Drug Class Review
on Estrogen Preparations

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INTRODUCTION

Estrogen production declines in women when ovarian function changes with aging or after surgical removal of the ovaries. This drop in estrogen levels can trigger a vasomotor response resulting in a sensation of flushing and sweating that interferes with function and sleep (hot flashes or flushes). Other symptoms, such as mood changes and urogenital atrophy, contribute to reduced quality of life for many women. Several other effects on health also occur because estrogen receptors are located in many areas of the body and estrogen has interactions with processes such as blood clotting. Studies conducted in recent years have identified additional health benefits of postmenopausal estrogen besides symptom management (osteoporosis) as well as potential harms (cardiovascular disease, breast cancer, cholecystitis). Estrogen was approved as a hormone supplement in the 1940s to treat estrogen withdrawal symptoms in menopausal women. A national survey conducted in 1995 indicated that 37% of women age 50 and older were using estrogen for multiple purposes.[1]

Several oral estrogen preparations are available, although conjugated equine estrogen (CEE) is the most commonly used in the U.S. Other routes of delivery, such as transdermal, intramuscular, and topical, are less common. Treatment with transdermal 17-beta estradiol (E2) provides higher estradiol levels than corresponding doses of CEE that provide higher levels of estrone and estrone sulfate.[2] This difference reflects the hormonal compositions of the different drugs as well as the consequences of the hepatic first-pass metabolism effect with oral use. It is not known if these differences result in important clinical effects.

A new transdermal vaginal ring (Femring, delivering E2 50 mcg or 100 mcg) was approved by the FDA in March 2003 for the treatment of moderate to severe vasomotor symptoms.

Recent research and current practice dictate that systemically administered estrogen be combined with a progestin or progesterone for a woman with a uterus to avoid endometrial hypertrophy and endometrial cancer associated with estrogen-only therapy. Both agents can be combined into one daily pill, although other regimens utilizing separate estrogen and progestin/progesterone pills taken together or distributed cyclically over a month are also used.

The current FDA approved indications for postmenopausal estrogen include treatment of menopausal symptoms and prevention of low bone density and fractures. The FDA recently added health warnings to its label including new data on health harms from the Women's Health

Initiative (WHI) trial published in July 2002.[3] The U.S. Preventive Services Task Force, as well as several professional organizations, are currently recommending against use of estrogen and progestin/progesterone for prevention of chronic conditions.[4] It is possible that the clinical uses of postmenopausal estrogen could change in the near future.

Scope and Key Questions

The purpose of this review is to address the following key questions:

1. What is the comparative efficacy of different estrogen preparations when used by perimenopausal and postmenopausal women for
    - Reducing symptoms of menopause: hot flashes/flushes, sleep disturbances/night sweats, mood changes (depression), urogenital atrophy, sexual function, and quality-of-life measures?
    - Preventing low bone density and fractures?

2. What is the comparative safety of different estrogen preparations when used by perimenopausal and postmenopausal women for
    - Short-term use (<5 years)?
    - Long-term use (5 or more years)?

3. Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion criteria

1. Study participants include women recruited from any health care setting or a population-based sample experiencing menopause. When possible, data were considered separately for women with natural vs. surgical menopause (oophorectomy) and for women in peri vs. postmenopause.
    - Perimenopausal women are those transitioning through natural menopause who had irregular menstrual periods within the last 12 months.

- Postmenopausal women are those with surgical or natural menopause and amenorrhea for more than 12 months.

Exclusions:

- Nonmenopausal women
- Major intercurrent disease
- Previous estrogen use within one month of commencement of the study

2. Interventions include oral and transdermal estrogens listed below for all symptoms, bone density, and fracture outcomes, and vaginal cream for urogenital atrophy, with or without concomitant use of progestin/progesterone administered as sequential or continuous regimens. Progestin/progesterone preparations will not be considered separately. Eligibility for review was determined by Oregon Health Plan (OHP) estrogen subcommittee members and Kathy Ketchum, OMAP DUR Board Coordinator, based on current practice and availability. These include:
   - 17-beta estradiol (E2): oral, transdermal, vaginal cream
   - Estradiol valerate (E2V): oral
   - Conjugated equine estrogen (CEE): oral, vaginal cream
   - Synthetic conjugated estrogen: oral
   - Esterified estrogen (EE): oral
   - Estropipate: oral

   Exclusions:
   - Agents or routes of administration not listed
   - Treatment period of less than 3 months for symptoms and less than 1 year for bone density and fractures
   - Estrogen content not clear
   - Co-interventions that may potentially affect outcomes (e.g., testosterone)

Note: The estrogens subcommittee decided not to include agents using an intravaginal ring route of administration, because there was little use of this type of preparation. At the time, such preparations were FDA-approved only for treatment of urogenital symptoms, not vasomotor symptoms. Studies of a new intravaginal ring are included in this updated report because it is a

new product that has been approved for a new indication (moderate to severe vasomotor symptoms) since the original report.

3. Outcome measures include the following:
    - Hot flashes or flushes defined as any otherwise unexplained sensation of flushing/sweating experienced by the woman being studied. Studies were included if they measured frequency, severity, presence versus absence, or a combination measure of frequency and severity as either primary or secondary outcomes at baseline, 3 months, and/or end of study.
    - Other symptoms such as sleep disturbances/night sweats, mood changes (depression), sexual function, urogenital atrophy, and quality-of-life measures.
    - Prevention of osteoporosis measured by improvement in bone density and fracture outcomes after at least 1 year of use.

4. Adverse Effects
    - Withdrawals
    - Withdrawals due to adverse effects
    - Withdrawals due to specific adverse effects

    For short-term use
    - Atypical bleeding; endometrial hypertrophy
    - Nausea and vomiting
    - Breast tenderness
    - Headaches
    - Weight changes
    - Dizziness
    - Thrombosis
    - Cardiovascular events
    - Rash and pruritis
    - Cholecystitis
    - Effects on the liver

For long-term use

- Cardiovascular events
- Breast cancer
- Thrombosis
- Cholecystitis
- Ovarian cancer/endometrial cancer

5. Treatment effects are defined as the difference in outcomes between the estrogen and placebo groups, or second estrogen group for head-to-head comparisons, at the end of the study. Measures of the difference between the changes from baseline for the 2 groups were not used. For cross-over trials, only results from the end of the first phase were used because of the potential carry-over effect.

6. Study Designs

   Include:

   - Symptoms: Double-blind, randomized controlled trials of at least 3 months duration of one estrogen preparation vs. another estrogen or vs. placebo.
   - Prevention of osteoporosis: Double-blind or open, randomized controlled trials of postmenopausal women who are treated for at least 1 year vs. another estrogen or vs. placebo.
   - Good quality systematic reviews and meta-analyses.

   Exclude:

   - No original data: non-systematic review, editorial, letter with no original data, etc.
   - Co-interventions that may potentially affect outcomes (e.g., testosterone, bisphophonates).

7. Special Populations

   - Elderly
   - Racial/ethnic groups
   - Co-morbidities (smokers, high-risk for ovarian and breast cancer, high-risk for osteoporosis)
   - Early oophorectomy (<45 years) or premature menopause (<35 years)

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Registry (2002, Issue 1), Medline (1966-2002), Embase (1980-2002), and reference lists of review articles (see Appendix A for complete search strategy). Pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the State of Oregon (http://www.ohppr.state.or.us/index.htm). All citations were imported into an electronic database (EndNote 5.0).

In August 2003 we conducted update searches of the Cochrane Library (2003, Issue 2), MEDLINE (through July 2003), and Embase (through July 2003) starting from the end-date of the original searches. Subcommittee members were invited to provide additional citations.

Study Selection

We included English-language randomized controlled trials and systematic evidence reviews of estrogen and treatment of menopausal symptoms or prevention of low bone density and fractures that used one or more of the estrogen preparations identified as eligible (listed above). The results of our electronic literature searches were also compared to reference lists of two recently published systematic evidence reviews listed in the Cochrane database.[5, 6]

Data Abstraction

One reviewer abstracted the following data from included trials: study design, population characteristics (including age, ethnicity, setting, peri vs. postmenopausal status, hysterectomy status), eligibility criteria, interventions (estrogen type, form, dose and duration, use of progestin/progesterone, cyclic or continuous regimen), comparisons, numbers enrolled and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results if available. Withdrawals due to adverse effects were characterized by type of specific adverse effect. Abbreviations and acronyms related to this review are listed in Appendix B.

