 3 months -Exclusion criteria: 1. Uncontrolled hypertension or hyperlipidemia 2. Use of medication known to affect lipids 3. Poorly controlled diabetes mellitus 4. Unstable angina or congestive heart failure, myocardial infarction within three months of study 5. Preexisting liver disease 6. Renal impairment 7. Hepatic adenoma 8. History of breast or uterine cancer 9. Gall bladder disease 10. History of thromboembolic events

Dobs 2002 (*Continued*)

Interventions	-EE 1.25 mg once a day -EE 1.25 mg plus mT 2.5 mg once a day -Route:oral -Co-intervention: no (a progestin was prescribed after the last study visit)
Outcomes	-Relevant outcomes: 1. Sense of well being: the Quality of Life at Menopause Scale 2. Sexual functioning(by means of BISF-W, SRS, and SIQ) 3. Lipid profile 4. Body composition: DEXA , anthropometry -Other outcomes: 1. Hormone measurements(total estrogen, estradiol, total testosterone and free testosterone, SHBG) 2. Strength testing 3. Safety data
Notes	-Baseline equality: no statistically significant differences between the E and E-T groups in age, race, surgical or natural menopause and weight. The E group seemed to have a healthier sexual function at baseline than the E-T group -The author was contacted and kindly supplied some information, but there was still some information unanswered.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Discontinuation rate <10%
Free of selective reporting?	No	One or more outcomes of interest in the review are reported incompletely
Free of other bias?	No	Baseline imbalance (sexual function)

Dow 1983

Methods	-Design: single-blind randomised(C), parallel group -No of centres: single -Duration: 16 weeks -Power calculation: not stated -Intention-to-treat analysis: not stated -No of participants randomised: 40(20 in each group) -No of participants completed and analysed: not stated -No of noncompliers and losses to follow up: not stated -Compliance assessment: -Source of funding: not stated
Participants	-Location: United Kingdom -Setting: hospital-based -Ethnicity: unspecified -Run-in period: not stated -Characteristics: surgically and naturally menopausal women with loss of libido -Age (range): 46.9(33-61) yr -Inclusion criteria: 1. Postmenopausal women with loss of libido and a regular sexual partner 2. No contraindication for HT -Exclusion criteria: 1. Gross primary marital disturbance or significant concurrent psychopathology or physical illness 2. Concurrent use of medication that might affect libido or interfere with the proposed HT
Interventions	-oestradiol 50 mg -oestradiol 50 mg plus T 100 mg -Route: implant -Co-intervention: women with an intact uterus were treated with cyclical norethisterone 5 mg orally for 7 days each month
Outcomes	-Relevant outcomes: 1. Sexual function: self-rating scales of sexual and marital satisfaction 2. Menopausal symptoms: menopausal symptoms scale (Greene 1976)
Notes	-Baseline equality: not stated -The author could not be contacted.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	C - Not stated
Allocation concealment?	Unclear	B - Unclear

Dow 1983 (*Continued*)

Blinding? All outcomes	Yes	Outcome assessment was blinded
Incomplete outcome data addressed? All outcomes	Unclear	number analysed not stated
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Unclear	insufficient information

El-Hage 2007

Methods	-Design: double-blind, randomised, placebo-controlled, crossover study -No of centres: single -Duration: 24 weeks -Power calculation: yes -Intention-to-treat analysis: yes -No of participants randomised: 36 -No of participants completed the study: 33 -No of participants analysed: 36 -No of noncompliers and losses to follow up: 3 (one moved out of State, one; no change to her condition, one; lost to follow up) -Compliance assessment:'not stated -Source of funding:pharmacological company
Participants	-Location: Australia -Setting: population-based -Ethnicity: Caucasian -Run-in period: 2 week run-in with transdermal oestrogen -Characteristics: surgically and naturally menopausal women with loss of libido -Age (range): 46.9 (33-61) yr -Inclusion criteria: 1. Hysterectomy 2. Decrease sexual motivation 3. In a stable relationship for at least 6 months 4. Normal thyroid function 5. Postmenopausal FSH level -Exclusion criteria: 1. Major illness 2. Taking antidepressants, steroid hormones 3. Severe depression 4. Dysfunctional relationship 5. Use of alternative therapy products which may influence hypoactive sexual desire disorder, mood, or energy

El-Hage 2007 (*Continued*)

Interventions	Transdermal HT plus 1% testosterone cream (10 mg of testosterone, Andro-Feme) versus transdermal HT plus placebo cream
Outcomes	Sexual function, mood, energy, lipid profile, discontinuation rate
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	No missing data
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possible free of other sources of bias

Farish 1984

Methods	-Design: double-blind randomised (A), parallel group -No of centres: two -Duration: 2 4 weeks -Power calculation: not stated -Intention-to-treat analysis: not stated -No of participants randomised: 31(14 in E group, 17 in E-T group) -No of participants completed the study: 31/31=100% -No of participants analysed: 100% for lipoprotein levels at baseline, 2 months, and 6 months. 30/31=96.8% for lipoprotein at 4 months. 19/31=61.3% (10 in E group, 9 in E-T group) for HDL subfraction -No of noncompliers and losses to follow up: 0/31 = 0% -Compliance assessment: not stated -Source of funding: not stated
Participants	

Farish 1984 (*Continued*)

	-Location: United Kingdom -Setting: hospital-based -Ethnicity: unspecified -Run-in period: no -Characteristics: surgically menopausal women with climacteric symptoms -Age(range): 46.4 (36-54) yr -Inclusion criteria: 1. TAH with BSO for non-malignant condition at least 6 weeks earlier -Exclusion criteria: 1. Receiving any hormone therapy prior to commencing treatment nor were taking any
Interventions	-17 beta-estradiol 50 mg -17 beta-estradiol 50 mg plus T 100 mg -Route: implant -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Lipid profile -Other outcomes: 1. Hormone measurements
Notes	-Baseline equality: not stated. However, baseline levels of lipid profiles were shown in the table and seemed to be similar in two groups. - The author was contacted and kindly provided further information.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A-Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	No missing data
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Unclear	insufficient information

Floter 2002a

Methods	See Floter 2002b
Participants	See Floter 2002b
Interventions	See Floter 2002b
Outcomes	See Floter 2002b
Notes	See Floter 2002b

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Floter 2002b
Allocation concealment?	Yes	See Floter 2002b
Blinding? All outcomes	Yes	See Floter 2002b
Incomplete outcome data addressed? All outcomes	No	See Floter 2002b
Free of selective reporting?	No	See Floter 2002b
Free of other bias?	No	See Floter 2002b

Floter 2002b

Methods	-Design: double-blind randomised (A), crossover study -No of centres: single -Duration: 24 weeks -Power calculation: yes -Intention-to-treat analysis: no -No of participants randomised: 50 -No of participants completed/analysed: 44/50 = 88%(22 in E-group, 22 in E-T group at the end of phrase 2 of the study) -No of noncompliers: 6/50 = 12%. Reasons were poor drug compliance(5/50= 10%), and migraine during E-P period(1/50=2%) -No of losses to follow up: 0% -Compliance assessment: not stated -Source of funding: partly funded by drug company

Floter 2002b (*Continued*)

Participants	-Location: Sweden -Setting: population-based -Ethnicity: unspecified -Run-in period: washout 2 months -Characteristics: healthy surgically menopausal women -Age (SD): 54 (2.9) yr -Inclusion criteria: 1. Age 45-60 years 2. History of TAH with BSO for benign disease 3. BMI 18-29 kg/m^2 4. BP < 170 mmHg systolic and/or 105 mmHg diastolic 5. Normal mammogram within the past year -Exclusion criteria: 1. Previous use of HT(< past 2 months), other medication taken at the same time 2. History of or present pre malignancies, liver disease, cardiovascular, cerebrovascular or thromboembolic disorders 3. Present psychiatric disease 4. Regular use of tranquillizers and/or antihistamines 5. Alcohol abuse or smoking of at least 10 cigarettes/day
Interventions	-oestradiol valerate 2mg once a day -oestradiol valerate 2mg plus testosterone undecanoate 40 mg once a day -Route: oral -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Sense of well being: Psychological General Well Being Index 2. Sexual function: McCoy's sex scale questionnaire 3. Hirsutism and acne 4. Blood count -Other outcomes: 1. Self-esteem: questionnaire concerning a woman's view of her own abilities in social life and work. 2. Other safety outcomes 3. Clitoral enlargement 4. Hormone measurements
Notes	-Baseline equality: not applicable -Differences between treatment periods were assessed using Fisher's permutation test. No significant treatment-by-sequence group interaction, indicating no 'carry-over effect'. - The author was contacted and kindly provided further information.

Risk of bias

Item	Authors' judgement	Description

Floter 2002b (*Continued*)

Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Free of selective reporting?	No	One or more outcomes of interest in the review are reported incompletely
Free of other bias?	No	Crossover trial, no washout period

Floter 2004

Methods	See Floter 2002b
Participants	See Floter 2002b
Interventions	See Floter 2002b
Outcomes	See Floter 2002b
Notes	See Floter 2002b

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	See Floter 2002b
Allocation concealment?	Yes	See Floter 2002b
Blinding? All outcomes	Yes	See Floter 2002b
Incomplete outcome data addressed? All outcomes	No	See Floter 2002b
Free of selective reporting?	No	See Floter 2002b
Free of other bias?	No	See Floter 2002b

Floter 2005

Methods	See Floter 2002b
Participants	See Floter 2002b
Interventions	See Floter 2002b
Outcomes	See Floter 2002b
Notes	See Floter 2002b

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Floter 2002b
Allocation concealment?	Yes	See Floter 2002b
Blinding? All outcomes	Yes	See Floter 2002b
Incomplete outcome data addressed? All outcomes	No	See Floter 2002b
Free of selective reporting?	No	See Floter 2002b
Free of other bias?	No	See Floter 2002b

Hickok 1993

Methods	-Design: double-blind randomised (A), parallel group -No of centres: single -Duration: 24 weeks -Power calculation: not stated -Intention-to-treat analysis: not stated -No of participants randomised: 26 (13 in each group) -No of participants completed and analysed: 26/26 =100% -No of noncompilers and losses to follow up: 0 -Compliance assessment: subjects had to take at least 75% of their assigned medication for 4 consecutive weeks. -Source of funding:partly funded by drug company
Participants	

Hickok 1993 (*Continued*)

	-Location: United States -Setting: hospital-based -Ethnicity: White -Run-in period: not stated -Characteristics: healthy postmenopausal women, unclear type of menopause -Age:E group 50, E-T group 52 -Inclusion criteria: 1. Age 40-60 years with no menstrual bleeding in the last 12 months 2. No history of steroid ingestion for 4 weeks, treatment with adrenergic agonists or antagonists, peripheral vasodilators, cholesterol-lowering agents, beta-blockers, beta-mimetics or thyroid hormones 3. Nonsmokers or ex-smokers who had not smoked in the past 12 months -Exclusion criteria: 1. History of genital tract disease 2. Current or previous estrogen-dependent malignancy 3. History of jaundice or elevated liver enzyme 4. Gall bladder disease 5. history of cardiovascular disease
Interventions	-EE 0.625 mg once a day -EE 0.625 mg plus mT 1.25 mg once a day -Route: oral -Co-intervention: not stated
Outcomes	-Relevant outcomes: 1. Vasomotor and menopausal symptoms: fifteen symptoms were evaluated(hot flushes, cold sweats, vaginal dryness, cold hands and feet, breast pain or tenderness, numbness and tingling, skin crawls, edema, increased facial or body hair, voice deepening, acne, trouble sleeping, pounding of the heart, dizzy spells, and pressure or tightness in the head or body 2. Lipid profile 3. Red blood cell count -Other outcomes: 1. Endometrial histology 2. Vaginal pathology 3. Other safety clinical laboratory evaluations
Notes	-Baseline equality: no statistically significant differences between the treatment groups with regard to age, time since menopause, the menopausal symptoms scale and lipid profiles. -The author was contacted and kindly provided further information.

