# Testosterone for peri- and postmenopausal women (Review)

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## ABSTRACT

**Background**
: The value of adding testosterone to hormone therapy (HT) for the management of peri- and postmenopausal women is controversial and has not been systematically reviewed.

**Objectives**
: To determine the benefits and risks of testosterone therapy for peri- and postmenopausal women taking hormone therapy.

**Search strategy**
: We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (1st November 2003), The Cochrane Library (Issue 2, 2003), MEDLINE (1966 to 1st November 2003), EMBASE (1980 to 1st November 2003), Biological Abstracts (1969 to 2002), PsycINFO (1972 to 1st November 2003), CINAHL (1982 to 1st November 2003), and reference lists of articles. We also contacted pharmaceutical companies and researchers in the field.

**Selection criteria**
: Studies that were randomized comparisons of testosterone plus hormone therapy versus hormone therapy alone in peri- or postmenopausal women.

**Data collection and analysis**
: Two review authors assessed the quality of the trials and extracted data independently. Where it was necessary, the corresponding authors of eligible trials were contacted for additional information. For dichotomous outcomes Peto odds ratios and 95% confidence intervals 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**
: Twenty-three trials with 1957 participants were included in the review. The median study duration was 6 months (range 1.5 to 24 months). Most of the trials were of adequate quality with regard to randomization and concealment of allocation sequence. The major methodological limitations were attrition bias and lack of a washout period in the cross-over studies. The pooled estimate from the studies suggested that the addition of testosterone to HT regimens improved sexual function scores for postmenopausal women. A significant adverse effect was a decrease in high-density lipoprotein (HDL) cholesterol levels. The discontinuation rate was not significantly greater with testosterone therapy (Peto odds ratio 1.01, 95% confidence interval 0.76 to 1.33) than with HT alone. There was insufficient evidence of a treatment effect for perimenopausal women or for other outcomes.

**Authors' conclusions**
: Only a limited number of studies could be pooled in the meta-analyses. This limited the power of the meta-analysis to provide conclusions about efficacy and safety. However, there is evidence that adding testosterone to HT has a beneficial effect on sexual function in postmenopausal women. There was a reduction in HDL cholesterol associated with the addition of testosterone to the HT regimens. The meta-analysis combined studies using different testosterone regimens. It is, therefore, difficult to estimate the effect of testosterone on sexual function in association with any individual hormone treatment regimen.

## PLAIN LANGUAGE SUMMARY

The role of testosterone therapy in peri-and postmenopausal women remains unclear.

The value of adding adjuvant testosterone to hormone therapy for peri-and postmenopausal women's health is controversial. This systematic review examines the benefits and the risks of such therapy. The small number of studies appropriate for inclusion in the meta-analysis is a limitation for every outcome looked at in this review. The available evidence is that adding testosterone to estrogen therapy, with or without progestin, appears to be effective in improving sexual function in postmenopausal women and is associated with a reduction in high-density lipoprotein (HDL) cholesterol. The impact of testosterone therapy on other health outcomes and for perimenopausal women remains unclear.

## BACKGROUND

Conventional hormone therapy for peri- and postmenopausal women. Conventional hormone therapy (HT), as estrogen alone or in combination with progestin, has been used for many years for the alleviation of symptoms that arise from sex-steroid insufficiency. It has been established that HT is beneficial for relieving vasomotor symptoms and results in a significant reduction in hot flushes in terms of frequency (mean 77%; 95% confidence interval (CI) 58.2 to 87.5) and severity (odds ratio (OR) 0.13, 95% CI 0.08 to 0.22) (MacLennan 2001). In postmenopausal women, sleep quality, urogenital atrophy and dyspareunia can also be improved with systemic or vaginal estrogen therapy (Cardozo 1998; Hays 2003; Moehrer 2003). HT inhibits bone mineral loss and reduces the risk of vertebral fracture and hip fracture (Beral 2002; Greendale 2000; Macedo 1998; Manson 2001; Rossouw 2002). However, it has been reported that up to 14.5% of users will still lose total hip bone mineral density (BMD), at a rate of 1.0% per year in the first three years of HT use (Greendale 2000).

### CONCERNS RAISED ABOUT HT USE BY THE WOMEN'S HEALTH INITIATIVE ESTROGEN-PROGESTIN (WHI) STUDY

Considerable concern exists that traditional HT conveys risks that may outweigh benefits in asymptomatic postmenopausal women. The gravest concern is that of an increase in cardiovascular events, particularly venous thromboembolic events, in the first year or two of using oral conjugated estrogen (CEE) combined with medroxyprogesterone acetate (MPA) (Grodstein 2001; Rossouw 2002). In addition, in the Women's Health Initiative Estrogen-Progestin (WHI-EP) study oral HT increased the risk of ischemic stroke (Wassertheil-Smoller). The estrogen-only arm also showed a significantly increased risk of stroke (Anderson 2004). The estimated hazard ratio was 1.39 (95%CI 1.10 to 1.77) (Anderson 2004). A statistically significant increase in the risk of breast cancer resulted in the premature termination of the WHI-EP study, an effect that was greatest for women using HT prior to commencing the study (Rossouw 2002; Chlebowski 2003). In contrast, the estrogen-only versus placebo arm of the WHI study did not show an increase in risk of breast cancer during the 6.8 years of the study (Anderson 2004). A substudy of the estrogen-progestin arm of this study, the Women's Health Initiative Memory Study (WHIMS), reported that oral CEE plus MPA increased the risk for probable dementia in postmenopausal women aged 65 years or older (Shumaker 2003). There is a separate WHI report on the effects of HT on global cognitive function in women over 65 years (Rapp 2003). Unfortunately this latter study had some fundamental methodological limitations as the investigators used the Modified Mini-Mental State Examination (3MSE), a screening instrument for detection of dementia. This tool is not considered appropriate as a measure of cognitive change (Rapp 2003).

Hays 2003 have proposed that oral CEE plus MPA therapy has no significant effects on general health, vitality, mental health, depressive symptoms or sexual satisfaction (Hays 2003). Not only were the majority of women in this study asymptomatic at baseline but also the tools used to evaluate the endpoints reported upon were mostly inappropriate; for example, sexual function was assessed by a single question about satisfaction (Hays 2003).

There is evidence that standard estrogen therapy has little effect on libido in women not suffering dyspareunia (Campbell 1977), although parameters of sexuality improve when extremely high doses of estrogen are administered (Davis 1995).

### THE ROLE OF TESTOSTERONE IN WOMEN

Biological data support important physiological effects of testosterone in women. Testosterone may act directly via androgen receptors throughout the body: in the brain, particularly the hypothalamus and amygdala; and important peripheral sites including bone; breast; skin; skeletal muscle; adipose, vascular and genital tissues (Davis 1999). The effects of testosterone are also mediated by aromatization to oestrogens, as androgens are the essential precursor hormones for estrogen biosynthesis in the ovaries and extra-gonadal tissues (Simpson 2000). Imbalances in androgen biosynthesis or metabolism in women may have undesirable effects on any or all of the above 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 1998). Recognised causes of low testosterone production include hypopituitism, adrenal insufficiency, premature ovarian failure, bilateral oophorectomy, oral glucocorticosteroid therapy

and oral oestrogen therapy (Bachmann 2002; Burger 1987; Davis 1996)

EFFECTS OF MENOPAUSE ON TESTOSTERONE LEVELS
There is inconclusive evidence regarding alteration in testosterone levels across the menopausal transition. Several cross-sectional and prospective studies have reported that serum total testosterone levels drop during this transition (Bancroft 1996; Burger 1995; Overlie 1999; Rannevik 1995; Rozenburg 1988) but results from a recent prospective study did not support this conclusion (Burger 2000). Testosterone levels are known to vary during the menstrual cycle (Judd 1973; Massafra 1999) with levels peaking in the middle third of the cycle, and remaining moderately elevated through to the mid luteal phase (Massafra 1999). In the late reproductive years there is failure of the midcycle rise in free testosterone, which characterizes the menstrual cycle in young ovulating women (Mushayandebvu 1996). Therefore, in order to establish whether levels do decline during the menopause transition it is necessary to measure testosterone in premenopausal women at times other than during the early follicular phase nadir. Furthermore, testosterone levels should be measured in the morning due to its diurnal variation (Vierhapper 1997). Sex hormone binding globulin (SHBG) is a pivotal determinant of the bioavailability of sex steroids, and variations in the plasma levels of SHBG impact significantly on the amount of free testosterone and other bound sex steroids (Dunn 1981). Free testosterone may be an important indicator of tissue androgen exposure and variations in SHBG levels in women can have dramatic effects on free testosterone levels (Bachmann 2002; Baird 1969; Vermeulen 1972). Direct testosterone immunoassays are limited by 'noise' from assay interference and by cross-reactivity with other steroids, which becomes worse at low testosterone concentrations (Klee 2000). The gold standard methodology for measurement of free testosterone is considered to be equilibrium dialysis. Measurement of free testosterone by analogue assays is notoriously unreliable, particularly at the lower end of the normal female range and is not recommended for use (Klee 2000). Of note, the two prospective studies that reported a decrease in testosterone across the menopausal transition did not specify the particular day of the menstrual cycle that blood samples were taken (Overlie 1999; Rannevik 1995). Burger et al used an insensitive assay method to measure total testosterone levels during day four to day eight of the menstrual cycle when levels are known to be low and compared levels in pre- and postmenopausal women (Burger 2000). Thus the effect of menopause on testosterone levels remains unclear.

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 wellbeing (Bachmann 2002; Davis 2000a). However, there are no substantial data to support this hypothesis and no 'cut-off' level for any circulating androgen has been demonstrated to be diagnostic of female androgen insufficiency. The concept of female androgen insufficiency is primarily supported by results from therapeutic trials. However, demonstration of clinical efficacy of testosterone therapy is only surrogate evidence for a female androgen insufficiency syndrome, which still remains to be appropriately researched.

TESTOSTERONE THERAPY FOR POSTMENOPAUSAL WOMEN
Results from many randomized controlled trials suggest that testosterone 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 androgen therapy include acne, excess facial and body hair, deepening of the voice, weight gain, emotional changes, and adverse effects on lipid profiles (Bachmann 2002). Lowered HDL cholesterol, increased blood hematocrit, and abnormal liver function tests have been reported with higher-dose 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). From a study that involved 572,794 women who were exposed to oral esterified estrogen plus methyltestosterone the incidence of toxic hepatitis was 3 per 100,000 person-years (Ettinger 1998). The long-term effects of testosterone on breast and other cancers, cardiovascular disease and stroke are unknown. As androgens are converted to estrogens in vivo, estrogenic side effects are also potential consequences of androgen therapy, such as effects on the breast and endometrium. However, these risks have not been formally evaluated.

While there is still controversy about female androgen insufficiency (FAI), the treatment of postmenopausal women with a variety of androgen formulations is becoming increasingly popular (Davis 2000a). This systematic review is, therefore, intended to ascertain the benefits and risks of adding testosterone to hormone therapy in peri- and postmenopausal women.

## OBJECTIVES

To determine the benefits and risks of testosterone therapy for peri- and postmenopausal women taking HT, as follows.
1. Benefits:
1.1. sense of wellbeing;
1.2. improvement of unexplained fatigue;
1.3. sexual functioning;
1.4. menopausal symptoms;
1.5. cognition;
1.6. body composition;
1.7. bone health.

2. Risks:

2.1. hirsutism;
2.2. acne;
2.3. mood alteration;
2.4. breast cancer;
2.5. coronary heart disease;
2.6. change in blood hematocrit;
2.7. adverse effects on blood lipid profile;
2.8. blood coagulation profile;
2.9. discontinuation rate.

HT was defined as unopposed estrogen therapy or estrogen therapy with combined cyclic- or continuous-progestin therapy. We aimed to test the following null hypotheses.
1) Testosterone plus HT does not improve sexual functioning, mood, bone health, body composition, cognition or menopausal symptoms more than what is achieved by HT alone.
2) Testosterone plus HT is not more likely than HT alone to adversely affect the lipid profile, coagulation profile, other markers of cardiovascular disease risk, hirsutism, acne or breast cancer.
In testing the above hypotheses we examined the effects of testosterone plus HT compared with HT alone.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

Only randomized controlled trials were considered for inclusion in the review.

### Types of participants

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

Diagnostic criteria were as follows.
1) A naturally menopausal woman was defined as:
1.1. a woman with an intact uterus who had had spontaneous amenorrhea for at least 12 months, and/or a low serum estradiol level, and/or an elevated serum level of follicle stimulating hormone (FSH) that was in the postmenopausal range;
1.2. a woman who has had a hysterectomy and who had one or both ovaries conserved at hysterectomy and a low serum estradiol level and/or (similar to 1.1) an elevated serum level of FSH that was in the postmenopausal range.

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 an elevated serum level of FSH that was in the postmenopausal range, and a final menstrual period that was less than 12 months prior to participating in the study.

We included all studies irrespective of prerequisite symptoms and signs for participants before randomization.

### Types of intervention

Testosterone plus hormone therapy (HT), in all forms of administration, versus HT alone in peri- or postmenopausal women. Studies that combined those interventions with other complementary therapies such as vitamin or mineral supplements, diet, or exercise were considered for inclusion. The minimum acceptable period of treatment was four weeks.

### Types of outcome measures

The following outcomes were recorded, if the information was available.
1. Primary outcomes
1.1 Sense of wellbeing - as measured and scored by validated questionnaires, for example the psychological general wellbeing index (PGWB)
1.2 Unexplained fatigue - as measured and scored by validated questionnaires
1.3 Sexual function - measured and scored in all aspects, including libido, activity, satisfaction, pleasure, fantasy and orgasm, by validated questionnaires

2. Secondary outcomes
2.1. Benefits:
2.1.1. bone health:
2.1.1.1. incidence of osteoporotic fractures,
2.1.1.2. biochemical markers,
2.1.1.3. bone mineral density;
2.1.2. body composition - measured in various aspects including body weight, skinfold thickness, hip and waist circumferences, subcutaneous fat, body mass index, muscle strength, and lean body mass;
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. hirsutism - 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. hematocrit;
2.2.8. lipid profile - measured as total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides;

2.2.9. coagulation parameters.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Menstrual Disorders and Subfertility Group methods used in reviews.

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

1) The Menstrual Disorders and Subfertility Group Trials Register was searched for any controlled trials by using a combination of search terms (menopause, postmenopause, testosterone, androgens, and estrogen) in the title, abstract or keywords sections. See the Review Group module on The Cochrane Library for more details about the specialized register.

2) The Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library Issue 2, 2003 was searched in all fields using the following words: postmenopause, androgens, testosterone, and estrogen.

3) The following electronic databases were searched using Ovid software:
MEDLINE (1966 to 1st November 2003);
EMBASE (1980 to 1st November 2003);
Bio Abstracts (1980 to 1st November 2003);
CINAHL (1982 to 1st November 2003);
PsycINFO (1974 to 1st November 2003).

The MEDLINE, Bio Abstracts, CINAHL, and PsycINFO databases were searched using the following subject headings and keywords.
1. randomised controlled trial.pt
2. controlled clinical trial.pt
3. randomised controlled trials/
4. random allocation/
5. double-blind method/
6. single-blind method
7. or/1-6
8. clinical trial.pt
9. exp clinical trials/
10. (clin$ adj25 trial$).tw.
11. ((singl$ or double$ or treb$ or tripl$) adj25 (blind$ or mask$)).tw.
12. placebos/
13. placebo$.tw.
14. random$.tw.
15. research design/
16. or/8-15
17. animal/ not (human/and animal)
18. 7 or 16
19. 18 not 17
20. testosterone.tw.
21. androgen?.tw.
22. menopaus$.tw.
23. post?menopaus$.tw.
24. estrogen$.tw.
25. oestrogen$.tw.
26. estradiol.tw.
27. oestradiol.tw.
28. or/20-21
29. or/22-23
30. or/24-27
31. 28 and 29
32. 30 and 31
33. 19 and 32

The EMBASE database was searched using the following subject headings and keywords.

1. Controlled study or Randomised Controlled Trial
2. Double Blind Procedure
3. Single blind Procedure
4. Crossover Procedure
5. Drug Comparison
6. Placebo
7. Random*
8. latin square*
9. crossover
10. cross-over
11. placebo*
12. (doubl* or singl* or trip* or trebl*) and (blind* or mask*)
13. (comparative*) and (trial*)
14. (clinical) and (trial*)
15. animal not (human and animal)
16. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
17. #16 not #15
18. testosterone
19. androgen?
20. menopaus*
21. post?menopaus*
22. estrogen*
23. oestrogen*
24. estradiol
25. oestradiol
26. #18 or #19
27. #20 or #21
28. #22 or #23 or #24 or #25
29. #26 and #27
30. #28 and #29
31. #17 and #30

4) 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: post menopause, androgen, testosterone, estrogen. 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 that are collected by the NHS Centre for Reviews and Dissemination.

5) Additional unpublished trials were identified from citation lists of relevant articles, communication with the corresponding authors of relevant articles, experts, and pharmaceutical companies.

## METHODS OF THE REVIEW

1) STUDY SELECTION
SOne of the reviewers (WS) selected trials for consideration after employing the search strategy described above. WS obtained copies of the full text articles and made copies for RB in which details of the authors and institutions had been struck out and the results section removed. Each study identified by the search strategy was independently assessed against the inclusion criteria by the two reviewers (RB and WS). If it was necessary, additional information was sought from the principal investigators of the study, by SD. If there was any study that did not contain enough detail to be examined, that study was listed in the awaiting assessment section.

2) ASSESSMENT OF METHODOLOGICAL QUALITY
Included trials were independently assessed by two of the reviewers (RB and WS) for quality criteria and methodological details. We used the standard checklist developed by the Menstrual Disorders and Subfertility Group. Any disagreement in eligibility or quality assessment was discussed in detail; and if it was not due to oversight or misinterpretation, MWS was to provide a third opinion. Assessment of agreement was done during the pilot phase. Major quality criteria were established to enable future sensitivity analyses.

*Trial Characteristics*
Assessment of methodological quality
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 analysis
B. No intention-to-treat analysis
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 less than 10% of the study population?
A. Losses and/or withdrawals of less than 10%
B. Losses and/or withdrawals of 10% or more
C. Not reported or unclear
1.9. Method of randomization
A. Truly randomized: centralised randomization scheme or on-site computer system with concealment of allocation or sequentially numbered, sealed opaque envelopes
B. Pseudo randomized: alternating record numbers or dates of birth, or an open list of random numbers or open envelopes/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 provided RB with the results sections of the included studies and both reviewers independently extracted information using the pro forma designed by the Review Group. Discrepancies were resolved by discussion, with a third reviewer (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 the outcome of interest), e.g. baseline sexual function score, wellbeing 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. type of therapies used
2. mode of administration
3. doses administered
4. duration of treatment

Outcomes relevant to this review;
-benefits: sense of wellbeing, improvement of unexplained fatigue, sexual functioning, bone health, body composition, cognition, menopausal symptoms
-risks: hirsutism, acne, mood alteration, breast cancer, coronary heart disease, hematocrit, lipid profile, coagulation profile, discontinuation rate

Where possible, missing data were sought from the authors.

4) ANALYSIS
Statistical analysis was performed in accordance with the guidelines for statistical analysis that were 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, if the information was available.

1. Primary outcomes
1.1. Sense of wellbeing - percentage of women who improved or did not improve, mean or median of per cent change
1.2. Unexplained fatigue - percentage of women who improved or did not improve, mean or median of per cent change
1.3. Sexual function - 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 fractures - the number of osteoporotic fractures per year in each treatment group,
2.1.1.2. biochemical markers - 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 - 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 (femur, lumbar spine, wrist);
2.1.2. body composition - percentage of women for whom there was an increase, no change, or decrease; mean or median of per cent change in each value;
2.1.3. cognition - percentage of women who improved or did not improve, mean or median of per cent change;
2.1.4. menopausal symptoms - percentage of women who improved or did not improve, mean or median of per cent change.

2.2. Adverse events:
2.2.1. hirsutism - percentage of women who did, or did not, have a change in score or reported this side effect;
2.2.2. acne - percentage of women who had or did not have this 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. mammographic findings - percentage of women with decreased, stable, or increased mammographic density,
2.2.4.2. incidence of breast cancer - percentage of women who did or did not develop breast cancer;
2.2.5. coronary heart disease - the number of events per year;
2.2.6. discontinuation rate - percentage of women who discontinued treatment;

2.2.7. hematocrit - percentage of women for whom there was an increase, no change, or decrease, mean or median of per cent 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 per cent change.
The criteria for improvement in the particular outcomes were defined by trialists.

For dichotomous data, results for each study were expressed as an odds ratio with 95% confidence intervals (95% CI). They were 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% confidence intervals (95% CI) and combined for meta-analysis. 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 with non-parametric tests of significance, the results were also reported in the other data section of the review. 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 homogeneity resulted in a P value of 0.05 or less), the random-effects model was performed and reasons for the heterogeneity were explored and discussed.

Where there was statistical heterogeneity trials were not pooled and sources for the heterogeneity were considered and commented on

Despite the lack of statistical heterogeneity differences in clinical parameters were considerable (clinical heterogeneity). These differences were taken into account when analyzing 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. The analyses 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 or postmenopause; oral or non-oral HT; methyltestosterone or testosterone; trial duration of less than three months, three to less than 12 months. or 12 months or more; placebo-controlled trials versus 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.

## DESCRIPTION OF STUDIES

1. Study inclusion
Sixty-four 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. Twenty-four articles were excluded, and thirty-four were included. Among the 34 included references there were 23 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. The results were included from of different articles of the same trials only if the different articles were reporting different outcomes.

Of the twenty-four excluded articles the reasons for exclusion were: non-randomization (nine studies), no HT group serving as a control group (eight studies), ineligible outcomes (five studies), ineligible intervention (one study), and ineligible participants (one study).

2. Participants
There was a total of 1956 participants randomized in the included trials. Five of 23 trials did not report the number of participants who completed the study (Davis 2003; Dow 1983; Garnett 1992; Regestein 2001; Watts 1995). Of the 1682 randomized participants from the remaining 18 trials there were 1314 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 analyzed for each outcome.

2.1 Setting
Nineteen trials were hospital-based studies or clinic-based studies. In five trials recruitment was from the general community (Floter 2002; Regestein 2001; Shepanek 1999; Davis 2003; Braunstein 2003).

2.2 Location
The trials were located in seven countries, specifically United States of America (13 trials) (Barrett-Connor 1999; Braunstein 2003; Dobs 2002; Hickok 1993; Lobo 2003; Miller 2000; Raisz 1996; Regestein 2001; Sarrel 1998; Shepanek 1999; Shifren 2000; Simon 1999; Watts 1995), United Kingdom (four trials) (Dow 1983; Farish 1984; Garnett 1992; Montgomery 1987), Australia (two trials) (Burger 1987; Davis 1995), Italy (one trial) (Penotti 2001), Canada (one trial)(Sherwin 1988), and Sweden (one trial)(Floter 2002). Only one trial was a multinational study (Davis 2003).

2.3 Ethnicity

There were eight trials that specified ethnicity (Barrett-Connor 1999; Dobs 2002; Hickok 1993; Lobo 2003; Sarrel 1998; Shepanek 1999; Shifren 2000; Watts 1995). From these trials, the most common ethnicity was Caucasian.

2.4 Disease status

Disease status was classified by considering participant characteristics required 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 the presence of symptoms (Barrett-Connor 1999; Dobs 2002; Floter 2002; Garnett 1992; Hickok 1993; Miller 2000; Penotti 2001; Raisz 1996; Regestein 2001; Shepanek 1999; Sherwin 1988; Simon 1999; Watts 1995). Six 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; Dow 1983; Lobo 2003), and dissatisfaction with HT alone (Sarrel 1998). Three studies included only surgically menopausal women who had impaired sexual function with low serum testosterone levels (Braunstein 2003; Davis 2003; Shifren 2000).

2.5 Type of menopause

The majority of trials included both surgically and naturally menopausal women. Nine trials included only surgically menopausal women (Barrett-Connor 1999; Braunstein 2003; Davis 2003; Farish 1984; Floter 2002; Shepanek 1999; Sherwin 1988; Shifren 2000; Watts 1995), and two trials were conducted in naturally menopausal women only (Penotti 2001; Simon 1999). 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 randomized clinical trials. The majority of trials were double-blind, placebo-controlled studies. There were two open randomized trials(Penotti 2001; Raisz 1996) and three single-blind trials(Burger 1987; Davis 1995; Dow 1983). In one trial blinding was unclear(Garnett 1992).

To ensure double blinding (participants and assessor), one trial used an identical form of medication (Miller 2000), four trials used placebo therapy (Braunstein 2003; Davis 2003; Sherwin 1988; Shifren 2000), six trials used double-dummy placebo tablets (Floter 2002; Hickok 1993; Lobo 2003; Regestein 2001; Sarrel 1998; Watts 1995), and two used an independent doctor, who did not assess outcomes, to provide medication (Farish 1984; Montgomery 1987). Four trials did not report the blinding method (Barrett-Connor 1999; Dobs 2002; Shepanek 1999; Simon 1999).

3.2 Crossover studies

Four trials were crossover studies (Floter 2002; Regestein 2001; Sherwin 1988; Shifren 2000). The principal problem with this kind of study is a carry-over effect after the treatment has been changed. Therefore, a period between treatments, known as a washout period, is needed as a means of minimising a carry-over effect. In addition, the statistical techniques used to demonstrate carry-over may not be satisfactory. Thus only a cross-over study that had a washout period was considered as an appropriate trial for this review. Accordingly, the trial conducted by Sherwin et al was recognized as a suitable crossover study (Sherwin 1988). Because of the possibility of a carry-over effect in the remaining studies, it was decided that only the first half of the study would be considered for inclusion. However, after contacting the corresponding authors of these studies it was established that the data from the first treatment periods were no longer available.

3.3 Centers

There were 11 single-center trials (Dobs 2002; Davis 1995; Dow 1983; Floter 2002; Hickok 1993; Miller 2000; Montgomery 1987; Penotti 2001; Regestein 2001; Sarrel 1998; Sherwin 1988), and the remaining trials were multicenter (more than 2) studies.

3.4 Source of funding

There were nine trials that were sponsored by pharmaceutical companies(Barrett-Connor 1999; Braunstein 2003; Davis 1995; Davis 2003; Regestein 2001; Sarrel 1998; Shepanek 1999; Shifren 2000; Watts 1995), seven trials partly funded by pharmaceutical companies(Dobs 2002; Burger 1987; Floter 2002; Garnett 1992; Hickok 1993; Miller 2000; Raisz 1996), and seven trials did not state their funding source(Dow 1983; Farish 1984; Lobo 2003; Montgomery 1987; Penotti 2001; Sherwin 1988; Simon 1999).

3.5 Duration of study

There were two trials with a study duration of less than three months (Raisz 1996; Sarrel 1998), 16 trials lasting from three to less than 12 months (Dobs 2002; Braunstein 2003; Burger 1987; Davis 2003; Dow 1983; Farish 1984; Floter 2002; Hickok 1993; Lobo 2003; Montgomery 1987; Penotti 2001; Regestein 2001; Shepanek 1999; Sherwin 1988; Shifren 2000; Simon 1999), and five studies of 12-months duration or more (Barrett-Connor 1999; Davis 1995; Garnett 1992; Miller 2000; Watts 1995).

4. Intervention

4.1 Route of administration

4.1.1 Hormone therapy - 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; Garnett 1992; Montgomery 1987), transdermal therapy (Davis 2003; Penotti 2001; Shifren 2000), and intramuscular injection (Sherwin 1988).

4.1.2 Testosterone-testosterone was most commonly administered orally. Non-oral administration included implants (Burger 1987; Davis 1995; Dow 1983; Farish 1984; Garnett 1992; Montgomery 1987), transdermal patches (Braunstein 2003; Davis 2003; Shifren 2000), sublingual tablets (Miller 2000), and intramuscular injection (Sherwin 1988). For orally administered testosterone, nine trials used methyltestosterone (Barrett-Connor 1999; Dobs 2002; Hickok 1993; Lobo 2003; Raisz 1996; Regestein 2001; Sarrel 1998; Shepanek 1999; Simon 1999; Watts 1995), and the remaining trials used testosterone undecanoate(Floter 2002; Penotti 2001).

4.2 Progestin use

In women with an intact uterus, seven 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) while seven trials used a progestin to oppose the estrogenic effects on the endometrium (Burger 1987; Davis 1995; Dow 1983; Garnett 1992; Miller 2000; Montgomery 1987; Penotti 2001).

4.3 Dosages of testosterone

4.3.1 Methyltestosterone-There were two dosages of methyltestosterone used in the included studies (1.25 and 2.5 mg). The lower (1.25 mg) dose was commonly used together with 0.625 mg of esterified estrogen or an equivalent dose of estrogen (Barrett-Connor 1999; Hickok 1993; Lobo 2003; Regestein 2001; Shepanek 1999; Simon 1999). The higher (2.5 mg) dose was used with 1.25 mg of esterified estrogen or an equivalent dose of estrogen (Barrett-Connor 1999; Dobs 2002; Raisz 1996; Sarrel 1998; Simon 1999; Watts 1995).

4.3.2 Non-methyl testosterone - 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

TThis review included a broad range of outcomes of interest. Data synthesis in each outcome was from descriptive analysis and/or meta-analysis, depending on the availability and appropriateness of data. For construct outcomes, only the available data that were measured by validated questionnaires were included for data synthesis and considered for meta-analysis. The construct outcomes were sense of wellbeing, unexplained fatigue, sexual function, mood, menopausal symptoms, hirsutism and acne. The available non-skewed data from parallel studies or crossover studies with a washout period were included for meta-analysis. Information about data that were not included in the meta-analysis was presented in '"the additional table of trial outcomes not included in the meta-analysis'.

5.1 Primary outcomes

5.1.1. Sense of wellbeing- There were eight trials that reported data pertaining to this outcome(Barrett-Connor 1999; Dobs 2002; Floter 2002; Montgomery 1987; Montgomery 1987; Penotti 2001; Regestein 2001; Sherwin 1988; Shifren 2000). Two of these did not provide comparative results (Dobs 2002; Penotti 2001). Therefore, only six trials were considered for data synthesis. All data were unsuitable for meta-analysis.

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

5.1.3. Sexual function - Sixteen trials reported the effects of testosterone on sexual function (Barrett-Connor 1999; Braunstein 2003; Burger 1987; Davis 1995; Davis 2003; Dobs 2002; Dow 1983; Floter 2002; Lobo 2003; Miller 2000; Penotti 2001; Regestein 2001;Sarrel 1998; Shepanek 1999; Sherwin 1988; Shifren 2000). One study did not report any data for this outcome that were suitable for descriptive data synthesis (Regestein 2001). Only three trials provided suitable data for meta-analysis (Davis 1995; Lobo 2003; Sarrel 1998). One of them was a single-blind study (Davis 1995), which provided data for all domains of sexual function except composite score. Only the study of Davis 1995 provided data for the domains of satisfaction, pleasure, orgasm, and fantasy. For the domain of sexual activity, responsiveness, and libido (or desire), there were between two and three studies included for each of the meta-analyses.

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. biochemical markers - there were two trials that reported this outcome (Miller 2000; Raisz 1996), and they were included for data synthesis. Only one trial had eligible data for meta-analysis (Miller 2000).

5.2.1.1.3. bone mineral density - five trials described this result (Barrett-Connor 1999; Davis 1995; Garnett 1992; Miller 2000; Watts 1995). There were three double-blind studies (Barrett-Connor 1999; Miller 2000; Watts 1995), one quasi-randomized study (Garnett 1992), and one single-blind study (Davis 1995). Only two trials provided appropriate data for meta-analysis (Davis 1995; Miller 2000). The remaining were included for descriptive data synthesis.

5.2.1.2. body composition - only two studies provided data pertaining to this outcome and the body weight gain data from these studies were suitable for meta-analysis (Davis 1995; Dobs 2002). Only one single-blind trial provided data for other aspects of body composition that were eligible for meta-analysis (Davis 1995). These parameters were total body fat mass, total body fat free mass (FFM), fat mass (FM) to FFM ratio, FM over abdomen, FFM over abdomen, FM to FFM over abdomen, waist circumference, hip circumference, and body mass index.

5.2.1.3. cognition - of the four randomized trials (Dobs 2002; Regestein 2001; Shepanek 1999; Sherwin 1988) that reported effects of testosterone on cognition, only one was eligible for meta-analysis (Dobs 2002). The remaining trials were considered for descriptive data synthesis.

5.2.1.4. menopausal symptoms - this outcome was reported on in 10 trials (Barrett-Connor 1999; Dow 1983; Hickok 1993; Miller 2000; Raisz 1996; Regestein 2001; Sarrel 1998; Sherwin 1988; Simon 1999; Watts 1995) but no trial provided data for meta-analysis. Therefore, only descriptive data synthesis was performed.

5.2.2. Adverse events
5.2.2.1. hirsutism - only the results of trials that used a standard method of assessment were included for data synthesis. Accordingly there were five eligible trials (Barrett-Connor 1999; Braunstein 2003; Floter 2002; Lobo 2003; Shifren 2000). However, only one trial provided suitable results for meta-analysis (Lobo 2003).

5.2.2.2. acne - only the results of trials that used a standard method of assessment were included for data synthesis. Accordingly there were five eligible trials (Barrett-Connor 1999; Braunstein 2003; Floter 2002; Lobo 2003; Shifren 2000). However only one trial provided suitable results for meta-analysis (Lobo 2003).

5.2.2.3. mood alteration, specifically aggression - only one trial reported the effects of testosterone on aggression, and the data were not appropriate for meta-analysis (Sherwin 1988). Therefore only descriptive data synthesis was performed.

5.2.2.4. Breast cancer
5.2.2.4.1. mammographic findings-No trial reported this outcome.

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. discontinuation rate - of 23 included trials, data from eight trials were incomplete (Davis 2003; Dow 1983; Garnett 1992; Miller 2000; Raisz 1996; Regestein 2001; Shepanek 1999; Watts 1995) and therefore sixteen trials were included in the meta-analysis.

5.2.2.7. hematocrit - there were five trials pertaining to this outcome but the data was not suitable for meta-analysis (Barrett-Connor 1999; Floter 2002; Hickok 1993; Shifren 2000; Watts 1995). Only descriptive data synthesis was performed.

5.2.2.8. lipid profile - there were 11 appropriate trials for inclusion in the meta-analysis (Barrett-Connor 1999; Dobs 2002; Davis 1995; Farish 1984; Hickok 1993; Lobo 2003; Penotti 2001; Raisz 1996; Shifren 2000; Watts 1995). Two trials did not provide enough data for the meta-analysis but they were included in the descriptive data synthesis (Dobs 2002; Miller 2000).

5.2.2.9. coagulation profile- Only one trial included this outcome, and it was suitable for meta-analysis (Dobs 2002).

## METHODOLOGICAL QUALITY

1. Randomization and concealment of allocation sequences
Randomization and concealment of allocation sequences were adequate in 12 trials(Barrett-Connor 1999; Dobs 2002; Davis 1995; Farish 1984; Floter 2002; Lobo 2003; Miller 2000; Penotti 2001; Regestein 2001; Sarrel 1998; Sherwin 1988; Shifren 2000) while in seven trials these were unclear (Braunstein 2003; Davis 2003; Dow 1983; Montgomery 1987; Raisz 1996; Shepanek 1999; Simon 1999). In two trials randomization was adequate but concealment was unclear(Burger 1987; Hickok 1993). In one study concealment was adequate but randomization was unclear(Watts 1995) while in another study randomization was inadequate and concealment was unclear(Garnett 1992).