Validity Assessment

For trials not included in either of two recently published Cochrane reviews,[5, 6] we assessed the internal validity (quality) based on the pre-defined criteria listed in Appendix C, which were submitted to the Health Resources Commission in December 2001. These criteria are based on those developed by the U.S. Preventive Services Task Force and the National Health Services Centre (UK).[7-9]

We rated the internal validity based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up, and the use of intention-to-treat analysis. Trials with a major limitation in one or more categories were rated poor quality; trials meeting all criteria were rated good quality; the remainder were rated fair quality. The "fair quality" category is broad and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. All trials included in the Cochrane reviews appear to be of at least fair quality by these criteria and were not rated in this review. Quality ratings for studies included in the Cochrane review on hot flashes or flushes are in Appendix D,[6] ratings for the Cochrane review on bone density and fractures are not yet available.[5]

External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Data Synthesis

We conducted a meta-analysis of trials reporting hot flash or flush outcomes in order to provide a more precise and standard measure of treatment effect. This outcome was the most

uniformly reported among studies of symptoms. Our meta-analysis differs from the Cochrane review because OHP defined a narrower range of oral agents, included transdermal forms, captured studies published after 2000, and included head-to-head comparisons. Trials that presented data on frequency of hot flash/flush outcomes after treatment in numerical format and provided standard deviations met criteria for the meta-analysis. DerSimonian-Laird weighted mean differences in mean weekly number of hot flashes/flushes were calculated to estimate pooled effects. This assumes a random effect, or between-study variation, in addition to within-study variation. The calculations were generated using StatsDirect statistical software version 1.9.14.[10] Funnel plots were constructed and indicated no evidence of publication bias, although they are a crude estimate and were limited by the small numbers of eligible studies.

RESULTS

Overview

Electronic searches identified 1,005 citations: 24 from the Cochrane Library, 666 from Medline, 315 from Embase. Hand searches identified 26 citations from reference lists, and 47 articles were received from pharmaceutical companies.

Update searches conducted in August 2003 resulted in 123 additional citations: 92 from Embase, 11 from the Cochrane Central Registry of Controlled Trials, 9 from Medline, and 11 from 3 pharmaceutical companies. Ninety-nine of these were excluded at the abstract stage. Of the remaining 24 citations, 12 met inclusion criteria. Twelve were excluded after full text review: 10 because the drug was not included, the intervention used combined drug therapy, or the study compared only different dosages of the same medication; one had a duration of less than 3 months, and one had already been cited in the original report. Two additional citations, a placebo-controlled trial of a newly-approved vaginal ring, and a report from the Women's Health Initiative, were published after the initial searches and were located through hand searching. One included study is reported only in abstract form, and another is a poster presentation.

What is the comparative efficacy of different estrogen preparations for reducing symptoms of menopause?

Symptoms considered in this review include hot flashes or flushes, sleep disturbances/night sweats, mood changes (depression), urogenital symptoms and sexual function, and quality-of-life measures. Numbers of included studies are summarized in Table 1. Trials of hot flashes/flushes predominated. Data from these studies were abstracted into Evidence Table 1 and eligible studies were combined in a meta-analysis. Quality scores are listed in Appendix E. Trials reporting other symptoms are qualitatively described in the text because outcome measures varied widely between studies.

Table 1. Number of studies of estrogens and menopausal symptoms

	Hot Flashes/ Flushes	Sleep Disturbances/ Night Sweats	Mood Changes	Urogenital Symptoms/ Sexual Function	Quality-of-Life Measures
Head-to-head comparisons					
Conjugated equine estrogen (CEE) and oral estradiol (E2)	1	0	0	0	0
Oral estradiol (E2) and estradiol valerate (E2V)	1	0	1	0	0
Conjugated equine estrogen (CEE) and transdermal estradiol (E2)	3	0	0	3	2
Vaginal estrogen creams	NA	NA	NA	3	NA
E2 intravaginal ring and oral E2	1	0	0	0	0
Placebo comparisons					
Estradiol (E2)					
Oral	12	0	1	0	2
Transdermal	11	3	1	4	4
Intravaginal ring	1	0	0	0	0
Estradiol valerate (E2V)	3	0	0	0	0
Conjugated equine estrogen (CEE)	6	1	5	2	1
Conjugated synthetic estrogen	0	0	0	0	0
Esterified estrogen (EE)	0	0	0	0	1
Estropipate	1	0	0	0	0

Hot Flashes/Flushes

A hot flash or flush refers to the spontaneous sensation of warmth, often associated with perspiration, resulting from a vasomotor response to declining estrogen levels. Although the term "flash" indicates a prodromal phase and "flush" the vasomotor dilation phase, they are combined in this report because they were reported inconsistently among the trials. These episodes are described in many ways in the estrogen trials. Most commonly, study participants recorded the number of episodes over a day or week period of time and changes indicated treatment responses. Other trials used measures such as percentage of participants experiencing symptoms or severity of symptoms, for example. A cumulative symptom score, the Kupperman Index,[11] was used in some studies to classify the severity of menopausal symptoms. It is based on the severity and intensity of hot flashes, paresthesias, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia/myalgia, headache, palpitation and formication. The maximum score is 51, a value of more than 20 indicates moderate to severe symptoms, and a score of 10 describes mild complaints. Hot flashes is the most important symptom in the index. However, the use of the score is controversial since it has not been validated. Trials described in Evidence Table 1 include all measures of hot flashes.

Head-to-head comparisons

Six trials compared estrogen preparations head-to-head including a trial of CEE compared to oral E2,[12] oral E2 compared to E2V,[13] a vaginal ring releasing E2 compared to oral E2,[14] and three trials comparing CEE to transdermal E2[2, 15, 16] (Evidence Table 1). All trials reported improved number and/or severity of hot flashes for all of the estrogen treatment groups compared to placebo or baseline. There were no statistically significant differences in treatment effects in any of the head-to-head estrogen comparisons in any of the trials.

Of three trials comparing CEE to transdermal E2, two were combined in a meta-analysis,[15, 16] and one excluded because data was provided in graph form.[2] The pooled weighted mean difference in hot flashes was not significantly different between E2 and CEE treatment groups, thereby favoring neither agent (-0.3; 95% CI: -3.4, 2.7).

In a good quality trial of 159 women receiving either a vaginal ring releasing 50 or 100 mcg of E2 compared to 1 mg oral E2 per day, the number of hot flushes/night sweats at 24 weeks was reduced in all groups and there were no significant differences between groups.[14]

Dose-response trends were demonstrated in three trials, with higher doses corresponding to bigger treatment effects.[12, 14, 15] In the intravaginal E2 ring trial, a dose response pattern was seen at 12 weeks, but not at 24 weeks.[14] Too few dose comparisons were conducted between estrogens to determine if differences exist.

Placebo comparisons

Thirty-four randomized controlled trials comparing an eligible estrogen preparation with placebo met criteria for this review (Evidence Table 1).

Characteristics of the trials include:

- Trials were conducted predominantly in the U.S. or W. Europe and most often recruited participants from general or gynecology practices.
- In general, each trial enrolled small numbers of participants and had multiple comparison groups.
- Entry criteria varied: some stated, "most" or a percentage of participants had symptoms, some required a certain threshold of symptoms such as "5 or more vasomotor symptoms per day."
- Trials often enrolled both peri- and postmenopausal women but did not separate them in the analysis so comparisons between them cannot be made. Ages ranged from the mid 40s to 60s; most trials reported mean ages in the early 50s.
- Hysterectomy status was clearly reported if the study criteria called for women either with or without hysterectomy. For trials including both types, the data were not separately reported so comparisons cannot be made.
- No trial specifically addressed treatment in women with premature ovarian failure. A limited number of trials focused on women with recent hysterectomy and oophorectomy, although ages varied.