Risk of bias

Item	**Authors' judgement**	**Description**

Hickok 1993 (*Continued*)

Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	No missing data
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possible free of other sources of bias

Hofling 2007

Methods	-Design: double-blind randomised (A), parallel group -No of centres: single centre -Duration: 24 weeks -Power calculation: not stated -Intention-to-treat analysis: no -No of participants randomised:49 in E2/NETA, 50 in E2/NETA+testosterone -No of participants completed the study: not stated -Number of participants analysed: 41 in E2/NETA, 47 in E2/NETA+testosterone -No of noncompilers: 8 in E2/NETA, 3 in E2/NETA+T (discontinued treatment or not having FNA biopsy) -No of losses to follow up: not stated -Compliance assessment: not stated -Source of funding:the Swedish Cancer Society, the Swedish Research Council (project 5982), and the Karolinska Institutet Research Funds. The clinical trial with the testosterone patch was supported by an unrestricted grant from Procter & Gamble Pharmaceuticals, Egham Surrey, UK.
Participants	-Characteristics: naturally menopausal women. -Age: 45-65 years -Location: Sweden -Setting: unclear -Ethnicity: Caucasian -Run-in period: no -Inclusion criteria: 1. postmenopausal for at least 12 months and had FSH > 40 IU/L 2. None of the women had taken any sex steroid hormones during the last 3 months before the study. 3. All the women had a normal mammogram within 1 month of entering the study. -Exclusion criteria:

Hofling 2007 (*Continued*)

	1. Previous history of cancer or previous breast disease 2. An abnormal mammogram 3. Hypertension (systolic blood pressure >170 mm Hg or diastolic >105 mm Hg), hyperlipidaemia (total cholesterol 98.0 mmol/L or triglycerides 93.0 mmol/L), diabetes mellitus 4. History of thromboembolic disease, undiagnosed vaginal bleeding, any sign of hepatic dysfunction, 5. Concomitant treatment known to influence the study medication (warfarin, rifampicin, carbamazepine, griseofulvin, hydantoins, primidone, barbiturates, and broad-spectrum antibiotics).
Interventions	17beta-estradiol (E2) 2 mg and norethisterone acetate (NETA) 1 mg plus testosterone patch releasing 300 kg/24 hours versus 17beta-estradiol (E2) 2 mg and norethisterone acetate (NETA) 1 mg plus placebo patch
Outcomes	Breast cell proliferation, dense breast, and discontinuation rate
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	C - Not stated
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possible free of other sources of bias

Leao 2006

Methods	-Design: double-blind randomised (A), parallel group -No of centres: multicentre -Duration: 52 weeks -Power calculation: not stated -Intention-to-treat analysis: yes by default -No of participants randomised: 37 (21 in E group, 16 in E-T group) -No of participants completed the study: 37 -No of participants analysed: 37 -No of non compilers: no -No of losses to follow up: no -Compliance assessment: not stated -Source of funding: not stated
Participants	-Characteristics: hysterectomised postmenopausal women. -Age: E group 52.57+6.26, E-T group 54.06+4.85 -Location: Brazil -Setting: unclear -Ethnicity: White(31.25), Black(37.5), Mulatto(31.25) -Run-in period: no -Inclusion criteria: with 1. < 65 year-old 2. Undertaken Hysterectomy 3. Serum FSH in the menopausal range (>40mIU/ml) -Exclusion criteria: 1. Acne or hirsutism classified as greater than a Ferriman-Galley score of 8 2. Impaired hepatic or renal function 3. Diabetes mellitus 4. Coronary disease 5. Systolic blood pressure > 180mmHg or diastolic blood pressure >110mmHg 6. use of any oestrogen formulation in the past 3 months 7. contraindications for oestrogen replacement
Interventions	- Estradiol gel 1mg/d plus methyltestosterone 1.25 mg/d - Estradiol gel 1mg/d plus placebo - Route: percutaneous oestrogen, oral T patch - Co-intervention: no
Outcomes	-Relevant outcomes: 1. Body composition 2. Lipid -Other outcomes: 1. Blood pressure 2. Fibrinogen levels

Leao 2006 (*Continued*)

Notes	-Baseline equality: no statistically significant differences across treatment groups with regard to age, ethnicity, and age at menopause -The author was contacted. No further information was supplied.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	No missing data
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possible free of other sources of bias

Lobo 2003

Methods	-Design: double-blind randomised(A), parallel group -No of centres: 20 -Duration: 16 weeks -Power calculation: not stated -Intention-to-treat analysis: no -No of participants randomised: 218(111 in E group, 107 in E-T) -No of participants completed the study: 182/218 = 83.5%(87 in E-T group, 95 in E) -No of participants analysed: 218 -No of non compilers: 36/218= 16.5%(20 in E-T group, 16 in E group). Reasons were adverse events(9 in E-T, 5 in E), lack of efficacy(2 in E-T, 3 in E), and administrative problem(9 in E-T, 8 in E) -No. of losses to follow up: not stated -Compliance assessment: not stated -Source of funding:Not stated
Participants	

Lobo 2003 (*Continued*)

	-Location: United States -Setting: hospital-based -Ethnicity: White (91.8%), Black (4.6%), Hispanic (2.3%), other (1.3%) -Run-in period: 2 weeks of receiving esterified oestrogen 0.625 mg per day -Characteristics: surgically and naturally menopausal women with hypoactive sexual desire associated with the onset of menopause -Age(SD):E group 53.8(5.7), E-T group 52.9(5.7) -Inclusion criteria: 1. Healthy postmenopausal women(natural or surgical for at least 6 months) 2. Age 45-65 years 3. Hypoactive sexual interest or desire associated with the onset of menopause 4. No overt mood disorders 5. A history of adequate sexual interest before the onset of menopause 6. Receiving the equivalent of 0.625 mg of conjugated equine estrogens for 3 or more months 7. A stable, monogamous, heterosexual relationship -Exclusion criteria: 1. Dyspareunia 2. Unresolved or recent sexual abuse 3. Depressive or anxiety symptoms or physical limitations that interfered with normal sexual functioning 4. An abnormal mammogram 5. Recent clinical laboratory test abnormalities
Interventions	-EE 0.625 mg once a day -EE 0.625 mg plus mT 1.25 mg once a day -Route:oral -Co-intervention: no (a progestin was prescribed after the last study visit)
Outcomes	-Relevant outcomes: 1. Sexual function: SIQ and BISF-W 2. Lipid profile 3. Hirsutism:the scale of Lorenzo 4. Acne:the scale of Palatsi
Notes	-Baseline equality: Two groups were similar in terms of age, BMI, race, time since menopause, type of menopause, marital status, percent of highest educational level, total and bioavailable testosterone. - The author was contacted and kindly provided further information. -The baseline sexual dimension scores, lipid profiles, hirsutism score and acne score seemed to be similar in the two groups.

Risk of bias

Item	Authors' judgement	Description

Lobo 2003 (*Continued*)

Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing data have been imputed using appropriate methods
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possible free of other sources of bias

Luciano 1998

Methods	See Miller 2000
Participants	See Miller 2000
Interventions	See Miller 2000
Outcomes	See Miller 2000
Notes	See Miller 2000

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Miller 2000
Allocation concealment?	Yes	See Miller 2000
Blinding? All outcomes	Yes	See Miller 2000
Incomplete outcome data addressed? All outcomes	No	See Miller 2000
Free of selective reporting?	No	See Miller 2000
Free of other bias?	Unclear	See Miller 2000

Luciano 1999

Methods	See Miller 2000
Participants	See Miller 2000
Interventions	See Miller 2000
Outcomes	See Miller 2000
Notes	See Miller 2000

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Miller 2000
Allocation concealment?	Yes	See Miller 2000
Blinding? All outcomes	Yes	See Miller 2000
Incomplete outcome data addressed? All outcomes	No	See Miller 2000
Free of selective reporting?	No	See Miller 2000
Free of other bias?	Unclear	See Miller 2000

Matthews 2005

Methods	-Design: double-blind randomised (A), parallel group -No of centres: single centre -Duration: 8 weeks -Power calculation: no -Intention-to-treat analysis: no -No. of participants randomised: Estratab 18; Estratab-Provera 18; Estratab-micronized progesterone 17; Estratest(combination oestrogen and androgen) 20; Placebo 16 -No. of participants completed the study: Estratab 16; Estratab-Provera 18; Estratab-micronized progesterone 16; Estratest 19; Placebo 16 -No. of participants analysed: unclear -No. of non compilers: unclear -No of losses to follow up: Estratab 2, Estratab-Provera 1, Estratab-micronized progesterone 1, Estratest 1 -Compliance assessment: not stated -Source of funding: drug company
Participants	-Characteristics: healthy postmenopausal women -Age: mean (SEM) Placebo 57.0 (0.94), Estratab 57.0 (1.1), Estratab-Provera 57.5 (0.90), Estratab-micronized progesterone 56.0 (0.89), Estratest 56.7 (0.79) yr -Location: US -Setting: population-based -Ethnicity: 80 Caucasians, 8 African Americans, 1 other -Run-in period: no -Inclusion criteria: 1. 48-65 year-old 2. Menopause -Exclusion criteria: 1. BW >30% than ideal body weight as determined by Metropolitan Life Tables 2. History of medication-dependent diabetes, heart disease, pulmonary embolism or deep vein thrombosis, liver or pancreatic disease, and hypertension 3. Use of lipid lowering drugs, and daily use of steroids, current use of medications that would affect cardiovascular function 4. Unwillingness to not smoke for 12 hr prior to testing 6. Having a menstrual period or any unexplained vaginal bleeding for 12 months prior to the study, 7. Use of hormone therapy in the 3 months 8. Contraindications for hormone therapy 9. An abnormal pap smear 10. Fasting serum triglyceride levels >250 mg/dl
Interventions	-Oral Estratab (1.25 mg/day) and placebo pill; Estratab (1.25 mg/day) and Provera continuous (5 mg); Estratab (1.25 mg/day) and Prometrium, micronized progesterone (100 mg/day); Estratest, combination oestrogen and androgen, and placebo pill; and two placebo pills -Route: oral -Co-intervention: no

Outcomes	-Relevant outcomes: 1. Sense of well being -Other outcomes: 1. Cardiovascular response to stress
Notes	-Baseline equality: no significant differences across treatment groups with regard to age, years of education, race, marital status, highest educational degree attained, current occupational status, family income, or family history of high blood pressure, diabetes, angina, myocardial infarction, other heart disease, stroke or cancer, baseline blood pressure or heart rate -The author was contacted and kindly provided the further information.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Discontinuation rate <10%
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Unclear	Insufficient information

Miller 2000

Methods	-Design: double-blind randomised (A), parallel group -No of centres: single -Duration: 12 months -Power calculation: not stated -Intention-to-treat analysis: no -No of participants randomised: 66 -No of participants completed the study: 57/66 = 86.4% (30 in HT group, 27 in HT-T) -No of participants analysed: 57 -No of noncompliers: 9/66 = 13.6%. Reasons were breakthrough uterine bleeding(3), skin rash/acne(2), weight gain(2), PMS symptoms(1), other illness(1) -No of losses to follow up: 0% -Compliance assessment: not stated -Source of funding:partly funded by drug company
Participants	-Location: United States -Setting: hospital-based -Ethnicity: unspecified -Run-in period: not stated -Characteristics: healthy surgically and naturally menopausal women -Age (SEM): E group 53.5(1), E-T group 54.6(1.2) yr -Inclusion criteria: 1. Postmenopausal women with no contraindications to HT -Exclusion criteria: 1. Patients who had taken any drug known to alter calcium or bone metabolism
Interventions	Patients with hysterectomy -micronised oestradiol 0.5 mg twice a day -micronised oestradiol 0.5 mg twice a day plus micronised testosterone 1.25 mg twice a day Patients with intact uterus -micronised oestradiol 0.5 mg twice a day plus micronised progesterone 100 mg -micronised oestradiol 0.5 mg twice a day plus micronised progesterone 100 mg plus micronised testosterone 1.25 mg twice a day -Route: sublingual -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Biochemical markers of bone metabolism; 1.1. Urinary markers: Dpd and NTx 1.2. Serum marker: BSAP 2. BMD of lumbar spines and hip: DEXA -Other outcomes: 1. Hormone measurements

Miller 2000 (*Continued*)