2. Baseline equality
TOf the included parallel studies for which this is applicable, six publications did not comment on baseline equality (Burger 1987; Davis 2003; Dow 1983; Farish 1984; Sarrel 1998; Simon 1999). Six 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; Braunstein 2003; Garnett 1992; two publications of Miller 2000; Watts 1995). Baseline equality in terms for age, menopausal status, and baseline values of the outcomes were reported in six publications (a publication of Dobs 2002; Hickok 1993; Lobo 2003; Miller 2000; Penotti 2001; Shepanek 1999). However, baseline inequality was documented in three trials for sexual function score (Dobs 2002), menopausal symptom scores (Raisz 1996), and age (Davis 1995; Raisz 1996).

3. Non-compliers and intention-to-treat analysis
Two studies reported no withdrawals (Farish 1984; Hickok 1993), and four reported a discontinuation rate of less than 10 percent (Davis 1995; Dobs 2002; Sarrel 1998; Simon 1999). The majority of trials reported a non-compliance rate of at least 10% (Barrett-Connor 1999; Braunstein 2003; Burger 1987; Floter 2002; Lobo 2003; Miller 2000; Montgomery 1987; Penotti 2001; Regestein 2001; Shepanek 1999; Sherwin 1988; Shifren 2000). The remaining studies did not report on discontinuation.

Three trials stated that analyses were performed on an intention-to-treat basis (Barrett-Connor 1999; Lobo 2003; Shifren 2000) but only one trial clearly described the method of intention-to-treat analysis. In this study both "visit-wise" (observed cases) and last-observation-carried-forward data were used for the intention-to-treat analysis (Lobo 2003). However, the number of participants analyzed (216) was still less than the number of participants randomized (218). For the other two trials the number of participants at analysis was obviously less than that at randomization (Barrett-Connor 1999; Shifren 2000). There are two criteria for an intention-to-treat analysis. Firstly trial participants should be analyzed in the groups to which they were randomized 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 was 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 wellbeing - of the relevant trials, one study used a self-rating scale (Penotti 2001); six used validated the questionnaires (Dobs 2002; Floter 2002; Montgomery 1987; Regestein 2001; Sherwin 1988; Shifren 2000), and one did not describe questionnaire used (Barrett-Connor 1999). The names of the validated questionnaires were: the Quality of Life at Menopause Scale (QUALMS), 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 2002; Sherwin 1988; Shifren 2000). As stated previously, this outcome was most commonly presented in the analysis of sense of wellbeing. Names of the validated questionnaires were the Psychological General Well Being Index (PGWB), and the Daily Menopausal Rating Scale (DMRS).

4.3 Sexual function - of 16 trials four studies used self-rating scales(Burger 1987; Miller 2000; Penotti 2001; Regestein 2001) and 10 studies used validated questionnaires(Braunstein 2003; Davis 1995; Davis 2003; Dobs 2002; Floter 2002; Lobo 2003; Sarrel 1998; Shepanek 1999; Sherwin 1988; Shifren 2000). 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), Sabbatsberg Revised Sexual Self-Rating Scale (SRS), Sexual Interest Questionnaire (SIQ), Sexual Activity Log (SAL), 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 trial (Sherwin 1988).

4.5 Cognition - all four studies used validated questionnaires (Dobs 2002; Regestein 2001; Shepanek 1999; Sherwin 1988).

4.6 Menopausal symptoms - four trials used validated questionnaires(Dow 1983; Montgomery 1987; Regestein 2001; Sherwin 1988). Four 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 used included the Greene scale and the Menopause Specific Quality of Life Questionnaire.

4.7 Hirsutism -two trials used standard scales for hirsutism evaluation (Lobo 2003; Shifren 2000); one trial used a modified scale(Barrett-Connor 1999), and two trials did not state the scale used (Braunstein 2003; Floter 2002).

4.8 Acne - two trials used original scales for acne evaluation (Lobo 2003; Shifren 2000); one trial used a modified scale(Barrett-Connor 1999), and two trials did not state the scale used (Braunstein 2003; Floter 2002).

## RESULTS

### Outcomes

1. Primary outcomes
1.1. Sense of wellbeing
1.1.1. Meta-analysis (comparison 1): no appropriate data available
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 wellbeing with the addition of 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 2002). These two trials measured sense of wellbeing using the Psychological General Well Being Index. For other trials that used different questionnaires, one crossover study reported no effect on anxiety with the addition of a testosterone by injection (Sherwin 1988); and two parallel trials (Montgomery 1987; Regestein 2001) reported no evidence of a significant difference for sense of wellbeing.

1.2. Unexplained fatigue
1.2.1. Meta-analysis (comparison 2): no appropriate data available
1.2.2. Descriptive data synthesis: data was available from three crossover studies in surgically menopausal women (Floter 2002; Sherwin 1988; Shifren 2000). One crossover study (with a washout period) found that women treated with estrogen alone reported significantly lower ratings of energy levels than those who received either of the androgen-containing preparations ( P value < 0.01) (Sherwin 1988). Two other studies (with no washout periods) found no significant difference between the treatments in term of vitality (Floter 2002; Shifren 2000). It is possible that lack of a washout period in these studies contributed to underestimation of a treatment effect.

1.3. Sexual function
1.3.1. Meta-analysis (comparison 3): there was an improved outcome, measured as a higher score, with testosterone for a number of domains of sexual function; in one of the domains, the parameters sexual activity and coital frequency were considered together.

The improvement as a standardized mean difference (SMD) was 0.45 (95% CI 0.19 to 0.71) for responsiveness, 1.01 (95% CI 0.42 to 1.60) for combined sexual activity and coital frequency, 0.42 (95% CI 0.18 to 0.66) for libido, and 0.41 (95% CI 0.15 to 0.67) for the composite sexual function score. One study provided data showing that use of testosterone was associated with an improved outcome (SMD 0.98 (95% CI 0.24 to 1.72) for satisfaction, 1.41 (95% CI 0.63 to 2.20) for pleasure, 1.01 (95% CI 0.27 to 1.75) for orgasm, and 1.37 (95% CI 0.59 to 2.15) for fantasy).

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

1.3.2. Descriptive data synthesis: of twelve available studies there were seven trials that used validated questionnaires for sexual function assessment. All of these trials reported positive effects of testosterone on sexual functioning (Braunstein 2003; Davis 2003; Dobs 2002; Floter 2002; 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 use progestin as a co-intervention during the study period. However, beneficial effects of testosterone on sexual function were reported when progestin was added to oppose the estrogenic effects on the endometrium (Burger 1987; Davis 1995).

2. Secondary outcomes

2.1. Benefits

2.1.1. Bone health - with regard to bone health, the ultimate outcome was 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 4-6): meta-analyses using either mean endpoint or change values, from two trials, showed no significant difference between treatment groups for lumbar BMD after 12 and 24 months of treatment. There were inconsistent results for femoral BMD between analyses using mean endpoint and change values at the 12-month treatment period: using the mean endpoint the WMD was -0.05 g/cm2 (95% CI -0.09 to -0.01); while for change in value the WMD 1.40 g/cm2 (95% CI 0.14 to 2.66). This inconsistency may be due to baseline BMD values. In a study conducted by Davisl, baseline femoral BMDs were 0.70 g/cm2 (standard deviation (SD) 0.13) in the estrogen plus testosterone group and 0.82 g/cm2 (SD 0.10) in the estrogen-only group (Davis 1995). In a study conducted by Miller, the baseline femoral BMDs were 0.87 g/cm2 (SD 0.11) and 0.92 g/cm2 (SD 0.09) in the T-HT group and the HT-alone group, respectively. The estrogen plus testosterone group had noticeably lower BMD values at baseline in both studies even though in the Miller study the difference in baseline values was not statistically significant. Both studies were conducted in naturally and surgically menopausal women and allowed progestin co-administration.

2.1.1.2. Descriptive data synthesis: three studies showed inconsistent results. Two studies showed that there was no significant difference between treatment groups for BMD of either the lumbar spine or femur (Garnett 1992; 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 when compared to the HT group (Barrett-Connor 1999).

The two types of biochemical markers of bone turnover are bone formation and bone resorption markers. Two eligible studies included in the descriptive data synthesis reported no significant effect on bone resorption markers by adding testosterone to an HT regimen. One open randomized study (Raisz 1996) reported a significant increase in all bone formation markers after estrogen plus testosterone therapy when compared to estrogen therapy. In contrast there was no between-group difference in percent change observed in serum bone-specific alkaline phosphatase in a double-blind study (Miller 2000).

2.1.2. Body composition

2.1.2.1. Meta-analysis (comparison 7): body weight gain had a tendency to be greater in the T-HT group than in the HT alone group; however, it did not achieve statistical significance (WMD 1.15 kg, 95% CI -0.24 to 2.54). For other parameters, data were derived from only one study in each case. Using mean or mean change in each value, results did not achieve a significant difference.

2.1.2.2. Descriptive data synthesis: results of other parameters of body composition measured in another study (Dobs 2002) were not included in the meta-analysis because standard deviations were unclear. This study reported that T-HT treatment, when compared with HT alone, significantly increased lean body mass in the arms, legs, and trunk. When changes in arms, legs, and trunk in each patient were analyzed together, the difference between treatments was significant for lean body mass (P value < 0.05) and percentage of fat tissue (P value < 0.05), but not for fat tissue (P value < 0.05).

2.1.3. Cognition

2.1.3.1. Meta-analysis (comparison 8): only data using identical pictures and shape memory in one trial were eligible for quantitative analysis; the results showed no statistically significant difference between treatments (difference in means -0.42 (95% CI -1.20 to 0.36) and 0.03 (95% CI -0.74 to 0.80) for identical pictures and shape memory, respectively) (Dobs 2002).

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 estrogen and methyl testosterone maintained a steady level of performance on the Building Memory task, whereas those receiving estrogen 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 estrogen plus testosterone group than in the estrogen 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 estrogen therapy on tasks involving spatial transformation or orientation, mathematics, or nonverbal reasoning (Shepanek 1999). Another crossover study did not report an effect on cognitive function of estrogen alone versus estrogen plus testosterone Sherwin 1988). No studies involved coadministered progestin during the study period.

2.1.4. Menopausal symptoms-
2.1.4.1. Meta-analysis (comparison 9): no appropriate data available
2.1.4.2. Descriptive data synthesis: menopausal symptoms were measured by validated questionnaires in three trials (Dow 1983; Regestein 2001; Sherwin 1988). Dow measured menopausal symptoms with 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 no mean overall outcome change score between treatments (Regestein 2001). Sherwin measured the symptoms by menopausal index and reported a significantly greater improvement in somatic and psychological symptoms in the combined testosterone-estrogen treated group compared with the estrogen alone group (Sherwin 1988). No comparative effects on hot flushes were provided in another report of the same trial (Sherwin 1984). Descriptive data synthesis from other studies that measured menopausal symptoms by modified scores or scales also found inconsistent results.

2.2. Adverse events
2.2.1. Hirsutism
2.2.1.1. Meta-analysis (comparison 10): one study eligible for meta-analysis (Lobo 2003) showed that the mean hirsutism 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 estrogen (0.625 mg) versus conjugated equine estrogen (0.625 mg) plus methyl-testosterone (1.25 mg)) (Barrett-Connor 1999). In the same study but with the high-dose groups (conjugated equine estrogen (1.25 mg) versus conjugated equine estrogen (1.25 mg) plus methyltestosterone (2.5 mg)) 10 T-HT treated participants and 3 HT treated participants reported hirsutism as an adverse event. Two crossover studies (with no washout period) reported no difference in hirsutism between treatment groups (Floter 2002; Shifren 2000).

2.2.2. Acne
2.2.2.1. Meta-analysis (comparison 11): One study eligible for meta-analysis(Lobo 2003) showed that the mean acne 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 the groups reported in two crossover studies (with no washout period) (Floter 2002; Shifren 2000). In the interim analysis of a two-year study, acne of mild or moderate severity was reported by 5 women (3%) in estrogen plus methyltestosterone treated participants; no participants receiving estrogen alone reported acne (Barrett-Connor 1999).

2.2.3. Mood alteration, specifically aggression
2.2.3.1. Meta-analysis( comparison 12): no appropriate data available
2.2.3.2. Descriptive data synthesis: no significant difference between treatments for hostility (Sherwin 1988).

2.2.4. Breast cancer (comparison 13 and 14): no trial reported an outcome for either mammographic findings or clinical breast cancer.

2.2.5. Coronary heart disease (comparison 15): no trial reported this as an outcome

2.2.6. Discontinuation rate
2.2.6.1. Meta-analysis (comparison 19 and 20): meta-analyses involving 15 trials showed that there was no statistically significant difference in discontinuation between treatments. For both the overall discontinuation rate and the discontinuation rate due to adverse events the Peto odds ratios were 1.01 (95% CI 0.76 to 1.33) and 1.28 (95% CI 0.85 to 1.92), respectively. Sensitivity analyses (comparisons 22 to 35) based on quality of randomization and concealment of allocation sequences, study size (by taking out three large studies with more than 100 participants), blinding, crossover studies, doses of testosterone, and doses of estrogen 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 also did not affect results.

2.2.7. Hematocrit
2.2.7.1. Meta-analysis (comparison 16): no appropriate data available
2.2.7.2. Descriptive data synthesis: two parallel studies involving methyltestosterone reported that there was no clinically significant difference in hematocrit (Barrett-Connor 1999; Watts 1995). Another parallel study also examining methyltestosterone showed that there was a statistically significant difference in hematocrit between the two treatment groups. However, the difference was small and levels remained within the normal range (Hickok 1993). Two crossover studies (with no washout period) where one study used testosterone undecanoate and the other used a testosterone patch revealed no significant change in hematocrit (Floter 2002; Shifren 2000).

2.2.8. Lipid profile
2.2.8.1. Meta-analysis (comparison 17): ffour periods of time - less than 3 months, 3 to 12 months, at 12 months, and at 24 months,

were analyzed for five lipid parameters. These parameters were total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, and the total cholesterol/HDL cholesterol ratio.

2.2.8.1.1. studies of less than 3 months: the direction of the results was different between the two eligible studies for total cholesterol, triglyceride, and LDL cholesterol. Furthermore, there was statistically significant heterogeneity for triglyceride, HDL cholesterol, and LDL cholesterol (P value 0.006, 0.03 and 0.002, respectively). Therefore, these trials were not pooled. Sources of heterogeneity were were possibly clinical diversity and/or methodological diversity. Baseline inequality was documented in the study conducted by Raisz in terms of age and total cholesterol levels (Raisz 1996). 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 value < 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 treatments (Farish 1984). Another possible source of heterogeneity was route of testosterone administration. In one study both hormones were administered orally (Raisz 1996) and by implant in the other (Farish 1984).

In contrast to other parameters, HDL cholesterol was significantly lower after treatment in the T-HT group than in the HT group in both trials. Differences in means were -24.50 mg/dl (95% CI -36.41 to -12.59) (Raisz 1996) and -8.9 mg/dl (95% CI -15.85 to -1.95) (Farish 1984).

2.2.8.1.2. studies at 3 to 12 months: six studies were eligible for this analysis. By using mean scores and/or change in scores, HDL cholesterol was consistently significantly lower in the T-HT group than in the HT group (total WMD -16.02 mg/dl, 95% CI -19.90 to -12.14) while LDL cholesterol was not significantly different between treatment groups. Using change in scores, total cholesterol and triglyceride were significantly lower in the T-HT group than in the HT group whereas there was no difference when using mean scores. When we combined the mean scores and the change in scores the decrease in total cholesterol was greater in the T-HT group than in the HT group (WMD -11.59 mg/dl, 95% CI -20.98 to -2.20). However, triglyceride levels were still not significantly different between treatment groups. Only one study was eligible for quantitative analysis of the total cholesterol to HDL cholesterol ratio and the decrease in the ratio was greater in the T-HT than in the HT group (difference in means 20.60 mg/dl, 95% CI 12.76 to 28.44). Because statistically significant heterogeneity was found by the chi square test, the random-effects model was used to estimate the treatment effects. The forest plot showed that the outlying results were from the studies that used a higher dose of methyltestosterone (Dobs 2002; Watts 1995)

2.2.8.1.3. studies at 12 months: using mean scores there were no differences between treatments in any parameter. 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 decreases in triglyceride and HDL cholesterol were significantly greater in the T-HT group (WMD -45.29 mg/dl (95% CI -80.17 to-10.40); -23.64 mg/dl (95% CI -28.95 to -18.33), respectively).

2.2.8.1.4 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 whereas triglyceride and HDL cholesterol levels were significantly lower in the T-HT group than in the HT group. The total cholesterol to HDL cholesterol ratio was significantly higher in the T-HT group at both 12 and 24 months.

For changes in scores the meta-analyses at both 12 and 24 months were limited to the interventions esterified estrogen (1.25 mg) versus esterified estrogen (1.25 mg) plus methyltestosterone (2.5 mg).

Subgroup analyses were not performed due to the limited number of studies.

2.2.8.2. Descriptive data synthesis: results from a study of esterified estrogen (1.25 mg) versus esterified estrogen (1.25 mg) plus methyltestosterone (2.5 mg) showed that after 16 weeks of treatment significant decreases in levels of total cholesterol, HDL cholesterol, and triglycerides occurred in the estrogen plus testosterone group; LDL cholesterol values were virtually unchanged (Dobs 2002). The estrogen group demonstrated different effects on lipids with a significant decrease in LDL cholesterol levels and no meaningful changes in the other lipid parameters (Dobs 2002). Results from a study of micronized estrogen progesterone) versus micronized estrogen plus micronized testosterone (both groups 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 estrogen-testosterone treated group In contrast, triglyceride levels decreased 9.0% and HDL cholesterol levels increased 9.0% with estrogen therapy.

2.2.9. Coagulation profile

2.2.9.1. Meta-analysis (comparison 18): data derived from one trial showed no significant difference between treatments for plasma viscosity (difference in means 0.05, 95%CI -0.10 to 0.00) or fibrinogen levels (difference in means 0.31, 95%CI -0.13 to 0.75).

2.2.9.2. Descriptive data synthesis: the relevant study was included in the quantitative analysis.

**Sensitivity analysis**

Sensitivity analyses were performed only for the discontinuation rate. This was due to the limited number of trials for each outcome. There was no substantial effect of methodological quality of trials,

excluding very large studies, length of treatment follow up, or doses used on the discontinuation rate.

**Publication bias**

Funnel plots were created to examine any possibility of publication bias. For the discontinuation rate the funnel plot was symmetrical shape around the overall effect indicating the absence of bias. However, visual examination of funnel plots of other outcomes had limited power because the number of studies was small.

## DISCUSSION

**Summary of results**

There were a limited number of studies included in the meta-analyses. This limited the power of the meta-analyses to provide conclusions about efficacy and safety. Based on the results of this review, adding testosterone to an HT regimen has beneficial effects on sexual function for the domains of sexual activity combined with coital frequency, responsiveness, libido (desire) and for composite sexual function score. The standardized mean differences were 1.01 (95% CI 0.42 to 1.60), 0.45 (95%CI 0.19 to 0.71), 0.42 (95% CI 0.18 to 0.66), and 0.41 (95% CI 0.15 to 0.67) respectively. The only clearly documented adverse effect of adding testosterone to estrogen therapy was a reduction in HDL cholesterol that was seen for all the study durations evaluated. However, the magnitude and precision of this effect varied with study duration. The discontinuation from treatment rate was not significantly greater with testosterone therapy (Peto OR 1.01, 95% CI 0.76 to1.33). There was no convincing evidence for testosterone effects on sense of wellbeing, unexplained fatigue, bone health, body composition, menopausal symptoms, cognition, hirsutism, acne, hostility, plasma viscosity, fibrinogen level or haematocrit. However, conclusions are limited by the paucity of studies that have included these outcomes. Evidence on long-term effects with respect to breast cancer and coronary heart disease were lacking.

**Other supporting evidence**

To support the effects of testosterone on sexual function, a dose-response relationship of testosterone and sexual function was reported by Shifren (Shifren 2000). Higher testosterone doses resulted in further increases in scores for thoughts-desire, frequency of sexual activity, and pleasure-orgasm as determined using the Brief Index of Sexual Functioning for women (Shifren 2000). There was no formal statistical analysis for the dose-response relationship provided. In addition, Lobo et al reported a significant association between changes in female sexual interest or desire and responsiveness and bioavailable testosterone (Lobo 2003). However, in this study it was difficult to determine the actual degree of association because the endocrine data from 41 patients (measured in another laboratory) were excluded from the analysis and the correlation coefficient was not reported.

**Quality of the evidence**

TThe methodological strengths of the included studies were that most had adequate randomization and concealment of allocation sequences in order 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 was evident by a significant number of non-compliers and 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 (Davis 1995; 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. Attrition bias, baseline inequality, and detection bias all may have caused inaccurate effect estimations in the meta-analyses; the inequality documented in Raisz's study might be an explanation for the heterogeneity found in the meta-analysis for the lipid outcome with less than three months of treatment. With respect to the crossover studies, included for data synthesis for the outcomes of sense of wellbeing, unexplained fatigue, cognition, hirsutism and acne, lack of a washout period is likely to have resulted in underestimation of treatment effect. This may have led to the inconclusive results. The different types of questionnaires used for outcome measurement of the construct variables may also have contributed to an underestimation of treatment effects.

Nevertheless, descriptive data synthesis of data from other double-blind studies confirmed 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 findings as the direction of the effects is consistent across the relevant studies that were not included in the meta-analyses.

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 consequently identified relevant studies, both published and unpublished, in electronic databases. This was achieved through contact with the corresponding authors of relevant articles, experts, and pharmaceutical companies, and through handsearching of relevant journals. In addition, there was a pre-determined strategy for study selection and quality assessment of included studies that was conducted by two independent assessors. These procedures were used to optimize the validity of the results of this review.

Limitations of this review include the small number of studies suitable for meta-analysis and the inclusion of different intervention regimens in the same analysis. The former contributed to the inconclusive results and limited the power of the meta-analysis to provide conclusions about efficacy and safety. The limitation of grouping interventions is that the effect estimate cannot be interpreted for a single treatment regimen.

Progestin was a co-intervention in seven 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 a study medication from other adverse events since there was inconsistent reporting of the classification of adverse events among studies. We did not review the effects of HT plus testosterone on liver function, endometrial histology or hormonal profiles.

**Applicability of the results**

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 reported with testosterone implants and methyltestosterone.

2) Characteristics of patients: 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 of study, or location of the study. There was no evidence available for perimenopausal 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, and 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 counseling, and medical therapy. Therefore, evidence from this systematic review provides information to be considered within the overall management of female sexual dysfunction.

## AUTHORS' CONCLUSIONS

**Implications for practice**

1) Based on the evidence provided by our review of published and unpublished data, an indication for adding testosterone to HT is to enhance sexual function in postmenopausal women. Expressed as a SMDand compared to HT, adding testosterone to HT improved the mean composite score of sexual function 0.41 units (95% confidence interval 0.15 to 0.67) and the score for sexual activity 1.01 units (95% confidence interval 0.42 to 1.60).
2) The overall reporting of side effects in the studies included in this review was inadequate. Hence testosterone therapy should be used with caution.
3) Close surveillance for changes in HDL cholesterol and other side effects is necessary. A documented adverse event of adding testosterone to hormone therapy is a significant decrease in HDL cholesterol levels. The changes were -15.92 (95% confidence interval -31.13 to -0.71) at less than 3 months of treatment and -17.63 (95% confidence interval -31.45 to -3.8) at 24 months. At the present time, testosterone therapy should be limited to short-term use as long-term studies are not available.

**Implications for research**

1) Study design: double-blind, randomized controlled studies will best estimate treatment effects for further research into the use of testosterone in women. 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, further research should measure outcomes as dichotomous or categorical outcomes such as the number who improve, are not improved, get worse, in addition to a continuous outcome, if possible.
3) Outcome of interest - the following outcomes remain unclear and should be further investigated by appropriate studies:
3.1. benefits of testosterone on wellbeing, unexplained fatigue, bone health (BMD and fracture rate), and cognition;
3.2. adverse effects on hirsutism, acne, deepening of voice, coagulation profile, hematocrit, 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 are available. More studies addressing the use of testosterone with estrogen 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-estrogen-progestin in naturally menopausal women require further study.
6) Target population: effects of testosterone therapy in perimenopausal women need 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.

## POTENTIAL CONFLICT 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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## References to ongoing studies

**Fem T (1)**

A phase III, multinational, randomized, double-blind, parallel-group, placebo-controlled study to evaluate efficacy and safety of transdermal testosterone (300 per day) for 52 weeks and safety for a further 28-week open-label period in women with hypoactive sexual desire disoder on concurrent estrogen replacement therapy who have undergone hysterectomy and bilateral oophorectomy. (Ongoing study).

**Fem T (2)**

A phase III, multinational, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of transdermal testosterone (300 mg/day) for 24-weeks in women with Hypoactive Sexual Desire Disorder on concurrent oral hormone replacement therapy who have undergone hysterectomy and bilateral oophorectomy. (Ongoing study).

**Fem T (3)**

A phase III, multinational, randomized, double-blind, parallel-group, placebo-controlled 52-week study followed by a 52-week open-label extension to transdermal testosterone (300 mg/day) in naturally menopausal women with Hypoactive Sexual Desire Disorder on concurrent oral hormone replacement therapy. (Ongoing study).

**Fem T (4)**

A phase III, multinational, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of transdermal testosterone (300 mg/day) for 24-weeks and safety for a further 28-weeks in naturally menopausal women with Hypoactive Sexual Desire Disorder on concurrent oral hormone replacement therapy. (Ongoing study).

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** Indicates the major publication for the study*

## TABLES

### Characteristics of included studies

| Study | Barrett-Connor 1999 |
|---|---|
| Methods | -Design:double-blind randomised (A), parallel group<br>-No. of centres:Multicentre<br>-Duration:2 years<br>-Power calculation:not stated<br>-Intention-to-treat analysis:no<br>-No. of participants randomised:331; E group 79, E-T group 81, E(high dose) group 78, E-T(high dose) 73<br>-No. of participants completed the study: 199<br>-No. of participants analysed: depended on outcomes, 196 for lipid profile, unclear for other outcomes.<br>-No. of non compliers: 122/311= 39.2%; Reasons were adverse events(45), non-drug event(24), protocol violation(21), lost to follow-up(22)<br>-No. of losses to follow-up:22/311=7.1%<br>-Compliance assessment:not stated<br>-Source of funding:drug company |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| Participants | -Location:US<br>-Setting:hospital-based<br>-Ethnicity:Caucasians<br>-Run-in period: no<br>-Characteristics: healthy surgically menopausal women<br>-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)<br>-Inclusion criteria:<br>1. Caucasian<br>2. Age 21-65 years<br>3. TAH with BSO at least 3 months but not more than 5 years<br>4. Body weight within 75-125% of ideal body weight<br>5. A stable personal relationship for at least 6 months<br>-Exclusion criteria:<br>1. Use of estrogen or hormone therapy in the previous six weeks<br>2. Use of psychotropic drugs in the previous four weeks<br>3. History of pelvic or breast malignancy<br>4. Dependence on alcohol, tobacco or illicit drugs |
| Interventions | -CEE 0.625 mg once a day<br>-CEE 1.25 mg once a day (high dose)<br>-CEE 0.625 mg plus mT 1.25 mg once a day<br>-CEE 1.25 mg plus mT 2.5 mg once a day (high dose)<br>-Route:oral<br>-Co-intervention: all participants received calcium supplement |
| Outcomes | -Relevant outcomes:<br>1. General well being<br>2. Sexual behavior and enjoyment<br>3. BMD of lumbar spines and hip: DEXA<br>4. Menopausal symptoms: scales modified from those developed by Sherwin and Kupperman<br>5. Lipid profile<br>6. Hematocrit<br>-Other outcomes:<br>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.<br>-The author was contacted. The further supplied infomation was not allowed by drug company. |
| Allocation concealment | A – Adequate |

| **Study** | **Braunstein 2003** |
|---|---|
| Methods | -Design:double-blind randomised(C), parallel group<br>-No. of centres:multicenter<br>-Duration:24 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: not stated<br>-No. of participants randomised:447(119 in E group, 107 in E-T150, 110 in E-T300, 111 in E-T450)<br>-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%)<br>-No. of participants analysed: not stated<br>-No. of non compliers: 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%)<br>-No of losses to follow-up: not stated<br>-Compliance assessment: not stated<br>-Source of funding:drug company |
| Participants | -Characteristics: surgically menopausal women with menopausal onset of low sexual desire with low serum T levels<br>-Age:E group 49, E-T150 group 50, E-T300 group 50, E-T450 group 49<br>-Location:US<br>-Setting:population-based<br>-Ethnicity: Caucasian 89%<br>-Run-in period: 8-week pretreatment baseline period<br>-Inclusion criteria:<br>1. 20-70 year-old<br>2. Generally good health<br>3. BMI 18-30 kg/m2<br>4. TAH with BSO at least 1 year<br>5. Stable relationship with partner present more than 50% of the time<br>6. Serum free-T < 3.5 pg/ml at baseline<br>7. Stable estrogen dose > 3 months<br>8. Menopause onset of low sexual desire<br>-Exclusion criteria:<br>1. >15 moderate to severe hot flushes per week<br>2. Recent androgen use<br>3. Hirsutism, virilization, severe acne<br>4. Positive screening for depression or hypothyroidism<br>5. Ongoing medical, psychiatric or relationship disturbance<br>6. Medications known to affect sexual function<br>7. Severe hyperlipidemia/metabolic disorders<br>8. Dyspareunia, physical limitations affecting sexual function |
| Interventions | - once a day -CEE once a day plus T 150 mg twice a week<br>-CEE once a day plus T 300 mg twice a week<br>-CEE plus T 450 mg<br>-Route:oral estrogen, transdermal T patch<br>-Co-intervention: no |
| Outcomes | -Relevant outcomes:<br>1. Sexual function: SAL and PFSF<br>2. Hirsutism<br>3. Acne<br>-Other outcomes:<br>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<br>-Conference proceeding.<br>-The author was contacted. The further supplied infomation was not allowed by the drug company. |
| Allocation concealment | B – Unclear |

**Characteristics of included studies** (*Continued*)

| **Study** | **Burger 1987** |
|---|---|
| Methods | -Design:single-blind randomised(A), parallel group<br>-No. of centres:two<br>-Duration:24 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: not stated<br>-No. of participants randomised:20(10 in each group)<br>-No. of participants completed: 18/20 = 90%<br>-No. of participants analysed: not stated<br>-No. of non compliers:2/10=20%<br>-No. of losses to follow-up:not stated<br>-Compliance assessment: not stated<br>-Source of funding:Drug company provided medication |
| Participants | -Location:Australia<br>-Setting:hospital-based<br>-Ethnicity:unspecified<br>-Run-in period:current treatment with oral estrogens was stopped for a duration of 2 weeks<br>-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<br>-Age(SD):E group 48.2(5.2), E-T group 43.5(7.6)<br>-Inclusion criteria: as above<br>-Exclusion criteria: not stated |
| Interventions | -estradiol 40 mg<br>-estradiol 40 mg plus T 50 mg<br>-Route:implant<br>-Co-intervention: norethisterone 2.5 mg daily for 10 days every month was prescribed for women with intact uterus |
| Outcomes | -Relevant outcomes:<br>1. Libido:self-rating analogue scales(0-100)<br>2. Sexual enjoyment : 0-3 rating scale<br>-Other outcomes:<br>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.<br>-The author was contacted and kindly supplied further information. |
| Allocation concealment | B – Unclear |

**Characteristics of included studies** (*Continued*)

| **Study** | **Davis 1995** |
|---|---|
| Methods | -Design:single-blind randomised(A), parallel group<br>-No. of centres:single<br>-Duration:2 years<br>-Power calculation:not stated<br>-Intention-to-treat analysis: no<br>-No. of participants randomised:34(17 in each group)<br>-No. of participants completed: 32/34 = 94.1%<br>-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).<br>-No. of non compliers: 2/34=5.9%. One woman discontinued for personal reasons early after commencement, and the other discontinued after 12 months because of weight gain.<br>-Compliance assessment:-<br>-Source of funding:not stated |
| Participants | -Location:Australia<br>-Setting:hospital-based<br>-Ethnicity:unspecified<br>-Characteristics: surgically and naturally menopausal women with indication for implants<br>-Age(SD):E group 51.3(5.7), E-T group 57.0(5.2)<br>-Inclusion criteria:<br>1. Postmenopausal women who had been on oral estrogen therapy at least 6 weeks and had an indication for an implant<br>-Exclusion criteria:<br>1. Serious endocrine disorders with systemic disease<br>2. Use of drugs which affect response to treatment<br>3. History of alcohol or drug abuse<br>4. A rapidly progressive fatal disease<br>5. Major contraindication to HT<br>6. Other abnormal findings which might affect the interpretation of the result. |
| Interventions | -estradiol 50 mg every three month<br>-estradiol 50 mg plus T 50 mg every three months<br>-Route:implant<br>-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:<br>1. Sexual function: Sabbatsberg self-rating scale<br>2. BMD of lumbar spines and hip: DEXA<br>3. Lipid profile<br>-Other outcomes:<br>1. Implant accumulation |
| 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.<br>-The author was contacted and kindly provided additional information. |
| Allocation concealment | A – Adequate |