- Reporting of concurrent medications, co-morbidities, or other potential confounders was minimal, although inclusion criteria generally focused on healthy, symptomatic women.
- Many different outcomes were reported and lack of standardization makes them difficult to compare. Frequency of hot flashes was the most common measure and there were enough trials to combine them in a meta-analysis. Other outcomes are described in Evidence Table 1.
- Women in placebo groups usually also had improvement of symptoms because the natural history of the estrogen withdrawal effect is gradual resolution of symptoms.
- Women with the most frequent or severe symptoms most often had the biggest treatment effect and trials that enrolled highly symptomatic women tended to have large mean treatment effects.
- All estrogen preparations generally improved symptoms among symptomatic women compared to placebo.

Eleven of twelve trials of oral E2 demonstrated statistically significant improvements in hot flash frequency and/or severity compared to placebo.[17-27] The one trial that reported no difference between groups was conducted in Chinese women in Hong Kong after oophorectomy.[28] Approximately 66% of women in this trial had vasomotor symptoms at baseline and 23-35% considered them "moderate to severe," a lower level than in some of the other trials. One trial reported that women in early (3-12 months amenorrhea) as well as late menopause (>12 months amenorrhea) had benefit.[17] Eight trials included concomitant progestin/progesterone use (continuous and cyclic norethidrone acetate [NETA], cyclic nomegestrol).[17-20, 22, 25-27]

Three trials of E2V reported statistically significant improvements in hot flash frequency and/or severity compared to placebo.[29-31] All three trials included concomitant progestin/progesterone use (continuous medroxyprogesterone acetate [MPA], cyclic and continuous cyproterone acetate).

All six trials of CEE reported statistically significant improvements in hot flash frequency and/or severity compared to placebo.[32-37] Two trials included treatment groups with concomitant progestin/progesterone use (cyclic and continuous MPA, cyclic micronized progesterone) as well as unopposed CEE and reported no differences in treatment effects.[36, 37] One trial included three

doses of CEE (0.3, 0.45, 0.626 mg/day) and noted dose-response relationships with higher doses corresponding to bigger treatment effects.[37]

One trial of estropipate indicated statistically significant improvements in hot flash frequency compared to placebo.[38] Women enrolled in this trial differed from the others because they had symptoms of depression as well as hot flashes.

All 11 trials of transdermal E2 reported statistically significant improvements in hot flash frequency and/or severity compared to placebo.[15, 39-47] Two trials included concomitant progestin/progesterone (cyclic NETA, continuous transdermal levonorgestrel).[42, 45]

There is one fair quality placebo-controlled trial of a transdermal vaginal ring releasing E2 for treatment of vasomotor symptoms.[48] Three hundred thirty-three women with at least 7 moderate to severe hot flushes per day, or at least 56 moderate to severe vasomotor symptoms per week, were randomized to a vaginal ring delivering the equivalent of 50 or 100 mcg E2 per day or a placebo vaginal ring. Symptoms were recorded by women on daily diary cards using a 4-point scale (0=no flushes, 1=mild, 2=moderate, and 3=severe). The efficacy analysis was not intention-to-treat; it included only women with a baseline measurement of moderate to severe vasomotor symptoms who had a vaginal ring inserted and who had at least one evaluation during the study (325/333 randomized). At 13 weeks, the percentage reduction from baseline in number of moderate to severe vasomotor symptoms per week was 79.9% in women randomized to the E2 50 mcg ring, 90.6% in those randomized to the E2 100 mcg ring, and 49.1% in those using a placebo vaginal ring ($p<0.05$ for both E2 groups compared to placebo).

Meta-analysis

Of 12 trials of oral E2 compared to placebo, five met criteria for the meta-analysis.[17, 19-21, 25] The pooled weighted mean difference in hot flashes is -16.8 (95% CI: -23.4, -10.2) per week compared to placebo. Combining only the four trials that included E2 and progestin/progesterone did not significantly change results (-19.1 ; 95% CI: -29.6, -8.6]).[17, 19, 20, 25] Trials were excluded from analysis because they did not provide data on frequency of hot flashes[18, 22, 26-28] or did not provide standard deviations.[23, 24]

Three trials of oral estradiol valerate did not meet criteria for the meta-analysis because they did not provide data on frequency of hot flashes.[29-31]

Of six trials of CEE compared to placebo, one met criteria for the meta-analysis.[35] This trial reported a mean reduction of -19.1 (95% CI: -33.0, -5.1) hot flashes per week after treatment compared to placebo. The other five trials were excluded from analysis because they did not provide data on frequency of hot flashes,[34, 36] provided data in a graph form,[32] or did not provide standard deviations.[32, 33, 37]

One trial of estropipate compared to placebo was identified from the search and met inclusion criteria.[38] This trial reported a mean difference in hot flashes of -11.4 (95% CI: -22.6, -0.2) per week.

Of 11 trials of transdermal E2 compared to placebo, six met criteria for the meta-analysis.[15, 39, 41, 43-45] The pooled weighted mean difference in hot flashes for these trials is -22.5 (95% CI: -39.4, -4.8) per week compared to placebo. Only one trial included E2 and progestin/progesterone and results were not significantly different than the others.[45] Trials were excluded because data was provided in a graph form,[42, 46] and the trials did not provide standard deviations.[24, 46]

Comparison with Cochrane meta-analysis

The results of the OHP review and meta-analysis are consistent with a Cochrane review and meta-analysis of oral estrogens and menopausal hot flashes that includes trials published prior to 2000.[6] The Cochrane review included double-blind, randomized, placebo-controlled trials of all forms of oral estrogen, alone or with progestin/progesterone, for at least 3 months duration. The meta-analysis reported weekly hot flash frequency and symptom severity. References were checked against the results of the OHP search. The OHP review differs from the Cochrane review because OHP defined a narrower range of oral agents, included transdermal forms, captured studies published after 2000, and included head-to-head comparisons.

The Cochrane meta-analysis indicated a significant reduction in the weekly hot flash frequency for estrogen compared to placebo with a pooled weighted mean difference of –17.5 (95% CI: -24.7, –10.2; 6 trials) per week, equivalent to a 77% reduction in frequency (95% CI: 58.2, 87.5). Severity of symptoms was also significantly reduced compared to placebo (odds ratio=0.13; 95% CI: 0.08, 0.22; 13 trials). Differences between types of estrogens were not determined, although trials of E2 and CEE predominated.

The review also found that the reduction in weekly hot flash frequency was similar for opposed and unopposed estrogen regimens compared to placebo (opposed: 77.1% reduction; 95% CI: 49.1, 89.7; unopposed: 76.8%; 95% CI: 59.4, 86.7). Symptom severity seemed to be better treated by opposed (odds ratio=0.10; 95% CI 0.06, 0.19; 10 trials) than by unopposed estrogen (odds ratio=0.35;95% CI: 0.22, 0.56; 4 trials). However, differences between trials could also contribute to this discrepancy.

Sleep Disturbances/Night Sweats

A trial of CEE in women with hot flashes and nighttime awakening at baseline indicated improvement in menopausal symptoms and measures of psychological well-being, but not in parameters of sleep quality such as total sleep time, sleep onset time, number of awakenings, and REM sleep duration compared to placebo.[49] Sleep disturbances were measured along with other quality-of-life measures in a subset of 1511 women enrolled in the WHI.[50] At one year of followup there was a small improvement (0.4 point on a 20-point scale) from baseline in women taking CEE compared with placebo, and no difference from placebo at 3 years.

A trial of transdermal E2 indicated significant improvement in sleep quality, sleep onset, and decreased nocturnal restlessness and awakenings compared to placebo.[51] In this trial, participants on E2 were less tired in the daytime, and had associated alleviation of vasomotor, somatic, and mood symptoms. Women with the worst insomnia had the best improvement with E2. Two other trials of transdermal E2 indicated significant declines in night sweats compared to placebo.[39, 41]

A head-to-head trial of an intravaginal ring delivering E2 compared with oral E2[14] found improvement on the combined endpoint of hot flushes/night sweats in both groups, but night sweats are not reported separately, so it is not possible to determine the effect of the interventions on this outcome alone.

Mood Changes

Eight trials of estrogen reporting mood outcomes met eligibility criteria including one trial comparing E2 and E2V,[13] one of oral E2,[18] one of transdermal E2[52] compared to placebo, and five of CEE compared to placebo.[36, 53-55]

In the head-to-head comparison trial of E2 and E2V, women were asked if symptoms of irritability, nervousness, anxiety, or depression were present or not before and after treatment cycles. Mood disturbances were more frequently reported by the E2 group (82%) than the E2V group (68%) at baseline.[13] At the end of treatment, symptoms were reduced to 52% in the E2 group compared to 44% in the E2V group (p=0.039).