Notes	-Baseline equality: no differences in age, height, weight, oestradiol and FSH levels, biochemical markers levels and BMD between the two groups. -The corresponding author was contacted and kindly supplied information.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Free of selective reporting?	No	One or more outcomes of interest in the review are reported incompletely
Free of other bias?	Unclear	insufficient information

Montgomery 1987

Methods	-Design: double-blind randomised (C), parallel group -No of centres: single -Duration: 16 weeks -Power calculation: not stated -Intention-to-treat analysis: no -No of participants randomised: 84 (29 in P group, 28 in E group, 27 in E-T) -No of participants completed the study: 70 (21 in P group, 25 in E, 24 in E-T) -No of participants analysed: 70 -No of noncompliers: 14/84 = 16.7%. Reasons: 1 acute cholecystitis (E group), 1 attempted suicide (E-T group), 6 symptoms not alleviated (P group), 6 lost to follow up (3 in P group, 2 in E-T group, 1 in E group) -No. of losses to follow up: 6/84=7.1%. -Compliance assessment: not stated -Source of funding: not stated
Participants	

Montgomery 1987 (*Continued*)

	-Location: United Kingdom -Setting: unclear -Ethnicity: unspecified -Run-in period: not stated -Characteristics: perimenopausal, surgically and naturally menopausal women with menopausal symptoms -Age: E group 46, E-T group 50, P group 48 -Inclusion criteria: 1. The [illegible]
Interventions	-estradiol 50 mg -estradiol 50 mg plus T 100 mg -placebo -Route:implant -Co-intervention:
Outcomes	-Relevant outcomes: 1. Psychiatric symptoms: the short version of Kellner and Sheffield's self rating scale of distress(SRD 30)
Notes	-Baseline equality: no differences between the three groups in age, menopausal status, or the presence of a uterus. -The study was designed to last for 6 months but many women withdrew after 4 months because they felt that the effects of the implant were wearing off. - The author could not be contacted.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	C - Not stated
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Free of selective reporting?	No	One or more outcomes of interest in the review (sense of well being) are reported incompletely.
Free of other bias?	Yes	Possible free of other sources of bias

Nathrost-Boos 2006

Methods	-Design: double-blind randomised (A), crossover study -No of centres: single centre -Duration: 24 (12/12) weeks -Power calculation: not stated -Intention-to-treat analysis: no -No of participants randomised: 60 -No of participants completed the study: 53 -No of participants analysed: 53 -No of noncompliers: 4 did not comply to medication, 1 had a fracture, 1 developed a skin disease, 1 had a carcinoma of the uterus -No of losses to follow up: no -Compliance assessment: not stated -Source of funding: drug company
Participants	-Characteristics: postmenopausal women with menopausal onset of low sexual desire with low serum T levels -Age: mean+SD 55.4+3.5 yr -Location: Sweden -Setting: unclear -Ethnicity: unclear -Run-in period: not stated -Inclusion criteria: 1. Postmenopausal women 2. Age 50-65 year-old 3. Generally good health 4. Complaining of total loss or significant decrease of libido during the postmenopausal period 5. Serum free-T < 2nmol/l at baseline 7. Stable estrogen dose > 3 months 8. Menopause onset of low sexual desire -Exclusion criteria: 1. Having a partner 2. Experience of previous androgen therapy 3. Medications known to affect sexual function 4. Heart disease, high blood pressure, malignant disease or other serious chronic disease
Interventions	-Percutanous treatment with testosterone gel 10 mg/d-hormone therapy -Placebo gel-hormone therapy -Route: percutaneous testosterone gel -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Sexual function 2. Sense of well being 3. Lipid profile 4. Hirsutism 5. Acne

Nathrost-Boos 2006 (*Continued*)

	6. Hematocrit -Other outcomes: 1. Skin-related side effect
Notes	-Baseline equality: not applicable -Conference proceeding. -The author was contacted and kindly provided the further information.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	No	Crossover trial, no washout period

Nguyen 1999

Methods	See Dobs 2002
Participants	See Dobs 2002
Interventions	See Dobs 2002
Outcomes	See Dobs 2002
Notes	See Dobs 2002

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Dobs 2002

Nguyen 1999 (*Continued*)

Allocation concealment?	Yes	See Dobs 2002
Blinding? All outcomes	Yes	See Dobs 2002
Incomplete outcome data addressed? All outcomes	Yes	See Dobs 2002
Free of selective reporting?	No	See Dobs 2002
Free of other bias?	No	See Dobs 2002

Penotti 2001

Methods	-Design: open randomised (A), parallel group -No of centres: single -Duration: 8 months -Power calculation: not stated -Intention-to-treat analysis: not stated -No of participants randomised: 40 -No of participants completed the study: 33/40 = 82.5% (18 in E group, 15 in E-T group) -No of participants analysed: not stated -No of non compilers: 7/40 = 17.5%. Reasons were having signs of hyperandrogenism(3 in E-T), on the advice of their general practitioners(2 in E-T), personal reasons(1 in E) and subsequent diagnosis of lymphoma(1 in E) -No of losses to follow up: 0 =0% -Compliance assessment: not stated -Source of funding: not stated
Participants	-Location: Italy -Setting: hospital-based -Ethnicity: unspecified -Run-in period: no -Characteristics: healthy naturally menopausal women -Age: E group 55.3, E-T group 57.4 yr -Inclusion criteria: 1. postmenopausal women already on HT at least 1 year -Exclusion criteria: 1. Major disease(Hypertension, heart disease, diabetes, renal or peripheral vascular diseases 2. surgical removal of uterus or ovaries

Interventions	-oestradiol 50 micrograms once a day plus MPA 10 mg/d for a duration of 2 weeks every two months -oestradiol 50 micrograms once a day plus MPA 10 mg/d for a duration of 2 weeks every two months plus testosterone undecanoate 40 mg once a day -Route: transdermal oestradiol, oral progestin, oral testosterone -Co-intervention: not stated
Outcomes	-Relevant outcomes: 1. Psychological well being: a 10-cm VAS 2. Sexual desire and satisfaction: a 10-cm VAS 3. Lipid profile -Other outcomes: 1. Pulsatility index of internal carotid artery and middle cerebral artery (primary outcome) 2. Endometrial thickness 3. Testosterone levels
Notes	-Baseline equality: no statistically significant differences between the two groups in terms of age, BMI, years of menopause, duration of HT, sexual desire and satisfaction scores. - The author was contacted and kindly supplied further information, but there was no data available (psychological well being, sexual function) for inclusion in the meta-analysis.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	Open randomised trial
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Free of selective reporting?	No	One or more outcomes of interest in the review (sense of well being) are reported incompletely
Free of other bias?	Yes	Possible free of other sources of bias

Penteado 2008

Methods	-Design: double-blind randomised (A), parallel group -No of centres: single -Duration: 52 weeks -Power calculation: yes -Intention-to-treat analysis: no -No of participants randomised: 60 -No of participants completed/analysed: 56 -No of non compilers: 2 in HT had abnormal uterine bleeding, 2 in HT+T fear of hormonal treatment -Compliance assessment: not stated -Source of funding: drug company
Participants	-Location: Sao Paulo Brazil -Setting: hospital-based -Ethnicity: 40 women in the group (66.7%) were Caucasian and 20 (33.3%) Afro-Brazilian. -Run-in period: no -Characteristics: naturally menopausal women with sexual problem after menopause -Age: 42 - 60 years -Inclusion criteria: 1. amenorrhoea for a minimum of 1 year 2. an intact uterus 3. a stable relationship with a partner capable of intercourse 4. appearance of sexual complaints after menopause. -Exclusion criteria: 1. hormone therapy 2. systemic diseases, endocrine and psychiatric illnesses 3. severe genital dystopia
Interventions	- Treatment: mMethyltestosterone 2 mg/day combined with HRT (conjugated equine estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day) - Control/Placebo: HRT (conjugated equine oestrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day -Route: oral -Co-intervention: no
Outcomes	Sexual function and discontinuation rate
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	C - Not stated
Allocation concealment?	Unclear	B - Unclear

Penteado 2008 (*Continued*)

Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Discontinuation rate <10%
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Unclear	insufficient information

Raisz 1996

Methods	-Design: open randomised (C), parallel group -No of centres: three -Duration: 6 weeks -Power calculation: not stated -Intention-to-treat analysis: not stated -No of participants randomised: 28 -No of participants analysed: 26 -No of noncompliers and losses to follow up: not stated -Compliance: not stated -Source of funding:partly funded by drug company
Participants	-Location: United States -Setting: hospital-based -Ethnicity: unspecified -Run-in period: 3 weeks of receiving calcium intake 1000-1500 mg per day by dietary adjustments or addition of calcium supplement -Characteristics: healthy surgically and naturally menopausal women -Age(range): E group 65.7(49.1-80.4), E-T group 59.8(46.6-78.5) -Inclusion criteria: 1. The same as stated in disease status 2. BMI within 25% of ideal body weight 3. Nonsmokers 4. Not taken estrogens within the last 6 months 5. No prior history of oestrogen-dependent cancer, hypercortisolism, hyperthyroidism, or metabolic bone disease 6. A negative mammogram and Pap smear within one year and normal ECG -Exclusion criteria: 1. Any prior treatment with drugs that might affect bone metabolism, other than calcium supplements and estrogens, or with drug known to alter hepatic enzymes
Interventions	

Raisz 1996 (*Continued*)

	-CEE 1.25 mg once a day -EE 1.25 mg plus mT 2.5 mg once a day -Postmenopausal women
Outcomes	-Relevant outcomes: 1. Menopausal symptoms: a modified menopausal index with a 0-3 scale 2. Bone formation markers (serum OC, BSAP, PICP) and bone resorption markers(pyridinoline, Dpd and hydroxyproline) 3. Lipid profile -Other outcomes: 1. Hormone measurement (oestrone, oestradiol, testosterone, DHT, SHBG, intact PTH, 25-hydroxy vitamin D 2. Adverse event (headache, breast pain, acne, vaginal bleeding) -Time points: 3, 6, 9 weeks
Notes	-Baseline equality: no significant differences in weight, height, BMD, menopause duration, oophorectomy status and prior HT duration between two groups. The E-T group was somewhat younger than the E group. There were no differences in general biochemical profiles or haematological measures. -The author was contacted, but the further information could not be provided.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	C-Not stated
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Open randomised trial
Incomplete outcome data addressed? All outcomes	Yes	Discontinuation rate <10%
Free of selective reporting?	No	One or more outcomes of interest in the review are reported incompletely.
Free of other bias?	No	Baseline imbalance (menopausal symptom score, age)

Regestein 2001

Methods	-Design: double-blind randomised(A), crossover study -No of centres: single -Duration: 16 weeks -Power calculation: not stated -Intention-to-treat analysis: no -No of participants randomised: not stated (assumed 42) -No of participants completed the study: not stated (35/42 = 83.3% had complete data set) -No of participants analysed: depended on outcomes -No of noncompliers: Reasons were unprecedented anxiety(1), poor feeling(1), and using Estring(1) -No of losses to follow up: no -Compliance assessment: a pill count was recorded to estimate treatment compliance. -Source of funding: drug company
Participants	-Location: United States -Setting: population-based -Ethnicity: unspecified -Run-in period: no -Characteristics: healthy surgically and naturally menopausal women -Age(range): 55.5 (38-65) yr -Inclusion criteria: 1. Natural or surgical menopause 2. Currently use HT 3. No prior androgen replacement therapy, psychotropic drugs and no major systemic disease 4. Used no more than three caffeinated drinks per day, two alcohol drinks per week, ten cigarette per day 5. BMI below 29 -Exclusion criteria:not stated
Interventions	-EE 0.625 mg once a day -EE 0.625 mg plus mT 1.25 mg once a day -Route:oral -Co-intervention: not stated
Outcomes	-Relevant outcomes: 1. Libido: an 80-mm VAS 2. Sexual enjoyment: a scale of 0-3 3. Anxiety: the State-Trait Anxiety Inventory, depression by the Zung Self-Rated Depression Inventory, somatization by the symptom Check List-90 Revised, and playfulness in the subjects' self-image by the Adult Playfulness Scale. 4. Menopausal symptoms: the Menopause-specific Quality of Life Questionnaire(MENQOL) 4. Neurobehavioral outcomes: computerized test 5. Complex verbal and associated fluency: the Possible Jobs and Alternate Uses measures -Other outcomes:

Regestein 2001 (*Continued*)

	1. Subjective sleep quality 2. Exercise levels
Notes	-Baseline equality: not applicable -The author was contacted and kindly provided further information.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	No	Cross-over trial, no washout period

Sarrel 1998

Methods	-Design: double-blind randomised (A), parallel group -No of centres: single -Duration: 8 weeks -Power calculation: not stated -Intention-to-treat analysis: not stated -No of participants randomised: 20 (10 in E-T, 10 in E) -No of participants completed/analysed: 19 -No of noncompliers: 1 in E -No of losses to follow up: 1 in E -Compliance assessment: not stated -Source of funding: drug company
Participants	

Sarrel 1998 (*Continued*)

	-Location: United States -Setting: hospital-based -Ethnicity: predominantly Caucasian -Run-in period: 2 weeks of receiving previous estrogens and then 2 weeks of placebo -Characteristics: surgically and naturally menopausal women dissatisfied with their concurrent treatment at least 4 months -Age (range): 52 (45-55) yr -Inclusion criteria: 1. As stated in disease status 2. Inadequate symptomatic relief included hot flashes, vaginal dryness, dyspareunia, decreased libido and decreased energy levels 3. BW above or below 25% of ideal BW -Exclusion criteria: 1. Clinically significant abnormal cervical cytology smear 2. Clinically significant abnormal mammograms within the past 12 months or clinically significant abnormal finding during pelvic examination 3. History of thromboembolic disorder or active thromboembolic disease in the past 12
Interventions	-EE 1.25 mg once a day -EE 1.25 mg plus mT 2.5 mg once a day -Route:oral -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Sexual behavior and enjoyment: the 10-item Sexual Activity and Libido Scale 2. Menopausal symptoms: the Menopausal Symptom Scale (modified from the original scale developed by Kupperman et al.) -Other outcomes: 1. Vaginal smear maturation index 2. Hormone measurements
Notes	-Baseline equality: not stated -The author was contacted and kindly provided further information; however, the menopausal symptom and quality of life data to enable to meta-analysis was no longer retrievable.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded

Sarrel 1998 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Discontinuation rate <10%
Free of selective reporting?	No	One or more outcomes of interest in the review (menopausal symptoms) are reported incompletely
Free of other bias?	Unclear	insufficient information

Shepanek 1999

Methods	-Design: double-blind randomised (C), parallel group -No of centres: two -Duration: 12 weeks -Power calculation: yes -Intention-to-treat analysis: no -No of participants randomised: 30 -No. of participants completed/analysed: 24/30=80% -No of noncompliers: 6/30 = 20%. Reasons were not stated. -No of losses to follow up: not stated -Compliance assessment: not stated -Source of funding: drug company provided medication
Participants	-Location: United States -Setting: population-based -Ethnicity: Caucasian 83.3% (14/24), Black African American 12.5% (3/24), Other 4.2% (1/24) -Run-in period: 30 days of placebo -Characteristics: healthy surgically menopausal women -Age (SD): E 53.74 (3.85), E-T 54.56 (5.13) yr -Inclusion criteria: the participants had to - 1. TAH with BSO 2. not be taking any prescription medications 3. have estimated IQ. of at least 80 based on the Symbol Digit Modalities Test 4. be a high school graduate or have an equivalent degree -Exclusion criteria: 1. A history of head injury with loss of consciousness greater than 30 minutes 2. a history of alcohol or drug abuse 3. any current Axis I psychotic level disorder 4. a history of central nervous system infection 5. a history of serious concurrent acute or chronic diseases of a severity to negatively impact cognitive ability 6. current use of medications known to adversely affect cognitive function 7. a learning disability 8. a first language other than English

Shepanek 1999 (*Continued*)

Interventions	-EE 0.625 mg once a day -EE 0.625 mg plus mT 1.25 mg once a day -Route:oral -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Sexual desire 2. Cognition: Symbol Digits Modality Test
Notes	-Baseline equality:Both groups had comparable demographics for personal characteristics (age, height, weight, length of menopause), group characteristics (education, race) and basic intelligence (as measured by the screening test, the Symbol Digit Modalities Test). -The author could not be contacted.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	C - Not stated
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possible free of other sources of bias

Sherwin 1984

Methods	See Sherwin 1988
Participants	See Sherwin 1988
Interventions	See Sherwin 1988
Outcomes	See Sherwin 1988
Notes	See Sherwin 1988

Risk of bias

Sherwin 1984 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Sherwin 1988
Allocation concealment?	Yes	See Sherwin 1988
Blinding? All outcomes	Yes	See Sherwin 1988
Incomplete outcome data addressed? All outcomes	No	See Sherwin 1988
Free of selective reporting?	No	See Sherwin 1988
Free of other bias?	Yes	See Sherwin 1988

Sherwin 1985a

Methods	See Sherwin 1988
Participants	See Sherwin 1988
Interventions	See Sherwin 1988
Outcomes	See Sherwin 1988
Notes	See Sherwin 1988

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Sherwin 1988
Allocation concealment?	Yes	See Sherwin 1988
Blinding? All outcomes	Yes	See Sherwin 1988
Incomplete outcome data addressed? All outcomes	No	See Sherwin 1988
Free of selective reporting?	No	See Sherwin 1988
Free of other bias?	Yes	See Sherwin 1988

Sherwin 1985b

Methods	See Sherwin 1988
Participants	See Sherwin 1988
Interventions	See Sherwin 1988
Outcomes	See Sherwin 1988
Notes	See Sherwin 1988

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Sherwin 1988
Allocation concealment?	Yes	See Sherwin 1988
Blinding? All outcomes	Yes	See Sherwin 1988
Incomplete outcome data addressed? All outcomes	No	See Sherwin 1988
Free of selective reporting?	No	See Sherwin 1988
Free of other bias?	Yes	See Sherwin 1988

Sherwin 1988

Methods	-Design: double-blind randomised (A), crossover study -No of centres: single -Duration: 4 months (1 month of placebo and then 3 months of intervention) -Power calculation: not stated -Intention-to-treat analysis: no -No of participants randomised: 49 -No of participants completed/analysed: 40 (10 in each treatment group) -No of noncompliers: 9/49 = 18.4% Reasons were unable to take time off from work for testing sessions and unwilling to comply with testing procedure for the entire course of the study. -No of losses to follow up: no -Compliance assessment: no -Source of funding: not stated

Sherwin 1988 (*Continued*)

Participants	-Location: Canada -Setting: hospital-based -Ethnicity: unspecified -Run-in period: no -Characteristics: healthy surgically menopausal women -Age: 45.4 for TAH with BSO, 36.6 for TAH -Inclusion criteria: 1. Women needed to undergo TAH with BSO for benign condition 2. In a state of good general health 3. No known contraindications to HT 4. They had completed at least nine years of formal education -Exclusion criteria: 1. Past or current psychological disturbance
Interventions	-estradiol valerate 10 mg -testosterone enanthate benzilic acid hydrozone 200 mg -estradiol dienanthate 7.5 mg plus estradiol benzoate 1 mg testosterone enanthate benzilic acid hydrozone 150 mg -placebo -no treatment (TAH patients) -Route:intramuscular injection -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Cognitive function(short and long-term memory): digit span, clerical Speed and Accuracy and the Abstract Reasoning Subtest of the Differential Aptitude Test
Notes	-Baseline equality: not applicable - The author was contacted and kindly supplied further information, but there was no longer data to enable inclusion in the meta-analysis.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size

Sherwin 1988 (*Continued*)

Free of selective reporting?	No	One or more outcomes of interest in the review are reported incompletely.
Free of other bias?	Yes	Possibly free of other sources of bias

Shifren 2000

Methods	-Design: double-blind randomised (A), crossover study -No of centres: nine -Duration: 12 weeks -Power calculation: not stated -Intention-to-treat analysis: no -No of participants randomised: 75 -No of participants completed/analysed: 65/75=86.7% -No of noncompliers: 18/75 = 24% Reason were adverse events (3 while receiving placebo, 1 while receiving T150, 2 while receiving T300), poor compliance with the telephone diary(6), or personal reasons(6) -No of losses to follow up: 0% -Compliance assessment: not stated -Source of funding: drug company
Participants	-Location: United States -Setting: hospital-based -Ethnicity: White (83%), Black (11%), Hispanic (5%), Asian (1%) -Run-in period: no -Characteristics: surgically menopausal women with impaired sexual function, low T levels and receiving adequate dose of estrogen therapy -Age (range): 47 (31-56) yr -Inclusion criteria: 1. Healthy surgically menopausal women with TAH at least 1 year but less than 10 year with impaired sexual function, free T concentration less than 3.5 pg/ml or serum T concentrations < 30 ng/dl and received conjugated equine estrogen at least 0.625 mg/day at least 2 months 2. A stable, monogamous, heterosexual relationship for at least 1 year 3. BMI between 19.5-33.5 -Exclusion criteria: 1. Use of oral, topical, or vaginal androgen therapy in the previous three months or injectable or implantable androgen therapy in the previous 6 months 2. More than 20 moderate or severe hot flashes per week 3. Severe acne(grade 3 on the scale of Palatsi et al) 4. Moderate or severe hirsutism(score of 6 or more on the scale of Lorenzo) 5. Hyperlipidemia 6. Psychiatric disease 7. Dyspareunia 8. Physical limitations that interfered with normal sexual functioning

Shifren 2000 (*Continued*)

	9. Use of glucocorticoids, selective serotonin-reuptake inhibitors, tricyclic antidepressants, antiandrogen agents, gingseng, yohimbine, phytoestrogens, dehydroepiandrosterone, or melatonin
Interventions	-CEE 0.625 mg once a day -CEE 0.625 mg once a day plus T 150 micrograms twice a week -CEE 0.625 mg once a day plus T 300 micrograms twice a week -Route:oral estrogen, transdermal patch testosterone -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Sexual function: the Brief Index of Sexual Functioning for Women 2. Mood: the Psychological General Well-Being Index 3. Hirsutism: the scale of Lorenzo and facial-deplication rate 4. Acne: the scale of Palatsi et al. 5. lipid profile 6. Blood counts -Other outcomes: 1. Hormone measurements (free testosterone, bioavailable testosterone, total testosterone, dihydrotestosterone and SHBG) 2. Other safety outcomes(fasting glucose concentrations, serum insulin concentrations, indicators of liver function, tolerance of the skin to transdermal systems and other adverse events -Time points:4, 8 and 12 weeks
Notes	-Baseline equality: not applicable - The author was contacted and kindly provided further information.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	No	Discontinuation >10%
Free of selective reporting?	Unclear	Insufficient information

Shifren 2000 (*Continued*)

Free of other bias?	No	Cross-over trial, no washout period

Shifren 2006

Methods	-Design: double-blind randomised (A), parallel group -No of centres: multicentre -Duration: 24 weeks -Power calculation: yes -Intention-to-treat analysis: no -No of participants randomised: 549 (273 in E group, 276 in E-T) -No of participants completed the study: E group 209/273 (76.6%), E-T 224/276 (81.2%) -No of participants analysed: 539 -No of non compilers: E group 59 (21.6%). Reasons were adverse event 19 (7.0%), voluntary 32 (11.7%), protocol violation 8 (2.9%) E-T 46 (16.7%). Reasons were adverse event 22(8%), voluntary 19(6.9%), protocol violation 5(1.8%) -No of losses to follow up: E group 5/273 (1.8%), E-T 6/276 (2.2%) -Compliance assessment: not stated -Source of funding: drug company
Participants	-Characteristics: postmenopausal women with menopausal onset of low sexual desire with low serum T levels -Age: E group 54+4.95, E-T 53.9+4.79 yr -Location: USA, Canada, Australia -Setting: population-based -Ethnicity: White 256(94), 260(94) black 8(3), 10(4) Hispanic -Run-in period: 8-week pretreatment baseline period -Inclusion criteria: 1. 40-70 year-old 2. Cessation of menstruation > 1 year 3. Generally good health 4. Stable monogamous relationship with a partner > 1 year 5. Partner present more than 50% of the time 6. Stable oestrogen dose > 3 months 8. Hypoactive sexual desire disorder -Exclusion criteria: 1. Recent androgen use 2. Positive screening for depression or hypothyroidism 3. Ongoing medical, psychiatric or relationship disturbance 4. Medications known to affect sexual function 5. Severe hyperlipidaemia/metabolic disorders 6. Dyspareunia, physical limitations affecting sexual function