**Characteristics of included studies** (*Continued*)

| **Study** | **Davis 2003** |
|---|---|
| Methods | -Design:double-blind randomised(C), parallel group<br>-No. of centres:multicenter<br>-Duration:24 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: not stated<br>-No. of participants randomised:77<br>-No. of participants completed and analysed: not stated<br>-No. of Losses to follow-up: not stated<br>-Compliance assessment: not stated<br>-Source of funding:drug company |
| Participants | -Location:Europe and Australia<br>-Setting:population-based<br>-Ethnicity:unspecified<br>-Run-in period:not stated<br>-Characteristics: surgically menopausal women with hypoactive sexual disorder with low T levels<br>-Age:not stated<br>-Inclusion criteria:not stated<br>-Exclusion criteria:not stated |
| Interventions | -estrogen (unknown dosage and frequency)<br>-estrogen (unknown dosage and frequency) plus T 150 mg twice a week<br>-Route:transdermal patch<br>-Co-intervention: not stated |
| Outcomes | -Relevant outcomes:<br>1. Sexual function:SAL and PFSF<br>-Other outcomes:<br>1. Safety outcomes(adverse events, clinical laboratory measurements, vital signs, and physical examinations. |
| Notes | -Baseline equality: not stated<br>-Conference proceedings<br>-The author was contacted. The further supplied infomation was not allowed by the drug company. |
| Allocation concealment | B – Unclear |

| **Study** | **Dobs 2002** |
|---|---|
| Methods | -Design:double-blind randomised(A), parallel group<br>-No. of centres:single<br>-Duration:16 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: no<br>-No. of participants randomised:40(20 in each group)<br>-No. of participants completed/analysed: 37(92.5%); 19 in E group, 18 in E-T group<br>-No. of non compliers: 3/40 = 7.5%. Reason was adverse events(two in the E-T group, one in E group)<br>-No. of losses to follow-up: 0/40 = 0%<br>-Compliance assessment: not stated<br>-Source of funding:partly funded by drug company |
| Participants | -Location:United States<br>-Setting:hospital-based<br>-Ethnicity: White(85%), Hispanic(5%), Black(2%)<br>-Run-in period:no<br>-Characteristics: healthy surgically and naturally menopausal women<br>-Age(SD):E group 55.4(6.6), E-T group 58.3(9.1)<br>-Inclusion criteria: |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| | 1. A postmenopausal woman being on a stable dose of estrogen at least 3 months<br>-Exclusion criteria:<br>1. Uncontrolled hypertension or hyperlipidemia<br>2. Use of medication known to affect lipids<br>3. Poorly controlled diabetes mellitus<br>4. Unstable angina or congestive heart failure, myocardial infarction within three months of study<br>5. Preexisting liver disease<br>6. Renal impairment<br>7. Hepatic adenoma<br>8. History of breast or uterine cancer<br>9. Gall bladder disease<br>10. History of thromboembolic events |
| Interventions | -EE 1.25 mg once a day<br>-EE 1.25 mg plus mT 2.5 mg once a day<br>-Route:oral<br>-Co-intervention: no (a progestin was prescribed after the last study visit) |
| Outcomes | -Relevant outcomes:<br>1. Sense of well being: the Quality of Life at Menopause Scale<br>2. Sexual functioning(by means of BISF-W, SRS, and SIQ)<br>3. Lipid profile<br>4. Body composition: DEXA , anthropometry<br>-Other outcomes:<br>1. Hormone measurements (total estrogen, estradiol, total testosterone and free testosterone, SHBG)<br>2. Strength testing<br>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<br>-The author was contacted and kindly supplied some information, but there was still some information unanswered. |
| Allocation concealment | A – Adequate |

| **Study** | **Dow 1983** |
|---|---|
| Methods | -Design:single-blind randomised(C), parallel group<br>-No. of centres:single<br>-Duration:16 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: not stated<br>-No. of participants randomised:40(20 in each group)<br>-No. of participants completed and analysed: not stated<br>-No. of non compliers and losses to follow-up: not stated<br>-Compliance assessment:-<br>-Source of funding:not stated |
| Participants | -Location:United Kingdom<br>-Setting:hospital-based<br>-Ethnicity:unspecified<br>-Run-in period:not stated<br>-Characteristics:surgically and naturally menopausal women with loss of libido<br>-Age(range):46.9(33-61)<br>-Inclusion criteria:<br>1. Postmenopausal women with loss of libido and a regular sexual partner |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| | 2. No contraindication for HT<br>-Exclusion criteria:<br>1. Gross primary marital disturbance or significant concurrent psychopathology or physical illness<br>2. Concurrent use of medication that might affect libido or interfere with the proposed HT |
| Interventions | -estradiol 50 mg<br>-estradiol 50 mg plus T 100 mg<br>-Route:implant<br>-Co-intervention: women with an intact uterus were treated with cyclical norethisterone 5 mg orally for 7 days each month |
| Outcomes | -Relevant outcomes:<br>1. Sexual function: self-rating scales of sexual and marital satisfaction<br>2. Menopausal symptoms: menopausal symptoms scale(Greene 1976) |
| Notes | -Baseline equality: not stated<br>-The author could not be contacted. |
| Allocation concealment | B – Unclear |

| **Study** | **Farish 1984** |
|---|---|
| Methods | -Design:double-blind randomised(A), parallel group<br>-No. of centres: two<br>-Duration:24 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: not stated<br>-No. of participants randomised:31(14 in E group, 17 in E-T group)<br>-No. of participants completed the study: 31/31=100%<br>-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<br>-No. of non compliers and losses to follow up: 0/31 = 0%<br>-Compliance assessment:not stated<br>-Source of funding:not stated |
| Participants | -Location:United Kingdom<br>-Setting:hospital-based<br>-Ethnicity:unspecified<br>-Run-in period:no<br>-Characteristics:surgically menopausal women with climacteric symptoms<br>-Age(range):46.4(36-54)<br>-Inclusion criteria:<br>1. TAH with BSO for non-malignant condition at least 6 weeks earlier<br>-Exclusion criteria:<br>1. Receiving any hormone therapy prior to commencing treatment nor were taking any drug to interfere with lipid metabolism<br>2. Renal or hepatic abnormalities |
| Interventions | -17 beta-estradiol 50 mg<br>-17 beta-estradiol 50 mg plus T 100 mg<br>-Route:implant<br>-Co-intervention: no |
| Outcomes | -Relevant outcomes:<br>1. Lipid profile<br>-Other outcomes:<br>1. Hormone measurements |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| Notes | -Baseline equality: not stated. However, baseline levels of lipid profiles were shown in the table and seemed to be similar in two groups.<br>- The author was contacted and kindly provided further information. |
| Allocation concealment | A – Adequate |

| **Study** | **Floter 2002** |
|---|---|
| Methods | -Design:Double-blind randomised(A), crossover study<br>-No. of centres:single<br>-Duration:24 weeks<br>-Power calculation:yes<br>-Intention-to-treat analysis: no<br>-No. of participants randomised:50<br>-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)<br>-No. of non compliers: 6/50 = 12%. Reasons were poor drug compliance(5/50= 10%), and migraine during E-P period(1/50=2%)<br>-No. of losses to follow-up: 0%<br>-Compliance assessment: not stated<br>-Source of funding:partly funded by drug company |
| Participants | -Location:Sweden<br>-Setting:population-base<br>-Ethnicity:unspecified<br>-Run-in period:washout 2 months<br>-Characteristics: healthy surgically menopausal women<br>-Age(SD):54(2.9)<br>-Inclusion criteria:<br>1. Age 45-60 years<br>2. History of TAH with BSO for benign disease<br>3. BMI 18-29 kg/m2<br>4. BP < 170 mmHg systolic and/or 105 mmHg diastolic<br>5. Normal mammogram within the past year<br>-Exclusion criteria:<br>1. Previous use of HT(< past 2 months), other medication taken at the same time<br>2. History of or present pre malignancies, liver disease, cardiovascular, cerebrovascular or thromboembolic disorders<br>3. Present psychiatric disease<br>4. Regular use of tranquillizers and/or antihistamines<br>5. Alcohol abuse or smoking of at least 10 cigarettes/day |
| Interventions | -estradiol valerate 2mg once a day<br>-estradiol valerate 2mg plus testosterone undecanoate 40 mg once a day<br>-Route:oral<br>-Co-intervention: no |
| Outcomes | -Relevant outcomes:<br>1. Sense of well being:Psychological General Well Being Index<br>2. Sexual function: McCoy's sex scale questionnaire<br>3. Hirsutism and acne<br>4. Blood count<br>-Other outcomes:<br>1. Self-esteem: questionnaire concerning a woman's view of her own abilities in social life and work.<br>2. Other safety outcomes<br>3. Clitoral enlargement |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| | 4. Hormone measurements |
| Notes | -Baseline equality: not applicable<br>-Differences between treatment periods were assessed using Fisher's permutation test. No significant treatment-by-sequence group interaction, indicating no 'carry-over effect'.<br>- The author was contacted and kindly provided further information. |
| Allocation concealment | A – Adequate |

| **Study** | **Garnett 1992** |
|---|---|
| Methods | -Design:randomised(B), parallel group unclear blinding<br>-No. of centres:two<br>-Duration:12 months<br>-Power calculation:not stated<br>-Intention-to-treat analysis: not stated<br>-No. of participants randomised:50 women requested HT and were alternately allocated to either E group(25) or E-T group(25).<br>-No. of participants completed/analysed: not stated<br>-No. of non compliers and losses to follow-up: not stated<br>-Compliance assessment:-<br>-Source of funding:partly funded by drug company |
| Participants | -Location:United Kingdom<br>-Setting:hospital-based<br>-Ethnicity:unspecified<br>-Run-in period:not stated<br>-Characteristics: healthy surgically and naturally menopausal women<br>-Age(SD):E group 54.3(6.9), E-T group 53.8(8.4)<br>-Inclusion criteria:<br>1. Healthy postmenopausal women<br>-Exclusion<br>criteria:<br>1. Excessive cigarette smoking (>20/day)<br>2. Excessive alcohol consumption (>300g/week)<br>3. medication known to affect bone metabolism<br>4. condition that likely to affect bone density<br>5. Hepatic or renal impairment |
| Interventions | -estradiol 75 mg<br>-estradiol 75 mg plus T 100 mg<br>-No treatment<br>-Route:implant every 6 months<br>-Co-intervention: women with an intact uterus received norethindrone acetate, 5 mg/day for the first 10 days of each month |
| Outcomes | -Relevant outcomes:<br>1. BMD of lumbar spines and hip: quantitative digital radiography<br>-Other outcomes:<br>1. Hormone measurements |
| Notes | -Baseline equality: no differences in age, years since menopause, height, weight, parity, hysterectomy, breast feeding, previous oral contraception, alcohol use, smoker and regular exercise.<br>-The corresponding author was contacted and the response was obtained but no additional information was provided. |
| Allocation concealment | B – Unclear |

**Characteristics of included studies** (*Continued*)

| **Study** | **Hickok 1993** |
|---|---|
| Methods | -Design:double-blind randomised(A), parallel group<br>-No. of centres:single<br>-Duration:24 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: not stated<br>-No. of participants randomised:26(13 in each group)<br>-No. of participants completed and analysed: 26/26 =100%<br>-No. of non compliers and losses to follow-up: 0<br>-Compliance assessment: subjects had to take at least 75% of their assigned medication for 4 consecutive weeks.<br>-Source of funding:partly funded by drug company |
| Participants | -Location:United States<br>-Setting:hospital-based<br>-Ethnicity: White<br>-Run-in period:not stated<br>-Characteristics: healthy postmenopausal women, unclear type of menopause<br>-Age:E group 50, E-T group 52<br>-Inclusion criteria:<br>1. Age 40-60 years with no menstrual bleeding in the last 12 months<br>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<br>3. Nonsmokers or ex-smokers who had not smoked in the past 12 months<br>-Exclusion criteria:<br>1. History of genital tract disease<br>2. Current or previous estrogen-dependent malignancy<br>3. History of jaundice or elevated liver enzyme<br>4. Gall bladder disease<br>5. history of cardiovascular disease<br>6. Current hypertriglyceridemia<br>7. Severe hypertension |
| Interventions | -EE 0.625 mg once a day<br>-EE 0.625 mg plus mT 1.25 mg once a day<br>-Route:oral<br>-Co-intervention: not stated |
| Outcomes | -Relevant outcomes:<br>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<br>2. Lipid profile<br>3. Red blood cell count<br>-Other outcomes:<br>1. Endometrial histology<br>2. Vaginal pathology<br>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.<br>-The author was contacted and kindly provided further information. |
| Allocation concealment | B – Unclear |

**Characteristics of included studies** (*Continued*)

| **Study** | **Lobo 2003** |
|---|---|
| Methods | -Design:double-blind randomised(A), parallel group<br>-No. of centres:twenty<br>-Duration:16 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: no<br>-No. of participants randomised:218(111 in E group, 107 in E-T)<br>-No. of participants completed the study: 182/218 = 83.5%(87 in E-T group, 95 in E)<br>-No. of participants analysed:218<br>-No. of non compliers: 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)<br>-No. of losses to follow-up: not stated<br>-Compliance assessment: not stated<br>-Source of funding:not stated |
| Participants | -Location:United States<br>-Setting:hospital-based<br>-Ethnicity: White(91.8%), Black(4.6%), Hispanic(2.3%), other(1.3%)<br>-Run-in period: 2 weeks of receiving esterified estrogen 0.625 mg per day<br>-Characteristics: surgically and naturally menopausal women with hypoactive sexual desire associated with the onset of menopause<br>-Age(SD):E group 53.8(5.7), E-T group 52.9(5.7)<br>-Inclusion criteria:<br>1. Healthy postmenopausal women(natural or surgical for at least 6 months)<br>2. Age 45-65 years<br>3. Hypoactive sexual interest or desire associated with the onset of menopause<br>4. No overt mood disorders<br>5. A history of adequate sexual interest before the onset of menopause<br>6. Receiving the equivalent of 0.625 mg of conjugated equine estrogens for 3 or more months<br>7. A stable, monogamous, heterosexual relationship<br>-Exclusion criteria:<br>1. Dyspareunia<br>2. Unresolved or recent sexual abuse<br>3. Depressive or anxiety symptoms or physical limitations that interfered with normal sexual functioning<br>4. An abnormal mammogram<br>5. Recent clinical laboratory test abnormalities<br>6. Recent previous high dose estrogen therapy or other sex hormones, lipid-lowering agents, antidepressants(including selective serotonin-reuptake inhibitors), anxiolytics, thyroid replacement medication(unless a stable dose), or antihypertensive drug.<br>4. |
| Interventions | -EE 0.625 mg once a day<br>-EE 0.625 mg plus mT 1.25 mg once a day<br>-Route:oral<br>-Co-intervention: no (a progestin was prescribed after the last study visit) |
| Outcomes | -Relevant outcomes:<br>1. Sexual function: SIQ and BISF-W<br>2. Lipid profile<br>3. Hirsutism:the scale of Lorenzo<br>4. Acne:the scale of Palatsi |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| 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.<br>- The author was contacted and kindly provided further information.<br>-The baseline sexual dimension scores, lipid profiles, hirsutism score and acne score seemed to be similar in the two groups. |
| Allocation concealment | A – Adequate |

| **Study** | **Miller 2000** |
|---|---|
| Methods | -Design:double-blind randomised(A), parallel group<br>-No. of centres:single<br>-Duration:12 months<br>-Power calculation:not stated<br>-Intention-to-treat analysis: no<br>-No. of participants randomised:66<br>-No. of participants completed the study: 57/66 = 86.4% (30 in HT group, 27 in HT-T)<br>-No. of participants analysed: 57<br>-No. of non compliers: 9/66 = 13.6%. Reasons were breakthrough uterine bleeding(3), skin rash/acne(2), weight gain(2), PMS symptoms(1), other illness(1)<br>-No. of losses to follow-up: 0%<br>-Compliance assessment: not stated<br>-Source of funding:partly funded by drug company |
| Participants | -Location:United States<br>-Setting:hospital-based<br>-Ethnicity:unspecified<br>-Run-in period:not stated<br>-Characteristics: healthy surgically and naturally menopausal women<br>-Age(SEM):E group 53.5(1), E-T group 54.6(1.2)<br>-Inclusion criteria:<br>1. Postmenopausal women with no contraindications to HT<br>-Exclusion criteria:<br>1. Patients who had taken any drug known to alter calcium or bone metabolism |
| Interventions | Patients with hysterectomy<br>-micronised estradiol 0.5 mg twice a day<br>-micronised estradiol 0.5 mg twice a day plus micronised testosterone 1.25 mg twice a day<br>Patients with intact uterus<br>-micronised estradiol 0.5 mg twice a day plus micronised progesterone 100 mg<br>-micronised estradiol 0.5 mg twice a day plus micronised progesterone 100 mg plus micronised testosterone 1.25 mg twice a day<br>-Route:sublingual<br>-Co-intervention: no |
| Outcomes | -Relevant outcomes:<br>1. Biochemical markers of bone metabolism;<br>1.1. Urinary markers: Dpd and NTx<br>1.2. Serum marker: BSAP<br>2. BMD of lumbar spines and hip: DEXA<br>-Other outcomes:<br>1. Hormone measurements |
| Notes | -Baseline equality: no differences in age, height, weight, estradiol and FSH levels, biochemical markers levels and BMD between the two groups.<br>-The corresponding author was contacted and kindly supplied information. |

Allocation concealment A – Adequate

| **Study** | **Montgomery 1987** |
|---|---|
| Methods | -Design:double-blind randomised(C), parallel group<br>-No. of centres:single<br>-Duration:16 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis:no<br>-No. of participants randomised:84(29 in P group, 28 in E group, 27 in E-T)<br>-No. of participants completed the study: 70(21 in P group, 25 in E, 24 in E-T)<br>-No. of participants analysed:70<br>-No. of non compliers: 14/84 = 16.7%. Reasons: 1acute 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)<br>-No. of losses to follow-up:6/84=7.1%.<br>-Compliance assessment:not stated<br>-Source of funding:not stated |
| Participants | -Location:United Kingdom<br>-Setting:unclear<br>-Ethnicity:unspecified<br>-Run-in period:not stated<br>-Characteristics: perimenopausal, surgically and naturally menopausal women with menopausal symptoms<br>-Age:E group 46, E-T group 50, P group 48<br>-Inclusion criteria:<br>1. The same as stated in disease status<br>-Exclusion criteria:<br>1. Women with a contraindication to estrogen therapy |
| Interventions | -estradiol 50 mg<br>-estradiol 50 mg plus T 100 mg<br>-placebo<br>-Route:implant<br>-Co-intervention: |
| Outcomes | -Relevant outcomes:<br>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.<br>-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.<br>- The author could not be contacted. |
| Allocation concealment | B – Unclear |

**Characteristics of included studies** (*Continued*)

| **Study** | **Penotti 2001** |
|---|---|
| Methods | -Design:Open randomised(A), parallel group<br>-No. of centres:single<br>-Duration:8 months<br>-Power calculation:not stated<br>-Intention-to-treat analysis: not stated<br>-No. of participants randomised:40<br>-No. of participants completed the study: 33/40 = 82.5% (18 in E group, 15 in E-T group)<br>-No. of participants analysed: not stated<br>-No. of non compliers: 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)<br>-No. of losses to follow-up: 0 =0%<br>-Compliance assessment: not stated<br>-Source of funding:not stated |
| Participants | -Location:Italy<br>-Setting:hospital-based<br>-Ethnicity:unspecified<br>-Run-in period:no<br>-Characteristics: healthy naturally menopausal women<br>-Age:E group 55.3, E-T group 57.4<br>-Inclusion criteria:<br>1. postmenopausal women already on HT at least 1 year<br>-Exclusion criteria:<br>1. Major disease(Hypertension, heart disease, diabetes, renal or peripheral vascular diseases<br>2. surgical removal of uterus or ovaries |
| Interventions | -estradiol 50 micrograms once a day plus MPA 10 mg/d for a duration of 2 weeks every two months<br>-estradiol 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<br>-Route:transdermal estradiol, oral progestin, oral testosterone<br>-Co-intervention: not stated |
| Outcomes | -Relevant outcomes:<br>1. Psychological well being:a 10-cm VAS<br>2. Sexual desire and satisfaction: a 10-cm VAS<br>3. Lipid profile<br>-Other outcomes:<br>1. Pulsatility index of internal carotid artery and middle cerebral artery (primary outcome)<br>2. Endometrial thickness<br>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.<br>- 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. |
| Allocation concealment | A – Adequate |

**Characteristics of included studies** (*Continued*)

| **Study** | **Raisz 1996** |
|---|---|
| Methods | -Design:Open randomised(C), parallel group<br>-No. of centres:three<br>-Duration:6 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis:not stated<br>-No. of participants randomised:28<br>-No. of participants analysed:26<br>-No. of non compliers and losses to follow-up:not stated<br>-Compliance: not stated<br>-Source of funding:partly funded by drug company |
| Participants | -Location:United States<br>-Setting:hospital-based<br>-Ethnicity:unspecified<br>-Run-in period: 3 weeks of receiving calcium intake 1000-1500 mg per day by dietary adjustments or addition of calcium supplement<br>-Characteristics: healthy surgically and naturally menopausal women<br>-Age(range):E group 65.7(49.1-80.4), E-T group 59.8(46.6-78.5)<br>-Inclusion criteria:<br>1. The same as stated in disease status<br>2. BMI within 25% of ideal body weight<br>3. Nonsmokers<br>4. Not taken estrogens within the last 6 months<br>5. No prior history of estrogen-dependent cancer, hypercortisolism, hyperthyroidism, or metabolic bone disease<br>6. A negative mammogram and Pap smear within one year and normal ECG<br>-Exclusion criteria:<br>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 | -CEE 1.25 mg once a day<br>-EE 1.25 mg plus mT 2.5 mg once a day<br>-Route:oral<br>-Co-intervention:no |
| Outcomes | -Relevant outcomes:<br>1. Menopausal symptoms: a modified menopausal index with a 0-3 scale<br>2. Bone formation markers(serum OC, BSAP, PICP) and bone resorption markers(pyridinoline, Dpd and hydroxyproline)<br>3. Lipid profile<br>-Other outcomes:<br>1. Hormone measurement(estrone, estradiol, testosterone, DHT, SHBG, intact PTH, 25-hydroxyvitamin D<br>2. Adverse event(headache, breast pain, acne, vaginal bleeding)<br>-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 hematological measures.<br>-The author was contacted, but the further information could not be provided. |
| Allocation concealment | B – Unclear |

**Characteristics of included studies** (*Continued*)

| **Study** | **Regestein 2001** |
|---|---|
| Methods | -Design:double-blind randomised(A), crossover study<br>-No. of centres:single<br>-Duration:16 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: no<br>-No. of participants randomised: not stated (assumed 42)<br>-No. of participants completed the study: not stated (35/42 = 83.3% had complete data set)<br>-No. of participants analysed: depended on outcomes<br>-No. of non compliers: Reasons were unprecedented anxiety(1), poor feeling(1), and using Estring(1)<br>-No. of losses to follow-up: no<br>-Compliance assessment: a pill count was recorded to estimate treatment compliance.<br>-Source of funding:drug company |
| Participants | -Location:United States<br>-Setting:population-based<br>-Ethnicity:unspecified<br>-Run-in period:no<br>-Characteristics: healthy surgically and naturally menopausal women<br>-Age(range):55.5(38-65)<br>-Inclusion criteria:<br>1. Natural or surgical menopause<br>2. Currently use HT<br>3. No prior androgen replacement therapy, psychotropic drugs and no major systemic disease<br>4. Used no more than three caffeinated drinks per day, two alcohol drinks per week, ten cigarette per day<br>5. BMI below 29<br>-Exclusion criteria:not stated |
| Interventions | -EE 0.625 mg once a day<br>-EE 0.625 mg plus mT 1.25 mg once a day<br>-Route:oral<br>-Co-intervention: not stated |
| Outcomes | -Relevant outcomes:<br>1. Libido: an 80-mm VAS<br>2. Sexual enjoyment: a scale of 0-3<br>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.<br>4. Menopausal symptoms: the Menopause-specific Quality of Life Questionnaire(MENQOL)<br>4. Neurobehavioral outcomes: computerized test<br>5. Complex verbal and associated fluency: the Possible Jobs and Alternate Uses measures<br>-Other outcomes:<br>1. Subjective sleep quality<br>2. Exercise levels |
| Notes | -Baseline equality: not applicable<br>-The author was contacted and kindly provided further information. |
| Allocation concealment | A – Adequate |

**Characteristics of included studies** (*Continued*)

| **Study** | **Sarrel 1998** |
|---|---|
| Methods | -Design:double-blind randomised(A), parallel group<br>-No. of centres:single<br>-Duration:8 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: not stated<br>-No. of participants randomised:20 (10 in E-T, 10 in E)<br>-No. of participants completed/analysed:19<br>-No. of non compliers: 1 in E<br>-No. of losses to follow-up: 1 in E<br>-Compliance assessment: not stated<br>-Source of funding:drug company |
| Participants | -Location:United States<br>-Setting:hospital-based<br>-Ethnicity:predominantly Caucasian<br>-Run-in period: 2 weeks of receiving previous estrogens and then 2 weeks of placebo<br>-Characteristics: surgically and naturally menopausal women dissatisfied with their concurrent treatment at least 4 months<br>-Age(range):52(45-55)<br>-Inclusion criteria:<br>1. As stated in disease status<br>2. Inadequate symptomatic relief included hot flashes, vaginal dryness, dyspareunia, decreased libido and decreased energy levels<br>3. BW above or below 25% of ideal BW<br>-Exclusion criteria:<br>1. Clinically significant abnormal cervical cytology smear<br>2. Clinically significant abnormal mammograms within the past 12 months or clinically significant abnormal finding during pelvic examination<br>3. History of thromboembolic disorder or active thromboembolic disease in the past 12 months<br>4. Active or previous estrogen-dependent breast, uterine or ovarian cancer, as well as undiagnosed uterine or vaginal bleeding at examination or in the past year |
| Interventions | -EE 1.25 mg once a day<br>-EE 1.25 mg plus mT 2.5 mg once a day<br>-Route:oral<br>-Co-intervention: no |
| Outcomes | -Relevant outcomes:<br>1. Sexual behavior and enjoyment: the 10-item Sexual Activity and Libido Scale<br>2. Menopausal symptoms: the Menopausal Symptom Scale (modified from the original scale developed by Kupperman et al.)<br>-Other outcomes:<br>1. Vaginal smear maturation index<br>2. Hormone measurements |
| Notes | -Baseline equality: not stated<br>-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. |
| Allocation concealment | A – Adequate |

**Characteristics of included studies** (*Continued*)

| **Study** | **Shepanek 1999** |
|---|---|
| Methods | -Design:double-blind randomised(C), parallel group<br>-No. of centres:two<br>-Duration:12 weeks<br>-Power calculation: yes<br>-Intention-to-treat analysis: no<br>-No. of participants randomised:30 -No. of participants completed/analysed: 24/30=80%<br>-No. of non compliers: 6/30 = 20%. Reasons were not stated.<br>-No. of losses to follow-up: not stated<br>-Compliance assessment: not stated<br>-Source of funding:drug company provided medication |
| Participants | -Location:United States<br>-Setting:population-based<br>-Ethnicity: Caucasian 83.3%(14/24), Black African American 12.5%(3/24), Other 4.2%(1/24)<br>-Run-in period: 30 days of placebo<br>-Characteristics: healthy surgically menopausal women<br>-Age(SD): E 53.74(3.85), E-T 54.56(5.13)<br>-Inclusion criteria: the participants had to<br>1. TAH with BSO<br>2. not be taking any prescription medications<br>3. have estimated IQ. of at least 80 based on the Symbol Digit Modalities Test<br>4. be a high school graduate or have an equivalent degree<br>-Exclusion criteria:<br>1. A history of head injury with loss of consciousness greater than 30 minutes<br>2. a history of alcohol or drug abuse<br>3. any current Axis I psychotic level disorder<br>4. a history of central nervous system infection<br>5. a history of serious concurrent acute or chronic diseases of a severity to negatively impact cognitive ability<br>6. current use of medications known to adversely affect cognitive function<br>7. a learning disability<br>8. a first language other than English |
| Interventions | -EE 0.625 mg once a day<br>-EE 0.625 mg plus mT 1.25 mg once a day<br>-Route:oral<br>-Co-intervention: no |
| Outcomes | -Relevant outcomes:<br>1. Sexual desire<br>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).<br>-The author could not be contacted. |
| Allocation concealment | B – Unclear |

**Characteristics of included studies** (*Continued*)

| **Study** | **Sherwin 1988** |
|---|---|
| Methods | -Design:double-blind randomised(A), crossover study<br>-No. of centres:single<br>-Duration:4 months (1 month of placebo and then 3 months of intervention)<br>-Power calculation:not stated<br>-Intention-to-treat analysis: no<br>-No. of participants randomised:49<br>-No. of participants completed/analysed: 40 (10 in each treatment group)<br>-No. of non compliers: 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.<br>-No. of losses to follow-up: no<br>-Compliance assessment: no<br>-Source of funding:not stated |
| Participants | -Location:Canada<br>-Setting:hospital-based<br>-Ethnicity:unspecified<br>-Run-in period:no<br>-Characteristics: healthy surgically menopausal women<br>-Age:45.4 for TAH with BSO, 36.6 for TAH<br>-Inclusion criteria:<br>1. Women needed to undergo TAH with BSO for benign condition<br>2. In a state of good general health<br>3. No known contraindications to HT<br>4. They had completed at least nine years of formal education<br>-Exclusion criteria:<br>1. Past or current psychological disturbance |
| Interventions | -estradiol valerate 10 mg<br>-testosterone enanthate benzilic acid hydrozone 200 mg<br>-estradiol dienanthate 7.5 mg plus estradiol benzoate 1 mg testosterone enanthate benzilic acid hydrozone 150 mg<br>-placebo<br>-no treatment (TAH patients)<br>-Route:intramuscular injection<br>-Co-intervention: no |
| Outcomes | -Relevant outcomes:<br>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<br>- The author was contacted and kindly supplied further information, but there was no longer data to enable inclusion in the meta-analysis. |
| Allocation concealment | A – Adequate |

**Characteristics of included studies** (*Continued*)

| **Study** | **Shifren 2000** |
|---|---|
| Methods | -Design:double-blind randomised(A), crossover study<br>-No. of centres:nine<br>-Duration:12 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: no<br>-No. of participants randomised:75<br>-No. of participants completed/analysed: 65/75=86.7%<br>-No. of non compliers: 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)<br>-No. of losses to follow-up: 0%<br>-Compliance assessment: not stated<br>-Source of funding:drug company |
| Participants | -Location:United States<br>-Setting:hospital-based<br>-Ethnicity:White(83%), Black(11%), Hispanic(5%), Asian(1%)<br>-Run-in period:no<br>-Characteristics: surgically menopausal women with impaired sexual function, low T levels and receiving adequate dose of estrogen therapy<br>-Age(range):47(31-56)<br>-Inclusion criteria:<br>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<br>2. A stable, monogamous, heterosexual relationship for at least 1 year<br>3. BMI between 19.5-33.5<br>-Exclusion criteria:<br>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<br>2. More than 20 moderate or severe hot flashes per week<br>3. Severe acne(grade 3 on the scale of Palatsi et al)<br>4. Moderate or severe hirsutism(score of 6 or more on the scale of Lorenzo)<br>5. Hyperlipidemia<br>6. Psychiatric disease<br>7. Dyspareunia<br>8. Physical limitations that interfered with normal sexual functioning<br>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<br>-CEE 0.625 mg once a day plus T 150 micrograms twice a week<br>-CEE 0.625 mg once a day plus T 300 micrograms twice a week<br>-Route:oral estrogen, transdermal patch testosterone<br>-Co-intervention: no |
| Outcomes | -Relevant outcomes:<br>1. Sexual function: the Brief Index of Sexual Functioning for Women<br>2. Mood: the Psychological General Well-Being Index<br>3. Hirsutism: the scale of Lorenzo and facial-deplication rate<br>4. Acne: the scale of Palatsi et al.<br>5. lipid profile<br>6. Blood counts<br>-Other outcomes: |

| | |
|---|---|
| | 1. Hormone measurements (free testosterone, bioavailable testosterone, total testosterone, dihydrotestosterone and SHBG)<br>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<br>-Time points:4, 8 and 12 weeks |
| Notes | -Baseline equality: not applicable<br>- The author was contacted and kindly provided further information. |
| Allocation concealment | A – Adequate |

| **Study** | **Simon 1999** |
|---|---|
| Methods | -Design:double-blind randomised(C), parallel group<br>-No. of centres:three<br>-Duration:12 weeks<br>-Power calculation:not stated<br>-Intention-to-treat analysis: not stated<br>-No. of participants randomised:93<br>-No. of participants completed the study: 89/93 = 95.7%<br>-No. of participants analysed: not stated<br>-No. of non compliers: 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.<br>-No. of losses to follow-up: 2/92 = 2.2%<br>-Compliance assessment: stated only "compliance and protocol adherence were excellent".<br>-Source of funding:not stated |
| Participants | -Location:United States<br>-Setting:hospital-based<br>-Ethnicity:unspecified<br>-Run-in period:4 weeks of placebo treatment<br>-Characteristics: healthy peri-and postmenopausal women<br>-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)<br>-Inclusion criteria:<br>1. Naturally menopausal women with both ovaries intact<br>2. Nonsmokers<br>3. BW within 25% of ideal BW<br>4. A stable heterosexual relationships of at least 1 year duration<br>-Exclusion criteria:<br>1. Use of estrogens, progestins, androgens, or anabolic steroids within 8 weeks of enrolment<br>2. No contraindication for HT |
| Interventions | -EE 0.625 mg once a day<br>-EE 1.25 mg once a day<br>-EE 0.625 mg plus mT 1.25 mg once a day<br>-EE 1.25 mg plus mT 2.5 mg once a day<br>-Route:oral<br>-Co-intervention: no |
| Outcomes | -Relevant outcomes:<br>1. Menopausal symptoms: the scale of Kupperman et al.<br>-Other outcomes:<br>1. Vaginal bleeding<br>2. Safety |

| | |
|---|---|
| | 2. Hormone measurements(estradiol, estrone, testosterone, dihydrotestosterone, androstenedione, DHEAS, SHBG<br>-Time points: 4, 8, and 12 weeks |
| 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.<br>-The author could not be contacted. |
| Allocation concealment | B – Unclear |

| **Study** | **Watts 1995** |
|---|---|
| Methods | -Design:double-blind randomised(C), parallel group<br>-No. of centres:three<br>-Duration:2 years<br>-Power calculation:not stated<br>-Intention-to-treat analysis: yes for safety analysis, no for efficacy analysis<br>-No. of participants randomised:66 (33 in each group)<br>-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)<br>-No. of non compliers: unclear<br>-No. of losses to follow-up: not stated<br>-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<br>-Source of funding:drug company |
| Participants | -Location:United States<br>-Setting:hospital-based<br>-Ethnicity:White(98.3%), Hispanic(1.7%)<br>-Run-in period:no<br>-Characteristics: healthy surgically menopausal women<br>-Age(SD):E group 45.0(8.0), E-T group 48.0(8.0)<br>-Inclusion criteria:<br>1. The same as stated in disease status<br>2. No concomitant illness<br>-Exclusion criteria: not stated |
| Interventions | -EE 1.25 mg once a day<br>-EE 1.25 mg plus mT 2.5 mg once a day<br>-Route:oral<br>-Co-intervention: no |
| Outcomes | -Relevant outcomes:<br>1. BMD of lumbar spines, radius and hip: DEXA<br>2. Menopausal symptoms: the scale modified from the original version developed by Kuppermann et al.<br>3. Lipid profile<br>4. Hematology<br>-Other outcomes:<br>1. Serum biochemistry and urinalysis tests<br>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 estrogen use in previous 2 years, menopausal symptoms scores and lipid profiles.<br>-The author was contacted and the response was obtained but no additional information was provided. |
| Allocation concealment | A – Adequate |

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 estrogen
-DEXA = dual-energy x-ray absorptiometry
-DHEAS = dehydroepiandrosterone sulfate
-DMRS = Daily menopausal Rating Scale
-Dpd = deoxypyridinoline
-E = estrogen(either with placebo or not) group; T group = testosterone(either with placebo or not) group; P group = placebo group; E-P group= estrogen plus progestogen(either with placebo or not) group, E-T group = estrogen plus testosterone(either with placebo or not) group; E-P-T group = estrogen plus progestogen plus testosterone(either with placebo or not) group
-ECG = electrocardiogram
-EE = esterified estrogen
-MPA = medroxyprogsterone 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

| Study | Reason for exclusion |
|---|---|
| Adamson 2001 | The study objective was to investigate the effect of esterified estrogens 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 estrogen/progestogen hormone therapy. The outcome was not eligible for this review. |
| Brincat 1984 | This study aimed to compare climacteric symptom control in 55 postmenopausal women treated with either estradiol 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 estrogen replacement by randomizing 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 estrogen groups with cyclical or continuous progestagen, and one transdermal estrogen regime with cyclical progestagen. Participants in the estradiol-testosterone implanted group were not randomised. |
| Girard 1995 | A RCT was undertaken to evaluate the effects of Fadiamone hormone cream (estrone and estradiol in combination with testosterone proprionate) on facial skin ageing. One group received Fadiamone and one group used placebo. There was no HT group serving as a control. |
| 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 (estrogen, progestogen and testosterone) in various doses. There was no combined estrogen plus progestogen therapy serving as a control group. |
| Kapetanakis 1982 | The study was carried out to assess the effect of pellets containing either estradiol or estradiol in combination with testosterone in ten women with various type of ovarian failure. The participants included women with gonadal dysgenesis. |
| 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 estradiol 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. |
| Passeri 1993 | The double-blind, randomized, 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 estrogen and estrogen plus testosterone on bone turnover. Estradiol 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. |
| Savvas 1988 | The non-randomised cohort study of postmenopausal women aimed to compare oral continuous treatment with cyclic estrogen plus progesterone preparation and subcutaneous implants of estradiol combined with testosterone for their effects in preventing postmenopausal osteoporosis. |