A trial of early postmenopausal women randomized to oral E2 reported significantly improved scores on the Beck Depression Inventory (21 items) as well as on the manic-depressive melancholia subscale (12 items), and the anxiety subscale (14 items), but not on the asthenia subscale or mania subscale.[18] A trial of oral E2 enrolled 50 women meeting DSM-IV criteria for major depressive disorder (26 women), dysthymic disorder (11), or minor depressive disorder (13).[52] Remission of depression, measured by the Montgomery-Asberg Depression Rating Scale, was observed in 68% of women using E2 compared with 20% using placebo (p=0.001).

Five trials of CEE indicated mixed results. One trial reported significantly positive effects of CEE measured by an overall symptom rating scale and depression and feelings of inadequacy subscales, but not other subscales relating to neuroticism and effects of life events.[53] Another trial of psychologically well-adjusted women reported significant improvement on the Beck Depression Inventory with CEE ($p<0.05$).[54] Women enrolled in the Heart and Estrogen/Progestin Replacement Study (HERS) with flushing who used CEE had significantly improved mental health and fewer depressive symptoms than those who used placebo, although women without flushing did not.[55] In the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI), women on CEE did not differ from those on placebo for anxiety and affective symptoms.[36] However, many women in PEPI were also taking progestins that have independent effects on mood. Another trial indicated that CEE did not improve scores on the Beck, General Health Questionnaire, or Eysenck personality scales compared to placebo.[33]

Urogenital Symptoms/Sexual Function

A head-to-head trial comparing CEE and transdermal E2 indicated that the majority of women reported either no change or improvement in vaginal dryness and itching, dyspareunia, and urinary pain and burning in all treatment groups with no major differences between groups.[2] All treatment groups demonstrated improved vaginal cytology, measured by the maturation index, with the biggest improvement in the higher dose E2 group (0.1 mg/day).

A head-to-head trial compared continuous low dose E2 released from a vaginal ring with CEE vaginal cream among women with signs and symptoms of urogenital atrophy.[56] Results indicated that the two agents were comparable for relief of vaginal dryness and dyspareunia, resolution of atrophic signs, improvement in vaginal mucosal maturation indices, and reduction in vaginal pH. The only outcome that differed significantly between agents was that participants found the ring more acceptable and preferred it to the cream. Similar findings were reported in another trial of the E2 vaginal ring and CEE cream[57] and a trial of the E2 tablet and CEE cream.[58]

A head-to-head trial of an intravaginal ring releasing E2 versus oral E2 that was designed to assess vasomotor symptoms also reported urogenital symptoms as a secondary outcome.[14] The mean intensity of vaginal dryness, involuntary loss of urine, and pain during intercourse decreased from baseline to 24 weeks in both groups.

A placebo-controlled trial,[48] examined urogenital symptoms in women randomized to a vaginal ring releasing the equivalent of 50 mcg or 100 mcg E2, or a placebo vaginal ring. There were some baseline differences among groups in vaginal irritation and itching (more severe in placebo group) and vaginal dryness (greater in placebo and 100 mcg vaginal ring groups). There was significant improvement in vaginal dryness at 4 and 8 weeks in the E2 vaginal ring 100 mcg group, and significant improvement in pain during intercourse at week 4 in both E2 groups and at week 13 in the E2 100 mcg group. There was a nonsignificant trend toward greater improvement of other urogenital symptoms in both E2 groups compared with placebo. In a subgroup of 60 women (18% of total) with signs and symptoms of vaginal atrophy at baseline, the maturation index was improved in both E2 groups compared with placebo at week 13.

A trial of transdermal E2, utilizing responses on the McCoy Sex Scale Questionnaire, indicated improvement in responses to five of nine items compared to placebo.[59] A correlation between improved sexual life and a quality-of-life questionnaire was also reported in this study. These findings were supported by another trial of transdermal E2 that indicated improvement in sexual problems and dysfunction as measured with the McCoy Sex Scale compared to placebo.[47] Another trial of transdermal E2 indicated improvement in vaginal dryness, but not dyspareunia, frequent urination, dysuria, stress incontinence, and nocturia, compared to placebo.[60] Another trial comparing transdermal E2 and placebo indicated no differences between groups for symptoms of vaginal discomfort, loss of libido, and incontinence.[44]

There are two brief reports from one head-to-head study that measured sexual functioning and sexual quality-of-life in 186 women randomized to transdermal E2 or oral E2. One of these is an abstract[61] and the other a poster presentation.[62] On some, but not all, measures of sexual function and sexual quality of life, there was more improvement in women who used transdermal E2 compared with oral E2. This study is not published in full-text form, and the brief reports do not provide sufficient detail to assess quality.

A trial of CEE reported significantly improved vaginal dryness and urinary frequency, but no significant improvement on six other items related to sexual function on a General Health Questionnaire compared to placebo.[33] The HERS trial found that women with at least one episode of incontinence per week at baseline and randomized to CEE/MPA had worsening incontinence after approximately 4 years of follow up compared to women taking placebo.[63]

Quality-of-Life

A head-to-head comparison of CEE vs. transdermal E2 utilizing the Menopause Specific Quality of Life Questionnaire indicated improvement in all areas with no significant differences between groups in any of the domains at baseline or after treatment.[64]

Quality of life measures were collected on a subgroup of women enrolled in the WHI (n=1,511).[50] Quality of life and functional status were assessed using the RAND 36-item Health Survey, which includes items about general health, physical functioning, limitations on usual role-related activities due to physical health problems, bodily pain, energy and fatigue, limitations on usual role-related activities due to emotional or mental problems, social function, and emotional or mental health. At one year, there were small but statistically significant positive effects of CEE on physical functioning, bodily pain, and sleep disturbance compared with placebo. There were no differences from placebo on any other quality of life measures, and by 3 years of followup there were no significant differences from placebo on any measure. Subgroup analyses found no interactions by baseline age, race, ethnicity, body mass index, or menopausal symptoms. In a subanalysis of women ages 50 to 54 years old who reported moderate to severe vasomotor symptoms at baseline, there was a positive effect on sleep disturbance, but no effect on other health-related quality of life measures, despite significant improvement in vasomotor symptoms.

Two trials of oral E2 reported improvements on Green and Beck scores[20] and on the General Health Questionnaire.[18] Four trials of transdermal E2 and placebo indicated improved health related quality-of-life and well-being measured by various instruments: Nottingham Health Profile, Psychological General Well-Being Index, Women Health Questionnaire, Kupperman's index, McCoy Sex Scale, psychological general well-being index.[47, 60, 65] One trial indicated that women with high well-being and no vasomotor symptoms at baseline had no improvement with treatment as measured by the Psychological General Well-Being Index.[66] The HERS trial (CEE), using non validated quality of life instruments (Duke Activity Status Index, RAND Mental Health Inventory, among others) found that quality of life scores were significantly lower among women who were older, had diabetes, hypertension, chest pain, or heart failure and use of CEE had little effect.[55] One trial of esterified estrogens reported improvement in the Quality of Life Menopause Scale compared to placebo.[67]

What is the comparative efficacy of different estrogen preparations for preventing low bone density and fractures?

Outcomes include bone density measurements at lumbar spine, forearm, and hip sites and/or fracture data from one or more sites. Numbers of included studies are summarized in Table 2, trials are described in Evidence Table 2, and quality ratings in Appendix F.