Shifren 2006 (*Continued*)

Interventions	-A stable dose of oral oestrogen with or without progestin plus T 300 microgram/d -A stable dose of oral oestrogen with or without progestin plus placebo -Route:oral oestrogen, transdermal T patch -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Sexual function: SAL and PFSF 2. Hirsutism 3. Acne -Other outcomes: 1. Clitoromegaly, deepening of voice
Notes	-Baseline equality: no significant differences across treatment groups with regard to age, ethnicity, BMI, duration of relationship, hysterectomy status, years since last menstrual period (non hysterectomy), SHBG and type of hormone therapy -The author was contacted and kindly provided the further information.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing data have been imputed using appropriate methods
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possible free of other sources of bias

Simon 1999

Methods	-Design: double-blind randomised (C), parallel group -No of centres: three -Duration: 12 weeks -Power calculation: not stated -Intention-to-treat analysis: not stated -No of participants randomised:93 -No of participants completed the study: 89/93 = 95.7% -No of participants analysed: not stated -No of non compilers: 3/93 = 3.2% All was assigned to E-T(high) group. Reasons were an adverse event(rash) and two of relocation and subsequently lost to follow up -No of losses to follow up: 2/92 = 2.2% -Compliance assessment: stated only "compliance and protocol adherence were excellent". -Source of funding: not stated
Participants	-Location: United States -Setting: hospital-based -Ethnicity: unspecified -Run-in period: 4 weeks of placebo treatment -Characteristics: healthy peri-and postmenopausal women -Age (SE): E (low dose) group 54.5 (1.2), E-T (low dose) group 52.0 (0.9), E (high dose) group 53.7 (0.9), E-T (high dose) group 54.3 (1.2) -Inclusion criteria: 1. Naturally menopausal women with both ovaries intact 2. Nonsmokers 3. BW within 25% of ideal BW 4. A stable heterosexual relationships of at least 1 year duration -Exclusion criteria: 1. Use of estrogens, progestins, androgens, or anabolic steroids within 8 weeks of enrolment 2. No contraindication for HT
Interventions	-EE 0.625 mg once a day -EE 1.25 mg once a day -EE 0.625 mg plus mT 1.25 mg once a day -EE 1.25 mg plus mT 2.5 mg once a day -Route:oral -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Menopausal symptoms: the scale of Kupperman et al. -Other outcomes: 1. Vaginal bleeding 2. Safety 2. Hormone measurements(estradiol, estrone, testosterone, dihydrotestosterone, androstenedione, DHEAS, SHBG -Time points: 4, 8, and 12 weeks

Simon 1999 (*Continued*)

Notes	-Baseline equality: patient characteristics were shown in table and they seemed to be similar in all groups in terms of age, BMI, duration of menopause and number of patients completing double-blind phase. -The author could not be contacted.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	C - Not stated
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Discontinuation rate <10%
Free of selective reporting?	No	One or more outcomes of interest in the review (menopausal symptoms) are reported incompletely
Free of other bias?	Unclear	insufficient information

Simon 2005

Methods	-Design: double-blind randomised (A), parallel group -No of centres: multicentre -Duration: 24 weeks -Power calculation: yes -Intention-to-treat analysis: available case analysis -No of participants randomised: 562 (E group 279, E-T group 283) -No of participants completed the study: E group 230/279 (82%), E-T group 221/283 (78%) -No of participants analysed: depended on outcome -No of noncompliers: E group 39(12%). The reasons were adverse events 19 (6.8%), protocol violation 3(1.1%), voluntary withdrawal 12(4.3%), investigator recommendation 5(1.8%). E-T group 54(19.2%). The reasons were adverse events 24(8.5%), protocol violation 3(1.1%), voluntary withdrawal 26(9.2%), investigator recommendation 1(0.4%). -No of losses to follow up: 18 [E group 10 (3.6%); E-T group 8 (2.8%)] -Compliance assessment: not stated -Source of funding: drug company
Participants	-Characteristics: surgically menopausal women with menopausal onset of low sexual desire -Age: E group 48.9+7.4, E-T group 49.2+7.7 49 yr -Location: US, Canada, Australia -Setting: population-based -Ethnicity: E group Caucasian 242 (87%) Black 27 (10%) Hispanic 8 (3%) Other 2 (1%); E-T group Caucasian 257 (91%), Black 19 (7%), Hispanic7 (2%), Other 0 (0%) -Run-in period: 8-week pretreatment baseline period -Inclusion criteria: 1. 20-70 year-old 2. Generally good health (normal mammogram if age > 40 yr, normal Pap smear, no physical impediment to sexual function) 3. BMI 18-30 kg/m2 4. TAH with BSO at least 6 months 5. Stable relationship with partner 6. Stable oestrogen dose > 3 months 7. Menopause onset of low sexual desire -Exclusion criteria:. 1. Drug or alcohol dependency 2. Recent androgen use 3. Hirsutism, virilization, severe acne 4. Positive screening for depression or hypothyroidism 5. Ongoing medical, psychiatric or relationship disturbance 6. Medications known to affect sexual function 7. Severe hyperlipidaemia/metabolic disorders 8. Dyspareunia, physical limitations affecting sexual function 9. Major life change interfering with sexual function

Simon 2005 (*Continued*)

	10. History of breast cancer or estrogen-dependent neoplasia, significant organic disease that could affect the outcome of the study, active gall bladder disease, diabetes, history of cerebrovascular disease or thromboembolic disorders, or abnormal levels of TSH, serum creatinine, or liver enzymes
Interventions	-Oestrogen plus T 300 microgram/d -Oestrogen plus placebo -Route: oral or transdermal oestrogen, transdermal T patch -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Sexual function 2. Hirsutism 3. Acne -Other outcomes: 1. Alopecia 2. Deepening of voice
Notes	-Baseline equality: no significant differences across treatment groups with regard to age, weight, height, BMI, ethnicity, route of administration of concomitant oestrogen, duration of relationship, years since oophorectomy, number of satisfying sexual episodes over 4 weeks, score on sexual desire domain, score on PDS -The author was contacted and kindly provided further information.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing data have been imputed using appropriate methods
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possible free of other sources of bias

Warnock 2005

Methods	-Design: double-blind randomised (C), parallel group -No of centres: multicentre -Duration: 8 weeks -Power calculation: yes -Intention-to-treat analysis: available case analysis -No of participants randomised: 102 (50 in E group, 52 in E-T group) -No of participants completed the study: E group 43/50 (86%), E-T group 44/50 (81%) -No of participants analysed: 100 -No of non compilers: E group 5. The reasons were adverse event 1, protocol violation 2, and other 2; E-T group 7. The reasons were adverse event 5, protocol violation 1, and ineffectiveness 1. -No of losses to follow up: E group 2, E-T group 0 -Compliance assessment: not stated -Source of funding: drug company
Participants	-Characteristics: surgically menopausal women with menopausal onset of low sexual desire -Age: E group 49.6 ? 6.6, E-T group 48.1 ? 7.6 yr -Location: US -Setting: unclear -Ethnicity: E group White 46(94%) Black 28(57.1%) Hispanic 0 (0%); E-T group White 46(90%), Black 24(47%), Hispanic3(6%) -Run-in period: a 2-week, open-label oestrogen (1.25 mg/day) lead-in phase -Inclusion criteria: 1. 25-65 year-old 2. Healthy surgically menopausal women (for a minimum of 3 months) 3. Receiving the equivalent of 0.625 to 1.25 mg of estrogens in oral, topical, or transdermal form for at least 3 months 4. Stable, monogamous relationship for at least 2 years 5. Hypoactive sexual interest/desire associated with the onset of surgical menopause -Exclusion criteria: 1. Sensitivity/contraindications to estrogens or androgens 2. History or concurrent diagnosis of psychiatric disorder, sexual aversion/phobic disorder related or unrelated to sexual trauma/abuse 3. BMI of at least 35 kg/m^2 4. Physical limitations interfered with normal sexual functioning 5. Clinical depression or a current depressive disorder 6. Abnormal mammogram or vaginal cytology 7. Undiagnosed abnormal vaginal bleeding/malignancy 8. Grade II or III vaginal vault prolapse 9. Relevant clinical laboratory test abnormalities 10. Receiving other hormones, selective oestrogen receptor modulators, lipid-lowering agents, liver enzyme-inducing drugs, anticoagulants, antidepressants (including selective serotonin reuptake inhibitors, anxiolytics, and herbal and holistic antidepressants), antihypertensive drugs, or herbal remedies claiming libido enhancement. 11. Clinically significant endocrine disease or inadequately controlled DM 12. Stable thyroid medications and antiepileptics for > 3 months.

Warnock 2005 (*Continued*)

Interventions	-Esterified oestrogens (1.25 mg) plus methyltestosterone (2.5 mg) once a day -Esterified oestrogens (1.25 mg) alone once a day -Route: oral oestrogen and methyltestosterone -Co-intervention: no
Outcomes	-Relevant outcomes: 1. Sexual function 2. Sense of well being 3. Hirsutism 4. Acne 5. Lipid profile
Notes	-Baseline equality: no significant differences across treatment groups with regard to age, ethnicity, years since oophorectomy, lipid levels and score of sexual questionnaire. -The author was contacted. No further information was supplied.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	C - Not stated
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	Participants and key personnel were blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing data have been imputed using appropriate methods
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	No	Baseline imbalance (age)

Watts 1995

Methods	-Design: double-blind randomised (C), parallel group -No of centres: three -Duration: 2 years -Power calculation: not stated -Intention-to-treat analysis: yes for safety analysis, no for efficacy analysis -No of participants randomised: 66 (33 in each group) -No of participants analysed: 66 for safety analysis, 48 for BMD(24 in each group), 45 for lipid profile(23 for E group, 22 for E-T Group) -No of non compilers: unclear -No of losses to follow up: not stated -Compliance assessment: patients were considered compliant if they had taken at least 75% of their medication as assessed by returned tablet counts and monthly phone call -Source of funding: drug company
Participants	-Location: United States -Setting: hospital-based -Ethnicity: White (98.3%), Hispanic (1.7%) -Run-in period: no -Characteristics: healthy surgically menopausal women -Age (SD): E group 45.0 (8.0), E-T group 48.0 (8.0) yr -Inclusion criteria: 1. The same as stated in disease status 2. No concomitant illness -Exclusion criteria: not stated
Interventions	-EE 1.25 mg once a day -EE 1.25 mg plus mT 2.5 mg once a day -Route: oral -Co-intervention: no
Outcomes	-Relevant outcomes: 1. BMD of lumbar spines, radius and hip: DEXA 2. Menopausal symptoms: the scale modified from the original version developed by Kuppermann et al. 3. Lipid profile 4. Haematology -Other outcomes: 1. Serum biochemistry and urinalysis tests 2. Vaginal cytology
Notes	-Baseline equality: the two groups were similar in terms of age, height, weight, race, time since oophorectomy, number of patients with oestrogen use in previous 2 years, menopausal symptoms scores and lipid profiles. -The author was contacted and the response was obtained but no additional information was provided.