## Characteristics of excluded studies (*Continued*)

| | |
|---|---|
| Savvas 1992 | This study was designed to investigate the effect on bone density when women change from oral estrogen 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. |
| Seed 2000 | This was semi-randomised study. The control groups included two historical groups of women who were randomly assigned to receive estrogen continuously or no treatment. The treatment groups comprised the two study groups; estrogen-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 estrogen 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 estrogen-androgen, estrogen or no treatment. The study design was not RCT. |
| 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. |
| 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 estrogen therapy received testosterone implant and 15 postmenopausal nonusers of HT served as control. The control group was not HT. |

## Characteristics of ongoing studies

| **Study** | **Fem T (1)** |
|---|---|
| Trial name or title | A phase III, multinational, randomized, double-blind, parallel-group, placebo-controlled study to evaluate efficacy and safety of transdermal testosterone (300 per day) for 52 weeks and safety for a further 28-week open-label period in women with hypoactive sexual desire disorder on concurrent estrogen replacement therapy who have undergone hysterectomy and bilateral oophorectomy |
| Participants | - 500 participants<br>- Eligible women must be surgically menopausal with low libido who have been receiving a stable dose estrogen replacement for at least 3 months. |
| Interventions | Transdermal Testosterone (300 mg/day) plus estrogen therapy versus hormone therapy alone |
| Outcomes | Libido, hormonal profile and safety data |
| Starting date | August 2002 |
| Contact information | Procter & Gamber Pharmaceuticals |
| Notes | |

| **Study** | **Fem T (2)** |
|---|---|
| Trial name or title | A phase III, multinational, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of transdermal testosterone (300 mg/day) for 24-weeks in women with Hypoactive Sexual Desire Disorder on concurrent oral hormone replacement therapy who have undergone hysterectomy and bilateral oophorectomy |
| Participants | - 500 participants<br>- Eligible women must be surgically menopausal with low libido who have been receiving a stable dose of oral continuous combined estrogen and progestin therapy for at least 3 months. |

**Characteristics of ongoing studies** (*Continued*)

| | |
|---|---|
| Interventions | Transdermal Testosterone (300 mg/day) plus estrogen therapy versus hormone therapy alone |
| Outcomes | Libido, hormonal profile and safety data |
| Starting date | August 2002 |
| Contact information | Procter & Gamber Pharmaceuticals |
| Notes | |

| **Study** | **Fem T (3)** |
|---|---|
| Trial name or title | A phase III, multinational, randomized, double-blind, parallel-group, placebo-controlled 52-week study followed by a 52-week open-label extension to transdermal testosterone (300 mg/day) in naturally menopausal women with Hypoactive Sexual Desire Disorder on concurrent oral hormone replacement therapy |
| Participants | - 600 participants<br>- Eligible women must be naturally menopausal (no spontaneous periods for 1 year) with low libido who have been receiving a stable dose of oral continuous combined estrogen and progestin therapy for at least 3 months. |
| Interventions | Transdermal Testosterone (300 mg/day) plus estrogen therapy versus hormone therapy alone |
| Outcomes | Libido, hormonal profile and safety data |
| Starting date | August 2002 |
| Contact information | Procter & Gamber Pharmaceuticals |
| Notes | |

| **Study** | **Fem T (4)** |
|---|---|
| Trial name or title | A phase III, multinational, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of transdermal testosterone (300 mg/day) for 24-weeks and safety for a further 28-weeks in naturally menopausal women with Hypoactive Sexual Desire Disorder on concurrent oral hormone replacement therapy |
| Participants | - 500 participants<br>- Eligible women must be naturally menopausal (no spontaneous periods for 1 year) with low libido who have been receiving a stable dose of oral continuous combined estrogen and progestin therapy for at least 3 months. |
| Interventions | Transdermal Testosterone (300 mg/day) plus estrogen therapy versus hormone therapy alone |
| Outcomes | Libido, hormonal profile and safety data |
| Starting date | August 2002 |
| Contact information | Procter & Gamber Pharmaceuticals |
| Notes | |

## ADDITIONAL TABLES

**Table 01. Trial outcomes not included in the meta-analysis**

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| Acne | Barrett-Connor 1996 | 291 | The data were not available. | - Acne of mild or moderate severity was reported by 5(3%) estrogen-testosterone treated participants, whereas no participants receiving estrogen reported acne. |
| Acne | Braunstein 2003 | 447 | The data were not available. | - Acne found 13% in the estrogen alone group, 9% in estrogen-testosterone 150 microgram, 18% in estrogen-testosterone 300 microgram. |
| Biochemical markers of bone metabolism | Miller 2000 | 57 | The data were 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 were not available. | - The effects of estrogen-testosterone and estrogen alone on markers of bone resorption were generally similar. The increase in bone formation markers after estrogen-testosterone treatment was significantly different from the effect of estrogen for all bone formation parameters. |
| Bone Mineral density of lumbar spine and femur | Barrett-Connor 1999 | 199 | The data were not available. | - BMD increased in the estrogen-testosterone(low dose) were comparable to those in the estrogen(low dose) group, while the BMD changes at 24 months in the estrogen-testosterone(high dose) group significantly exceeded those in estrogen(high dose) group(p=0.014 for lumbar spine, BMD and p=0.009 for total hip BMD). |
| Bone Mineral density | Garnett 1992 | 50 | The data were not available. | - There were no significant differences in bone density at any of the sites measured between women receiving estrogen alone and those receiving estrogen-testosterone. No treated subjects had a significant bone loss(more than twice the measurement precision) at either |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| | | | | spine or femoral neck at 1 year, but three in each treated group showed a small but nonsignificant decrease at both sites. |
| Bone Mineral Density of L1-L4, femur and forearm | Watts 1995 | 48 | The data were not available. | - The estrogen-testosterone showed significant increases in spinal BMD at 12 and 24 months($p<0.01$). The estrogen group demonstrated a nonsignificant 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 estrogen 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 estrogen-testosterone group but not the estrogen alone group. When changes in arms, legs, and trunk in each patient were analyzed simultaneously, the difference between treatments was significant for lean body mass($p=0.007$) and percentage of fat tissue($p=0.077$). |
| Cognition and psychological well being | Regestein 2001 | 42 | A cross-over 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.<br>- There were no other effects of added methyltestosterone found on psychological, |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| | | | | sleep, and exercise measures. |
| Cognition | Sherwin 1988 | 49 | The data were not available. | - There were no comparative effects between estrogen-testosterone and estrogen alone groups.<br>- 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 were likely to be skewed. | - No significant interactions were found showing an advantage for estrogen-testosterone treated group as contrasted to estrogen-treated group. |
| Cognition (Cube Comparisons and Building Memory) | Wisniewski 2002 | 26 | The data were 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 were not available. | - There was no clinically significant difference in hematology. |
| Hematocrit | Floter 2002 | 50 | A cross-over study with no washout period | - They reported that there was no change in |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| | | | | blood counts during the study. |
| Hematocrit | Hickok 1993 | 26 | The data were 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. |
| Hematocrit | Watts 1995 | 48 | The data were not available. | - No clinically significant changes in hematologic indices. |
| Hirsutism | Barrett-Connor 1999 | 199 | The data were not available. | - Changes in hair growth in the estrogen-testosterone(low dose) group were similar to those in the estrogen(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 estrogen-testosterone and two treated with estrogen reported hirsutism as an adverse event at month 12. At 24 months, 10 estrogen-testosterone-treated and 3 estrogen-treated participants reported hirsutism as an adverse event. |
| Hirsutism | Braunstein 2003 | 447 | The data were not available. | - Hirsutism was reported 2%, 1% and 5% in the estrogen group, estrogen-testosterone 150 microgram group and estrogen-testosterone 300 microgram group, respectively. |
| Hirsutism and acne | Floter 2002 | 50 | A cross-over study with no washout period | - Incidences of hirsutism and acne were similar in two treatment groups. |
| Hirsutism and acne | Shifren 2000 | 67 | A cross-over 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 |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| | | | | 300 microgram. |
| Lipid profile | Dobs 2002 | 40 | The data were 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 estrogen group demonstrated the opposite effect on lipids, with a significant decrease in LDL and no meaningful change in the other lipid parameters. |
| Lipid profile | Luciano 1998a | 56 | The data were 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 estrogen therapy triglyceride levels decreased 9.0% and HDL cholesterol levels increased 9.0%. |
| 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 nonsignificant trend toward greater improvement in well-being and sexual interest and higher scores on the modified menopausal rating scale in the estrogen-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 | 26 | The data were non-normal distribution. | - There was no statistically significant difference between two treatments in menopausal symptoms. |
| Menopausal symptoms | Luciano 1999 | 51 | The data were not available. | - Vasomotor symptoms were reduced by at least 75% after treatment in all groups. |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| Menopausal symptoms | Raisz 1996 | 28 | The data were 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 were not available. | - There was no statistical difference between the estrogen-testosterone groups versus the estrogen group. |
| Menopausal symptoms | Sherwin 1984 | 49 | The data were not available. | - There was no result for the comparative effect on hot flushes between estrogen-testosterone and estrogen alone. |
| Menopausal symptoms | Sherwin 1985a | 43 | The data were not available. | - Menopausal index:<br>1. Somatic symptoms: The scores of the estrogen-testosterone, androgen alone groups were lower than those of the estrogen alone and placebo groups (p<0.01).<br>2. Psychosomatic symptoms: There were no significant changes in any of the groups across time.<br>3. Psychological symptoms: The scores of the estrogen-alone and placebo groups were significantly higher than those of the estrogen-testosterone, androgen-alone groups during both treatment phases (p<0.01).<br>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 were not available. | - In general, estrogen-testosterone therapy provided greater relief from these symptoms than estrogen 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 |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| | | | | 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 estrogen 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 patients. |
| Mood (hostility) | Sherwin 1985c | 36 | The data were not available. | - Hostility scores did not differ significantly in the two groups (testosterone-estrogen or estrogen alone). |
| Sense of well being | Dobs 2002 | 40 | The data were not available. | - With regard to QUALMS questionnaire, the estrogen-testosterone group showed significant improvement from baseline in somatic symptoms(week 10,p=0.003; week 16, p=0.073). The estrogen 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 2002 | 50 | A cross-over 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 1985c | 43 | The data were not available. | - Anxiety: There were no differences among |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| | | | | any of the groups across time.<br>- Depression: Mean group scores fell within the normal range. Depression scores in the placebo group were significantly higher than those in estrogen-testosterone(p<0.05), A(p<0.01), E(p<0.05) groups during both treatment phases.<br>- Hostility: hostility scores did not differ significantly in the two groups (testosterone-estrogen versus estrogen alone) |
| Sense of well being | Shifren 2000 | 65 | A cross-over study with no washout period | - Adding 300 microgram patch into oral estrogen has a significant improvement in general well being by means of PGWB (p=0.04). There also were significant increases with estrogen-testosterone 300 microgram treatment for sub scales of positive well being and depressed mood. |
| Sexual function | Braunstein 2003 | 447 | The data were not available. | - Total satisfying sexual activity measured by SAL and sexual desire measured by PFSF at 24 weeks of treatments significantly increased in estrogen-testosterone 300 micrograms treated group when compared to estrogen-treated group. Linear dose effect was marginally significant for total satisfying sexual activity from SAL(p=0.062) and the sexual desire domain of the PFSF(p=0.059). |
| Sexual function | Burger 1987 | 20 | The data were 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. |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| Sexual function | Davis 2003 | ? | The data were not available. | - There was a 43% increase in the frequency of total satisfying sexual activity for those receiving estrogen-testosterone versus estrogen(p=0.06). The mean change for the estrogen-testosterone group corresponded to a 110% increase over baseline(p<0.05). There was also a statistically significant increase in the sexual desire score of the PFSF compared with estrogen(16 versus 6 units, p<0.05). The mean change for the testosterone group corresponded to a 75% increase over baseline(p<0.05). |
| Sexual function | Dobs 2002 | 40 | The data were 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 estrogen-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 estrogen-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.<br>-The SRS total score in the estrogen-testosterone group improved significantly at each visit, whereas scores in the estrogen group did not change significantly. The SIQ score for the estrogen-testosterone group |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| | | | | also increased significantly for interest in sex at weeks 10(p=0.031) and 16(p=0.014) when compared with before menopause. The estrogen group showed no significant change from baseline. |
| Sexual function (total McCoy score) | Floter 2002 | 44 | A cross-over 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 | Luciano 1999 | 51 | The data were 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(desire and satisfaction) | Penotti 2001 | 33 | The data were not available. | - No difference between two groups was observed at any of the considered time points. |
| Sexual function | Shepanek 1999 | 30 | The data were likely to be skewed. | - Estrogen-testosterone-treated participants reported significantly less lack of sexual desire or interest to engage in sexual activity, compared to participants receiving estrogen alone. |
| Sexual function | Sherwin 1985b | 43 | The data were 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 |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| | | | | than did women in the estrogen 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-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) percent of the normative mean at baseline and decreased to 98(49) percent during treatment with estrogen plus 300 microgram of testosterone(p=0.07 for the comparison with estrogen-alone). |
| Sexual function (the prevalence of particular types of sexual behavior) | Shifren 2000 | 65 | A cross-over study with no washout period | - The percentage of women who reported having sexual fantasies at least once a week was 12 percent at baseline, 10 percent during estrogen treatment, 18 percent during estrogen plus testosterone 150 microgram, and 24 percent during treatment with |

**Table 01. Trial outcomes not included in the meta-analysis** (*Continued*)

| Outcome | Study ID | N | Reason | Conclusion |
|---|---|---|---|---|
| | | | | 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 percent at baseline, 35 percent during treatment with either estrogen-alone or estrogen plus 150 microgram of testosterone, and 41 percent during treatment with estrogen plus 300 microgram of testosterone. |
| Unexplained fatigue (vitality) | Floter 2002 | 50 | A cross-over study with no washout period | - There was no significant difference between the treatments in vitality. |
| Unexplained fatigue (vitality) | Shifren 2000 | 67 | A cross-over study with no washout period | - Vitality improved in women treated with testosterone patch combined with oral conjugated equine estrogen. |
| Unexplained fatigue and sense of well being | Sherwin 1985a | 43 | The data were 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 ($p<0.01$). |

## ANALYSES

### Comparison 03. HT plus testosterone versus HT on sexual function

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Change scores of sexual function | | | Standardised Mean Difference (Fixed) 95% CI | Subtotals only |

### Comparison 05. HT plus testosterone versus HT on biochemical markers of bone turnover

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Biochemical markers of bone turnover at 12 months | | | Weighted Mean Difference (Fixed) 95% CI | Subtotals only |

### Comparison 06. HT plus testosterone versus HT on bone mineral density

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Lumbar BMDs at 12 months | | | Weighted Mean Difference (Fixed) 95% CI | Subtotals only |
| 02 Lumbar BMDs at 24 months | 1 | 32 | Weighted Mean Difference (Fixed) 95% CI | -0.08 [-0.19, 0.03] |
| 03 Femur BMDs at 12 months | | | Weighted Mean Difference (Fixed) 95% CI | Subtotals only |
| 04 Femur BMDs at 24 months | | | Weighted Mean Difference (Fixed) 95% CI | Subtotals only |

### Comparison 07. HT plus testosterone versus HT on body composition

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Body composition | | | Weighted Mean Difference (Fixed) 95% CI | Subtotals only |
| 02 Weight | 1 | 37 | Weighted Mean Difference (Fixed) 95% CI | 1.18 [-0.25, 2.61] |
| 03 Body mass index | 0 | 0 | Weighted Mean Difference (Fixed) 95% CI | Not estimable |

### Comparison 08. HT plus testosterone versus HT on cognition

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Cognitive performance | | | Weighted Mean Difference (Fixed) 95% CI | Subtotals only |

### Comparison 10. HT plus testosterone versus HT on hirsutism

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Mean scores of hirsutism | | | Weighted Mean Difference (Fixed) 95% CI | Subtotals only |

### Comparison 11. HT plus testosterone versus HT on acne

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Mean scores of acne | 1 | 216 | Weighted Mean Difference (Fixed) 95% CI | 0.10 [-0.03, 0.23] |

**Comparison 17. HT plus testosterone versus HT on lipid profile**

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Total cholesterol at less than 3 months | | | Weighted Mean Difference (Fixed) 95% CI | Totals not selected |
| 02 Triglyceride at less than 3 months | | | Weighted Mean Difference (Random) 95% CI | Totals not selected |
| 03 LDL cholesterol at less than 3 months | | | Weighted Mean Difference (Random) 95% CI | Totals not selected |
| 04 HDL cholesterol at less than 3 months | 2 | 57 | Weighted Mean Difference (Random) 95% CI | -15.92 [-31.13, -0.71] |
| 05 Total cholesterol/ HDL at less than 3 months | 0 | 0 | Weighted Mean Difference (Fixed) 95% CI | Not estimable |
| 06 Total cholesterol at 3-12 months | 6 | 391 | Weighted Mean Difference (Random) 95% CI | -11.59 [-20.98, -2.20] |
| 07 Triglyceride at 3-12 months | 6 | 391 | Weighted Mean Difference (Random) 95% CI | -16.01 [-35.25, 3.23] |
| 08 LDL cholesterol at 3-12 months | 6 | 391 | Weighted Mean Difference (Random) 95% CI | 7.74 [-3.88, 19.36] |
| 09 HDL cholesterol lipid profiles at 3-12 months | 6 | 391 | Weighted Mean Difference (Random) 95% CI | -16.02 [-19.90, -12.14] |
| 10 Total cholesterol/HDL at 3-12 months | 1 | 45 | Weighted Mean Difference (Fixed) 95% CI | 20.60 [12.76, 28.44] |
| 11 Total cholesterol at 12 months | 3 | 194 | Weighted Mean Difference (Random) 95% CI | -8.79 [-28.01, 10.44] |
| 12 Triglyceride at 12 months | 3 | 194 | Weighted Mean Difference (Random) 95% CI | -33.88 [-67.18, -0.59] |
| 13 LDL cholesterol at 12 months | 3 | 194 | Weighted Mean Difference (Fixed) 95% CI | 9.32 [2.30, 16.34] |
| 14 HDL cholesterol at 12 months | 3 | 194 | Weighted Mean Difference (Random) 95% CI | -16.25 [-29.15, -3.34] |
| 15 Total cholesterol/HDL at 12 months | 1 | 45 | Weighted Mean Difference (Fixed) 95% CI | 15.40 [4.40, 26.40] |
| 16 Total cholesterol at 24 months | 3 | 167 | Weighted Mean Difference (Random) 95% CI | -11.69 [-32.36, 8.97] |
| 17 Triglyceride at 24 months | 3 | 167 | Weighted Mean Difference (Random) 95% CI | -47.53 [-77.18, -17.89] |
| 18 LDL cholesterol at 24 months | 3 | 167 | Weighted Mean Difference (Fixed) 95% CI | 9.15 [1.09, 17.20] |
| 19 HDL cholesterol at 24 months | 3 | 167 | Weighted Mean Difference (Random) 95% CI | -17.63 [-31.45, -3.80] |
| 20 Total cholesterol/HDL at 24 months | 1 | 45 | Weighted Mean Difference (Fixed) 95% CI | 20.80 [11.00, 30.60] |

**Comparison 18. HT plus testosterone versus HT on coagulation profile**

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Mean levels of plasma viscosity and fibrinogen levels | | | Weighted Mean Difference (Fixed) 95% CI | Subtotals only |

**Comparison 19. HT plus testosterone versus HT on discontinuation rate**

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Discontinuation rate (overall) | 15 | 1364 | Peto Odds Ratio 95% CI | 1.01 [0.76, 1.33] |
| 02 Discontinuation rate (type of menopause) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 03 Discontinuation rate (menopausal status) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 04 Discontinuation rate (route of hormone therapy) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 05 Discontinuation rate (type of testosterone) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 06 Discontinuation rate (duration of treatment) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 07 Discontinuation rate (blinding) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 08 Discontinuation rate (disease status) | | | Peto Odds Ratio 95% CI | Subtotals only |

**Comparison 20. HT plus testosterone versus HT on discontinuation rate due to adverse events**

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Discontinuation rate due to adverse events (overall) | 15 | 1364 | Peto Odds Ratio 95% CI | 1.28 [0.85, 1.92] |
| 02 Discontinuation rate due to adverse events (type of menopause) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 03 Discontinuation rate due to adverse events (menopausal status) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 04 Discontinuation rate due to adverse events (route of hormone therapy) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 05 Discontinuation rate due to adverse events (type of testosterone) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 06 Discontinuation rate due to adverse events (duration of treatment) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 07 Discontinuation rate due to adverse events (blinding) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 08 Discontinuation rate due to adverse events (disease status) | | | Peto Odds Ratio 95% CI | Subtotals only |

**Comparison 22. HT-T versus HT on discontinuation rate (sensitivity analysis)**

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Discontinuation rate (allocation quality) | 10 | 964 | Peto Odds Ratio 95% CI | 0.96 [0.69, 1.33] |
| 02 Discontinuation rate due to adverse events (allocation quality) | 10 | 964 | Peto Odds Ratio 95% CI | 1.31 [0.80, 2.14] |
| 03 Discontinuation rate (quality of randomization) | 12 | 1010 | Peto Odds Ratio 95% CI | 0.93 [0.67, 1.29] |
| 04 Discontinuation rate due to adverse events (quality of randomization) | 12 | 1010 | Peto Odds Ratio 95% CI | 1.31 [0.80, 2.14] |
| 05 Discontinuation rate (blinding method) | 11 | 1239 | Peto Odds Ratio 95% CI | 0.97 [0.73, 1.28] |
| 06 Discontinuation rate due to adverse events (blinding method) | 11 | 1239 | Peto Odds Ratio 95% CI | 1.21 [0.79, 1.84] |
| 07 Discontinuation rate (large studies) | 12 | 609 | Peto Odds Ratio 95% CI | 1.28 [0.73, 2.25] |
| 08 Discontinuation rate due to adverse events (large studies) | 12 | 609 | Peto Odds Ratio 95% CI | 1.30 [0.48, 3.53] |
| 09 Discontinuation rate (crossover studies) | 12 | 1094 | Peto Odds Ratio 95% CI | 1.02 [0.76, 1.37] |
| 10 Discontinuation rate due to adverse events (crossover studies) | 12 | 1094 | Peto Odds Ratio 95% CI | 1.39 [0.91, 2.11] |
| 11 Discontinuation rate (methyltestosterone doses) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 12 Discontinuation rate due to adverse events (methyltestosterone doses) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 13 Discontinuation rate (estrogen doses) | | | Peto Odds Ratio 95% CI | Subtotals only |
| 14 Discontinuation rate due to adverse events (estrogen doses) | | | Peto Odds Ratio 95% CI | Subtotals only |

## 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; Testosterone [*administration & dosage; adverse effects; blood]

### MeSH check words

Female; Humans

## COVER SHEET

**Title** Testosterone for peri- and postmenopausal women

| | |
|---|---|
| **Authors** | Somboonporn W, Davis S, Seif MW, Bell R |
| **Contribution of author(s)** | 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<br>Davis S: reviewing selection of studies, reviewing data extraction, co-drafting of the protocol and review, supervision of data presentation, results interpretation, and publication<br>Bell R: review of searching, selection of studies, appraising quality of articles, data extraction, co-drafting of the protocol/review, assistance with statistics and data analysis<br>Seif M: design of the review, developing search strategies, appraising quality of papers, providing gynaecological clinical perspective, screening studies against inclusion and exclusion criteria, writing of review. |
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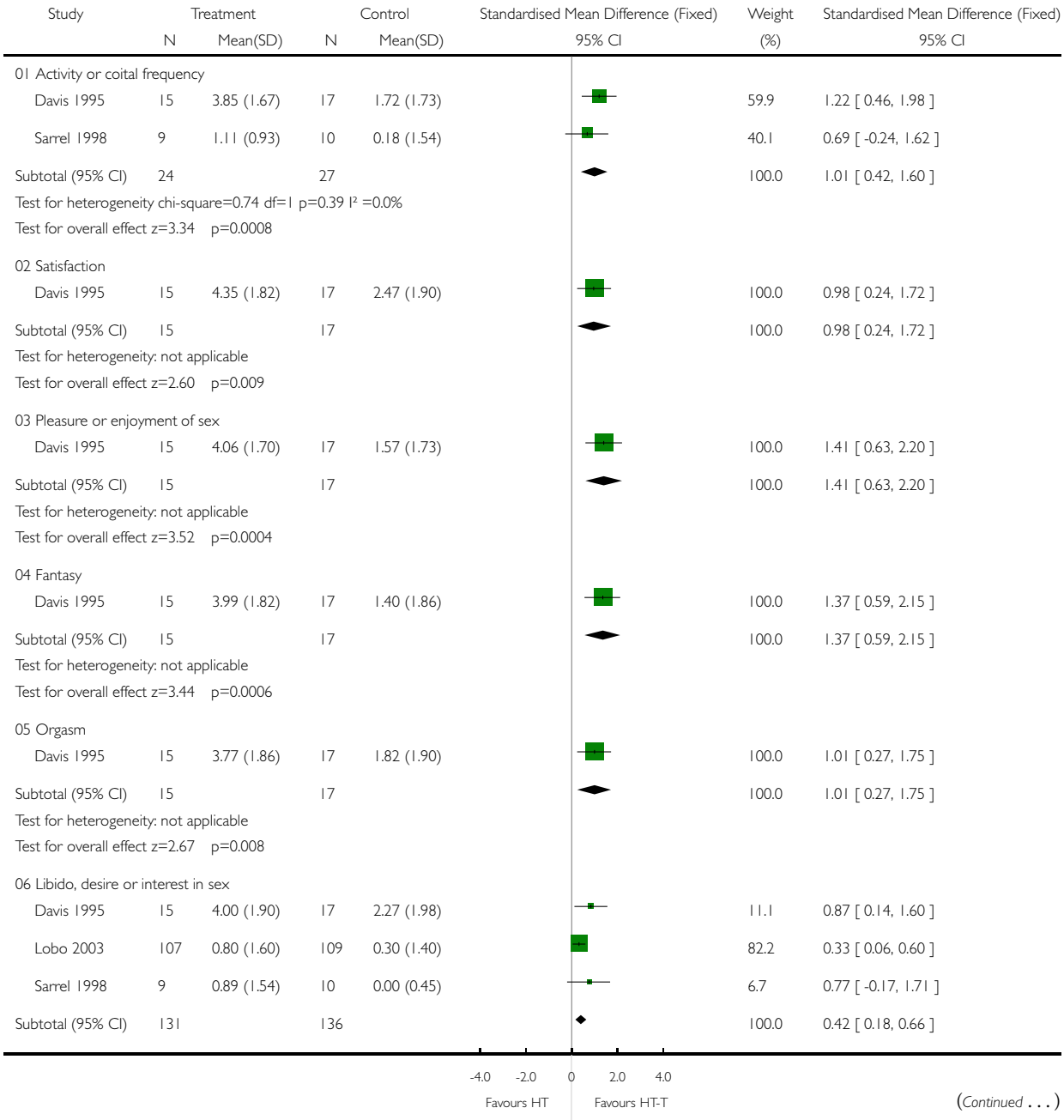
## GRAPHS AND OTHER TABLES

## Analysis 03.01. Comparison 03 HT plus testosterone versus HT on sexual function, Outcome 01 Change scores of sexual function

Review: Testosterone for peri- and postmenopausal women

Comparison: 03 HT plus testosterone versus HT on sexual function

Outcome: 01 Change scores of sexual function

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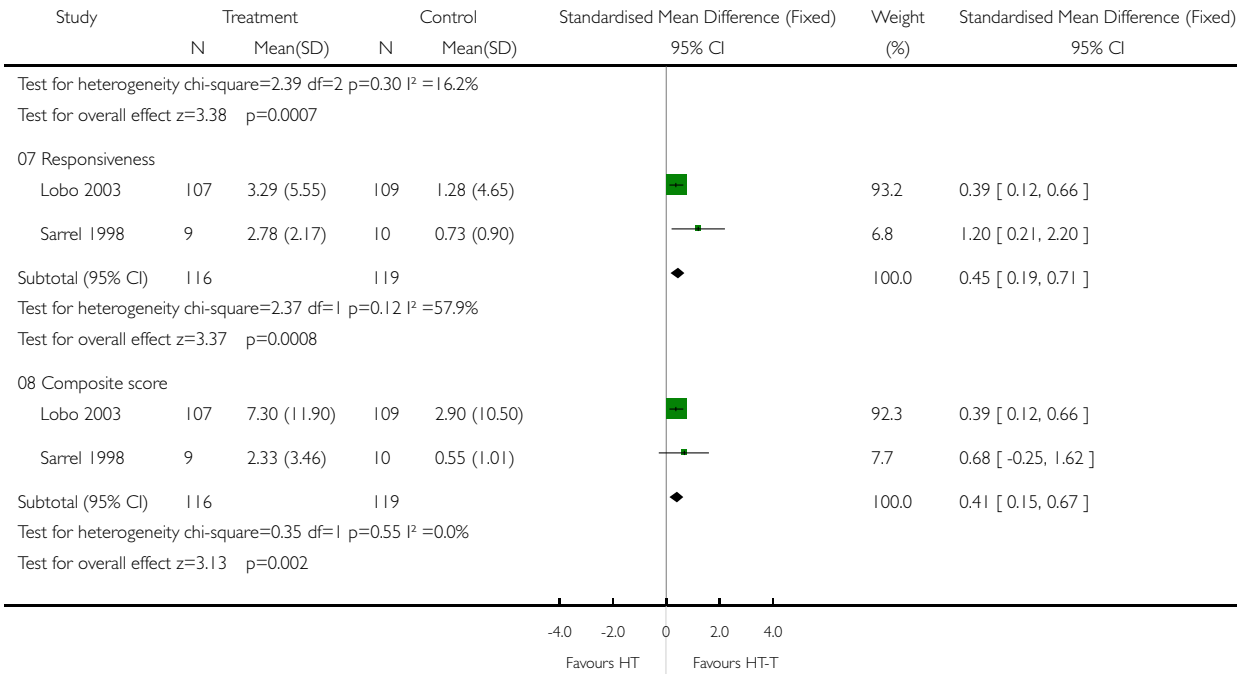
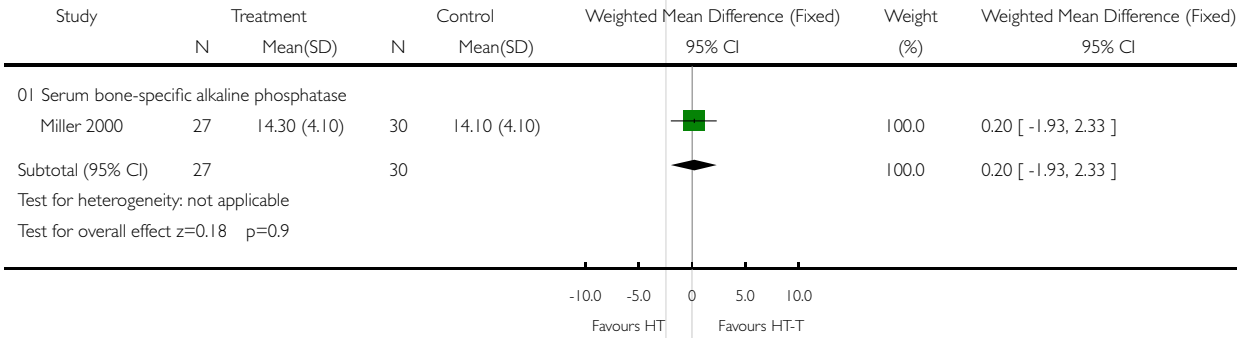



## Analysis 05.01. Comparison 05 HT plus testosterone versus HT on biochemical markers of bone turnover, Outcome 01 Biochemical markers of bone turnover at 12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 05 HT plus testosterone versus HT on biochemical markers of bone turnover

Outcome: 01 Biochemical markers of bone turnover at 12 months

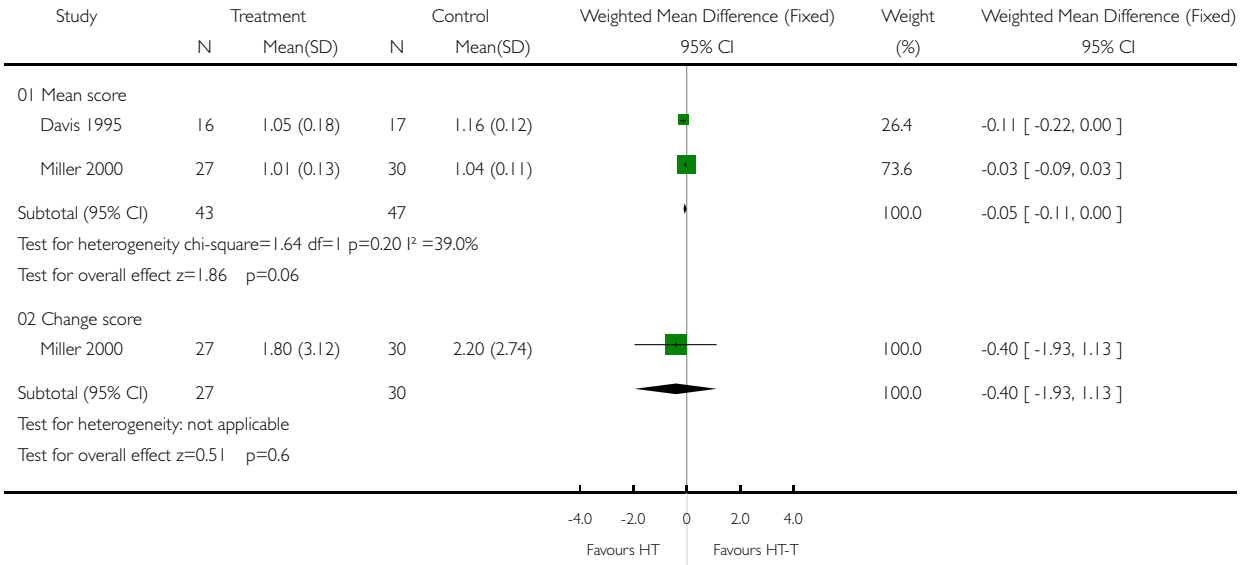


### Analysis 06.01. Comparison 06 HT plus testosterone versus HT on bone mineral density, Outcome 01 Lumbar BMDs at 12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 06 HT plus testosterone versus HT on bone mineral density