Table 2. Number of studies of estrogens with bone density or fracture outcomes

	Total	Bone Density	Fractures
Head-to-head comparisons			
CEE and transdermal E2	2	2	0
Transdermal E2 and estradiol valerate (E2V)	1	1	0
Placebo comparisons			
Estradiol (E2)			
Oral	10	10	1
Transdermal	13	13	2
Estradiol valerate (E2V)	5	5	1
Conjugated equine estrogen (CEE)	26	23	8
Conjugated synthetic estrogen	0	0	0
Esterified estrogen (EE)	1	1	0
Estropipate	0	0	0

Characteristics of the trials include:

- Three trials with bone density outcomes compared estrogens head-to-head.
- 56 trials with bone density outcomes compared an estrogen preparation to placebo.
- 12 trials with fracture outcomes compared an estrogen preparation to placebo.
- Trials often included concurrent calcium and vitamin D supplementation for both estrogen and placebo groups.
- Five different forms of estrogen were used in these trials.
- All fracture outcomes were verified by x-rays.
- Bone density was measured in grams per centimeter or grams per centimeter squared by single-photon absorptiometry, dual-photon absorptiometry, dual x-ray absorptiometry (DXA), or quantitative computed tomography (QCT) at the lumbar spine, forearm, or hip sites.
- Both prevention and treatment trials are included. Treatment refers to studies of women with pre-existing fractures or a diagnosis of osteoporosis at baseline.
- The majority of studies were 1 or 2 years in duration although the longest trial was 5.2 years.
- Both open and double-blinded studies are included because bone density and fracture outcomes are less prone to bias than self-reported symptom outcomes.

Bone Density

Head-to-head comparisons

Three head-to-head trials compared different estrogen preparations including two trials of CEE compared to transdermal E2,[68, 69] and one trial of transdermal E2 compared to estradiol valerate.[70]

Two trials comparing CEE to transdermal E2 (0.05 mg/day for 25 days/month). evaluated two regimens of CEE (0.625 mg/day for 30 vs. 25 days/month). [68, 69] All groups also received 2.5 mg/day of MPA for the last 12 days of treatment each month. In one trial, women using either CEE for 30 days or transdermal E2 for 25 days/month had an increase in lumbar spine bone mineral content compared to placebo (CEE: +4.4%, $p<0.05$: E2: +7.1%, $p<0.01$).[68] Use of CEE for 25 days/month did not show a significant change (+1.3%, NS). Similar results were found when using these regimens in 118 women with prior hysterectomies.[69]

One study of 73 healthy postmenopausal women age 45 to 54 years compared the effects of oral E2 and E2V on forearm and spinal bone density.[70] Both groups significantly gained bone density compared to placebo, and no significant differences between groups were found at any site.

Placebo comparisons

Fifty-two randomized controlled trials comparing an eligible estrogen preparation with placebo and reporting bone density outcome data met criteria for this review. These studies are described in Evidence Table 2.

Characteristics of the trials include:

- Trials were conducted predominantly in the U.S. or W. Europe and most often recruited participants from general or gynecology practices.
- Both prevention and treatment trials were included and provided a broad patient population for this review by including healthy postmenopausal women as well as those with pre-existing fractures.
- Hysterectomy status was sometimes reported. For trials including both types, the data were not separately reported so comparisons cannot be made.
- The number of study subjects in trials ranged from 21 to over 16,000; trials ranged from 1 to over 5 years in duration.
- 28 trials of estradiol in three forms were included: 10 trials of oral E2, 13 trials of transdermal E2, and 5 trials of E2V.
- 26 trials of CEE and one trial of esterified estrogen were included.
- All estrogen preparations generally increased bone density or slowed its loss when compared to the placebo group.
- Most results were reported as the mean difference between treatment and placebo groups or as percent change from baseline.

Eight of 10 studies of oral E2 demonstrated statistically significant improvements in bone density compared with placebo.[71-78] One trial did not report treatment and placebo group differences, but stated that forearm bone density in the treatment group was statistically

significantly increased from baseline while the placebo group showed no change.[79] Another trial reported a trend in E2 groups towards increased bone density, however statistical significance was not reached for between group comparisons.[80]

All 13 trials of transdermal E2 reported statistically significant improvements in bone density compared to placebo.[81-93] Only three trials did not use concomitant progestin/progesterone.[83, 88, 92]

Five trials of E2V with concomitant progestin/progesterone reported bone density outcomes.[70, 94-97] Four of the five trials noted improvement in treatment groups compared to placebo.[70, 94-96] and one did not.[97]

Twenty-three trials evaluated the effect of CEE on bone density outcomes.[98-120] All trials reported significant within group changes in bone density at multiple sites for various doses with higher doses showing greater changes. In one small (N=135) trial[103] CEE 0.625 mg increased bone density over 3 years at the femoral neck ($p=0.02$), total femur ($p<0.001$), and trochanter ($p<0.001$), but not at the lumbar spine (0.84% difference in increase from baseline compared with placebo, $p=0.39$). Some trials reported that doses lower than 0.625 mg were less effective in maintaining or increasing bone density.[99, 106, 110-112]

One study of esterified estrogen and bone density met criteria for this review.[121] The treatment groups used three doses (0.3, 0.625, and 1.25 mg/day) and reported lumbar spine and hip bone density outcomes. All doses showed statistically significant increases in lumbar spine and total hip bone density compared to placebo ($p<0.05$) although the 1.25 mg/day dose was significantly more effective in increasing bone density at the lumbar spine than the lower doses.[121]

Effect on bone density of discontinuation of estrogen

Two studies reported the effect on bone density after discontinuing the use of estrogen to determine if bone density gains were sustained after discontinuation, or if there was evidence that bone loss was accelerated in women who had used estrogen therapy when compared with those who had not used it.[122, 123] Both found the rate of bone loss after stopping estrogen was similar to that of women who did not receive estrogen treatment and are described below.

A followup study from the PEPI trial [122] measured bone density for an average of 4 years in women using CEE for 3 years. Further bone density gains were not observed in women after

discontinuation of estrogen therapy, but there was also no evidence of accelerated bone loss when compared with those who had taken placebo. The second study reported the effect on bone mineral density of discontinuation of estrogen therapy for one year after 5 years of treatment in women enrolled in a randomized placebo-controlled trial of raloxifene and estrogen for prevention of postmenopausal bone loss.[123] This study also found that changes in bone density after one year of discontinuation were not significantly different in women using CEE compared with women randomized to placebo.

Comparison with Cochrane meta-analysis

A recently published Cochrane review and meta-analysis of estrogen and bone density and fractures was reviewed for this report.[5] Fifteen of the trials included in this review did not meet inclusion criteria for the OHP review because they used ineligible estrogen preparations.[124-138]

Results of the Cochrane meta-analysis include:

- The pooled percent change in bone density was statistically significantly increased with estrogen compared to placebo at all measurement sites when combining results for all prevention and treatment trials and for both opposed and unopposed regimens.
- After 1 year, the percent change in bone density was higher in the estrogen groups compared to placebo (5.4% at the lumbar spine, 3.0% at the forearm, and 2.5% at the femoral neck).
- After 2 years of treatment, the estrogen groups had further increases in bone density compared to placebo (6.8% lumbar spine, 4.5% forearm, and 4.1% femoral neck).
- At each of the sites, the percent differences between trials for prevention and treatment were not statistically significant.
- There were no significant differences when opposed and unopposed estrogen trials were compared at 1 and 2 years.
- A dose-response relationship was identified at each site at 2 years when low, medium, and high doses were compared.
    - For low-dose estrogen (equivalent to 0.3 mg CEE), the percent change in bone density was 3.9% at the lumbar spine, 3.1% forearm, and 2.0% femoral neck.

- For high-dose estrogen (equivalent to 0.9 mg CEE) the percent change was 8.0% lumbar spine, 4.5% forearm, and 4.7% femoral neck.

- When different estrogen preparations were evaluated, including CEE, oral E2 and transdermal E2, they all demonstrated significantly improved bone density compared to placebo and there were no significant differences between them. For the lumbar spine, the differences between estrogen and placebo groups were:
  - 5.45% (95% CI: 3.31, 7.59) for transdermal E2,
  - 5.36% (95% CI: 3.99, 6.75) for oral E2,
  - 5.62% (95% CI: 4.64, 6.60) for oral CEE.

Fractures

Head-to-head comparisons

No head-to-head trials were found.