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	C - Not stated
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Participants and key personnel were blinded.
Incomplete outcome data addressed? All outcomes	No	Plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size.
Free of selective reporting?	No	One or more outcomes of interest in the review are reported incompletely.
Free of other bias?	Unclear	Insufficient information

Wisniewski 2002

Methods	See Dobs 2002
Participants	See Dobs 2002
Interventions	See Dobs 2002
Outcomes	See Dobs 2002
Notes	See Dobs 2002

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	See Dobs 2002
Allocation concealment?	Yes	See Dobs 2002
Blinding? All outcomes	Yes	See Dobs 2002
Incomplete outcome data addressed? All outcomes	Yes	See Dobs 2002

Wisniewski 2002 (*Continued*)

Free of selective reporting?	No	See Dobs 2002
Free of other bias?	No	See Dobs 2002

Zang 2006

Methods	-Design: open randomised (A), parallel group -No of centres: single centre -Duration: 12 weeks -Power calculation: not stated -Intention-to-treat analysis: yes by default -No of participants randomised: 63(T group 21, E group 22, E-T group 20) -No of participants completed the study: 63 -No of participants analysed: 63 -No of non compilers: 0 -No of losses to follow up: 0 -Compliance assessment: not stated -Source of funding: drug company
Participants	-Characteristics: naturally menopausal women -Age: T group 54.8+4.0, E group 55.4+4.7, E-T group 55.7 +4.5 yr -Location: Sweden -Setting: population-based -Ethnicity: unclear -Run-in period: washout periods: 8 weeks for oral HT, 4 weeks for transdermal HT or local oestrogen applications, and 6 months for progestin implants or injections. -Inclusion criteria: 1. 44-64 year-old 2. BMI 20-32 kg/m^2 3. last menstrual bleeding > 12 months or FSH levels > 30 IU/L 4. Nonsmoker -Exclusion criteria: 1. Liver, biliary, or renal disease 2. Uncontrolled high blood pressure 3. Endocrine disorder 4. History or presence of thromboembolic disorder and malignancy
Interventions	-Testosterone undecanoate (40 mg every second day) -oestradiol valerate (2 mg daily) -The combination of testosterone undecanoate and oestradiol valerate -Route:oral oestrogen and testosterone -Co-intervention: no

Zang 2006 (*Continued*)

Outcomes	-Relevant outcomes: 1. BMD 2. Body composition -Other outcomes: 1. Glucose and insulin levels
Notes	-Baseline equality: no statistically significant differences across treatment groups with regard to age, weight, BMI, waist-to-hip ratio, blood pressure, serum hormone levels, and previous use of HT -The author was contacted and kindly provided further information.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	A - Adequate
Allocation concealment?	No	C - Inadequate
Blinding? All outcomes	No	Open randomised trial
Incomplete outcome data addressed? All outcomes	Yes	No missing data
Free of selective reporting?	Unclear	Insufficient information
Free of other bias?	Yes	Possible free of other sources of bias

Definition:
-Run-in period for this review means a period where any intervention was identically administration to all participants in the same period of time.
-Relevancy means a score of the importance of sexuality in the woman's life.

Abbreviation:
-BISF-W = Brief Index of Sexual Functioning for Women
-BP = blood pressure
-BMD = bone mineral density
-BMI = body mass index
-BSAP = serum bone-specific alkaline phosphatase
-BSO = bilateral salpingo-oophorectomy
-BW = body weight
-CEE = conjugated equine oestrogen
-DEXA = dual-energy x-ray absorptiometry
-DHEAS = dehydroepiandrosterone sulphate
-DMRS = Daily menopausal Rating Scale
-Dpd = deoxypyridinoline
-E = oestrogen(either with placebo or not) group; T group = testosterone(either with placebo or not) group; P group = placebo group; E-P group= oestrogen plus progestogen(either with placebo or not) group, E-T group = oestrogen plus testosterone(either with placebo or not) group; E-P-T group = oestrogen plus progestogen plus testosterone(either with placebo or not) group
-ECG = electrocardiogram
-EE = esterified oestrogen
-MPA = medroxyprogesterone acetate
-mT = methyl testosterone
-No. = number
-NTx = Cross-linked N-terminal telopeptide of type I collagen
-Pap smear = Papanicolaou smear
- PFSF = Profile of Female Sexual Function
- PMS = premenstrual like symptom
- QUALMS = Quality of Life at Menopause Scale
- SAL = Sexual Activity Log
- SIQ = Sexual Interest Questionnaire
- SRS = Sabbatsberg Revised Sexual Self-Rating Scale
- TAH = total abdominal hysterectomy
- SD = standard deviation
- SEM = standard error of mean
- T= testosterone
- VAS =visual analogue scale
Notes:
The published articles that were from the same trials were as follows:
1. Davis 1995 and Davis 2000
2. Basaria 2002, Dobs 2002, Nguyen 1999, and Wisniewski 2002
3 Miller 2000, Luciano 1998a, and Luciano 1999
4. Barrett-Conner 1996 and Barrett-Conner 1999
The published articles of Sherwin included the similar set of participants.

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

Adamson 2001	The study objective was to investigate the effect of esterified oestrogens combined with methyltestosterone on quality of life. The comparison group was placebo not hormone therapy.
Bachmann 1996	The objective of this study was to compare the effect of the addition of androgen on the incidence and severity of breakthrough bleeding in postmenopausal women receiving conventional regimens of continuous combined oestrogen/progestogen hormone therapy. The outcome was not eligible for this review.
Barton 2007	The phase III randomised, placebo-controlled crossover clinical trial was aimed to evaluate whether transdermal testosterone would increase sexual desire in female cancer survivors. The population was not healthy postmenopausal women.
Brincat 1984	This study aimed to compare climacteric symptom control in 55 postmenopausal women treated with either oestradiol plus testosterone implants or placebo. The control group was not HT.
Buckler 1998	This was a pharmacokinetic study on the two existing testosterone preparations (oral testosterone undecanoate and subcutaneous testosterone pellets). One of sub studies was a 6 months double-blind randomised parallel group study but the main outcome was testosterone concentration which was not relevant to the review.
Buckler 2003	The objective of the study was to assess the efficacy (in terms of drug tolerance and doses) of intravaginal rings for androgen replacement in postmenopausal women who were receiving adequate oestrogen replacement by randomising them to either 0.5 or 1 mg testosterone/day added to HT. There was no HT only group serving as a control.
Burger 1984	An open study aimed to evaluate the effectiveness of combined estradiol and testosterone implants in alleviating menopausal symptoms not responding to standard oral oestrogens. The treatment group was the group of women who complained of persistent symptoms and then received testosterone plus estradiol implants. They were asked to return at monthly intervals for symptomatic assessment. The study design was not RCT.
Castelo-Branco 2000	This was an open parallel group study aimed to investigate long-term bone changes, lipid changes and sexual activity. Subjects were allocated randomly to one of three treatment groups or as controls. The treatment regimens were two oral oestrogen groups with cyclical or continuous progestogen, and one transdermal oestrogen regime with cyclical progestogen. Participants in the estradiol-testosterone implanted group was not randomised.
Davis 2003	The study was conducted to elicit women's perceptions of the effects of testosterone therapy. The study was not RCT.
Frisoli 2005	The study was conducted to evaluate the effect of nandrolone decanoate on bone mineral density. The comparison group was not hormone therapy.
Frisoli 2005a	The study was conducted to evaluate the effect of nandrolone decanoate on bone mineral density. The comparison group was not hormone therapy.
Garnett 1992	The study was quasi-randomised trial.

(*Continued*)

Gruber 1998	This study was carried out to assess the effect of topical androgen replacement therapy on body composition and body weight. The treatment group was androgen gel, not testosterone plus HT while the control group was placebo, not HT.
Imparato 1973	The aim of this study was to determine the efficacy and side effects of a combined hormone preparation (oestrogen, progestogen and testosterone) in various doses. There was no combined oestrogen plus progestogen therapy serving as a control group.
Kapetanakis 1982	The study was carried out to assess the effect of pellets containing either oestradiol or oestradiol in combination with testosterone in ten women with various type of ovarian failure. The participants included women with gonadal dysgenesis.
Krug 2003	The placebo-controlled crossover study was carried out to assess the effects of oestrogen or testosterone in postmenopausal women with constantly low levels of gonadal steroids on in divergent thinking. The treatment group was testosterone only, not testosterone plus oestrogen.
Lane 2003	The study was to investigate the effects on large artery function of testosterone replacement in addition to conventional hormone therapy in postmenopausal women. It was not a randomised control trial.
Luciano 1998b	The purpose of this study was to evaluate the pharmacokinetics and the therapeutic responses of micronized estradiol, progesterone and testosterone administered sublingually as a single tablet. The outcome was not eligible for this review.
Magos 1985	A regimen of subcutaneous implants of oestradiol and testosterone in combination with continuous oral norethisterone was investigated in 71 non-hysterectomized postmenopausal women in order to evaluate endometrial and menstrual response. There was no HT group serving as a control.
Nathorst-Böös 2005	The purpose of this study was to evaluate the pharmacokinetics of percutaneous administration of testosterone gel. The outcome was not eligible for this review.
Passeri 1993	The double-blind, randomised, placebo-controlled study was conducted in 46 postmenopausal women with established osteoporosis in order to assess the long-term effects of nandrolone decanoate on the bone mineral density and biochemical markers of bone turnover. The patients received intramuscular injections of placebo or 50 mg nandrolone decanoate every 3 weeks for 18 months. The treatment was not testosterone plus HT and the control group was not on HT.
Sands 2000	This was an interventional study, but not a randomised controlled trial, aimed to compare the short-term effects of oestrogen and oestrogen plus testosterone on bone turnover. Oestradiol was given at baseline and then followed by the combination of estradiol plus testosterone.
Sarrel 1997	The primary outcomes, vaginal and fingertip blood flow, were not objectives of this review. In addition, the study participants were the same as those in Sarrel 1998 which was included in our review.

(*Continued*)

Savvas 1988	The non-randomised cohort study of postmenopausal women aimed to compare oral continuous treatment with cyclic oestrogen plus progesterone preparation and subcutaneous implants of estradiol combined with testosterone for their effects in preventing postmenopausal osteoporosis.
Savvas 1992	This study was designed to investigate the effect on bone density when women change from oral oestrogen replacement therapy to subcutaneous hormone implants. The treatment group was the group of women who were complaining of problems with depression, loss of energy and loss of libido although the vasomotor symptoms were controlled while the control group was the group of women who were happy to continue with oral HT. The study design was not RCT.
Scott 2005	This retrospective study was designed to determine whether systemic replacement with combined esterified oestrogen and methyltestosterone would reduce symptoms and promote clinical improvement in postmenopausal women with dry eye syndrome. The study design was not RCT.
Seed 2000	This was semi-randomised study. The control groups included two historical groups of women who were randomly assigned to receive oestrogen continuously or no treatment. The treatment groups comprised the two study groups; oestrogen-androgens and tibolone.
Sherwin 1987a	The study was undertaken in order to investigate whether surgically menopausal women who had been chronically receiving a combined estrogen-androgen drug long term would differ in aspects of their sexual functioning from women who had been receiving oestrogen alone and from those who remained untreated for several years. The study design was not RCT.
Sherwin 1987b	The study aimed to compare lipid concentration in surgically menopausal women who received either oestrogen-androgen, oestrogen or no treatment. The study design was not RCT.
Soares-Welch 2005	This randomised, double-blind crossover study was carried out to test the effect of increased testosterone availability on impoverished GH/IGF-I secretion. The treatment group was not HT-T.
Taskin 1999	The prospective, randomised placebo controlled double blind study aimed to investigate and compare the effects of testosterone, tibolone, hormone therapy on diastolic cardiac functions and lipid peroxidation in postmenopausal women. The outcomes were not eligible for this review.
van Anders 2005	The study examined effects of testosterone on hypoactive sexual desire in pre- and postmenopausal women (treated) compared with an age-matched reference group). The design was not RCT.
Worboys 2001	The study aimed to investigate the effects of testosterone implant therapy on arterial reactivity encompassing endothelial-dependent and -independent vasodilation in women using HT. Thirty-three postmenopausal women stabilized on oestrogen therapy received testosterone implant and 15 postmenopausal nonusers of HT served as control. The control group was not HT.