Outcome: 01 Lumbar BMDs at 12 months

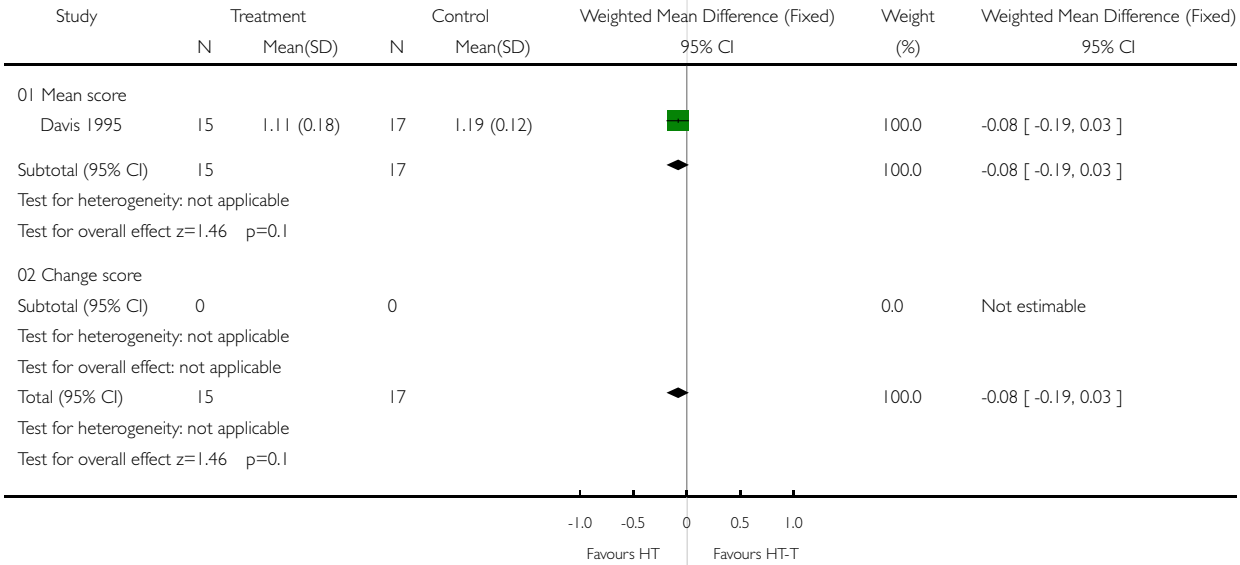



### Analysis 06.02. Comparison 06 HT plus testosterone versus HT on bone mineral density, Outcome 02 Lumbar BMDs at 24 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 06 HT plus testosterone versus HT on bone mineral density

Outcome: 02 Lumbar BMDs at 24 months



## Analysis 06.03. Comparison 06 HT plus testosterone versus HT on bone mineral density, Outcome 03 Femur BMDs at 12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 06 HT plus testosterone versus HT on bone mineral density

Outcome: 03 Femur BMDs at 12 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean score | | | | | | | |
| Davis 1995 | 16 | 0.76 (0.13) | 17 | 0.83 (0.09) | | 32.8 | -0.07 [ -0.15, 0.01 ] |
| Miller 2000 | 27 | 0.89 (0.12) | 30 | 0.93 (0.08) | | 67.2 | -0.04 [ -0.09, 0.01 ] |
| Subtotal (95% CI) | 43 | | 47 | | | 100.0 | -0.05 [ -0.09, -0.01 ] |
| Test for heterogeneity chi-square=0.39 df=1 p=0.53 $I^2$ =0.0% | | | | | | | |
| Test for overall effect z=2.22 p=0.03 | | | | | | | |
| 02 Change score | | | | | | | |
| Miller 2000 | 27 | 1.80 (2.60) | 30 | 0.40 (2.19) | | 100.0 | 1.40 [ 0.14, 2.66 ] |
| Subtotal (95% CI) | 27 | | 30 | | | 100.0 | 1.40 [ 0.14, 2.66 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=2.19 p=0.03 | | | | | | | |

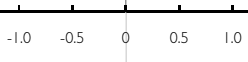

## Analysis 06.04. Comparison 06 HT plus testosterone versus HT on bone mineral density, Outcome 04 Femur BMDs at 24 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 06 HT plus testosterone versus HT on bone mineral density

Outcome: 04 Femur BMDs at 24 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean score | | | | | | | |
| Davis 1995 | 15 | 0.77 (0.14) | 17 | 0.84 (0.10) | | 100.0 | -0.07 [ -0.16, 0.02 ] |
| Subtotal (95% CI) | 15 | | 17 | | | 100.0 | -0.07 [ -0.16, 0.02 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=1.61 p=0.1 | | | | | | | |
| 02 Change score | | | | | | | |
| Subtotal (95% CI) | 0 | | 0 | | | 0.0 | Not estimable |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |



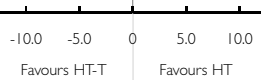
## Analysis 07.01. Comparison 07 HT plus testosterone versus HT on body composition, Outcome 01 Body composition

Review: Testosterone for peri- and postmenopausal women

Comparison: 07 HT plus testosterone versus HT on body composition

Outcome: 01 Body composition

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Total body fat mass | | | | | | | |
| Davis 1995 | 15 | 35.90 (8.00) | 17 | 35.10 (6.60) | | 100.0 | 0.80 [ -4.32, 5.92 ] |
| Subtotal (95% CI) | 15 | | 17 | | | 100.0 | 0.80 [ -4.32, 5.92 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.31 p=0.8 | | | | | | | |
| 02 Total body fat free mass | | | | | | | |
| Davis 1995 | 15 | 27.90 (5.90) | 17 | 28.20 (5.80) | | 100.0 | -0.30 [ -4.36, 3.76 ] |
| Subtotal (95% CI) | 15 | | 17 | | | 100.0 | -0.30 [ -4.36, 3.76 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.14 p=0.9 | | | | | | | |
| 03 Fat mass: fat-free mass ratio | | | | | | | |
| Davis 1995 | 15 | 1.38 (0.52) | 17 | 1.31 (0.42) | | 100.0 | 0.07 [ -0.26, 0.40 ] |
| Subtotal (95% CI) | 15 | | 17 | | | 100.0 | 0.07 [ -0.26, 0.40 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.42 p=0.7 | | | | | | | |
| 04 Fat mass over abdomen | | | | | | | |
| Davis 1995 | 15 | 1.64 (0.65) | 17 | 1.43 (0.59) | | 100.0 | 0.21 [ -0.22, 0.64 ] |
| Subtotal (95% CI) | 15 | | 17 | | | 100.0 | 0.21 [ -0.22, 0.64 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.95 p=0.3 | | | | | | | |
| 05 FFM over abdomen | | | | | | | |
| Davis 1995 | 15 | 3.31 (0.38) | 17 | 3.30 (0.52) | | 100.0 | 0.01 [ -0.30, 0.32 ] |
| Subtotal (95% CI) | 15 | | 17 | | | 100.0 | 0.01 [ -0.30, 0.32 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.06 p=1 | | | | | | | |
| 06 FM:FFM over the abdomen | | | | | | | |
| Davis 1995 | 15 | 0.51 (0.21) | 17 | 0.42 (0.14) | | 100.0 | 0.09 [ -0.04, 0.22 ] |
| Subtotal (95% CI) | 15 | | 17 | | | 100.0 | 0.09 [ -0.04, 0.22 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=1.41 p=0.2 | | | | | | | |
| 07 WHO abdominal circumference | | | | | | | |
| Davis 1995 | 15 | 89.90 (9.30) | 17 | 88.40 (11.80) | | 100.0 | 1.50 [ -5.82, 8.82 ] |

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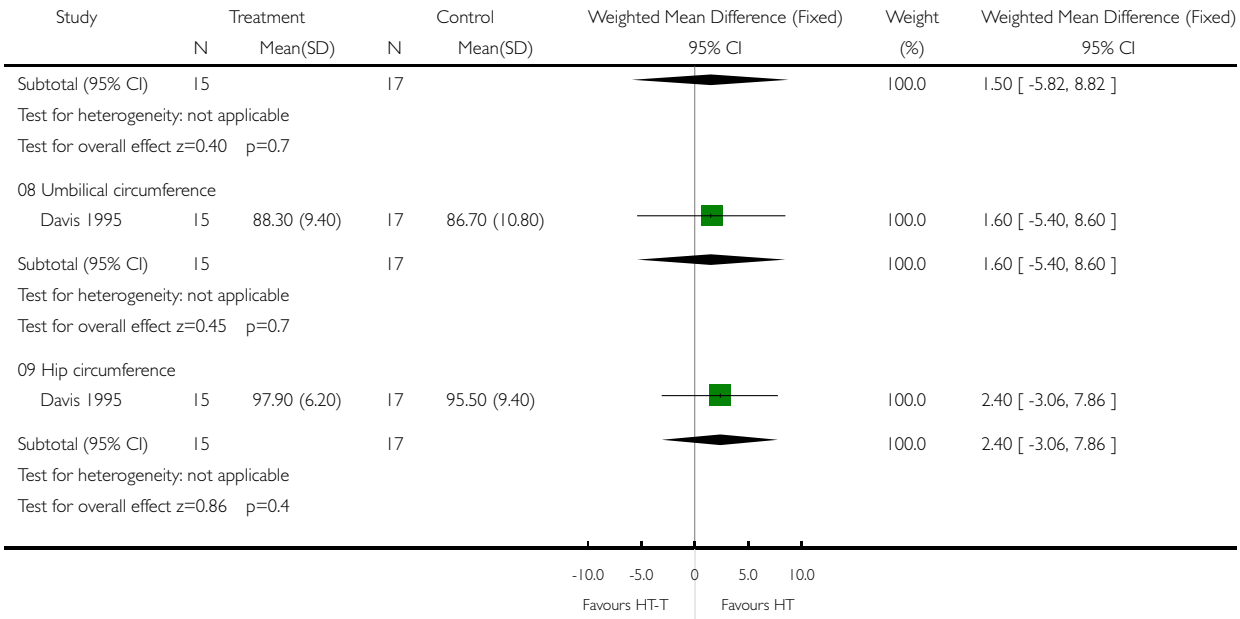
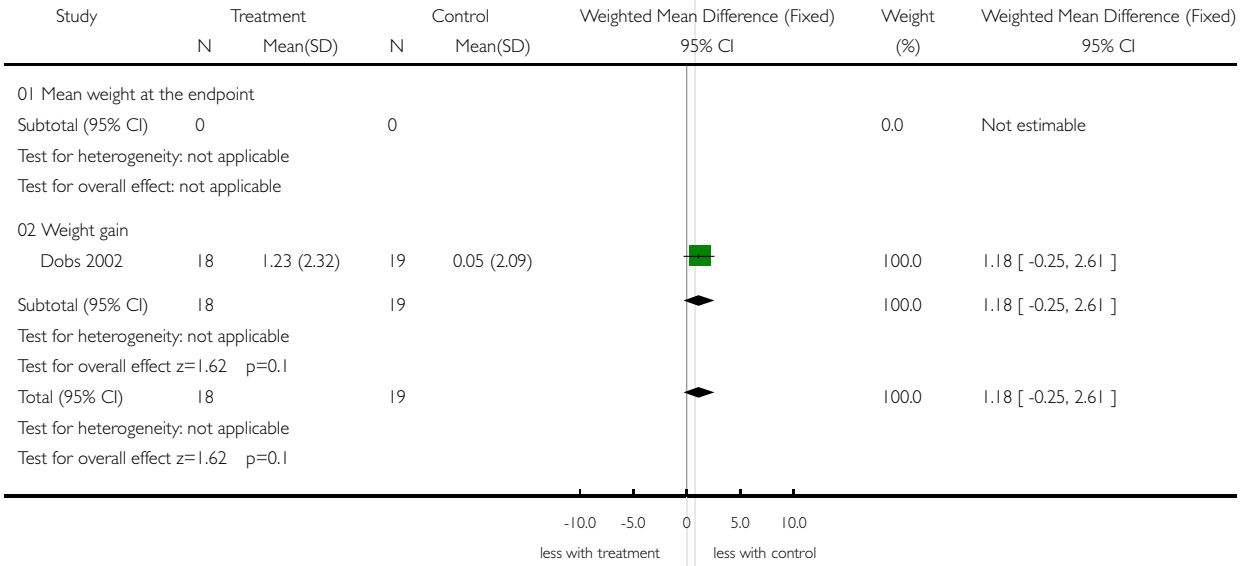



## Analysis 07.02. Comparison 07 HT plus testosterone versus HT on body composition, Outcome 02 Weight

Review: Testosterone for peri- and postmenopausal women

Comparison: 07 HT plus testosterone versus HT on body composition

Outcome: 02 Weight



### Analysis 07.03. Comparison 07 HT plus testosterone versus HT on body composition, Outcome 03 Body mass index

Review: Testosterone for peri- and postmenopausal women

Comparison: 07 HT plus testosterone versus HT on body composition

Outcome: 03 Body mass index

| Study | Treatment N Mean(SD) | Control N Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|
| Total (95% CI) | 0 | 0 | | 0.0 | Not estimable |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |


### Analysis 08.01. Comparison 08 HT plus testosterone versus HT on cognition, Outcome 01 Cognitive performance

Review: Testosterone for peri- and postmenopausal women

Comparison: 08 HT plus testosterone versus HT on cognition

Outcome: 01 Cognitive performance

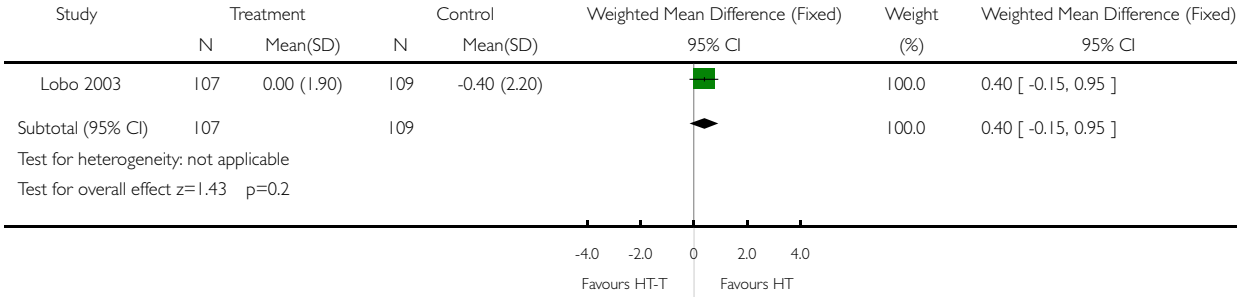
| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Identical Pictures | | | | | | | |
| Dobs 2002 | 13 | 21.80 (6.50) | 13 | 24.20 (4.40) | | 100.0 | -2.40 [ -6.67, 1.87 ] |
| Subtotal (95% CI) | 13 | | 13 | | | 100.0 | -2.40 [ -6.67, 1.87 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=1.10 p=0.3 | | | | | | | |
| 02 Shape Memory | | | | | | | |
| Dobs 2002 | 13 | 12.20 (2.20) | 13 | 12.10 (3.60) | | 100.0 | 0.10 [ -2.19, 2.39 ] |
| Subtotal (95% CI) | 13 | | 13 | | | 100.0 | 0.10 [ -2.19, 2.39 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.09 p=0.9 | | | | | | | |

### Analysis 10.01. Comparison 10 HT plus testosterone versus HT on hirsutism, Outcome 01 Mean scores of hirsutism

Review: Testosterone for peri- and postmenopausal women

Comparison: 10 HT plus testosterone versus HT on hirsutism

Outcome: 01 Mean scores of hirsutism

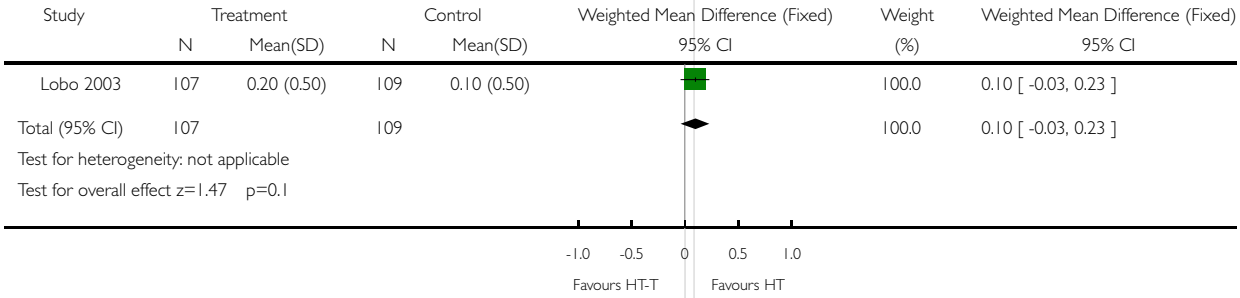



### Analysis 11.01. Comparison 11 HT plus testosterone versus HT on acne, Outcome 01 Mean scores of acne

Review: Testosterone for peri- and postmenopausal women

Comparison: 11 HT plus testosterone versus HT on acne

Outcome: 01 Mean scores of acne

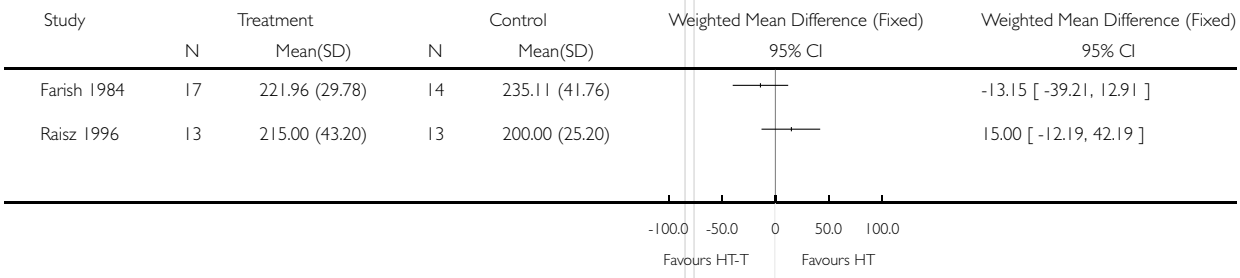



### Analysis 17.01. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 01 Total cholesterol at less than 3 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 01 Total cholesterol at less than 3 months



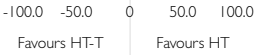
### Analysis 17.02. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 02 Triglyceride at less than 3 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 02 Triglyceride at less than 3 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|
| Farish 1984 | 17 | 114.26 (38.09) | 14 | 104.50 (32.78) | | 9.76 [ -15.19, 34.71 ] |
| Raisz 1996 | 13 | 94.00 (57.60) | 13 | 157.00 (64.80) | | -63.00 [ -110.13, -15.87 ] |




### Analysis 17.03. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 03 LDL cholesterol at less than 3 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 03 LDL cholesterol at less than 3 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|
| Farish 1984 | 17 | 148.88 (24.75) | 14 | 158.56 (40.99) | | -9.68 [ -34.16, 14.80 ] |
| Raisz 1996 | 13 | 154.00 (39.66) | 13 | 104.00 (32.40) | | 50.00 [ 22.16, 77.84 ] |


### Analysis 17.04. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 04 HDL cholesterol at less than 3 months

Review: Testosterone for peri- and postmenopausal women

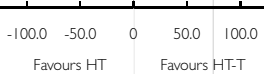
Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 04 HDL cholesterol at less than 3 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| Farish 1984 | 17 | 57.23 (11.21) | 14 | 66.13 (8.51) | | 55.0 | -8.90 [ -15.85, -1.95 ] |
| Raisz 1996 | 13 | 45.10 (9.40) | 13 | 69.60 (19.80) | | 45.0 | -24.50 [ -36.41, -12.59 ] |
| Total (95% CI) | 30 | | 27 | | | 100.0 | -15.92 [ -31.13, -0.71 ] |

Test for heterogeneity chi-square=4.91 df=1 p=0.03 $I^2$ =79.7%

Test for overall effect z=2.05 p=0.04



### Analysis 17.05. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 05 Total cholesterol/ HDL at less than 3 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 05 Total cholesterol/ HDL at less than 3 months

| Study | Treatment N Mean(SD) | Control N Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|
| Total (95% CI) | 0 | 0 | | 0.0 | Not estimable |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |

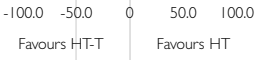

### Analysis 17.06. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 06 Total cholesterol at 3-12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 06 Total cholesterol at 3-12 months

| Study | Treatment N | Mean(SD) | Control N | Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean score | | | | | | | |
| Dobs 2002 | 20 | 212.69 (38.67) | 20 | 208.82 (19.34) | | 13.0 | 3.87 [ -15.08, 22.82 ] |
| Farish 1984 | 17 | 223.51 (36.74) | 14 | 232.79 (47.18) | | 7.1 | -9.28 [ -39.54, 20.98 ] |
| Penotti 2001 | 15 | 223.50 (33.30) | 18 | 226.30 (24.61) | | 12.1 | -2.80 [ -23.13, 17.53 ] |
| Subtotal (95% CI) | 52 | | 52 | | | 32.2 | -0.97 [ -13.58, 11.63 ] |
| Test for heterogeneity chi-square=0.57 df=2 p=0.75 I² =0.0% | | | | | | | |
| Test for overall effect z=0.15 p=0.9 | | | | | | | |
| 02 Change score | | | | | | | |
| Hickok 1993 | 13 | -33.31 (16.84) | 13 | -6.15 (15.00) | | 18.8 | -27.16 [ -39.42, -14.90 ] |
| Lobo 2003 | 106 | -16.80 (26.10) | 110 | 2.40 (26.10) | | 24.0 | -19.20 [ -26.16, -12.24 ] |
| Watts 1995 | 22 | -14.80 (11.18) | 23 | -9.30 (8.73) | | 25.0 | -5.50 [ -11.38, 0.38 ] |
| Subtotal (95% CI) | 141 | | 146 | | | 67.8 | -16.47 [ -28.71, -4.24 ] |
| Test for heterogeneity chi-square=14.42 df=2 p=0.0007 I² =86.1% | | | | | | | |
| Test for overall effect z=2.64 p=0.008 | | | | | | | |
| Total (95% CI) | 193 | | 198 | | | 100.0 | -11.59 [ -20.98, -2.20 ] |
| Test for heterogeneity chi-square=18.19 df=5 p=0.003 I² =72.5% | | | | | | | |
| Test for overall effect z=2.42 p=0.02 | | | | | | | |



## Analysis 17.07. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 07 Triglyceride at 3-12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 07 Triglyceride at 3-12 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean score | | | | | | | |
| Dobs 2002 | 20 | 115.14 (62.00) | 20 | 159.43 (70.86) | | 11.3 | -44.29 [ -85.55, -3.03 ] |
| Farish 1984 | 17 | 112.48 (31.00) | 14 | 100.97 (46.06) | | 15.5 | 11.51 [ -16.76, 39.78 ] |
| Penotti 2001 | 15 | 94.00 (29.43) | 18 | 85.30 (36.49) | | 17.7 | 8.70 [ -13.79, 31.19 ] |
| Subtotal (95% CI) | 52 | | 52 | | | 44.5 | -3.71 [ -32.50, 25.07 ] |
| Test for heterogeneity chi-square=5.61 df=2 p=0.06 I² =64.3% | | | | | | | |
| Test for overall effect z=0.25 p=0.8 | | | | | | | |
| 02 Change score | | | | | | | |
| Hickok 1993 | 13 | 3.38 (38.86) | 13 | 8.15 (36.69) | | 15.2 | -4.77 [ -33.82, 24.28 ] |
| Lobo 2003 | 106 | -31.10 (51.80) | 110 | -7.50 (50.00) | | 20.9 | -23.60 [ -37.18, -10.02 ] |
| Watts 1995 | 22 | -29.80 (22.60) | 23 | 15.20 (38.30) | | 19.3 | -45.00 [ -63.28, -26.72 ] |
| Subtotal (95% CI) | 141 | | 146 | | | 55.5 | -26.60 [ -46.29, -6.92 ] |
| Test for heterogeneity chi-square=6.18 df=2 p=0.05 I² =67.6% | | | | | | | |
| Test for overall effect z=2.65 p=0.008 | | | | | | | |
| Total (95% CI) | 193 | | 198 | | | 100.0 | -16.01 [ -35.25, 3.23 ] |
| Test for heterogeneity chi-square=20.86 df=5 p=0.0009 I² =76.0% | | | | | | | |
| Test for overall effect z=1.63 p=0.1 | | | | | | | |

## Analysis 17.08. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 08 LDL cholesterol at 3-12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 08 LDL cholesterol at 3-12 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean score | | | | | | | |
| Dobs 2002 | 20 | 158.55 (34.80) | 20 | 119.88 (19.34) | | 15.5 | 38.67 [ 21.22, 56.12 ] |
| Farish 1984 | 17 | 150.04 (30.94) | 14 | 153.52 (44.86) | | 10.1 | -3.48 [ -31.20, 24.24 ] |
| Penotti 2001 | 15 | 153.30 (37.18) | 18 | 141.90 (23.33) | | 13.0 | 11.40 [ -10.28, 33.08 ] |
| Subtotal (95% CI) | 52 | | 52 | | | 38.6 | 17.21 [ -7.63, 42.06 ] |
| Test for heterogeneity chi-square=7.67 df=2 p=0.02 I² =73.9% | | | | | | | |
| Test for overall effect z=1.36 p=0.2 | | | | | | | |
| 02 Change score | | | | | | | |
| Hickok 1993 | 13 | -19.31 (14.96) | 13 | -10.08 (16.53) | | 18.9 | -9.23 [ -21.35, 2.89 ] |
| Lobo 2003 | 106 | 1.70 (23.10) | 110 | 1.00 (24.00) | | 22.3 | 0.70 [ -5.58, 6.98 ] |
| Watts 1995 | 22 | -5.90 (21.10) | 23 | -16.80 (11.70) | | 20.2 | 10.90 [ 0.87, 20.93 ] |
| Subtotal (95% CI) | 141 | | 146 | | | 61.4 | 1.22 [ -8.42, 10.86 ] |
| Test for heterogeneity chi-square=6.45 df=2 p=0.04 I² =69.0% | | | | | | | |
| Test for overall effect z=0.25 p=0.8 | | | | | | | |
| Total (95% CI) | 193 | | 198 | | | 100.0 | 7.74 [ -3.88, 19.36 ] |
| Test for heterogeneity chi-square=23.33 df=5 p=0.0003 I² =78.6% | | | | | | | |
| Test for overall effect z=1.30 p=0.2 | | | | | | | |

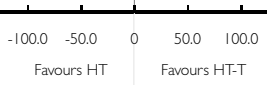
### Analysis 17.09. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 09 HDL cholesterol lipid profiles at 3-12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 09 HDL cholesterol lipid profiles at 3-12 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean score | | | | | | | |
| Dobs 2002 | 20 | 30.94 (3.87) | 20 | 54.14 (15.47) | | 14.8 | -23.20 [ -30.19, -16.21 ] |
| Farish 1984 | 17 | 58.39 (13.15) | 14 | 65.74 (9.28) | | 13.0 | -7.35 [ -15.27, 0.57 ] |
| Penotti 2001 | 15 | 52.30 (11.23) | 18 | 62.70 (8.91) | | 14.8 | -10.40 [ -17.42, -3.38 ] |
| Subtotal (95% CI) | 52 | | 52 | | | 42.6 | -13.76 [ -23.35, -4.16 ] |
| Test for heterogeneity chi-square=10.37 df=2 p=0.006 I² =80.7% | | | | | | | |
| Test for overall effect z=2.81 p=0.005 | | | | | | | |
| 02 Change score | | | | | | | |
| Hickok 1993 | 13 | -14.54 (4.77) | 13 | 2.15 (5.40) | | 22.1 | -16.69 [ -20.61, -12.77 ] |
| Lobo 2003 | 106 | -12.40 (11.40) | 110 | 3.20 (11.00) | | 24.4 | -15.60 [ -18.59, -12.61 ] |
| Watts 1995 | 22 | -18.40 (19.50) | 23 | 5.50 (10.90) | | 10.8 | -23.90 [ -33.19, -14.61 ] |
| Subtotal (95% CI) | 141 | | 146 | | | 57.4 | -16.80 [ -19.78, -13.82 ] |
| Test for heterogeneity chi-square=2.80 df=2 p=0.25 I² =28.5% | | | | | | | |
| Test for overall effect z=11.03 p<0.00001 | | | | | | | |
| Total (95% CI) | 193 | | 198 | | | 100.0 | -16.02 [ -19.90, -12.14 ] |
| Test for heterogeneity chi-square=14.07 df=5 p=0.02 I² =64.5% | | | | | | | |
| Test for overall effect z=8.09 p<0.00001 | | | | | | | |



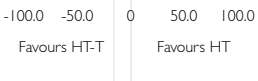

### Analysis 17.10. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 10 Total cholesterol/HDL at 3-12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 10 Total cholesterol/HDL at 3-12 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Change score | | | | | | | |
| Watts 1995 | 22 | 7.10 (16.40) | 23 | -13.50 (9.30) | | 100.0 | 20.60 [ 12.76, 28.44 ] |
| Total (95% CI) | 22 | | 23 | | | 100.0 | 20.60 [ 12.76, 28.44 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=5.15 p<0.00001 | | | | | | | |



## Analysis 17.11. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 11 Total cholesterol at 12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 11 Total cholesterol at 12 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean score | | | | | | | |
| Davis 1995 | 16 | 232.02 (40.60) | 17 | 224.29 (29.39) | | 25.0 | 7.73 [ -16.58, 32.04 ] |
| Subtotal (95% CI) | 16 | | 17 | | | 25.0 | 7.73 [ -16.58, 32.04 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.62 p=0.5 | | | | | | | |
| 02 Change score | | | | | | | |
| Barrett-Connor 1999 | 55 | -23.40 (28.20) | 61 | 3.50 (36.60) | | 35.9 | -26.90 [ -38.73, -15.07 ] |
| Watts 1995 | 22 | -12.00 (15.20) | 23 | -9.30 (9.70) | | 39.1 | -2.70 [ -10.19, 4.79 ] |
| Subtotal (95% CI) | 77 | | 84 | | | 75.0 | -14.35 [ -38.05, 9.35 ] |
| Test for heterogeneity chi-square=11.48 df=1 p=0.0007 I² =91.3% | | | | | | | |
| Test for overall effect z=1.19 p=0.2 | | | | | | | |
| Total (95% CI) | 93 | | 101 | | | 100.0 | -8.79 [ -28.01, 10.44 ] |
| Test for heterogeneity chi-square=13.31 df=2 p=0.001 I² =85.0% | | | | | | | |
| Test for overall effect z=0.90 p=0.4 | | | | | | | |

## Analysis 17.12. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 12 Triglyceride at 12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 12 Triglyceride at 12 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean score | | | | | | | |
| Davis 1995 | 16 | 150.57 (93.00) | 17 | 150.57 (3.54) | | 25.2 | 0.00 [ -45.60, 45.60 ] |
| Subtotal (95% CI) | 16 | | 17 | | | 25.2 | 0.00 [ -45.60, 45.60 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.00 p=1 | | | | | | | |
| 02 Change score | | | | | | | |
| Barrett-Connor 1999 | 55 | -20.80 (58.20) | 61 | 42.30 (80.30) | | 37.4 | -63.10 [ -88.45, -37.75 ] |
| Watts 1995 | 22 | -20.80 (47.10) | 23 | 6.70 (38.80) | | 37.4 | -27.50 [ -52.77, -2.23 ] |
| Subtotal (95% CI) | 77 | | 84 | | | 74.8 | -45.29 [ -80.17, -10.40 ] |
| Test for heterogeneity chi-square=3.80 df=1 p=0.05 $I^2$ =73.7% | | | | | | | |
| Test for overall effect z=2.54 p=0.01 | | | | | | | |
| Total (95% CI) | 93 | | 101 | | | 100.0 | -33.88 [ -67.18, -0.59 ] |
| Test for heterogeneity chi-square=7.08 df=2 p=0.03 $I^2$ =71.7% | | | | | | | |
| Test for overall effect z=1.99 p=0.05 | | | | | | | |

## Analysis 17.13. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 13 LDL cholesterol at 12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 13 LDL cholesterol at 12 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean score | | | | | | | |
| Davis 1995 | 16 | 143.08 (37.51) | 17 | 135.35 (25.91) | | 10.1 | 7.73 [ -14.39, 29.85 ] |
| Subtotal (95% CI) | 16 | | 17 | | | 10.1 | 7.73 [ -14.39, 29.85 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.68 p=0.5 | | | | | | | |
| 02 Change score | | | | | | | |
| Barrett-Connor 1999 | 55 | -8.20 (23.80) | 61 | -17.90 (28.90) | | 53.4 | 9.70 [ 0.10, 19.30 ] |
| Watts 1995 | 22 | -3.90 (24.60) | 23 | -13.10 (13.20) | | 36.5 | 9.20 [ -2.41, 20.81 ] |
| Subtotal (95% CI) | 77 | | 84 | | | 89.9 | 9.50 [ 2.10, 16.90 ] |
| Test for heterogeneity chi-square=0.00 df=1 p=0.95 $I^2$ =0.0% | | | | | | | |
| Test for overall effect z=2.52 p=0.01 | | | | | | | |
| Total (95% CI) | 93 | | 101 | | | 100.0 | 9.32 [ 2.30, 16.34 ] |
| Test for heterogeneity chi-square=0.03 df=2 p=0.99 $I^2$ =0.0% | | | | | | | |
| Test for overall effect z=2.60 p=0.009 | | | | | | | |

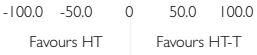
## Analysis 17.14. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 14 HDL cholesterol at 12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 14 HDL cholesterol at 12 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean score | | | | | | | |
| Davis 1995 | 16 | 58.01 (17.01) | 17 | 61.87 (15.47) | | 31.0 | -3.86 [ -14.98, 7.26 ] |
| Subtotal (95% CI) | 16 | | 17 | | | 31.0 | -3.86 [ -14.98, 7.26 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.68 p=0.5 | | | | | | | |
| 02 Change score | | | | | | | |
| Barrett-Connor 1999 | 55 | -12.70 (9.80) | 61 | 12.20 (10.50) | | 38.9 | -24.90 [ -28.59, -21.21 ] |
| Watts 1995 | 22 | -16.60 (21.20) | 23 | 1.20 (19.00) | | 30.1 | -17.80 [ -29.58, -6.02 ] |
| Subtotal (95% CI) | 77 | | 84 | | | 69.0 | -23.64 [ -28.95, -18.33 ] |
| Test for heterogeneity chi-square=1.27 df=1 p=0.26 $I^2$ =21.3% | | | | | | | |
| Test for overall effect z=8.73 p<0.00001 | | | | | | | |
| Total (95% CI) | 93 | | 101 | | | 100.0 | -16.25 [ -29.15, -3.34 ] |
| Test for heterogeneity chi-square=13.03 df=2 p=0.001 $I^2$ =84.7% | | | | | | | |
| Test for overall effect z=2.47 p=0.01 | | | | | | | |