Placebo comparisons

Our review identified 11 studies of estrogen that included outcome data on fractures (Evidence Table 2). Seven were included[82, 89, 96, 107, 108, 120, 139] in a recent Cochrane meta-analysis,[5] while four were not because they were recently published.[3, 76, 101, 140]

Only one study of oral E2 evaluated fracture outcomes and found a statistically significant risk reduction for forearm fractures (RR=0.45; 95% CI: 0.22, 0.90) but not overall fractures (RR=0.82; 95% CI: 0.53, 1.29).[76] Both studies of transdermal E2 indicated no significant improvement in vertebral[82, 89] and non-vertebral fractures.[82] One trial of E2V in early postmenopausal women reported a significant decrease in nonvertebral (RR=0.29; 95% CI: 0.10, 0.90) but not vertebral fractures.[96]

Seven studies examined CEE preparations.[3, 107, 108, 115, 120, 139, 140] Although some of these studies showed a trend toward reduction of fractures at various sites in the treatment groups, only one showed a significant result.[3] In the Women's Health Initiative (WHI), a large study conducted in the U.S., 16,608 postmenopausal women over age 50 were given 0.625 mg/day of CEE with 2.5 mg/day of MPA and followed for over 5 years. When compared with the placebo group, total fractures for women on CEE were significantly reduced (RR=0.76; CI: 0.63, 0.92).[3] Risks were also reduced for site-specific fractures of the hip and vertebra, although adjusted confidence intervals included 1. A more recent update of fracture data from the WHI was

published in October 2003.[101] During an average of 5.6 years of followup, 8.6% of women in the CEE group vs 11.1% in the placebo group had a fracture at any site (hazard ratio 0.76; 95% CI 0.69-0.83). CEE reduced the risk of hip fracture by 33% (hazard ratio 0.67; 95% CI 0.47-0.96) This effect did not differ in women stratified by age, body mass index, smoking status, history of falls, personal and family history of fracture, total calcium intake, past use of hormone therapy, bone density, or summary fracture risk score.

Comparison with Cochrane meta-analysis

Seven studies[82, 89, 96, 107, 108, 120, 139] reporting fracture outcomes were included in the recently published Cochrane review. [5] Two trials indicating significant fracture risk reduction, including the WHI, were not included because they were published after the Cochrane analysis.[76] Findings include:

- Four of five studies measuring vertebral fracture outcomes indicated non-statistically significant reductions in estrogen groups (RR=0.66; 95% CI: 0.41, 1.07).
- Five studies measured the effect of estrogen on nonvertebral fractures.[82, 96, 108, 120, 139]
    - One study indicated a statistically significant relative risk reduction for nonvertebral fractures with estrogen use.[96]
    - Three of the other studies had a risk reduction that was not statistically significant,[82, 108, 139] and the other had a RR of 1.0.[120]
- When all studies were pooled, there was a nonsignificant reduction in nonvertebral fractures (RR=0.87;95% CI: 0.71, 1.08).

What is the comparative safety of different estrogen preparations for short-term use (<5 years)?

All of the trials of symptoms and most of the trials of bone density and fractures were less than 5 years in duration and few enrolled more than 200 participants. Withdrawals, withdrawals due to adverse effects, and withdrawals due to specific adverse effects are summarized in Evidence Table 3 for trials of hot flashes and Evidence Table 4 for trials of bone density and fractures. Specific adverse effects include atypical bleeding and endometrial hypertrophy, nausea and vomiting, breast tenderness, headache, weight change, dizziness, venous thromboembolic events (VTE), cardiovascular events, rash and pruritis, cholecystitis,

liver effects, and others including breast cancer and additional problems. These outcomes were reported unevenly across studies and cannot be combined in summary statistics.

Head-to-head comparison trials provided insufficient evidence to determine the relative adverse effects of different estrogens. One trial of CEE and oral E2 reported that the incidence of possible drug-related adverse experiences ranged from 20% in placebo, E2 1 mg/day, and CEE 0.625 mg/day groups to 35% in E2 2 mg/day and CEE 1.25 mg/day groups with no statistically significant differences between groups.[12] In a head-to-head trial of an intravaginal ring delivering E2 compared with oral E2 for treatment of vasomotor symptoms, there were no significant differences between groups in the frequency of the most common adverse events.[14] Among trials with placebo groups, comparisons between types of estrogens cannot be made with the data provided.

The most notable differences between estrogen and placebo groups were breast tenderness and vaginal bleeding and both symptoms were more frequent among women with higher compared to lower doses of estrogen regardless of type of estrogen. Reports of bleeding varied depending on concomitant progestin/progesterone use and regimen (cyclic or continuous). Several of the other symptoms, such as headache and mood changes, were common for both estrogen and placebo groups. Adverse skin reactions were most common among women using transdermal forms of E2. Withdrawals were often high among the placebo group in the hot flash trials because of lack of treatment effect among women who were enrolled based on the presence of symptoms.

The WHI is the largest trial to evaluate adverse effects of postmenopausal estrogen use (continuous CEE and MPA).[3] The WHI was designed as a primary prevention trial, not a trial of menopausal symptom treatment. Important harms that occurred early in the trial included venous thromboembolic events (RR 3.60; no CI provided) and coronary heart disease events (RR 1.78; no CI provided). Risks remained elevated throughout the trial for both outcomes. These findings were also noted in the early years of the HERS trial, a secondary coronary heart disease prevention trial using CEE/MPA, for cardiac events (RR=1.51; 95% CI: 1.00, 2.27) and venous thromboembolic events (RR=3.28; 95% CI: 1.07, 10.1).[140, 141] In HERS, risks remained elevated for thromboemobolic events only. A recent review and meta-analysis of studies of estrogen and venous thromboembolic events confirmed these findings. Although studies with several

different estrogen preparations were included, data from the studies were not stratified by preparation.[142]

The HERS/HERS II trial reported increased risks for biliary tract surgery among estrogen users early in the study (RR=1.39; 95% CI: 1.00, 1.93).[140] This outcome has not yet been reported by the WHI, but is supported by results of the Nurse's Health Study, a large prospective observational study of estrogen users compared to nonusers (RR=1.8; 95% CI: 1.6, 2.0).[143]

What is the comparative safety of different estrogen preparations for long-term use (5 or more years)?

No head-to-head studies are available that compare adverse effects of different estrogen preparations after 5 or more years of use. The WHI and HERS/HERS II studies provide the best evidence of long-term adverse effects for postmenopausal estrogen use and both use continuous regimens of CEE/MPA.[3, 140, 141]

Cardiovascular Events

The WHI is the first large randomized controlled trial to report a statistically significant increase in coronary heart disease events among estrogen users without known heart disease (RR=1.29; 95% CI: 1.02, 1.63).[3] Mortality from these events was not elevated. Events occurred early in the trial and persisted throughout the 5.2-year follow-up period. Risks were elevated for all age groups, although it is not yet known how risks varied with other cardiac risk factors. Absolute increases in coronary heart disease cases are estimated at 7 per 10,000 when using WHI estimates. Risk was not significantly elevated after 6.8 years of follow-up in HERS/HERS II (RR=0.97; 95% CI: 0.82, 1.14).[141]

Risk for stroke was not significantly elevated in the WHI (RR=1.41; 95% CI: 0.86, 2.31) and HERS/HERS II (RR=1.09; 95% CI: 0.88, 1.35). A systematic review and meta-analysis of other studies of estrogen and stroke indicated a significant increase in stroke risk (RR=1.12; 95% CI: 1.01, 1.23).[144] Absolute increases in stroke are estimated at 8 per 10,000 when using WHI estimates.

Venous Thromboembolism

Risk for venous thromboembolism continued to be elevated with long-term use in the WHI, although at a lower rate than in the first year or two of use (RR=2.11; 95% CI: 1.26, 3.55).[3] This estimate is supported by results from HERS/HERS II as well as a meta-analysis of other studies.[140, 142] Absolute increases in venous thromboembolic events are estimated at 18 per 10,000 when using WHI estimates.

Breast Cancer

The WHI reported increased risks for breast cancer at 5.2 years of follow-up (RR=1.26; 95% CI: 1.00, 1.59).[3] HERS/HERS II indicated no increase after 6.8 years (RR=1.27; 95% CI: 0.84, 1.94).[140] Mortality from breast cancer was not elevated in these studies. This increased risk is consistent with estimates based on meta-analyses of other studies (RR 1.23 to 1.35).[144] Absolute increases in breast cancer cases are estimated at 8 per 10,000 when using WHI estimates. Comparisons between estrogen preparations have not been conducted because of the limited data about types of preparations provided in the studies.