(*Continued*)

Zang 2007	The aim of this study was to investigate the treatment effects of testosterone and oestrogen on endometrium and the expression of proteins and genes involved in adipocyte signal transduction to lipolysis in abdominal subcutaneous adipose tissue of postmenopausal women. The outcomes were not eligible not our review.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Alaghband-Zadeh 2003

Methods	Unspecified
Participants	Postmenopausal women
Interventions	Exogenous testosterone
Outcomes	Psychological and metabolic effects
Notes	Published in National register trial. No data is available for evaluation

Montgomery 1986

Methods	Prospective randomised study
Participants	Menopausal women
Interventions	Oestradiol and, oestradiol and testosterone implants
Outcomes	Psychiatric and psychosexual problems
Notes	Data could not be evaluated

Montgomery 1990

Methods	Not specified
Participants	climacteric women with sexual dysfunction
Interventions	implanted oestradiol alone and in combination with testosterone
Outcomes	Not specified
Notes	Data could not be evaluated

Montgomery 1991

Methods	Not specified
Participants	Decreased libido in climacteric women
Interventions	Oestradiol implant alone and in combination with testosterone

Montgomery 1991 (*Continued*)

Outcomes	Not specified
Notes	Data could not be evaluated

Myers 1990

Methods	A 10-week, double-blind, hormone replacement study
Participants	40 naturally menopausal women (mean age 58.3 yr)
Interventions	Basal and stimulated vaginal vaso congestion and daily self-reports of mood, physical symptoms, sexual behavior, and perceived sexual pleasure
Outcomes	Daily treatments were either conjugated equine oestrogen, i.e. Premarin (P; 0.625 mg), Premarin and medroxyprogesterone acetate, i.e. Provera (PP; 0.625 and 5 mg, respectively), Premarin and methyltestosterone (PT; 0.625 and 5 mg, respectively), or placebo (PL).
Notes	Data could not be evaluated

Sands 2003

Methods	Unspecified
Participants	Postmenopausal women
Interventions	Subcutaneous testosterone
Outcomes	Benefits
Notes	Published in National register trial. No data is available for evaluation.

DATA AND ANALYSES

Comparison 1. HT plus testosterone versus HT on sense of well being

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sense of well-being	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 sexual function	2	160	Std. Mean Difference (IV, Fixed, 95% CI)	0.47 [0.15, 0.80]
1.2 Cognitive difficulty	1	95	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 Somatic or physical symptoms	2	164	Std. Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.11, 0.54]
1.4 Anxiety or fear	1	95	Std. Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.70, 0.11]
1.5 Depressed mood	1	95	Std. Mean Difference (IV, Fixed, 95% CI)	0.26 [-0.14, 0.67]
1.6 Vasomotor symptoms	2	166	Std. Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.08, 0.56]
1.7 Sleep problems	1	95	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.35, 0.45]
1.8 Menstrual symptoms	1	95	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.52, 0.29]
1.9 Attractiveness	1	95	Std. Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.23, 0.58]
1.10 Psychosocial	1	70	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.57, 0.47]

Comparison 2. HT plus testosterone versus HT on sexual function

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change scores of sexual function	9		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Number of satisfying	5	1893	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [0.20, 0.38]
1.2 Number of activity	7	1946	Std. Mean Difference (IV, Fixed, 95% CI)	0.25 [0.17, 0.34]
1.3 Number of orgasms	5	1893	Std. Mean Difference (IV, Fixed, 95% CI)	0.30 [0.21, 0.39]
1.4 Libido, desire or interest in sex	9	2215	Std. Mean Difference (IV, Fixed, 95% CI)	0.35 [0.26, 0.43]
1.5 Orgasm	6	1872	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [0.19, 0.37]
1.6 Arousal	5	1845	Std. Mean Difference (IV, Fixed, 95% CI)	0.36 [0.27, 0.45]
1.7 Pleasure or enjoyment of sex	6	1641	Std. Mean Difference (IV, Fixed, 95% CI)	0.33 [0.22, 0.43]
1.8 Sexual concerns	5	1852	Std. Mean Difference (IV, Fixed, 95% CI)	0.32 [0.22, 0.41]
1.9 Responsiveness	8	2171	Std. Mean Difference (IV, Fixed, 95% CI)	0.32 [0.23, 0.40]
1.10 Sexual self-image	5	1839	Std. Mean Difference (IV, Fixed, 95% CI)	0.26 [0.16, 0.35]
1.11 Satisfaction	1	32	Std. Mean Difference (IV, Fixed, 95% CI)	0.98 [0.24, 1.72]
1.12 Fantasy	1	32	Std. Mean Difference (IV, Fixed, 95% CI)	1.37 [0.59, 2.15]
1.13 Frequency of desire	1	96	Std. Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.19, 0.61]
1.14 Composite score	3	330	Std. Mean Difference (IV, Fixed, 95% CI)	0.41 [0.19, 0.63]
2 Change scores of Personal Distress Scale	5	1845	Mean Difference (IV, Fixed, 95% CI)	-8.13 [-10.59, -5.67]
2.1 Personal Distress Scale	5	1845	Mean Difference (IV, Fixed, 95% CI)	-8.13 [-10.59, -5.67]

Comparison 3. HT plus testosterone versus HT on bone mineral density

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lumbar BMDs at 12 months	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Mean score	2	90	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.11, 0.00]
1.2 Change score	1	57	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.93, 1.13]
2 Lumbar BMDs at 24 months	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Mean score	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 Change score	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.19, 0.03]
3 Femur BMDs at 12 months	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Mean score	2	90	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.09, -0.01]
3.2 Change score	1	57	Mean Difference (IV, Fixed, 95% CI)	1.4 [0.14, 2.66]
4 Femur BMDs at 24 months	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Mean score	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.16, 0.02]
4.2 Change score	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 4. HT plus testosterone versus HT on body composition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Mean weight at the endpoint (3 months)	1	42	Mean Difference (IV, Fixed, 95% CI)	1.30 [-3.86, 6.46]
1.2 Mean weight at the endpoint (6 months)	1	37	Mean Difference (IV, Fixed, 95% CI)	5.40 [-4.79, 15.59]
1.3 Mean weight at the endpoint (12 months)	1	37	Mean Difference (IV, Fixed, 95% CI)	6.30 [-3.83, 16.43]
1.4 Weight gain	1	37	Mean Difference (IV, Fixed, 95% CI)	1.18 [-0.25, 2.61]
2 Body mass index	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Body mass index at 3 months	1	42	Mean Difference (IV, Fixed, 95% CI)	1.0 [-0.64, 2.64]
2.2 Body mass index at 6 months	1	37	Mean Difference (IV, Fixed, 95% CI)	1.60 [-2.31, 5.51]
2.3 Body mass index at 12 months	1	37	Mean Difference (IV, Fixed, 95% CI)	2.10 [-1.83, 6.03]
3 Waist:hip ratio	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 At 6 months	1	37	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.08, -0.02]
3.2 At 12 months	1	37	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.06, 0.00]

Comparison 5. HT plus testosterone versus HT on cognition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cognitive performance	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Identical Pictures	1	26	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-6.67, 1.87]
1.2 Shape Memory	1	26	Mean Difference (IV, Fixed, 95% CI)	0.10 [-2.19, 2.39]
2 Cognition difficulty	1	95	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 6. HT plus testosterone versus HT on menopausal symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vasomotor symptom	2	166	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.18, 0.37]

Comparison 7. HT plus testosterone versus HT on facial and body hair growth

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean scores of facial and body hair growth	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Incidence of facial and body hair growth	7	2127	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [1.07, 2.17]

Comparison 8. HT plus testosterone versus HT on acne

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean scores of acne	1	216	Mean Difference (IV, Fixed, 95% CI)	0.1 [-0.03, 0.23]
2 Incidence of acne	7	2127	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.51 [1.07, 2.14]

Comparison 9. HT plus testosterone versus HT on mammographic findings

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of increased breast density	1	87	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.46, 3.95]
2 Area of dense breast	1	87	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 10. HT plus testosterone versus HT on lipid profile

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total cholesterol at less than 3 months	4	231	Mean Difference (IV, Random, 95% CI)	-14.92 [-27.81, -2.03]
2 Triglyceride at less than 3 months	4		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 LDL cholesterol at less than 3 months	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 HDL cholesterol at less than 3 months	4	231	Mean Difference (IV, Random, 95% CI)	-17.11 [-23.47, -10.75]
5 Total cholesterol at 3 - <6 months	2	256	Mean Difference (IV, Random, 95% CI)	-9.42 [-31.76, 12.93]
5.1 Mean score	1	40	Mean Difference (IV, Random, 95% CI)	3.87 [-15.08, 22.82]
5.2 Change score	1	216	Mean Difference (IV, Random, 95% CI)	-19.2 [-26.16, -12.24]
6 Triglyceride at 3 - <6 months	2	256	Mean Difference (IV, Fixed, 95% CI)	-25.62 [-38.53, -12.72]
6.1 Mean score	1	40	Mean Difference (IV, Fixed, 95% CI)	-44.29 [-85.55, -3.03]
6.2 Change score	1	216	Mean Difference (IV, Fixed, 95% CI)	-23.6 [-37.18, -10.02]
7 LDL cholesterol at 3 - <6 months	2	256	Mean Difference (IV, Random, 95% CI)	18.78 [-18.39, 55.94]
7.1 Mean score	1	40	Mean Difference (IV, Random, 95% CI)	38.67 [21.22, 56.12]
7.2 Change score	1	216	Mean Difference (IV, Random, 95% CI)	0.7 [-5.58, 6.98]
8 HDL cholesterol at 3 - <6 months	2	256	Mean Difference (IV, Random, 95% CI)	-18.72 [-26.04, -11.39]
8.1 Mean score	1	40	Mean Difference (IV, Random, 95% CI)	-23.2 [-30.19, -16.21]
8.2 Change score	1	216	Mean Difference (IV, Random, 95% CI)	-15.60 [-18.59, -12.61]
9 Total cholesterol/HDL cholesterol at 3 - <6 months	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
10 Total cholesterol at 6 - <12 months	10	1910	Mean Difference (IV, Random, 95% CI)	-2.93 [-7.18, 1.32]
10.1 Mean score	3	101	Mean Difference (IV, Random, 95% CI)	-6.27 [-20.41, 7.88]

10.2 Change score	7	1809	Mean Difference (IV, Random, 95% CI)	-2.74 [-7.47, 2.00]
11 Triglyceride at 6 - <12 months	10	1909	Mean Difference (IV, Random, 95% CI)	-5.79 [-14.25, 2.67]
11.1 Mean score	3	101	Mean Difference (IV, Random, 95% CI)	7.00 [-8.74, 22.74]
11.2 Change score	7	1808	Mean Difference (IV, Random, 95% CI)	-8.64 [-18.40, 1.11]
12 LDL cholesterol at 6 - <12 months	10	1906	Mean Difference (IV, Fixed, 95% CI)	1.86 [-0.15, 3.87]
12.1 Mean score	3	101	Mean Difference (IV, Fixed, 95% CI)	3.24 [-10.76, 17.23]
12.2 Change score	7	1805	Mean Difference (IV, Fixed, 95% CI)	1.83 [-0.20, 3.86]
13 HDL cholesterol at 6 - <12 months	10	1907	Mean Difference (IV, Random, 95% CI)	-5.84 [-9.10, -2.58]
13.1 Mean score	3	101	Mean Difference (IV, Random, 95% CI)	-9.38 [-13.64, -5.12]
13.2 Change score	7	1806	Mean Difference (IV, Random, 95% CI)	-4.74 [-8.42, -1.07]
14 Total cholesterol/HDL at 6 - <12 months	1	45	Mean Difference (IV, Fixed, 95% CI)	20.6 [12.76, 28.44]
14.1 Change score	1	45	Mean Difference (IV, Fixed, 95% CI)	20.6 [12.76, 28.44]
15 Total cholesterol at 12 months	4	231	Mean Difference (IV, Random, 95% CI)	-7.99 [-23.45, 7.48]
15.1 Mean score	2	70	Mean Difference (IV, Random, 95% CI)	1.75 [-15.03, 18.52]
15.2 Change score	2	161	Mean Difference (IV, Random, 95% CI)	-14.35 [-38.05, 9.35]
16 Triglyceride at 12 months	4	231	Mean Difference (IV, Random, 95% CI)	-23.38 [-55.53, 8.76]
16.1 Mean score	2	70	Mean Difference (IV, Random, 95% CI)	3.92 [-21.60, 29.43]
16.2 Change score	2	161	Mean Difference (IV, Random, 95% CI)	-45.29 [-80.17, -10.40]
17 LDL cholesterol at 12 months	4	231	Mean Difference (IV, Fixed, 95% CI)	8.84 [2.13, 15.54]
17.1 Mean score	2	70	Mean Difference (IV, Fixed, 95% CI)	5.81 [-10.02, 21.64]
17.2 Change score	2	161	Mean Difference (IV, Fixed, 95% CI)	9.50 [2.10, 16.90]
18 HDL cholesterol at 12 months	4	231	Mean Difference (IV, Random, 95% CI)	-14.49 [-25.28, -3.70]
18.1 Mean score	2	70	Mean Difference (IV, Random, 95% CI)	-7.22 [-13.99, -0.45]
18.2 Change score	2	161	Mean Difference (IV, Random, 95% CI)	-23.64 [-28.95, -18.33]
19 Total cholesterol/HDL at 12 months	1	45	Mean Difference (IV, Fixed, 95% CI)	15.40 [4.40, 26.40]
19.1 Mean score	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
19.2 Change score	1	45	Mean Difference (IV, Fixed, 95% CI)	15.40 [4.40, 26.40]
20 Total cholesterol at 24 months	3	167	Mean Difference (IV, Random, 95% CI)	-11.69 [-32.36, 8.97]
20.1 Mean change	1	32	Mean Difference (IV, Random, 95% CI)	3.87 [-24.74, 32.48]
20.2 Change score	2	135	Mean Difference (IV, Random, 95% CI)	-16.63 [-42.67, 9.42]
21 Triglyceride at 24 months	3	167	Mean Difference (IV, Fixed, 95% CI)	-52.46 [-69.58, -35.35]
21.1 Mean change	1	32	Mean Difference (IV, Fixed, 95% CI)	Not estimable
21.2 Change score	2	135	Mean Difference (IV, Fixed, 95% CI)	-58.11 [-76.12, -40.09]
22 LDL cholesterol at 24 months	3	167	Mean Difference (IV, Fixed, 95% CI)	9.15 [1.09, 17.20]
22.1 Mean change	1	32	Mean Difference (IV, Fixed, 95% CI)	3.87 [-20.94, 28.68]
22.2 Change score	2	135	Mean Difference (IV, Fixed, 95% CI)	9.77 [1.26, 18.29]
23 HDL cholesterol at 24 months	3	167	Mean Difference (IV, Random, 95% CI)	-17.63 [-31.45, -3.80]