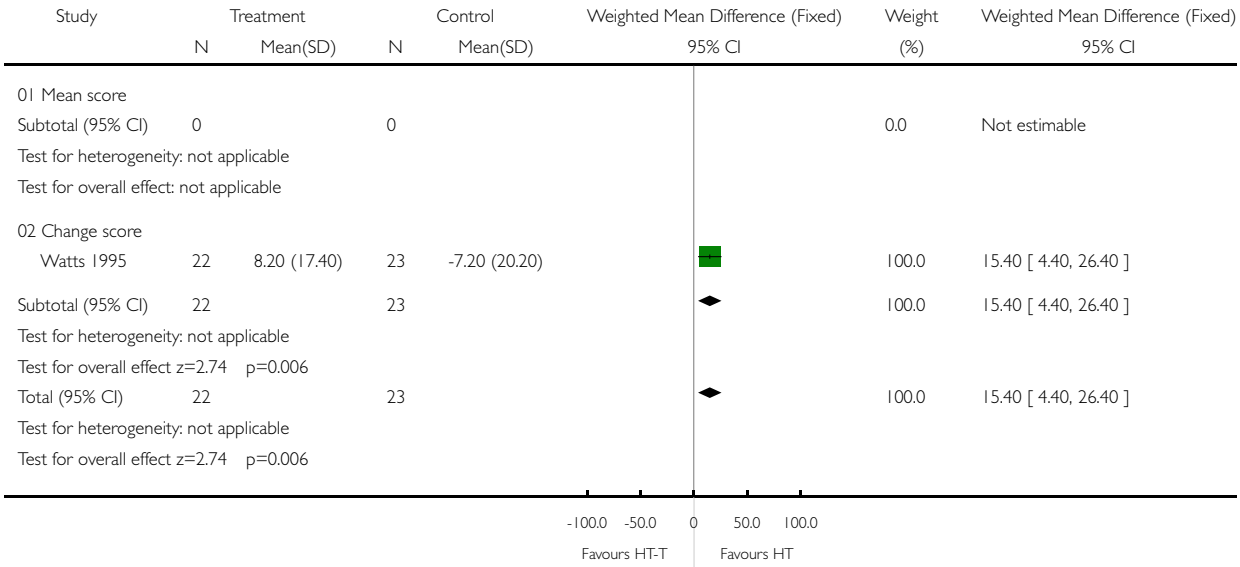


### Analysis 17.15. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 15 Total cholesterol/HDL at 12 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 15 Total cholesterol/HDL at 12 months

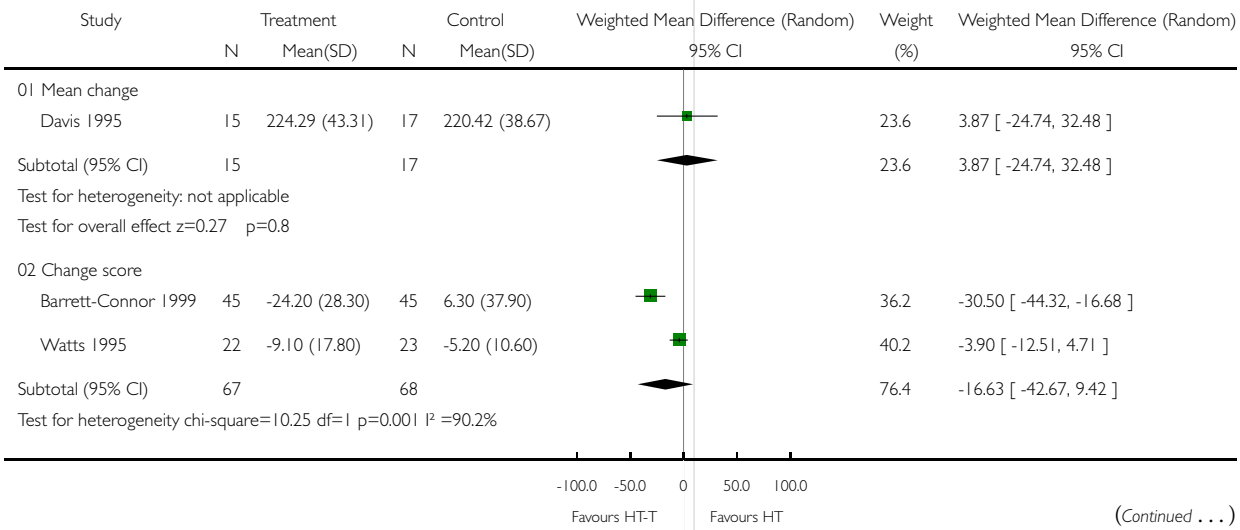



### Analysis 17.16. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 16 Total cholesterol at 24 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 16 Total cholesterol at 24 months

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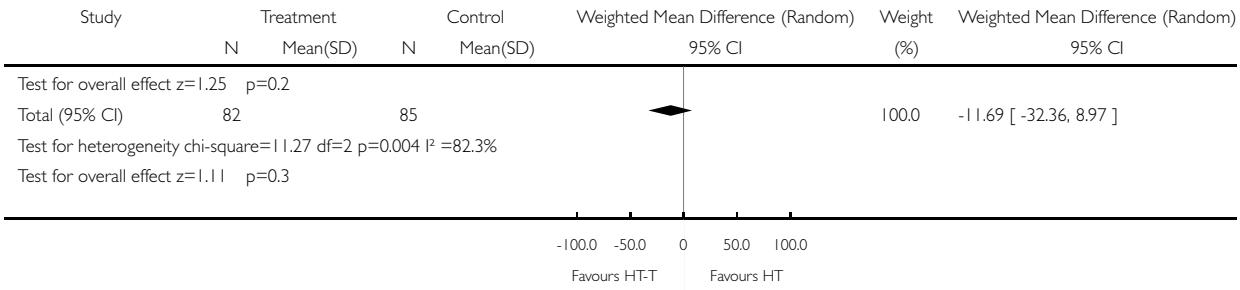
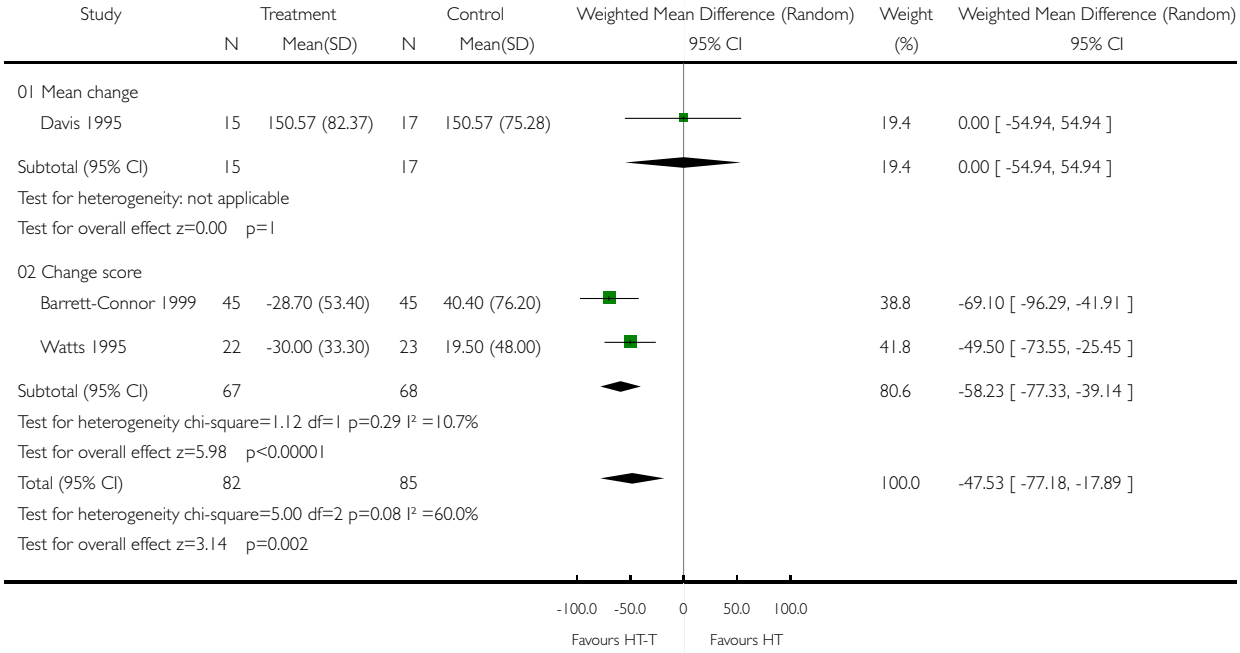



## Analysis 17.17. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 17 Triglyceride at 24 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 17 Triglyceride at 24 months



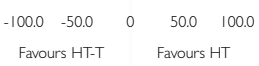
## Analysis 17.18. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 18 LDL cholesterol at 24 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 18 LDL cholesterol at 24 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean change | | | | | | | |
| Davis 1995 | 15 | 131.48 (35.19) | 17 | 127.61 (36.35) | | 10.5 | 3.87 [ -20.94, 28.68 ] |
| Subtotal (95% CI) | 15 | | 17 | | | 10.5 | 3.87 [ -20.94, 28.68 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.31 p=0.8 | | | | | | | |
| 02 Change score | | | | | | | |
| Barrett-Connor 1999 | 45 | -6.00 (22.50) | 45 | -13.10 (30.10) | | 53.8 | 7.10 [ -3.88, 18.08 ] |
| Watts 1995 | 22 | 1.90 (28.80) | 23 | -11.90 (14.90) | | 35.7 | 13.80 [ 0.31, 27.29 ] |
| Subtotal (95% CI) | 67 | | 68 | | | 89.5 | 9.77 [ 1.26, 18.29 ] |
| Test for heterogeneity chi-square=0.57 df=1 p=0.45 $I^2$ =0.0% | | | | | | | |
| Test for overall effect z=2.25 p=0.02 | | | | | | | |
| Total (95% CI) | 82 | | 85 | | | 100.0 | 9.15 [ 1.09, 17.20 ] |
| Test for heterogeneity chi-square=0.76 df=2 p=0.68 $I^2$ =0.0% | | | | | | | |
| Test for overall effect z=2.23 p=0.03 | | | | | | | |



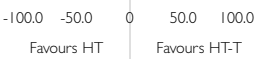
## Analysis 17.19. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 19 HDL cholesterol at 24 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 19 HDL cholesterol at 24 months

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Mean change | | | | | | | |
| Davis 1995 | 15 | 61.87 (18.95) | 17 | 61.87 (14.31) | | 29.9 | 0.00 [ -11.76, 11.76 ] |
| Subtotal (95% CI) | 15 | | 17 | | | 29.9 | 0.00 [ -11.76, 11.76 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.00 p=1 | | | | | | | |
| 02 Change score | | | | | | | |
| Barrett-Connor 1999 | 45 | -17.30 (10.00) | 45 | 9.70 (9.40) | | 37.0 | -27.00 [ -31.01, -22.99 ] |
| Watts 1995 | 22 | -16.40 (17.40) | 23 | 6.70 (12.50) | | 33.0 | -23.10 [ -31.99, -14.21 ] |
| Subtotal (95% CI) | 67 | | 68 | | | 70.1 | -26.34 [ -30.00, -22.69 ] |
| Test for heterogeneity chi-square=0.61 df=1 p=0.43 $I^2$ =0.0% | | | | | | | |
| Test for overall effect z=14.12 p<0.00001 | | | | | | | |
| Total (95% CI) | 82 | | 85 | | | 100.0 | -17.63 [ -31.45, -3.80 ] |
| Test for heterogeneity chi-square=18.20 df=2 p=0.0001 $I^2$ =89.0% | | | | | | | |
| Test for overall effect z=2.50 p=0.01 | | | | | | | |

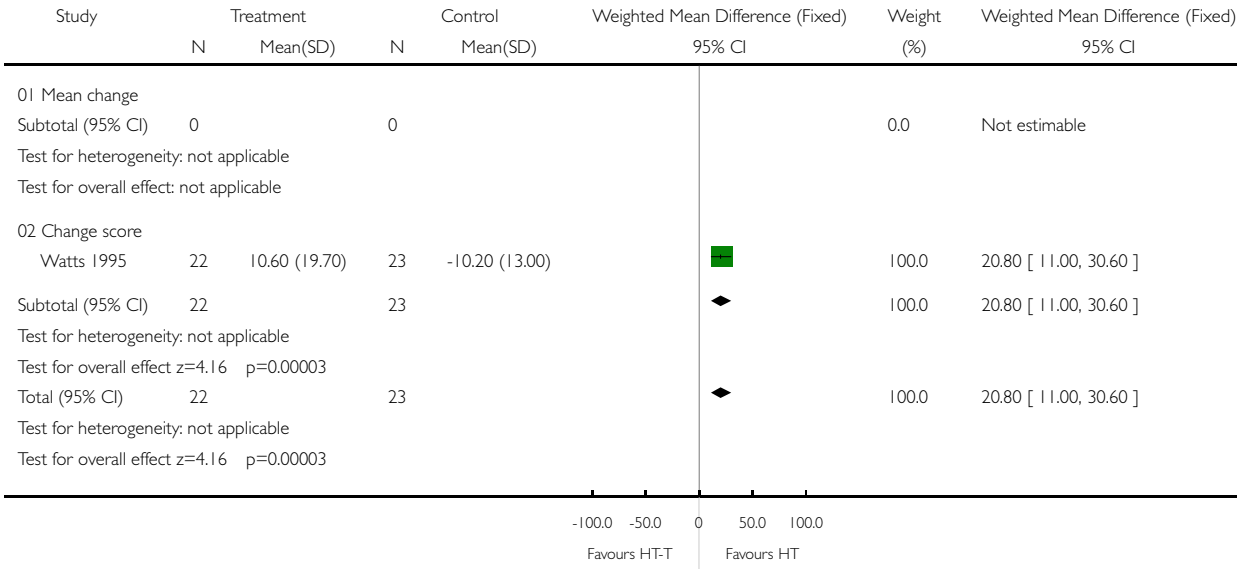


### Analysis 17.20. Comparison 17 HT plus testosterone versus HT on lipid profile, Outcome 20 Total cholesterol/HDL at 24 months

Review: Testosterone for peri- and postmenopausal women

Comparison: 17 HT plus testosterone versus HT on lipid profile

Outcome: 20 Total cholesterol/HDL at 24 months

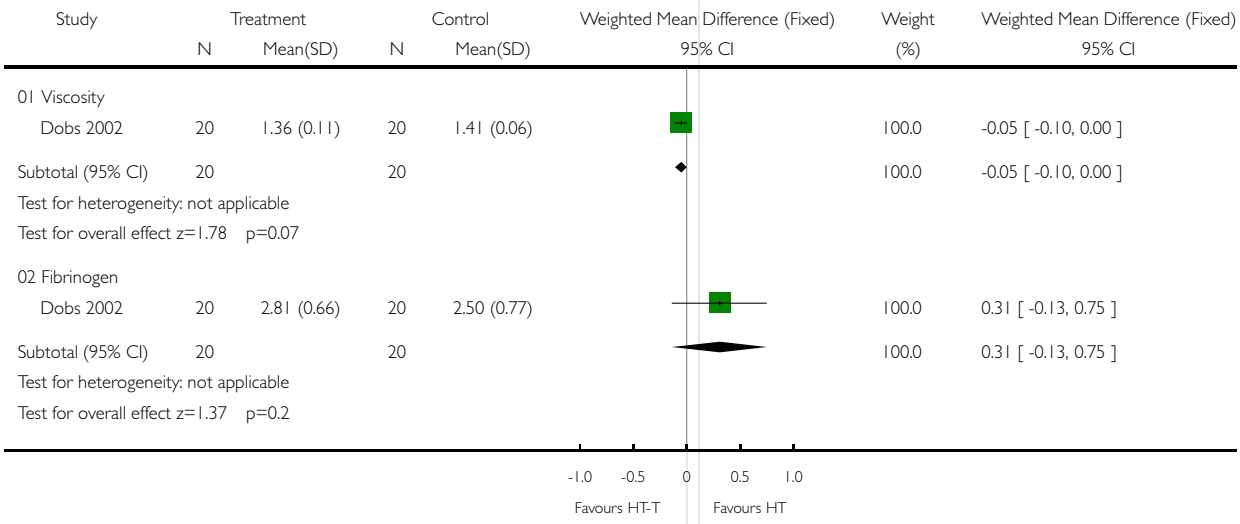



### Analysis 18.01. Comparison 18 HT plus testosterone versus HT on coagulation profile, Outcome 01 Mean levels of plasma viscosity and fibrinogen levels

Review: Testosterone for peri- and postmenopausal women

Comparison: 18 HT plus testosterone versus HT on coagulation profile

Outcome: 01 Mean levels of plasma viscosity and fibrinogen levels



## Analysis 19.01. Comparison 19 HT plus testosterone versus HT on discontinuation rate, Outcome 01 Discontinuation rate (overall)

Review: Testosterone for peri- and postmenopausal women

Comparison: 19 HT plus testosterone versus HT on discontinuation rate

Outcome: 01 Discontinuation rate (overall)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Barrett-Connor 1999 | 51/154 | 64/157 | | 36.0 | 0.72 [ 0.46, 1.14 ] |
| Braunstein 2003 | 35/107 | 38/119 | | 24.5 | 1.04 [ 0.59, 1.81 ] |
| Burger 1987 | 0/10 | 2/10 | | 0.9 | 0.12 [ 0.01, 2.09 ] |
| Davis 1995 | 2/17 | 0/17 | | 1.0 | 7.87 [ 0.47, 131.27 ] |
| Dobs 2002 | 2/20 | 1/20 | | 1.4 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 3/50 | 3/50 | | 2.8 | 1.00 [ 0.19, 5.17 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 20/107 | 16/111 | | 14.9 | 1.36 [ 0.67, 2.78 ] |
| Montgomery 1987 | 3/27 | 2/28 | | 2.3 | 1.60 [ 0.26, 9.91 ] |
| Penotti 2001 | 5/20 | 2/20 | | 2.9 | 2.75 [ 0.55, 13.79 ] |
| Sarrel 1998 | 1/10 | 0/10 | | 0.5 | 7.39 [ 0.15, 372.38 ] |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 13/75 | 15/75 | | 11.3 | 0.84 [ 0.37, 1.90 ] |
| Simon 1999 | 3/37 | 0/36 | | 1.4 | 7.61 [ 0.77, 75.55 ] |
| Total (95% CI) | 674 | 690 | | 100.0 | 1.01 [ 0.76, 1.33 ] |

Total events: 138 (Treatment), 143 (Control)

Test for heterogeneity chi-square=13.16 df=11 p=0.28 $I^2$ =16.4%

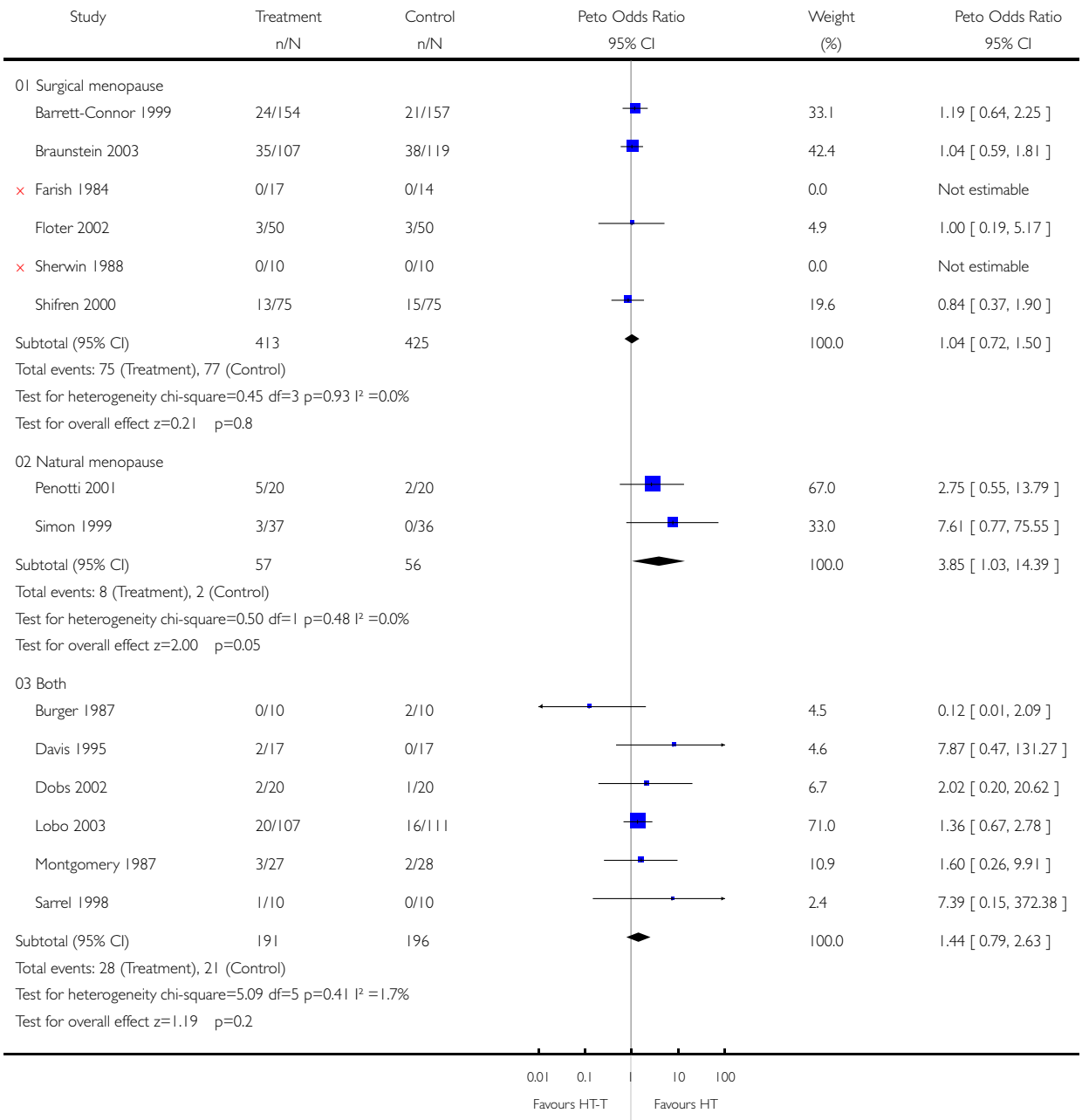
Test for overall effect z=0.05 p=1

## Analysis 19.02. Comparison 19 HT plus testosterone versus HT on discontinuation rate, Outcome 02 Discontinuation rate (type of menopause)

Review: Testosterone for peri- and postmenopausal women

Comparison: 19 HT plus testosterone versus HT on discontinuation rate

Outcome: 02 Discontinuation rate (type of menopause)

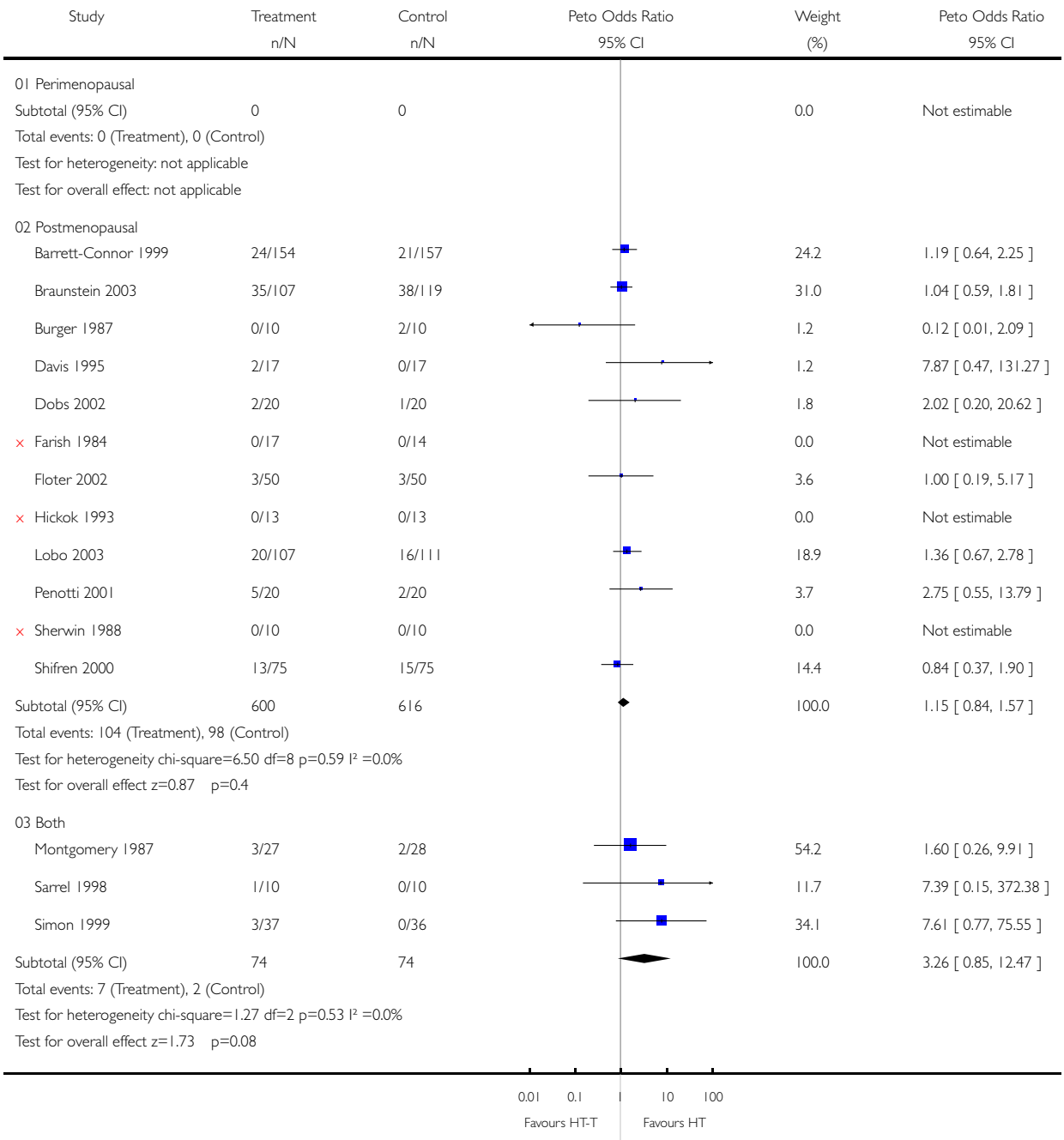


## Analysis 19.03. Comparison 19 HT plus testosterone versus HT on discontinuation rate, Outcome 03 Discontinuation rate (menopausal status)

Review: Testosterone for peri- and postmenopausal women

Comparison: 19 HT plus testosterone versus HT on discontinuation rate

Outcome: 03 Discontinuation rate (menopausal status)

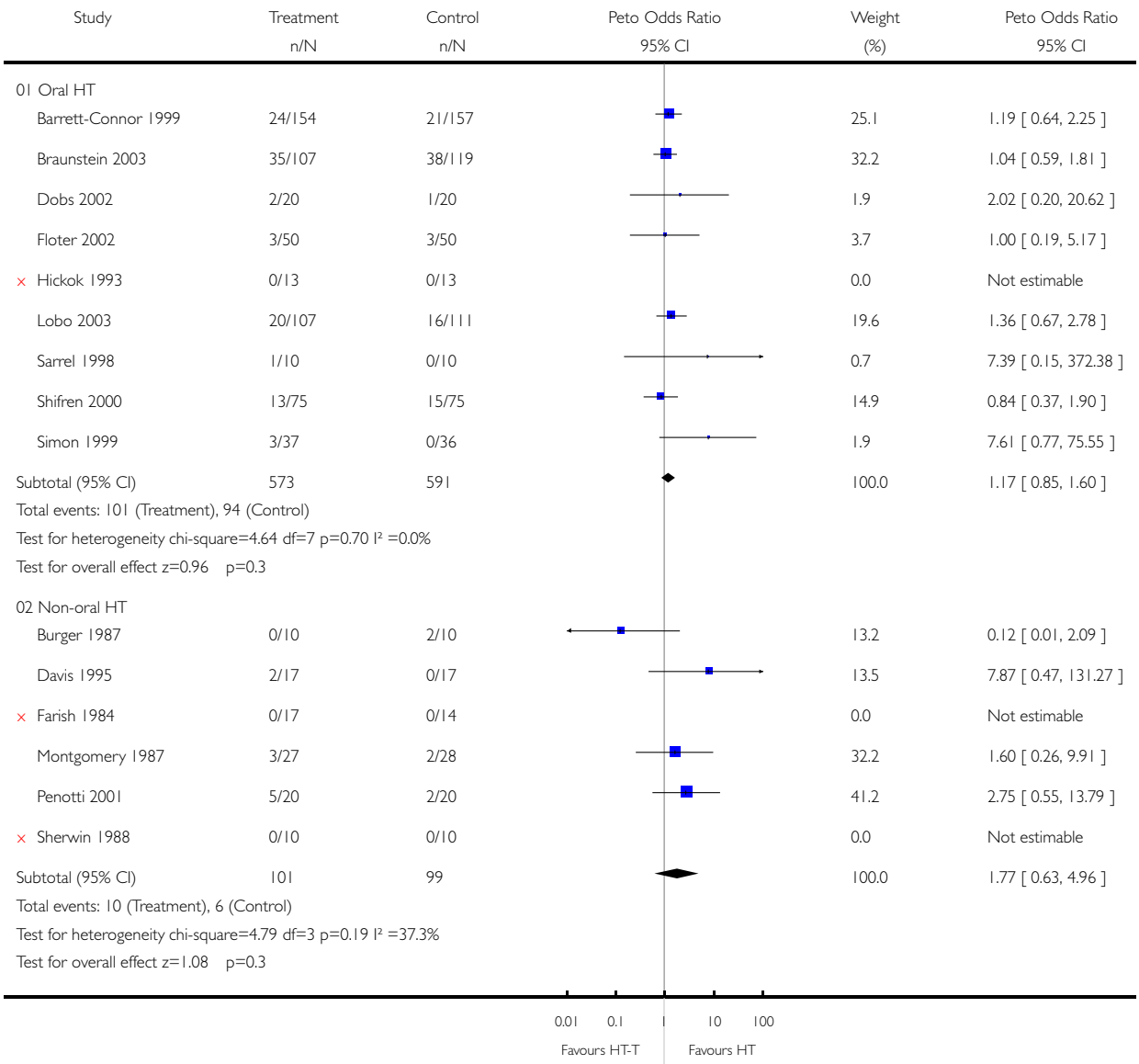


## Analysis 19.04. Comparison 19 HT plus testosterone versus HT on discontinuation rate, Outcome 04 Discontinuation rate (route of hormone therapy)

Review: Testosterone for peri- and postmenopausal women

Comparison: 19 HT plus testosterone versus HT on discontinuation rate

Outcome: 04 Discontinuation rate (route of hormone therapy)

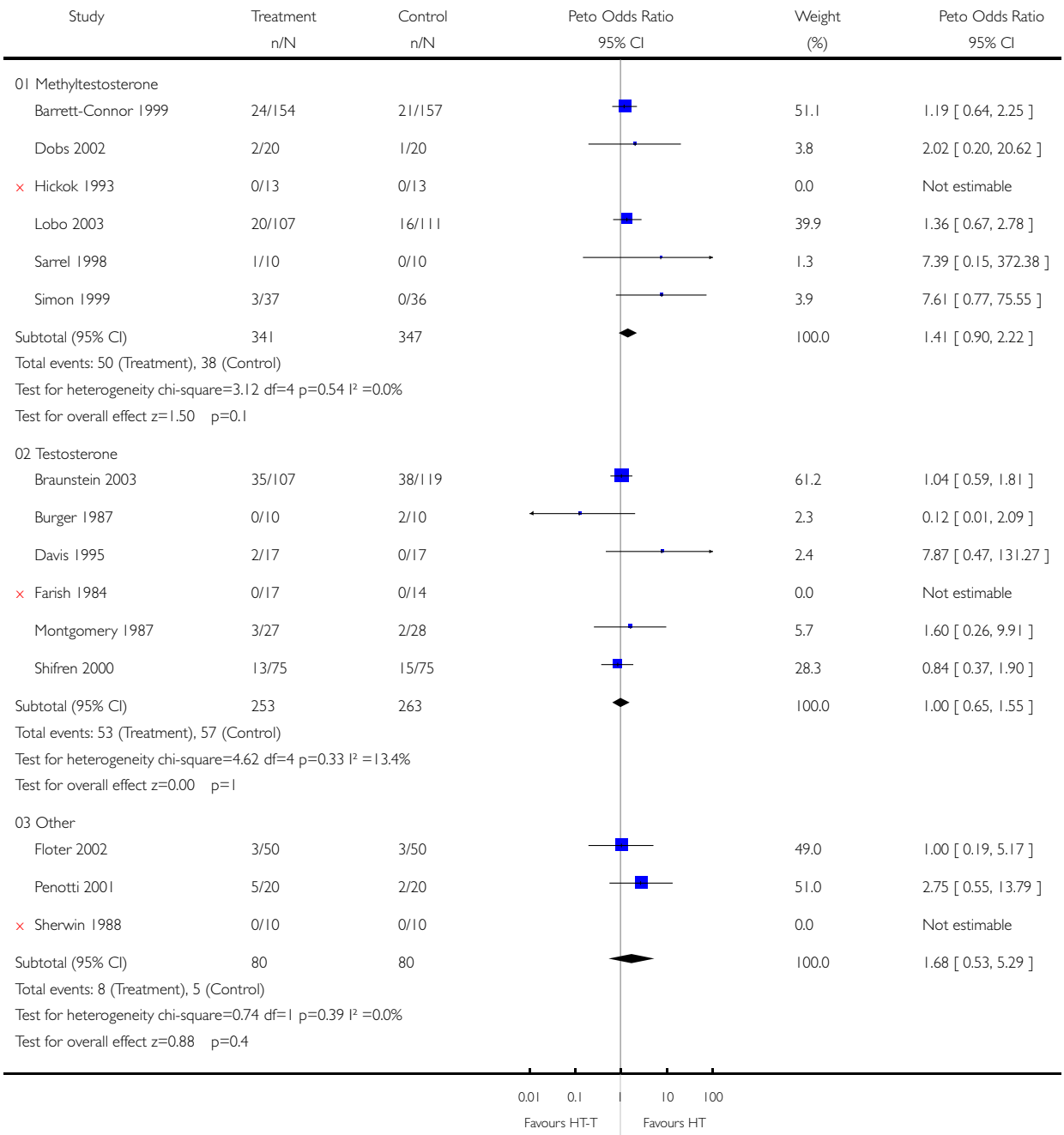


## Analysis 19.05. Comparison 19 HT plus testosterone versus HT on discontinuation rate, Outcome 05 Discontinuation rate (type of testosterone)

Review: Testosterone for peri- and postmenopausal women

Comparison: 19 HT plus testosterone versus HT on discontinuation rate

Outcome: 05 Discontinuation rate (type of testosterone)



## Analysis 19.06. Comparison 19 HT plus testosterone versus HT on discontinuation rate, Outcome 06 Discontinuation rate (duration of treatment)