A cohort study followed 3,175 French women, users and non-users of estrogen, for 8.9 years for incidence of breast cancer.[145] Women who had used any type of estrogen therapy were eligible for the study; the most commonly prescribed regimen in France is transdermal E2 combined with oral progesterone or progestins. The relative risk of breast cancer associated with HRT use, adjusted for calendar period of treatment, date of birth, and age at menopause was 0.98 (95% CI 0.73-1.75) compared with non-users. The risk was similar in the subgroup using combined therapy (adjusted relative risk 1.10 , 95% CI 0.73-1.66). Results are not presented by type of estrogen, so this study does not provide additional information about comparative risk.

Cholecystitis

HERS/HERS II reported increased risks for biliary tract surgery among estrogen users with long-term use (RR=1.44; 95% CI: 1.10, 1.90).[140] The Nurse's Health Study also reported an increased risk with long-term use (RR=2.5; 95% CI: 2.0, 2.9).[143] Data from this study also suggests that risk for cholecystitis increases with duration of estrogen use.

Ovarian Cancer/Endometrial Cancer

The WHI and HERS/HERS II report no increase in ovarian or endometrial cancer.[3, 140] Other studies of unopposed estrogen have indicated increased endometrial cancer for a woman with a uterus.[146] Observational studies of estrogen imply an increased risk for ovarian cancer [147, 148] while others do not.[149]

Are there subgroups of patients for which one medication or preparation is more effective or associated with fewer adverse effects?

Age groups

Trials of estrogen and menopausal symptoms were usually conducted among women ranging in age from 40 to 60 years old with the mean age in the early 50s. Data were not stratified by age and direct within-study comparisons cannot be made. Generally, women with the most symptoms had the most benefit. Trials of estrogen and bone density and fractures were conducted predominantly in older women in order to detect significant treatment effects because the prevalence of low bone density and fractures is higher among older women.

The most comprehensive trials of adverse effects (WHI and HERS/HERS II) enrolled older women with mean ages of 63 and 67 at baseline respectively. Data were not stratified by age in HERS/HERS II. In the WHI,[101] there was no evidence that the effect of CEE in reducing fracture risk differed by age or time since menopause. It is not clear how well the findings of these trials relate to younger women using estrogen for short-term relief of symptoms.

Racial/ethnic groups

Most trials enrolled white women in the U.S. or W. Europe who were recruited through clinical practices. The few trials conducted in nonwhite women took place in countries where lifestyle factors are substantial and could also influence outcomes. The WHI reported a subanalysis by race.[101] Among black women (N=1124), CEE plus MPA reduced the risk of total fractures by 42%. This was not statistically significant because of the small number of fractures in this subgroup. There was no evidence of an interaction between treatment and race/ethnicity.

Co-morbidities

The WHI reported that risks for breast cancer were not different among estrogen users with high risk compared to average risk, as defined by the Gail score or family history.[3, 101] No trials consider smokers, women at high-risk for ovarian cancer, or other risk factors and co-morbidities separately. The bone density trials include populations of women with and without pre-existing osteoporotic fractures and indicate that both groups benefit.

Early oophorectomy (<45 years) or premature menopause (<35 years)

No trials compare women with early oophorectomy or premature menopause with women undergoing menopause at an older age.

SUMMARY

A summary of the evidence is outlined in Table 3.

Table 3. Summary of evidence

Key Question	Level of Evidence	Internal Validity	External Validity
1. What is the comparative efficacy of different estrogen preparations for reducing symptoms of menopause?	RCT	Fair: moderate to high drop-out rates.	Fair: small numbers in most studies; recruited from clinics.
2. What is the comparative efficacy of different estrogen preparations for preventing low bone density and fractures?	RCT	Fair-good	Fair: small numbers in most studies; recruited from clinics.
3. What is the comparative safety of different estrogen preparations for short-term use (<5 years)?	RCT	Poor-fair: studies report adverse effects incompletely and nonuniformly..	Fair: small numbers in most studies; recruited from clinics.
4. What is the comparative safety of different estrogen preparations for long-term use (5 or more years)?	RCT	Fair: based on data from WHI and HERS/HERS II; moderate to high drop-out rates.	Fair-good: based on data from the WHI., with subgroup analyses by age, race/ethnicity, and risk factors.
5. Are there subgroups of patients for which one medication or preparation is more effective or associated with fewer adverse effects?	RCT	Fair: based on data from WHI; moderate to high drop-out rates.	Fair-good: based on data from the WHI., with subgroup analyses by age, race/ethnicity, and risk factors.

The results of these studies indicate that several forms of postmenopausal estrogen are more effective than placebo in relieving a variety of menopausal symptoms (hot flashes/flushes, sleep disturbances/night sweats, mood changes, urogenital symptoms and sexual function, and quality-of-life measures). Most published trials include E2 or CEE. Head-to-head comparisons do not identify one agent as more effective than another although very few trials exist that compare two active estrogen agents. Available trials also do not allow comparisons of opposed vs. unopposed and cyclic vs. continuous regimens.

Results of trials measuring bone density outcomes also indicate that several forms of estrogen are more effective than placebo in improving bone density, and limited head-to-head trials do not favor specific agents. Data for fracture prevention indicates lack of effectiveness in most studies, although most studies have important methodologic limitations.

Trials report adverse effects in incomplete and nonstandardized ways. Several short-term and long-term adverse health outcomes have been described, although data are insufficient to determine if they are better or worse for specific agents.

Currently available data are derived from trials enrolling predominantly healthy white women with access to health care in the U.S. or W. Europe. Comparisons of the efficacy and safety of different preparations in these women with women of different age groups, racial or ethnic groups, co-morbidities, and risk factors are not possible.

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Evidence Table 1. Trials of estrogen with hot flash/flush outcomes

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial	Main outcomes/results
Head-to-Head Comparisons								
Oral estrogens								
Archer 1992*	128 in 5 groups	Post and perimenopausal women with 5 or more vasomotor symptoms/day; Mean age 50.6 (40-60); General and gyn practices in USA	NR	CEE: 0.625, 1.25 mg/day; E2: 1, 2 mg/day	None	DB RCT	12 weeks	Mean % change in daily frequency of vasomotor events: CEE 0.625 mg/day= -80.3 CEE 1.25 mg/day= -94.8 E2 1 mg/day= -91.2 E2 2 mg/day= -91.7 All significantly different from placebo, no differences between groups.
Saure 2000	376 in 2 groups	Perimenopausal women with symptoms; Mean age 49; Denmark	0/376	E2: 1.5 mg/day for 24 days; E2V: 2 mg/day for 21 days	Desogestrel: 0.15 mg/day for 12 days/mo with E2; MPA: 10 mg/day for 10 days/mo with E2V	DB RCT cross-over	12 weeks	Hot flashes, night sweats: decreased in both Rx groups; no difference between groups.
Oral CEE compared with transdermal E2								
Good 1999	321 in 4 groups	Postmenopausal women recruited from general population; 60 or more hot flashes per week; 70% white; Mean age 50-51; USA	147/321	E2: 0.05, 0.1 mg/day; CEE 0.625, 1.25 mg/day	None	DB RCT	12 weeks	Reduction of hot flashes by 90% for both Rx; no sig differences between Rx at comparable doses; data provided in graphs.
Gordon 1995	604 in 6 groups	Postmenopausal women with symptoms; Mean age approx. 50 (25-74); USA	382/604	E2: 0.05, 0.1 mg/day (Climera); CEE: 0.625 mg/day oral	None	DB RCT	11 weeks	Number and severity of hot flashes: all groups decreased, Rx groups had sig decline compared to placebo (67-72% decrease, $p<0.05$); no sig difference between Rx groups but some dose-response trends for 2 doses of E2.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 1. Trials of estrogen with hot flash/flush outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial	Main outcomes/results
Head-to-Head Comparisons								
Oral CEE compared with transdermal E2								
Studd 1995	214 in 2 groups	Postmenopausal women with symptoms (at least 21 hot flashes per week); Mean age approx. 52 (40-65)	1%	E2: 0.05 mg/day (Menorest); CEE: 0.625 mg/day	Dydrogesterone: 10 mg/day days 16-28	DB RCT	12 weeks	Mean number of hot flashes per day: sig decrease from baseline in both Rx groups (E2 7.1 to 0.9 per day, CEE 6.7 to 0.5 per day), no sig differences between groups.
Vaginal E2 compared with oral E2								
Al-Azzawi, 2003	159 in 2 groups	Postmenopausal women younger than age 65 with 20 or more hot flushes/night sweats per week. Mean age 51 (31-63)	71/159	vaginal E2: vaginal ring releasing 50 mcg/day. Oral E2: 1 mg/day	Norethisterone 1 mg/day for last 12 days of each 28-day cycle.	DB RCT	24 weeks	Percent change from baseline in number per week of hot flushes/night sweats at Week 24: 50 mcg vaginal ring vs 1 mg oral E2 95% vs 94% 50 mcg then 100 mcg vs 1 mg then 2 mg E2: 93% vs 89% No significant differences between groups at 12 or 24 weeks