23.1 Mean change	1	32	Mean Difference (IV, Random, 95% CI)	Not estimable
23.2 Change score	2	135	Mean Difference (IV, Random, 95% CI)	-26.34 [-28.00, -22.69]
24 Total cholesterol/HDL at 24 months	1	45	Mean Difference (IV, Fixed, 95% CI)	20.80 [11.00, 30.60]
24.1 Mean change	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
24.2 Change score	1	45	Mean Difference (IV, Fixed, 95% CI)	20.80 [11.00, 30.60]

Comparison 11. HT plus testosterone versus HT on lipid profile (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total cholesterol	17	2488	Mean Difference (IV, Random, 95% CI)	-7.59 [-13.08, -2.10]
1.1 Testosterone patch	5	1738	Mean Difference (IV, Random, 95% CI)	0.08 [-2.37, 2.52]
1.2 Testosterone implant	2	63	Mean Difference (IV, Random, 95% CI)	-2.34 [-23.12, 18.45]
1.3 Oral testosterone	10	687	Mean Difference (IV, Random, 95% CI)	-14.02 [-21.63, -6.40]
2 HDL cholesterol	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Testosterone patch	5	1735	Mean Difference (IV, Random, 95% CI)	-1.09 [-1.98, -0.19]
2.2 Testosterone implant	2	63	Mean Difference (IV, Random, 95% CI)	-5.01 [-11.72, 1.70]
2.3 Oral testosterone	10	687	Mean Difference (IV, Random, 95% CI)	-18.63 [-22.18, -15.08]
3 LDL cholesterol	16	2406	Mean Difference (IV, Random, 95% CI)	4.41 [0.76, 8.07]
3.1 Testosterone patch	5	1734	Mean Difference (IV, Random, 95% CI)	1.77 [-0.34, 3.87]
3.2 Testosterone implant	2	64	Mean Difference (IV, Random, 95% CI)	3.37 [-13.92, 20.66]
3.3 Oral testosterone	9	608	Mean Difference (IV, Random, 95% CI)	10.39 [1.46, 19.32]
4 Triglyceride	17	2487	Mean Difference (IV, Random, 95% CI)	-14.80 [-23.24, -6.36]
4.1 Testosterone patch	5	1737	Mean Difference (IV, Random, 95% CI)	-3.64 [-8.73, 1.44]
4.2 Testosterone implant	2	63	Mean Difference (IV, Random, 95% CI)	9.10 [-16.04, 34.24]
4.3 Oral testosterone	10	687	Mean Difference (IV, Random, 95% CI)	-27.07 [-41.44, -12.70]
5 Total cholesterol/HDL	1	45	Mean Difference (IV, Fixed, 95% CI)	20.80 [11.00, 30.60]
5.1 Testosterone patch	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.2 Testosterone implant	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.3 Oral testosterone	1	45	Mean Difference (IV, Fixed, 95% CI)	20.80 [11.00, 30.60]

Comparison 12. HT plus testosterone versus HT on discontinuation rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation rate (overall)	21	3124	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.83, 1.19]
2 Discontinuation rate (type of menopause)	20		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Surgical menopause	8	1942	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.87, 1.36]
2.2 Natural menopause	5	764	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.60, 1.29]
2.3 Both	7	419	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.79, 2.63]
3 Discontinuation rate (menopausal status)	22		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Perimenopausal	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.2 Postmenopausal	19	3076	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.86, 1.25]
3.3 Both	3	148	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.26 [0.85, 12.47]
4 Discontinuation rate (route of hormone therapy)	22		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Oral HT	13	1840	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.79, 1.30]
4.2 Non-oral HT	7	289	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.62, 2.82]
4.3 Oral and non-oral HT	2	1095	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.82, 1.46]
5 Discontinuation rate (type of testosterone)	22		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 Methyl testosterone	10	955	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.89, 1.98]
5.2 Testosterone	9	2087	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.79, 1.21]
5.3 Other	3	182	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [0.53, 5.29]
6 Discontinuation rate (duration of treatment)	22		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Less than 3 months	3	195	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.46, 3.10]
6.2 3 - <6 months	5	428	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [0.87, 2.99]
6.3 6 - < 12 months	10	2164	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.80, 1.21]
6.4 12 - < 24 months	2	92	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.12, 6.98]
6.5 24 months	2	345	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.71, 2.42]
7 Discontinuation rate (blinding)	22		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Double-blind	18	3088	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.87, 1.26]
7.2 Open or single-blind	4	136	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [0.53, 6.49]
8 Discontinuation rate (disease status)	21		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 Inadequate symptom control	9	2048	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.80, 1.25]
8.2 Low T plus inadequate symptom control	2	303	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.62, 1.67]
8.3 No symptom	10	771	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.90, 2.46]

Comparison 13. HT plus testosterone versus HT on discontinuation rate due to adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation rate due to adverse events (overall)	20	3096	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.95, 1.62]
2 Discontinuation rate due to adverse events (type of menopause)	19		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Surgical menopause	8	1942	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.85, 1.59]
2.2 Natural menopause	4	704	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.72, 2.39]
2.3 Both	7	424	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [0.79, 4.78]
3 Discontinuation rate due to adverse events (menopausal status)	20		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Perimenopausal	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.2 Postmenopausal	17	2948	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.95, 1.61]
3.3 Both	3	148	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.99 [0.20, 19.45]
4 Discontinuation rate due to adverse events (route of hormone therapy)	19		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Oral HT	11	1707	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.92, 1.86]
4.2 Non-oral HT	7	294	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.48, 4.20]
4.3 Oral and non-oral HT	2	606	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.57, 1.92]
5 Discontinuation rate due to adverse events (type of testosterone)	20		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 Methyl testosterone	8	827	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [0.94, 2.57]
5.2 Testosterone	9	2087	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.82, 1.55]
5.3 Other	3	182	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.25, 9.35]
6 Discontinuation rate due to adverse events (duration of treatment)	20		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Less than 3 months	2	122	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.90 [0.76, 20.16]
6.2 3 - < 6 months	5	428	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [0.79, 4.77]
6.3 6 - < 12 months	10	2164	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.82, 1.54]
6.4 12 - <24 months	1	37	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
6.5 24 months	2	345	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.67, 2.33]
7 Discontinuation rate due to adverse events (blinding)	20		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Double-blind	16	2960	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.93, 1.59]
7.2 Open or single-blind	4	136	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.59 [0.59, 21.94]
8 Discontinuation rate due to adverse events (disease status)	19		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 Inadequate symptom control	8	1988	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.85, 1.67]
8.2 Low T plus inadequate symptom control	2	303	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.52, 2.12]
8.3 No symptom	9	703	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.36 [0.77, 2.39]

Comparison 14. HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation rate (allocation quality)	14	2773	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.81, 1.17]
2 Discontinuation rate due to adverse events (allocation quality)	14	2778	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.91, 1.57]
3 Discontinuation rate (quality of randomisation))	17	2902	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.81, 1.16]
4 Discontinuation rate due to adverse events (quality of randomisation)	17	2931	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.95, 1.61]
5 Discontinuation rate (blinding method)	17	3057	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.81, 1.17]
6 Discontinuation rate due to adverse events (blinding method)	15	2929	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.93, 1.59]
7 Discontinuation rate (large studies)	15	723	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.77, 2.49]
8 Discontinuation rate due to adverse events (large studies)	13	595	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.57, 3.64]
9 Discontinuation rate (methyl testosterone doses)	10		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Methyl testosterone, all doses	10	955	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.68, 1.35]
9.2 Methyl testosterone 1.25mg	5	473	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.55, 1.43]
9.3 Methyl testosterone 2 mg	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.12, 6.98]
9.4 Methyl testosterone 2.5mg	6	431	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.57, 1.58]
10 Discontinuation rate due to adverse events (methyl testosterone doses)	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 Methyl testosterone, all doses	8	827	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.92, 2.22]
10.2 Methyl testosterone 1.25mg	5	477	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.71, 2.23]
10.3 Methyl testosterone 2.5mg	5	358	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.60 [0.80, 3.23]
11 Discontinuation rate (estrogen doses)	24		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
11.1 Estrogen, all doses	24	3394	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.82, 1.17]
11.2 Conjugated estrogen 0.625mg or equivalent doses of other estrogens	7	766	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.70, 1.41]
11.3 Conjugated estrogen 1.25mg or equivalent doses of other estrogens	15	907	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.68, 1.52]

12 Discontinuation rate due to adverse events (estrogen doses)	22		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
12.1 Estrogen, all doses	22	3266	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.93, 1.58]
12.2 Conjugated estrogen 0.625mg or equivalent doses of other estrogens	6	706	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [0.80, 2.24]
12.3 Conjugated estrogen 1.25mg or equivalent doses of other estrogens	14	839	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.76, 2.65]

WHAT'S NEW

Last assessed as up-to-date: 17 April 2007.

21 October 2008	New search has been performed	There were 18 new studies. These trials were incorporated into the updated review. Personal distress, an important domain for measuring sexual function, is added into the updated review. Some intermediate outcomes were removed, such as coagulation factor, haematocrit, and biochemical markers of bone turnover.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 4, 2005

18 April 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Somboonporn W: searching, selection of studies, data extraction, drafting and co-drafting of the protocol and review, data analysis, data presentation, result interpretation, and publication.

Davis S: reviewing selection of studies, reviewing data extraction, co-drafting of the protocol and review, supervision of data presentation, results interpretation, and publication.

Bell R: review of searching, selection of studies, appraising quality of articles, data extraction, co-drafting of the protocol and review, assistance with statistics and data analysis.

DECLARATIONS OF INTEREST

Professor Susan Davis has acted as a consultant for the following companies that have testosterone therapies for women: Procter and Gamble, Solvay Pharmaceuticals, Acrux Ltd, Cellergy, and Organon and has received honoraria for lectures sponsored by Procter and Gamble and Organon. Currently Professor Davis is undertaking research supported either directly or indirectly by each of these named companies.

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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Androgens [*administration & dosage; adverse effects; blood]; Estrogen Replacement Therapy [adverse effects]; Hormone Replacement Therapy [adverse effects; *methods]; Perimenopause [blood; *drug effects; physiology]; Postmenopause [blood; *drug effects; physiology]; Randomized Controlled Trials as Topic; Testosterone [*administration & dosage; adverse effects; blood]

MeSH check words

Female; Humans