Review: Testosterone for peri- and postmenopausal women

Comparison: 19 HT plus testosterone versus HT on discontinuation rate

Outcome: 06 Discontinuation rate (duration of treatment)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 01 Less than 3 months | | | | | |
| Sarrel 1998 | 1/10 | 0/10 | | 100.0 | 7.39 [ 0.15, 372.38 ] |
| Subtotal (95% CI) | 10 | 10 | | 100.0 | 7.39 [ 0.15, 372.38 ] |
| Total events: 1 (Treatment), 0 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=1.00 p=0.3 | | | | | |
| 02 3 to 12 months | | | | | |
| Braunstein 2003 | 35/107 | 38/119 | | 39.1 | 1.04 [ 0.59, 1.81 ] |
| Burger 1987 | 0/10 | 2/10 | | 1.5 | 0.12 [ 0.01, 2.09 ] |
| Dobs 2002 | 2/20 | 1/20 | | 2.2 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 3/50 | 3/50 | | 4.5 | 1.00 [ 0.19, 5.17 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 20/107 | 16/111 | | 23.9 | 1.36 [ 0.67, 2.78 ] |
| Montgomery 1987 | 3/27 | 2/28 | | 3.7 | 1.60 [ 0.26, 9.91 ] |
| Penotti 2001 | 5/20 | 2/20 | | 4.7 | 2.75 [ 0.55, 13.79 ] |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 13/75 | 15/75 | | 18.1 | 0.84 [ 0.37, 1.90 ] |
| Simon 1999 | 3/37 | 0/36 | | 2.3 | 7.61 [ 0.77, 75.55 ] |
| Subtotal (95% CI) | 493 | 506 | | 100.0 | 1.16 [ 0.82, 1.65 ] |
| Total events: 84 (Treatment), 79 (Control) | | | | | |
| Test for heterogeneity chi-square=7.42 df=8 p=0.49 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.85 p=0.4 | | | | | |
| 03 12-24 months | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 | Not estimable |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 04 24 months | | | | | |
| Barrett-Connor 1999 | 24/154 | 21/157 | | 95.2 | 1.19 [ 0.64, 2.25 ] |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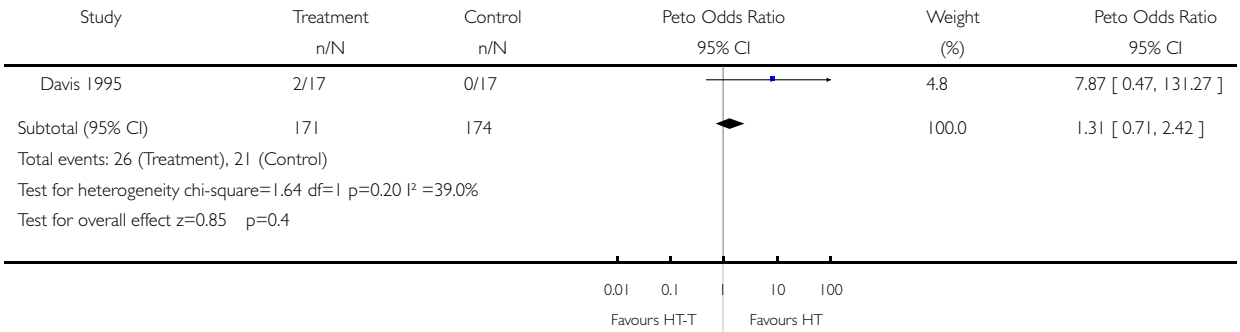
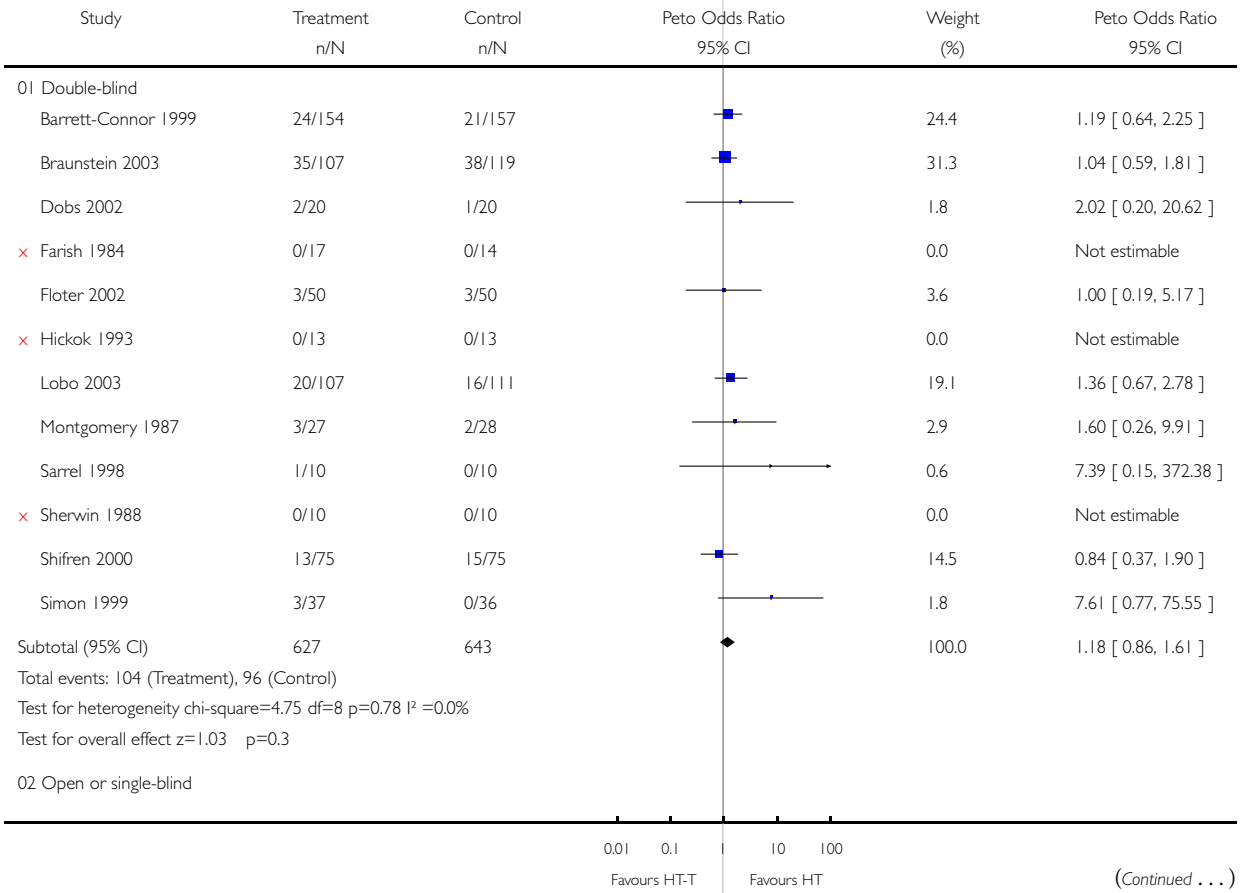



## Analysis 19.07. Comparison 19 HT plus testosterone versus HT on discontinuation rate, Outcome 07 Discontinuation rate (blinding)

Review: Testosterone for peri- and postmenopausal women

Comparison: 19 HT plus testosterone versus HT on discontinuation rate

Outcome: 07 Discontinuation rate (blinding)

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| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Burger 1987 | 0/10 | 2/10 | | 19.4 | 0.12 [ 0.01, 2.09 ] |
| Davis 1995 | 2/17 | 0/17 | | 19.9 | 7.87 [ 0.47, 131.27 ] |
| Penotti 2001 | 5/20 | 2/20 | | 60.7 | 2.75 [ 0.55, 13.79 ] |
| Subtotal (95% CI) | 47 | 47 | | 100.0 | 1.85 [ 0.53, 6.49 ] |
| Total events: 7 (Treatment), 4 (Control) | | | | | |
| Test for heterogeneity chi-square=4.77 df=2 p=0.09 $I^2$ =58.1% | | | | | |
| Test for overall effect z=0.96 p=0.3 | | | | | |

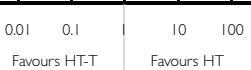

## Analysis 19.08. Comparison 19 HT plus testosterone versus HT on discontinuation rate, Outcome 08 Discontinuation rate (disease status)

Review: Testosterone for peri- and postmenopausal women

Comparison: 19 HT plus testosterone versus HT on discontinuation rate

Outcome: 08 Discontinuation rate (disease status)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 01 Inadequate symptom control | | | | | |
| Burger 1987 | 0/10 | 2/10 | | 5.0 | 0.12 [ 0.01, 2.09 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Lobo 2003 | 20/107 | 16/111 | | 80.0 | 1.36 [ 0.67, 2.78 ] |
| Montgomery 1987 | 3/27 | 2/28 | | 12.3 | 1.60 [ 0.26, 9.91 ] |
| Sarrel 1998 | 1/10 | 0/10 | | 2.7 | 7.39 [ 0.15, 372.38 ] |
| Subtotal (95% CI) | 171 | 173 | | 100.0 | 1.29 [ 0.68, 2.44 ] |
| Total events: 24 (Treatment), 20 (Control) | | | | | |
| Test for heterogeneity chi-square=3.49 df=3 p=0.32 $I^2$ =14.0% | | | | | |
| Test for overall effect z=0.77 p=0.4 | | | | | |
| 02 Low T plus inadequate symptom control | | | | | |
| Braunstein 2003 | 35/107 | 38/119 | | 68.3 | 1.04 [ 0.59, 1.81 ] |
| Shifren 2000 | 13/75 | 15/75 | | 31.7 | 0.84 [ 0.37, 1.90 ] |
| Subtotal (95% CI) | 182 | 194 | | 100.0 | 0.97 [ 0.61, 1.54 ] |
| Total events: 48 (Treatment), 53 (Control) | | | | | |
| Test for heterogeneity chi-square=0.17 df=1 p=0.68 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.13 p=0.9 | | | | | |

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| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 03 No symptom | | | | | |
| Barrett-Connor 1999 | 24/154 | 21/157 | | 66.6 | 1.19 [ 0.64, 2.25 ] |
| Davis 1995 | 2/17 | 0/17 | | 3.3 | 7.87 [ 0.47, 131.27 ] |
| Dobs 2002 | 2/20 | 1/20 | | 4.9 | 2.02 [ 0.20, 20.62 ] |
| Floter 2002 | 3/50 | 3/50 | | 9.8 | 1.00 [ 0.19, 5.17 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Penotti 2001 | 5/20 | 2/20 | | 10.2 | 2.75 [ 0.55, 13.79 ] |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Simon 1999 | 3/37 | 0/36 | | 5.0 | 7.61 [ 0.77, 75.55 ] |
| Subtotal (95% CI) | 321 | 323 | | 100.0 | 1.53 [ 0.92, 2.57 ] |
| Total events: 39 (Treatment), 27 (Control) | | | | | |
| Test for heterogeneity chi-square=4.59 df=5 p=0.47 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.63 p=0.1 | | | | | |

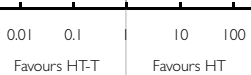

**Analysis 20.01. Comparison 20 HT plus testosterone versus HT on discontinuation rate due to adverse events, Outcome 01 Discontinuation rate due to adverse events (overall)**

Review: Testosterone for peri- and postmenopausal women

Comparison: 20 HT plus testosterone versus HT on discontinuation rate due to adverse events

Outcome: 01 Discontinuation rate due to adverse events (overall)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Barrett-Connor 1999 | 24/154 | 21/157 | | 42.1 | 1.19 [ 0.64, 2.25 ] |
| Braunstein 2003 | 14/107 | 14/119 | | 26.8 | 1.13 [ 0.51, 2.49 ] |
| × Burger 1987 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Davis 1995 | 1/17 | 0/17 | | 1.1 | 7.39 [ 0.15, 372.38 ] |
| Dobs 2002 | 2/20 | 1/20 | | 3.1 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 0/50 | 1/50 | | 1.1 | 0.14 [ 0.00, 6.82 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 9/107 | 5/111 | | 14.3 | 1.91 [ 0.65, 5.63 ] |

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| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Montgomery 1987 | 1/27 | 1/28 | | 2.1 | 1.04 [ 0.06, 17.04 ] |
| Penotti 2001 | 3/20 | 1/20 | | 4.0 | 2.95 [ 0.38, 22.72 ] |
| × Sarrel 1998 | 0/10 | 0/10 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 4.3 | 0.36 [ 0.05, 2.61 ] |
| Simon 1999 | 1/37 | 0/36 | | 1.1 | 7.19 [ 0.14, 362.59 ] |
| Total (95% CI) | 674 | 690 | | 100.0 | 1.28 [ 0.85, 1.92 ] |
| Total events: 56 (Treatment), 47 (Control) | | | | | |
| Test for heterogeneity chi-square=5.83 df=9 p=0.76 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.17 p=0.2 | | | | | |


**Analysis 20.02. Comparison 20 HT plus testosterone versus HT on discontinuation rate due to adverse events, Outcome 02 Discontinuation rate due to adverse events (type of menopause)**

Review: Testosterone for peri- and postmenopausal women

Comparison: 20 HT plus testosterone versus HT on discontinuation rate due to adverse events

Outcome: 02 Discontinuation rate due to adverse events (type of menopause)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 01 Surgical menopause | | | | | |
| Barrett-Connor 1999 | 24/154 | 21/157 | | 56.7 | 1.19 [ 0.64, 2.25 ] |
| Braunstein 2003 | 14/107 | 14/119 | | 36.1 | 1.13 [ 0.51, 2.49 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 0/50 | 1/50 | | 1.5 | 0.14 [ 0.00, 6.82 ] |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 5.8 | 0.36 [ 0.05, 2.61 ] |
| Subtotal (95% CI) | 413 | 425 | | 100.0 | 1.06 [ 0.66, 1.70 ] |
| Total events: 39 (Treatment), 39 (Control) | | | | | |
| Test for heterogeneity chi-square=2.36 df=3 p=0.50 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.23 p=0.8 | | | | | |
| 02 Natural menopause | | | | | |
| Penotti 2001 | 3/20 | 1/20 | | 78.7 | 2.95 [ 0.38, 22.72 ] |


(*Continued* . . . )

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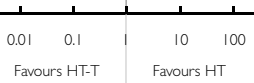
| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Simon 1999 | 1/37 | 0/36 | | 21.3 | 7.19 [ 0.14, 362.59 ] |
| Subtotal (95% CI) | 57 | 56 | | 100.0 | 3.57 [ 0.58, 21.81 ] |
| Total events: 4 (Treatment), 1 (Control) | | | | | |
| Test for heterogeneity chi-square=0.16 df=1 p=0.69 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.38 p=0.2 | | | | | |
| 03 Both | | | | | |
| × Burger 1987 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Davis 1995 | 1/17 | 0/17 | | 5.3 | 7.39 [ 0.15, 372.38 ] |
| Dobs 2002 | 2/20 | 1/20 | | 15.0 | 2.02 [ 0.20, 20.62 ] |
| Lobo 2003 | 9/107 | 5/111 | | 69.4 | 1.91 [ 0.65, 5.63 ] |
| Montgomery 1987 | 1/27 | 1/28 | | 10.3 | 1.04 [ 0.06, 17.04 ] |
| × Sarrel 1998 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Subtotal (95% CI) | 191 | 196 | | 100.0 | 1.94 [ 0.79, 4.78 ] |
| Total events: 13 (Treatment), 7 (Control) | | | | | |
| Test for heterogeneity chi-square=0.64 df=3 p=0.89 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.45 p=0.1 | | | | | |



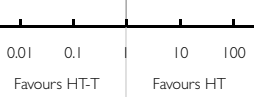
## Analysis 20.03. Comparison 20 HT plus testosterone versus HT on discontinuation rate due to adverse events, Outcome 03 Discontinuation rate due to adverse events (menopausal status)

Review: Testosterone for peri- and postmenopausal women

Comparison: 20 HT plus testosterone versus HT on discontinuation rate due to adverse events

Outcome: 03 Discontinuation rate due to adverse events (menopausal status)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 01 Perimenopausal | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 | Not estimable |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 02 Postmenopausal | | | | | |
| Barrett-Connor 1999 | 24/154 | 21/157 | | 43.5 | 1.19 [ 0.64, 2.25 ] |
| Braunstein 2003 | 14/107 | 14/119 | | 27.7 | 1.13 [ 0.51, 2.49 ] |
| × Burger 1987 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Davis 1995 | 1/17 | 0/17 | | 1.1 | 7.39 [ 0.15, 372.38 ] |
| Dobs 2002 | 2/20 | 1/20 | | 3.2 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 0/50 | 1/50 | | 1.1 | 0.14 [ 0.00, 6.82 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 9/107 | 5/111 | | 14.8 | 1.91 [ 0.65, 5.63 ] |
| Penotti 2001 | 3/20 | 1/20 | | 4.2 | 2.95 [ 0.38, 22.72 ] |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 4.4 | 0.36 [ 0.05, 2.61 ] |
| Subtotal (95% CI) | 600 | 616 | | 100.0 | 1.26 [ 0.83, 1.91 ] |
| Total events: 54 (Treatment), 46 (Control) | | | | | |
| Test for heterogeneity chi-square=5.06 df=7 p=0.65 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.08 p=0.3 | | | | | |
| 03 Both | | | | | |
| Montgomery 1987 | 1/27 | 1/28 | | 66.2 | 1.04 [ 0.06, 17.04 ] |
| × Sarrel 1998 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Simon 1999 | 1/37 | 0/36 | | 33.8 | 7.19 [ 0.14, 362.59 ] |
| Subtotal (95% CI) | 74 | 74 | | 100.0 | 1.99 [ 0.20, 19.45 ] |
| Total events: 2 (Treatment), 1 (Control) | | | | | |
| Test for heterogeneity chi-square=0.62 df=1 p=0.43 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.59 p=0.6 | | | | | |



## Analysis 20.04. Comparison 20 HT plus testosterone versus HT on discontinuation rate due to adverse events, Outcome 04 Discontinuation rate due to adverse events (route of hormone therapy)

Review: Testosterone for peri- and postmenopausal women

Comparison: 20 HT plus testosterone versus HT on discontinuation rate due to adverse events

Outcome: 04 Discontinuation rate due to adverse events (route of hormone therapy)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 01 Oral HT | | | | | |
| Barrett-Connor 1999 | 24/154 | 21/157 | | 45.4 | 1.19 [ 0.64, 2.25 ] |
| Braunstein 2003 | 14/107 | 14/119 | | 28.9 | 1.13 [ 0.51, 2.49 ] |
| Dobs 2002 | 2/20 | 1/20 | | 3.3 | 2.02 [ 0.20, 20.62 ] |
| Floter 2002 | 0/50 | 1/50 | | 1.2 | 0.14 [ 0.00, 6.82 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 9/107 | 5/111 | | 15.5 | 1.91 [ 0.65, 5.63 ] |
| × Sarrel 1998 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 4.6 | 0.36 [ 0.05, 2.61 ] |
| Simon 1999 | 1/37 | 0/36 | | 1.2 | 7.19 [ 0.14, 362.59 ] |
| Subtotal (95% CI) | 573 | 591 | | 100.0 | 1.21 [ 0.79, 1.85 ] |
| Total events: 51 (Treatment), 45 (Control) | | | | | |
| Test for heterogeneity chi-square=4.33 df=6 p=0.63 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.88 p=0.4 | | | | | |
| 02 Non-oral HT | | | | | |
| × Burger 1987 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Davis 1995 | 1/17 | 0/17 | | 15.0 | 7.39 [ 0.15, 372.38 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Montgomery 1987 | 1/27 | 1/28 | | 29.5 | 1.04 [ 0.06, 17.04 ] |
| Penotti 2001 | 3/20 | 1/20 | | 55.5 | 2.95 [ 0.38, 22.72 ] |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Subtotal (95% CI) | 101 | 99 | | 100.0 | 2.49 [ 0.54, 11.38 ] |
| Total events: 5 (Treatment), 2 (Control) | | | | | |
| Test for heterogeneity chi-square=0.70 df=2 p=0.71 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.18 p=0.2 | | | | | |

## Analysis 20.05. Comparison 20 HT plus testosterone versus HT on discontinuation rate due to adverse events, Outcome 05 Discontinuation rate due to adverse events (type of testosterone)

Review: Testosterone for peri- and postmenopausal women

Comparison: 20 HT plus testosterone versus HT on discontinuation rate due to adverse events

Outcome: 05 Discontinuation rate due to adverse events (type of testosterone)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 01 Methyltestosterone | | | | | |
| Barrett-Connor 1999 | 24/154 | 21/157 | | 69.4 | 1.19 [ 0.64, 2.25 ] |
| Dobs 2002 | 2/20 | 1/20 | | 5.1 | 2.02 [ 0.20, 20.62 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 9/107 | 5/111 | | 23.7 | 1.91 [ 0.65, 5.63 ] |
| × Sarrel 1998 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Simon 1999 | 1/37 | 0/36 | | 1.8 | 7.19 [ 0.14, 362.59 ] |
| Subtotal (95% CI) | 341 | 347 | | 100.0 | 1.42 [ 0.84, 2.40 ] |
| Total events: 36 (Treatment), 27 (Control) | | | | | |
| Test for heterogeneity chi-square=1.32 df=3 p=0.72 I² =0.0% | | | | | |
| Test for overall effect z=1.30 p=0.2 | | | | | |
| 02 Testosterone | | | | | |
| Braunstein 2003 | 14/107 | 14/119 | | 78.1 | 1.13 [ 0.51, 2.49 ] |
| × Burger 1987 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Davis 1995 | 1/17 | 0/17 | | 3.2 | 7.39 [ 0.15, 372.38 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Montgomery 1987 | 1/27 | 1/28 | | 6.2 | 1.04 [ 0.06, 17.04 ] |
| Shifren 2000 | 1/75 | 3/75 | | 12.5 | 0.36 [ 0.05, 2.61 ] |
| Subtotal (95% CI) | 253 | 263 | | 100.0 | 1.03 [ 0.51, 2.08 ] |
| Total events: 17 (Treatment), 18 (Control) | | | | | |
| Test for heterogeneity chi-square=2.10 df=3 p=0.55 I² =0.0% | | | | | |
| Test for overall effect z=0.09 p=0.9 | | | | | |
| 03 Other | | | | | |
| Floter 2002 | 0/50 | 1/50 | | 21.3 | 0.14 [ 0.00, 6.82 ] |
| Penotti 2001 | 3/20 | 1/20 | | 78.7 | 2.95 [ 0.38, 22.72 ] |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Subtotal (95% CI) | 80 | 80 | | 100.0 | 1.53 [ 0.25, 9.35 ] |
| Total events: 3 (Treatment), 2 (Control) | | | | | |
| Test for heterogeneity chi-square=1.87 df=1 p=0.17 I² =46.5% | | | | | |
| Test for overall effect z=0.46 p=0.6 | | | | | |

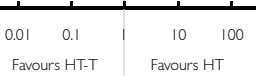
## Analysis 20.06. Comparison 20 HT plus testosterone versus HT on discontinuation rate due to adverse events, Outcome 06 Discontinuation rate due to adverse events (duration of treatment)

Review: Testosterone for peri- and postmenopausal women

Comparison: 20 HT plus testosterone versus HT on discontinuation rate due to adverse events

Outcome: 06 Discontinuation rate due to adverse events (duration of treatment)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 01 Less than 3 months | | | | | |
| × Sarrel 1998 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Subtotal (95% CI) | 10 | 10 | | 0.0 | Not estimable |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 02 3 to 12 months | | | | | |
| Braunstein 2003 | 14/107 | 14/119 | | 47.1 | 1.13 [ 0.51, 2.49 ] |
| × Burger 1987 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Dobs 2002 | 2/20 | 1/20 | | 5.5 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 0/50 | 1/50 | | 1.9 | 0.14 [ 0.00, 6.82 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 9/107 | 5/111 | | 25.2 | 1.91 [ 0.65, 5.63 ] |
| Montgomery 1987 | 1/27 | 1/28 | | 3.8 | 1.04 [ 0.06, 17.04 ] |
| Penotti 2001 | 3/20 | 1/20 | | 7.1 | 2.95 [ 0.38, 22.72 ] |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 7.5 | 0.36 [ 0.05, 2.61 ] |
| Simon 1999 | 1/37 | 0/36 | | 1.9 | 7.19 [ 0.14, 362.59 ] |
| Subtotal (95% CI) | 493 | 506 | | 100.0 | 1.30 [ 0.75, 2.23 ] |
| Total events: 31 (Treatment), 26 (Control) | | | | | |
| Test for heterogeneity chi-square=5.02 df=7 p=0.66 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.94 p=0.3 | | | | | |
| 03 12-24 months | | | | | |
| Subtotal (95% CI) | 0 | 0 | | 0.0 | Not estimable |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 04 24 months | | | | | |
| Barrett-Connor 1999 | 24/154 | 21/157 | | 97.5 | 1.19 [ 0.64, 2.25 ] |

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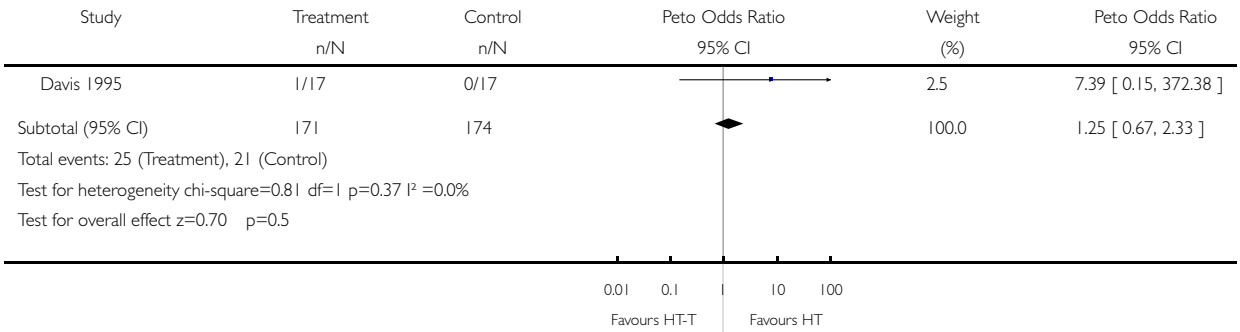
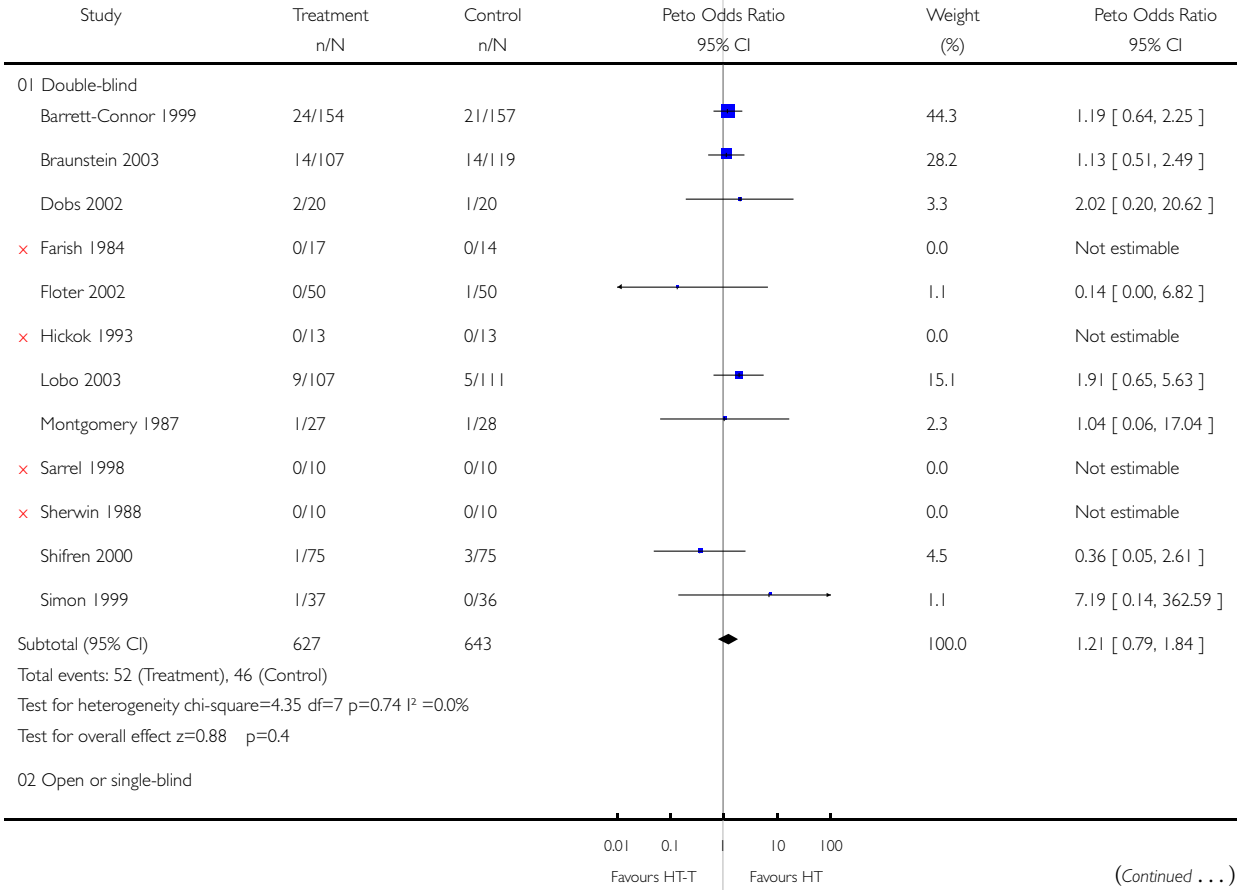



### Analysis 20.07. Comparison 20 HT plus testosterone versus HT on discontinuation rate due to adverse events, Outcome 07 Discontinuation rate due to adverse events (blinding)

Review: Testosterone for peri- and postmenopausal women

Comparison: 20 HT plus testosterone versus HT on discontinuation rate due to adverse events

Outcome: 07 Discontinuation rate due to adverse events (blinding)

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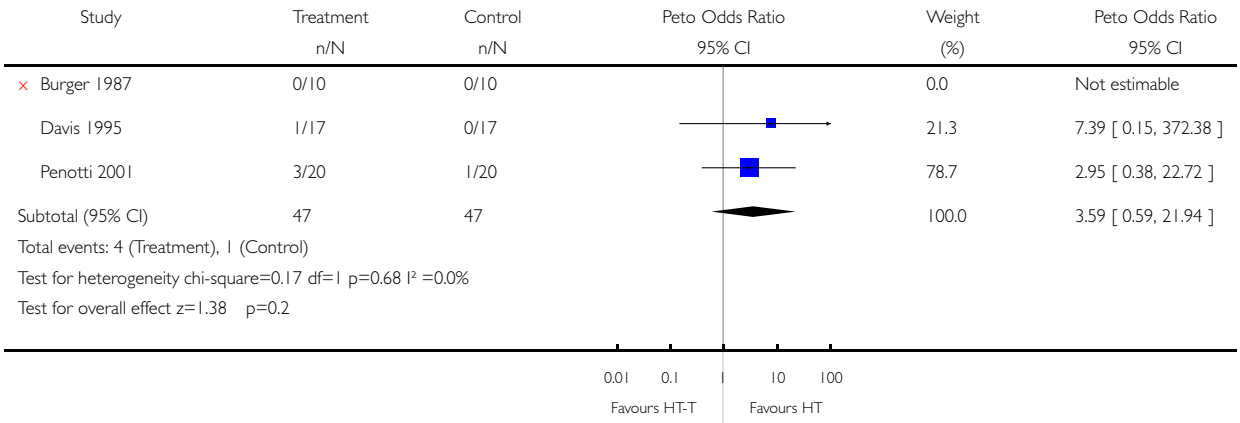
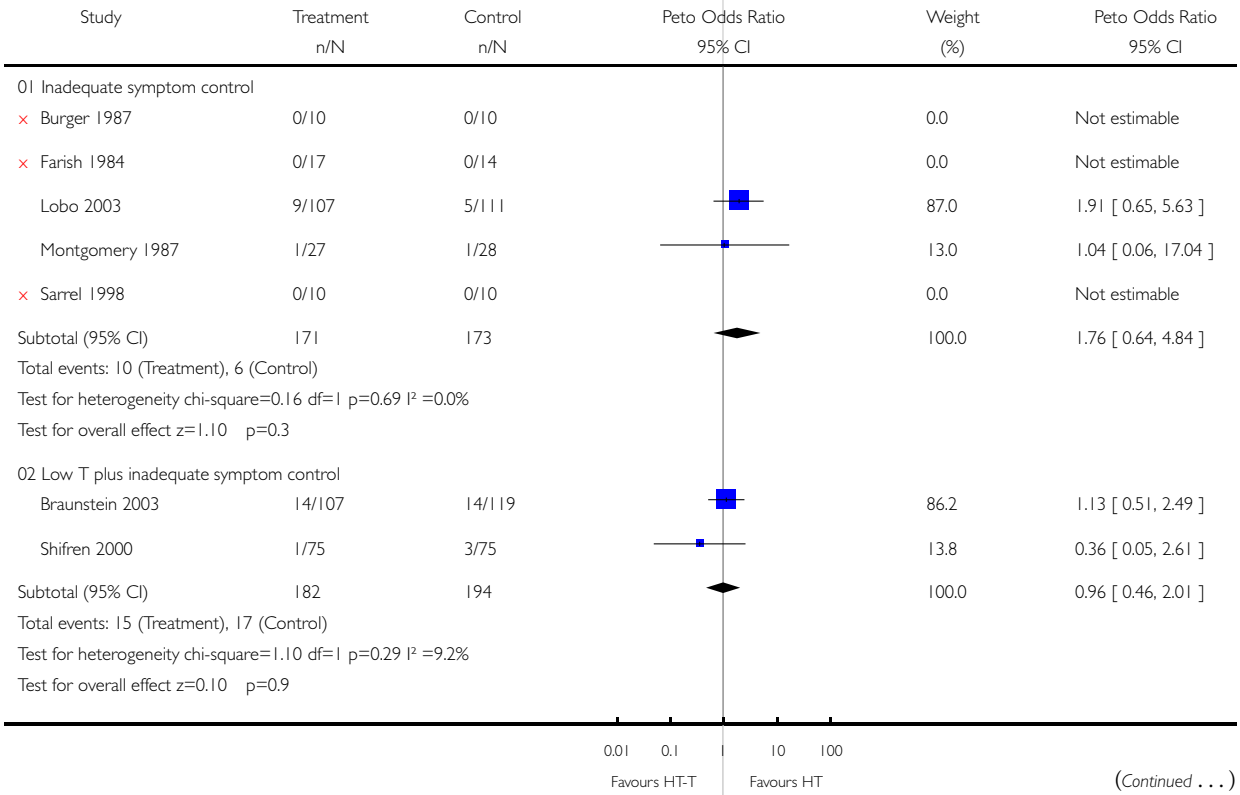



**Analysis 20.08. Comparison 20 HT plus testosterone versus HT on discontinuation rate due to adverse events, Outcome 08 Discontinuation rate due to adverse events (disease status)**

Review: Testosterone for peri- and postmenopausal women

Comparison: 20 HT plus testosterone versus HT on discontinuation rate due to adverse events

Outcome: 08 Discontinuation rate due to adverse events (disease status)

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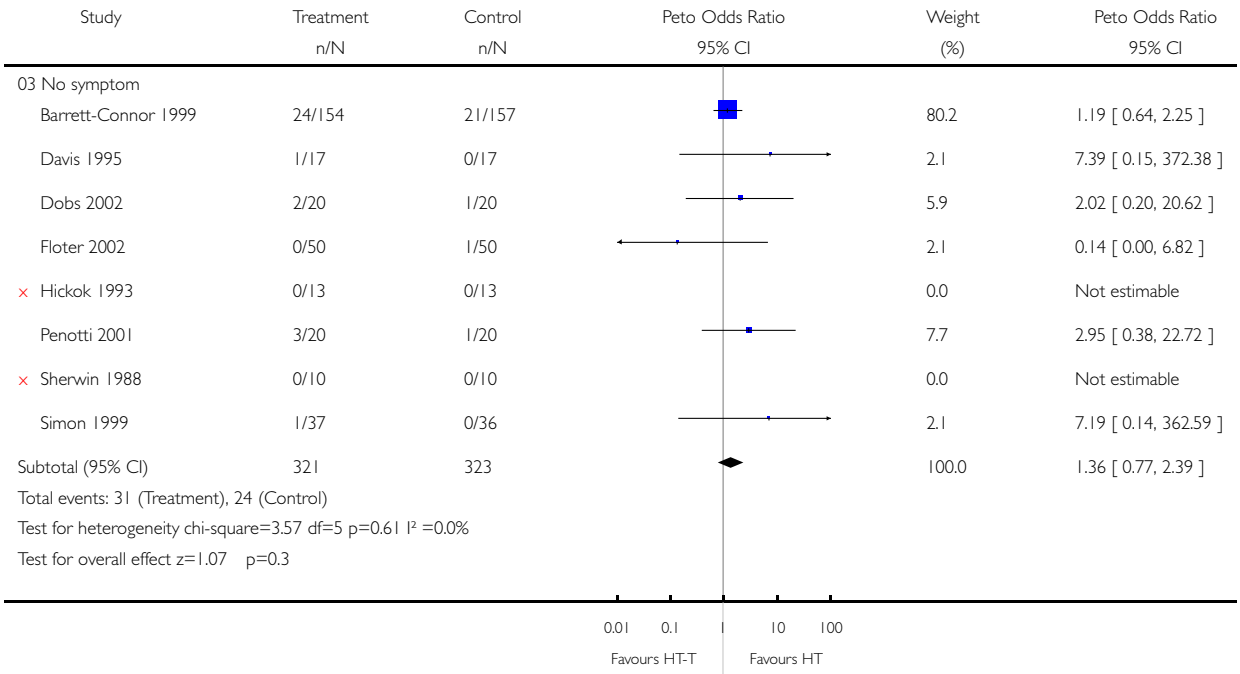
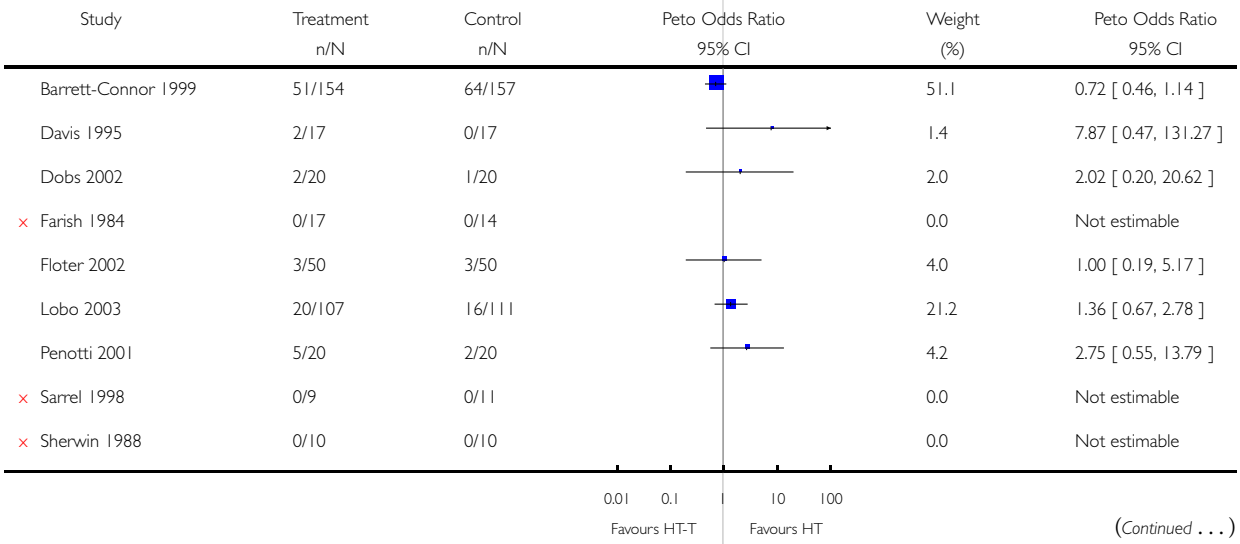



## Analysis 22.01. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 01 Discontinuation rate (allocation quality)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 01 Discontinuation rate (allocation quality)

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| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Shifren 2000 | 13/75 | 15/75 | | 16.1 | 0.84 [ 0.37, 1.90 ] |
| Total (95% CI) | 479 | 485 | | 100.0 | 0.96 [ 0.69, 1.33 ] |
| Total events: 96 (Treatment), 101 (Control) | | | | | |
| Test for heterogeneity chi-square=6.70 df=6 p=0.35 $I^2$ =10.4% | | | | | |
| Test for overall effect z=0.27 p=0.8 | | | | | |


## Analysis 22.02. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 02 Discontinuation rate due to adverse events (allocation quality)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 02 Discontinuation rate due to adverse events (allocation quality)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Barrett-Connor 1999 | 24/154 | 21/157 | | 60.1 | 1.19 [ 0.64, 2.25 ] |
| Davis 1995 | 1/17 | 0/17 | | 1.6 | 7.39 [ 0.15, 372.38 ] |
| Dobs 2002 | 2/20 | 1/20 | | 4.4 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 0/50 | 1/50 | | 1.6 | 0.14 [ 0.00, 6.82 ] |
| Lobo 2003 | 9/107 | 5/111 | | 20.5 | 1.91 [ 0.65, 5.63 ] |
| Penotti 2001 | 3/20 | 1/20 | | 5.7 | 2.95 [ 0.38, 22.72 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 6.1 | 0.36 [ 0.05, 2.61 ] |
| Total (95% CI) | 479 | 485 | | 100.0 | 1.31 [ 0.80, 2.14 ] |
| Total events: 40 (Treatment), 32 (Control) | | | | | |
| Test for heterogeneity chi-square=4.96 df=6 p=0.55 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.08 p=0.3 | | | | | |

## Analysis 22.03. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 03 Discontinuation rate (quality of randomization)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 03 Discontinuation rate (quality of randomization)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Barrett-Connor 1999 | 51/154 | 64/157 | | 50.4 | 0.72 [ 0.46, 1.14 ] |
| Burger 1987 | 0/10 | 2/10 | | 1.3 | 0.12 [ 0.01, 2.09 ] |
| Davis 1995 | 2/17 | 0/17 | | 1.3 | 7.87 [ 0.47, 131.27 ] |
| Dobs 2002 | 2/20 | 1/20 | | 2.0 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 3/50 | 3/50 | | 4.0 | 1.00 [ 0.19, 5.17 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 20/107 | 16/111 | | 20.9 | 1.36 [ 0.67, 2.78 ] |
| Penotti 2001 | 5/20 | 2/20 | | 4.1 | 2.75 [ 0.55, 13.79 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 13/75 | 15/75 | | 15.9 | 0.84 [ 0.37, 1.90 ] |
| Total (95% CI) | 502 | 508 | | 100.0 | 0.93 [ 0.67, 1.29 ] |

Total events: 96 (Treatment), 103 (Control)

Test for heterogeneity chi-square=8.69 df=7 p=0.28 $I^2$ =19.5%

Test for overall effect z=0.44 p=0.7

## Analysis 22.04. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 04 Discontinuation rate due to adverse events (quality of randomization)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 04 Discontinuation rate due to adverse events (quality of randomization)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Barrett-Connor 1999 | 24/154 | 21/157 | | 60.1 | 1.19 [ 0.64, 2.25 ] |
| × Burger 1987 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Davis 1995 | 1/17 | 0/17 | | 1.6 | 7.39 [ 0.15, 372.38 ] |
| Dobs 2002 | 2/20 | 1/20 | | 4.4 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 0/50 | 1/50 | | 1.6 | 0.14 [ 0.00, 6.82 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 9/107 | 5/111 | | 20.5 | 1.91 [ 0.65, 5.63 ] |
| Penotti 2001 | 3/20 | 1/20 | | 5.7 | 2.95 [ 0.38, 22.72 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 6.1 | 0.36 [ 0.05, 2.61 ] |
| Total (95% CI) | 502 | 508 | | 100.0 | 1.31 [ 0.80, 2.14 ] |

Total events: 40 (Treatment), 32 (Control)

Test for heterogeneity chi-square=4.96 df=6 p=0.55 $I^2$ =0.0%

Test for overall effect z=1.08 p=0.3

## Analysis 22.05. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 05 Discontinuation rate (blinding method)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 05 Discontinuation rate (blinding method)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Barrett-Connor 1999 | 51/154 | 64/157 | | 38.0 | 0.72 [ 0.46, 1.14 ] |
| Braunstein 2003 | 35/107 | 38/119 | | 25.9 | 1.04 [ 0.59, 1.81 ] |
| Dobs 2002 | 2/20 | 1/20 | | 1.5 | 2.02 [ 0.20, 20.62 ] |
| Floter 2002 | 3/50 | 3/50 | | 3.0 | 1.00 [ 0.19, 5.17 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 20/107 | 16/111 | | 15.8 | 1.36 [ 0.67, 2.78 ] |
| Montgomery 1987 | 3/27 | 2/28 | | 2.4 | 1.60 [ 0.26, 9.91 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 13/75 | 15/75 | | 12.0 | 0.84 [ 0.37, 1.90 ] |
| Simon 1999 | 3/37 | 0/36 | | 1.5 | 7.61 [ 0.77, 75.55 ] |
| Total (95% CI) | 609 | 630 | | 100.0 | 0.97 [ 0.73, 1.28 ] |

Total events: 130 (Treatment), 139 (Control)

Test for heterogeneity chi-square=6.41 df=7 p=0.49 $I^2$ =0.0%

Test for overall effect z=0.24 p=0.8

## Analysis 22.06. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 06 Discontinuation rate due to adverse events (blinding method)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 06 Discontinuation rate due to adverse events (blinding method)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Barrett-Connor 1999 | 24/154 | 21/157 | | 44.3 | 1.19 [ 0.64, 2.25 ] |
| Braunstein 2003 | 14/107 | 14/119 | | 28.2 | 1.13 [ 0.51, 2.49 ] |
| Dobs 2002 | 2/20 | 1/20 | | 3.3 | 2.02 [ 0.20, 20.62 ] |
| Floter 2002 | 0/50 | 1/50 | | 1.1 | 0.14 [ 0.00, 6.82 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 9/107 | 5/111 | | 15.1 | 1.91 [ 0.65, 5.63 ] |
| Montgomery 1987 | 1/27 | 1/28 | | 2.3 | 1.04 [ 0.06, 17.04 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 4.5 | 0.36 [ 0.05, 2.61 ] |
| Simon 1999 | 1/37 | 0/36 | | 1.1 | 7.19 [ 0.14, 362.59 ] |
| Total (95% CI) | 609 | 630 | | 100.0 | 1.21 [ 0.79, 1.84 ] |

Total events: 52 (Treatment), 46 (Control)

Test for heterogeneity chi-square=4.35 df=7 p=0.74 $I^2$ =0.0%

Test for overall effect z=0.88 p=0.4

## Analysis 22.07. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 07 Discontinuation rate (large studies)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 07 Discontinuation rate (large studies)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Burger 1987 | 0/10 | 2/10 | | 3.9 | 0.12 [ 0.01, 2.09 ] |
| Davis 1995 | 2/17 | 0/17 | | 4.0 | 7.87 [ 0.47, 131.27 ] |
| Dobs 2002 | 2/20 | 1/20 | | 5.8 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 3/50 | 3/50 | | 11.7 | 1.00 [ 0.19, 5.17 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Montgomery 1987 | 3/27 | 2/28 | | 9.5 | 1.60 [ 0.26, 9.91 ] |
| Penotti 2001 | 5/20 | 2/20 | | 12.1 | 2.75 [ 0.55, 13.79 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 13/75 | 15/75 | | 47.0 | 0.84 [ 0.37, 1.90 ] |
| Simon 1999 | 3/37 | 0/36 | | 6.0 | 7.61 [ 0.77, 75.55 ] |
| Total (95% CI) | 305 | 304 | | 100.0 | 1.28 [ 0.73, 2.25 ] |

Total events: 31 (Treatment), 25 (Control)

Test for heterogeneity chi-square=8.73 df=7 p=0.27 $I^2$ =19.8%

Test for overall effect z=0.87 p=0.4

## Analysis 22.08. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 08 Discontinuation rate due to adverse events (large studies)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 08 Discontinuation rate due to adverse events (large studies)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| × Burger 1987 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Davis 1995 | 1/17 | 0/17 | | 6.5 | 7.39 [ 0.15, 372.38 ] |
| Dobs 2002 | 2/20 | 1/20 | | 18.5 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 0/50 | 1/50 | | 6.5 | 0.14 [ 0.00, 6.82 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Montgomery 1987 | 1/27 | 1/28 | | 12.7 | 1.04 [ 0.06, 17.04 ] |
| Penotti 2001 | 3/20 | 1/20 | | 23.9 | 2.95 [ 0.38, 22.72 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 25.4 | 0.36 [ 0.05, 2.61 ] |
| Simon 1999 | 1/37 | 0/36 | | 6.5 | 7.19 [ 0.14, 362.59 ] |
| Total (95% CI) | 305 | 304 | | 100.0 | 1.30 [ 0.48, 3.53 ] |

Total events: 9 (Treatment), 7 (Control)

Test for heterogeneity chi-square=5.16 df=6 p=0.52 $I^2$ =0.0%

Test for overall effect z=0.52 p=0.6

## Analysis 22.09. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 09 Discontinuation rate (crossover studies)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 09 Discontinuation rate (crossover studies)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| Barrett-Connor 1999 | 51/154 | 64/157 | | 42.1 | 0.72 [ 0.46, 1.14 ] |
| Braunstein 2003 | 35/107 | 38/119 | | 28.7 | 1.04 [ 0.59, 1.81 ] |
| Burger 1987 | 0/10 | 2/10 | | 1.1 | 0.12 [ 0.01, 2.09 ] |
| Davis 1995 | 2/17 | 0/17 | | 1.1 | 7.87 [ 0.47, 131.27 ] |
| Dobs 2002 | 2/20 | 1/20 | | 1.6 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 20/107 | 16/111 | | 17.5 | 1.36 [ 0.67, 2.78 ] |
| Montgomery 1987 | 3/27 | 2/28 | | 2.7 | 1.60 [ 0.26, 9.91 ] |
| Penotti 2001 | 5/20 | 2/20 | | 3.4 | 2.75 [ 0.55, 13.79 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| Simon 1999 | 3/37 | 0/36 | | 1.7 | 7.61 [ 0.77, 75.55 ] |
| Total (95% CI) | 538 | 556 | | 100.0 | 1.02 [ 0.76, 1.37 ] |

Total events: 121 (Treatment), 125 (Control)

Test for heterogeneity chi-square=11.97 df=8 p=0.15 $I^2$ =33.2%

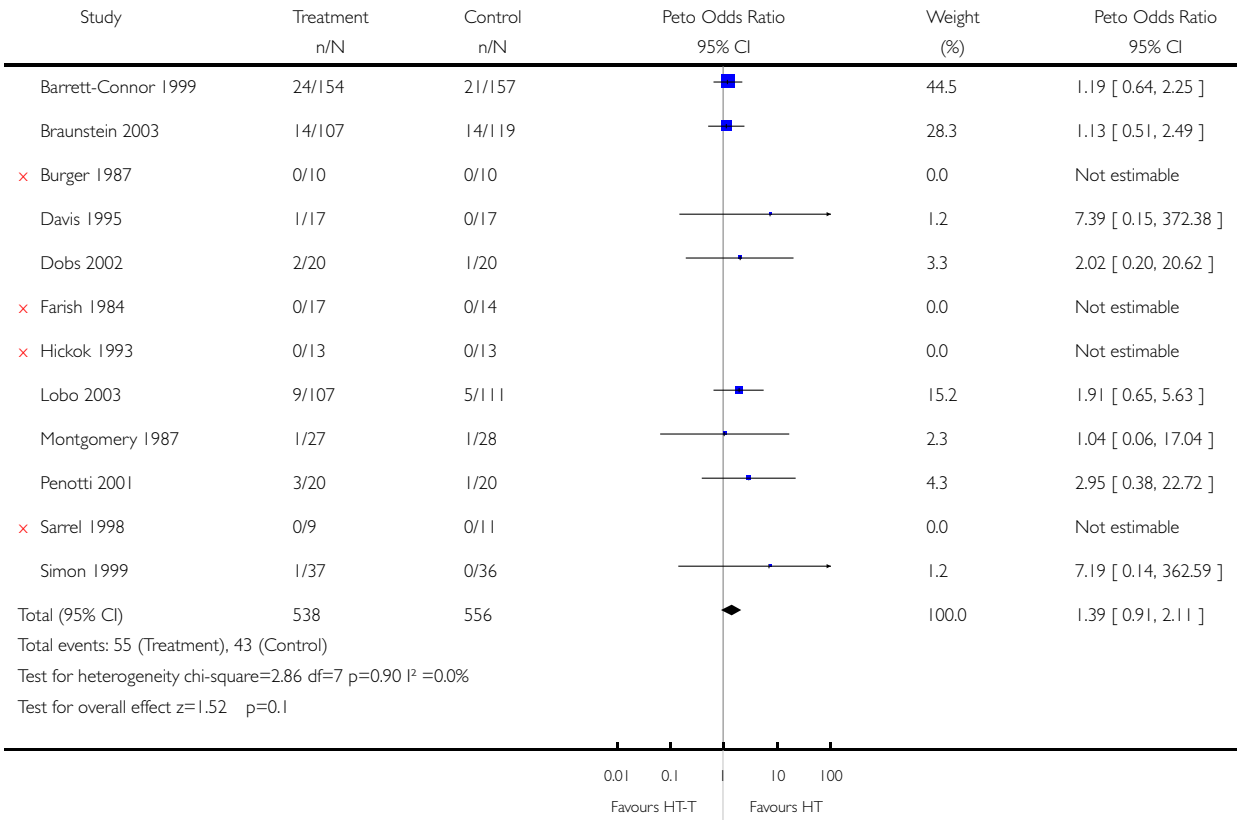
Test for overall effect z=0.13 p=0.9

## Analysis 22.10. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 10 Discontinuation rate due to adverse events (crossover studies)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 10 Discontinuation rate due to adverse events (crossover studies)

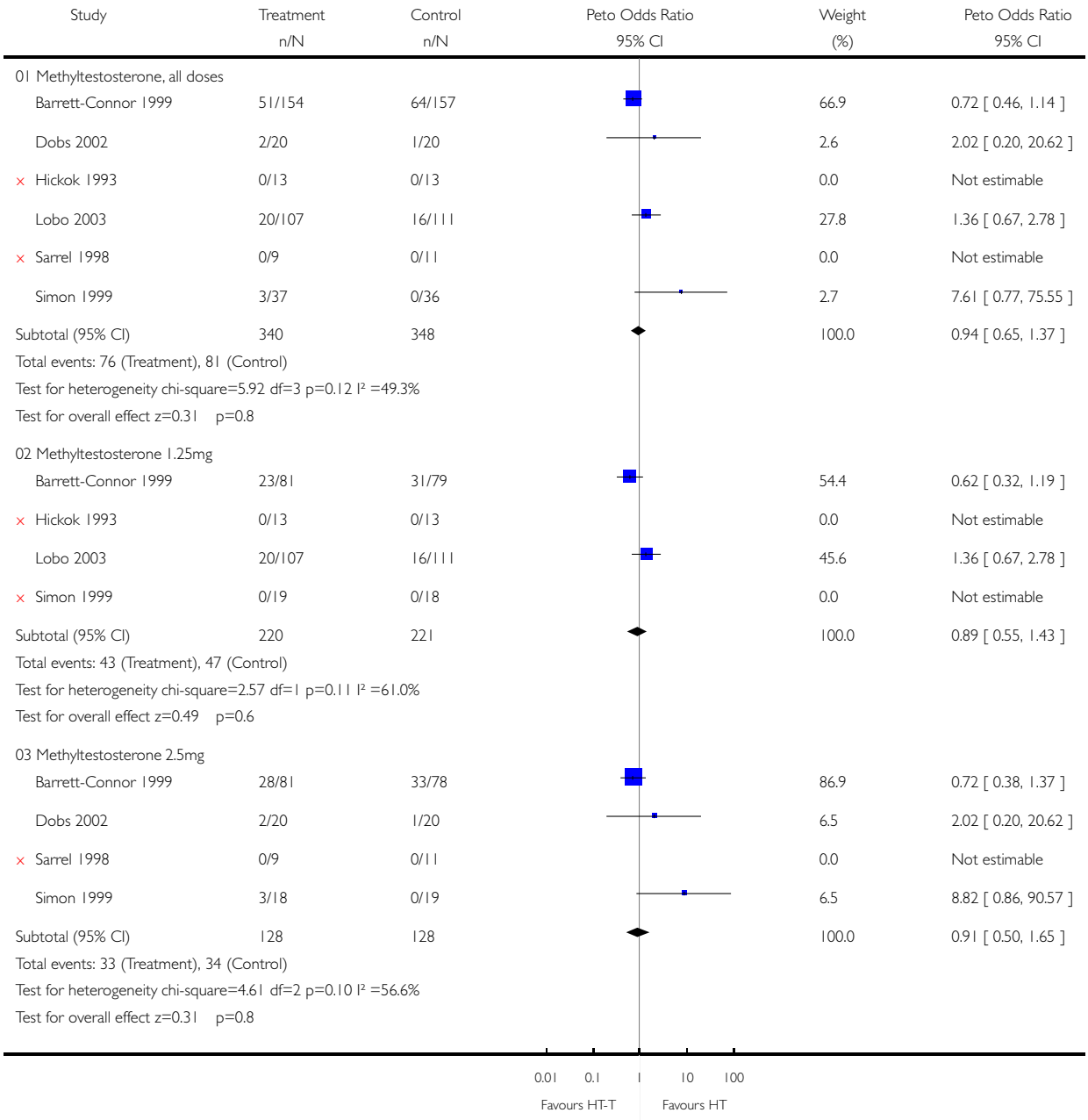


## Analysis 22.11. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 11 Discontinuation rate (methyltestosterone doses)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 11 Discontinuation rate (methyltestosterone doses)



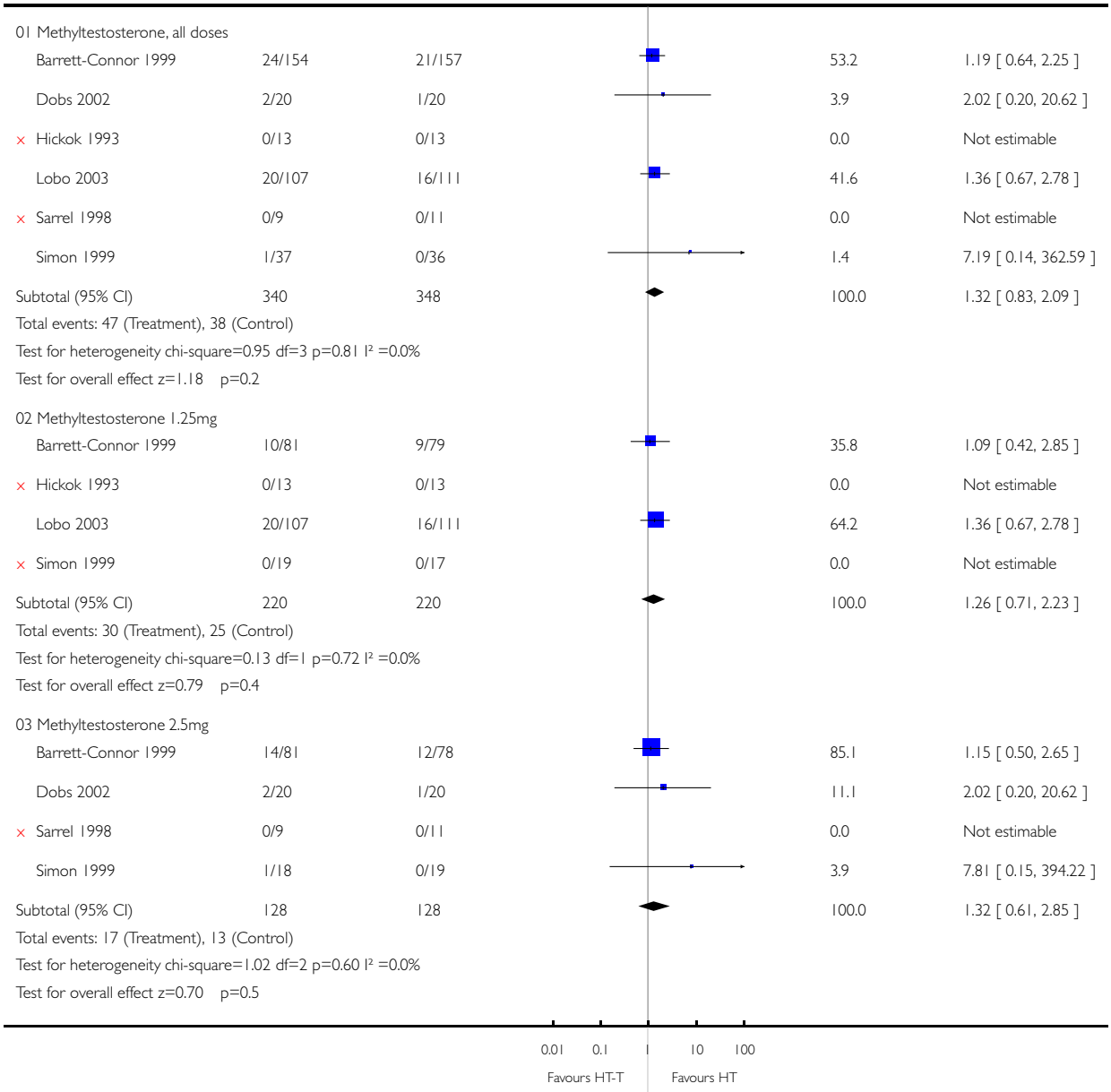
## Analysis 22.12. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 12 Discontinuation rate due to adverse events (methyltestosterone doses)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 12 Discontinuation rate due to adverse events (methyltestosterone doses)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 01 Methyltestosterone, all doses | | | | | |
| Barrett-Connor 1999 | 24/154 | 21/157 | | 53.2 | 1.19 [ 0.64, 2.25 ] |
| Dobs 2002 | 2/20 | 1/20 | | 3.9 | 2.02 [ 0.20, 20.62 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 20/107 | 16/111 | | 41.6 | 1.36 [ 0.67, 2.78 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| Simon 1999 | 1/37 | 0/36 | | 1.4 | 7.19 [ 0.14, 362.59 ] |
| Subtotal (95% CI) | 340 | 348 | | 100.0 | 1.32 [ 0.83, 2.09 ] |
| Total events: 47 (Treatment), 38 (Control) | | | | | |
| Test for heterogeneity chi-square=0.95 df=3 p=0.81 I² =0.0% | | | | | |
| Test for overall effect z=1.18 p=0.2 | | | | | |
| 02 Methyltestosterone 1.25mg | | | | | |
| Barrett-Connor 1999 | 10/81 | 9/79 | | 35.8 | 1.09 [ 0.42, 2.85 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 20/107 | 16/111 | | 64.2 | 1.36 [ 0.67, 2.78 ] |
| × Simon 1999 | 0/19 | 0/17 | | 0.0 | Not estimable |
| Subtotal (95% CI) | 220 | 220 | | 100.0 | 1.26 [ 0.71, 2.23 ] |
| Total events: 30 (Treatment), 25 (Control) | | | | | |
| Test for heterogeneity chi-square=0.13 df=1 p=0.72 I² =0.0% | | | | | |
| Test for overall effect z=0.79 p=0.4 | | | | | |
| 03 Methyltestosterone 2.5mg | | | | | |
| Barrett-Connor 1999 | 14/81 | 12/78 | | 85.1 | 1.15 [ 0.50, 2.65 ] |
| Dobs 2002 | 2/20 | 1/20 | | 11.1 | 2.02 [ 0.20, 20.62 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| Simon 1999 | 1/18 | 0/19 | | 3.9 | 7.81 [ 0.15, 394.22 ] |
| Subtotal (95% CI) | 128 | 128 | | 100.0 | 1.32 [ 0.61, 2.85 ] |
| Total events: 17 (Treatment), 13 (Control) | | | | | |
| Test for heterogeneity chi-square=1.02 df=2 p=0.60 I² =0.0% | | | | | |
| Test for overall effect z=0.70 p=0.5 | | | | | |



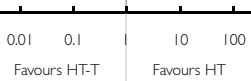
## Analysis 22.13. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 13 Discontinuation rate (estrogen doses)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 13 Discontinuation rate (estrogen doses)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 01 Estrogen, all doses | | | | | |
| Barrett-Connor 1999 | 51/154 | 64/157 | | 36.1 | 0.72 [ 0.46, 1.14 ] |
| Braunstein 2003 | 35/107 | 38/119 | | 24.6 | 1.04 [ 0.59, 1.81 ] |
| Burger 1987 | 0/10 | 2/10 | | 0.9 | 0.12 [ 0.01, 2.09 ] |
| Davis 1995 | 2/17 | 0/17 | | 1.0 | 7.87 [ 0.47, 131.27 ] |
| Dobs 2002 | 2/20 | 1/20 | | 1.4 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 3/50 | 3/50 | | 2.8 | 1.00 [ 0.19, 5.17 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 20/107 | 16/111 | | 15.0 | 1.36 [ 0.67, 2.78 ] |
| Montgomery 1987 | 3/27 | 2/28 | | 2.3 | 1.60 [ 0.26, 9.91 ] |
| Penotti 2001 | 5/20 | 2/20 | | 2.9 | 2.75 [ 0.55, 13.79 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 13/75 | 15/75 | | 11.4 | 0.84 [ 0.37, 1.90 ] |
| Simon 1999 | 3/37 | 0/36 | | 1.4 | 7.61 [ 0.77, 75.55 ] |
| Subtotal (95% CI) | 673 | 691 | | 100.0 | 1.00 [ 0.76, 1.31 ] |
| Total events: 137 (Treatment), 143 (Control) | | | | | |
| Test for heterogeneity chi-square=12.16 df=10 p=0.27 $I^2$ =17.7% | | | | | |
| Test for overall effect z=0.02 p=1 | | | | | |
| 02 Conjugated estrogen 0.625mg or equivalent doses of other estrogens | | | | | |
| Barrett-Connor 1999 | 23/81 | 31/79 | | 24.9 | 0.62 [ 0.32, 1.19 ] |
| Braunstein 2003 | 35/107 | 38/119 | | 34.2 | 1.04 [ 0.59, 1.81 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 20/107 | 16/111 | | 20.9 | 1.36 [ 0.67, 2.78 ] |
| Penotti 2001 | 5/20 | 2/20 | | 4.1 | 2.75 [ 0.55, 13.79 ] |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 13/75 | 15/75 | | 15.9 | 0.84 [ 0.37, 1.90 ] |

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| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| × Simon 1999 | 0/19 | 0/17 | | 0.0 | Not estimable |
| Subtotal (95% CI) | 432 | 444 | | 100.0 | 0.97 [ 0.70, 1.35 ] |
| Total events: 96 (Treatment), 102 (Control) | | | | | |
| Test for heterogeneity chi-square=4.49 df=4 p=0.34 $I^2$ =10.9% | | | | | |
| Test for overall effect z=0.18 p=0.9 | | | | | |
| 03 Conjugated estrogen 1.25mg or equivalent doses of other estrogens | | | | | |
| Barrett-Connor 1999 | 28/73 | 33/78 | | 46.1 | 0.85 [ 0.44, 1.62 ] |
| Burger 1987 | 0/10 | 2/10 | | 2.4 | 0.12 [ 0.01, 2.09 ] |
| Davis 1995 | 2/17 | 0/17 | | 2.4 | 7.87 [ 0.47, 131.27 ] |
| Dobs 2002 | 2/20 | 1/20 | | 3.6 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 3/50 | 3/50 | | 7.2 | 1.00 [ 0.19, 5.17 ] |
| Montgomery 1987 | 3/27 | 2/28 | | 5.8 | 1.60 [ 0.26, 9.91 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 13/75 | 15/75 | | 28.9 | 0.84 [ 0.37, 1.90 ] |
| Simon 1999 | 3/18 | 0/19 | | 3.6 | 8.82 [ 0.86, 90.57 ] |
| Subtotal (95% CI) | 326 | 332 | | 100.0 | 1.00 [ 0.65, 1.56 ] |
| Total events: 54 (Treatment), 56 (Control) | | | | | |
| Test for heterogeneity chi-square=8.55 df=7 p=0.29 $I^2$ =18.1% | | | | | |
| Test for overall effect z=0.02 p=1 | | | | | |

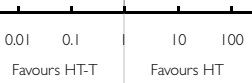
## Analysis 22.14. Comparison 22 HT-T versus HT on discontinuation rate (sensitivity analysis), Outcome 14 Discontinuation rate due to adverse events (estrogen doses)

Review: Testosterone for peri- and postmenopausal women

Comparison: 22 HT-T versus HT on discontinuation rate (sensitivity analysis)

Outcome: 14 Discontinuation rate due to adverse events (estrogen doses)

| Study | Treatment n/N | Control n/N | Peto Odds Ratio 95% CI | Weight (%) | Peto Odds Ratio 95% CI |
|---|---|---|---|---|---|
| 01 Estrogen, all doses | | | | | |
| Barrett-Connor 1999 | 24/154 | 21/157 | | 42.1 | 1.19 [ 0.64, 2.25 ] |
| Braunstein 2003 | 14/107 | 14/119 | | 26.8 | 1.13 [ 0.51, 2.49 ] |
| × Burger 1987 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Davis 1995 | 1/17 | 0/17 | | 1.1 | 7.39 [ 0.15, 372.38 ] |
| Dobs 2002 | 2/20 | 1/20 | | 3.1 | 2.02 [ 0.20, 20.62 ] |
| × Farish 1984 | 0/17 | 0/14 | | 0.0 | Not estimable |
| Floter 2002 | 0/50 | 1/50 | | 1.1 | 0.14 [ 0.00, 6.82 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 9/107 | 5/111 | | 14.3 | 1.91 [ 0.65, 5.63 ] |
| Montgomery 1987 | 1/27 | 1/28 | | 2.1 | 1.04 [ 0.06, 17.04 ] |
| Penotti 2001 | 3/20 | 1/20 | | 4.0 | 2.95 [ 0.38, 22.72 ] |
| × Sarrel 1998 | 0/9 | 0/11 | | 0.0 | Not estimable |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 4.3 | 0.36 [ 0.05, 2.61 ] |
| Simon 1999 | 1/37 | 0/36 | | 1.1 | 7.19 [ 0.14, 362.59 ] |
| Subtotal (95% CI) | 673 | 691 | | 100.0 | 1.28 [ 0.85, 1.92 ] |
| Total events: 56 (Treatment), 47 (Control) | | | | | |
| Test for heterogeneity chi-square=5.83 df=9 p=0.76 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.17 p=0.2 | | | | | |
| 02 Conjugated estrogen 0.625mg or equivalent doses of other estrogens | | | | | |
| Barrett-Connor 1999 | 10/81 | 9/79 | | 27.1 | 1.09 [ 0.42, 2.85 ] |
| Braunstein 2003 | 14/107 | 14/119 | | 39.5 | 1.13 [ 0.51, 2.49 ] |
| × Hickok 1993 | 0/13 | 0/13 | | 0.0 | Not estimable |
| Lobo 2003 | 9/107 | 5/111 | | 21.2 | 1.91 [ 0.65, 5.63 ] |
| Penotti 2001 | 3/20 | 1/20 | | 5.9 | 2.95 [ 0.38, 22.72 ] |
| × Sherwin 1988 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Shifren 2000 | 1/75 | 3/75 | | 6.3 | 0.36 [ 0.05, 2.61 ] |

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