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 1. Trials of estrogen with hot flash/flush outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial	Main outcomes/results
Placebo Comparisons								
Oral E2								
Baerug 1998*	119 in 3 groups	Post and perimenopausal women in gyn clinics with "moderate to severe" symptoms; Mean age 51 (45-61); Norway	NR	E2: 1 mg/day	NETA: 0.25, 0.5 mg/day (CCT)	DB RCT	12 weeks	Hot flash frequency (mean): E2= 6-9 over 2 weeks (sig different from placebo, includes all levels of hot flash intensity, no differences between progestin groups); vasomotor severity (Kupperman's Index, Greene's Climacteric Score): E2= sig improvement compared to placebo on Kupperman Index and Greene scales (vasomotor and psychological subscales). Women in early (3-12 months amenorrhea) as well as late menopause (>12 months ammenorrhea) had benefit.
Bech 1998*	151 in 3 groups	Post and perimenopausal women from community; Age not reported; Denmark	NR	E2: 2 mg/day (CCT), 2 mg/day days 1-12, then 1 mg/day days 23-28 (cyclic)	NETA: 1 mg/day (CCT & cyclic)	DB RCT	1 year	Hot flash severity: Kupperman scores sig different (E2= 3-3.7, placebo=9; p<0.01), no difference between CCT and cyclic.
Chung 1996*	100 in 2 groups	Chinese women post TAHBSO 66% had vasomotor symptoms at baseline (23-35% considered moderate to severe); Mean age 43.8; Hong Kong	100/100	E2: 2 mg/day	None	DB RCT cross-over	1 year	Vasomotor severity score, number with hot flashes, number with moderate to severe hot flashes: no sig differences between Rx and placebo.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 1. Trials of estrogen with hot flash/flush outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial	Main outcomes/results
Conard 1995*	57 in 3 groups	Post and perimenopausal women from hospital clinics; all with symptoms, 93% with "moderate to severe" symptoms; Mean age 51.8 (44-61);	0/57	E2: 1, 1.5 mg/day days 1-24	Nomegestrol acetate: 2.5, 3.75 days 11-24 (cyclic)	DB RCT	3 months	Daily hot flash frequency, vasomotor severity score, number with hot flashes: sig decreased among all groups, sig better effect in Rx groups compared to placebo, no difference between Rx groups.
Derman 1995*	82 in 2 groups	Post and perimenopausal women; at least 20 vasomotor events/week; Mean age 50 (40-60); USA	0/82	E2: 2 mg/day days 1-12, 1 mg/day days 23-28	NETA 1 mg/day days 13-22 (cyclic)	DB RCT	16 weeks	Hot flash frequency: decrease in both groups (Rx from 7 to 1.3/day; placebo 6 to 4.2/day; sig diff); also sig differnces between Rx and placebo for Kupperman, Greene, and Beck scores.
Freedman 2002	24 in 2 groups	Healthy postmenopausal women reporting 5 or more hot flashes per day in university setting; Mean age 52; US	NR	E2: 1 mg/day	None	DB RCT	3 months	Hot flash frequency: sig decline with E2, increased in placebo (determined by laboratory measures rather than self-report).
Gelfand 2003	119 in 2 groups	Postmenopausal women with a Kupperman Index of at least 15, at least 20 hot flushes per week, serum E1 of 100 pmol/L or less, and serum FSH of 30 IU/L or more. Mean age 52.6	0/119	E2: 1 mg/day	norgestimate 90 mcg/day for 3 days on, 3 days off.	DB RCT	90 days	Change in Kupperman Index at 90 days (lower score means improvement): E2 vs placebo -16.8 vs -7.8 ($p<0.001$) at 45 days: -14.8 vs -7.2

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 1. Trials of estrogen with hot flash/flush outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial	Main outcomes/results
Jensen J 1983*	100 in 4 groups	Postmenopausal women; 62% had hot flashes at baseline; Mean age 51.5 (46-55); Denmark	0/100	E2: 1 mg/day days 1-12	NETA 1 mg/day days 13-22 (cyclic)	RCT	1 year	Hot flash severity and frequency: decrease in all Rx groups compared to placebo, dose-reponse relationship.
Notelovitz 2000a	333 in 5 groups	Menopausal women with moderate or severe hot flashes; Mean age 51 (40-60); US	0/333	E2: 0.25, 0.5, 1, 2 mg/day	None	DB RCT	12 weeks	Number and severity of hot flashes: all Rx and placebo groups had reduction; sig difference for 0.5, 1 mg, 2 mg Rx groups compared to placebo, not sig for 0.25 mg group. Demonstrated dose-response relationship.
Notelovitz, 2000b	145 in 3 groups	Menopausal women with 8 or more hot flashes/day; Mean age 49 (31-63); US	101/145	E2: 0.5, 1 mg/day	None	DB RCT	12 weeks	% change from baseline in number of hot flashes: -83.2% 1 mg/day, -65.5 0.5 mg/day, stat sig lower than placebo.
Viklyleva 1997* English abstract	64 in 2 groups	Perimenopausal women; moderate to severe symptoms; Age 39-56; Moscow, Russia	NR	E2: 2 mg/day days 1-22, 1 mg/day days 23-28	NETA: 1 mg/day days 13-22 (cyclic)	DB RCT	24 weeks	Hot flash frequency: improvement on Kupperman index for Rx group vs placebo (p=0.01).
Yang, 2002	56 in 2 groups	Postmenopausal women Mean age 50 (47-52)	0/56	E2: 2 mg/day	norethisterone acetate 1 mg/day	DB RCT	4 months	Change in Greene Climacteric Scale at 4 months (decrease means improvement): E2 vs placebo -3.3 (+/-4.5) vs +3.2 (+/-8.0) p=0.009

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 1. Trials of estrogen with hot flash/flush outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial	Main outcomes/results
Transdermal E2								
Bacchi-Modena 1997	109 in 2 groups	Menopausal women with symptoms (7 or more hot flashes/day); Mean age 51.9 (39-61); Italy	NR	E2: 0.05 mg/day (Estraderm, MX 50)	None	DB RCT	12 weeks	Mean number of moderate to severe hot flashes per 24 hours: sig reduced compared to placebo (-8 from baseline for Rx, -4 for placebo, p<0.001); Kupperman index: -18 for Rx, -9 for placebo (p<0.001).
De Aloysio, 2000	156 in 3 groups	Menopausal women with at least 5 hot flashes/day; Mean age 53-54; Italy	8/156	E2: 0.25, 0.375 mg/day	None	DB RCT	12 weeks	% decrease in number of hot flashes: 83-84% in E2 groups, 58% placebo (p<0.05).
de Vrijer 1999	254 in 3 groups	Menopausal women with symptoms (7 or more hot flashes/day); Mean age 52 (40-64); Netherlands	89/254	E2: 0.05, 0.10 mg/day (Estraderm MX 50, 100)	None	DB RCT	12 weeks	Mean number of moderate to severe hot flashes per 24 hours: similar for both Rx groups, sig reduced compared to placebo (-5 to -5.3 for Rx, -0.3 for placebo, p<0.001); Kupperman index and night sweats also sig decreased for both Rx groups compared to placebo (presented in graph).
Gordon 1995	604 in 6 groups	Postmenopausal women with symptoms; Mean age approx. 50 (25-74); US	382/604	E2: 0.05, 0.1mg/day; CEE: 0.625 mg/day oral	None	DB RCT	11 weeks	Number and severity of hot flashes: all groups decreased, Rx groups had sig decline compared to placebo (67-72% decrease, p<0.05); no sig differece between Rx groups but some dose-response trends for 2 doses of E2.
Notelovitz 2000c	220 in 2 groups	Postmenopasual women with 8 or more hot flashes per day; Mean age approx. 53	0/220	E2: 0.05 mg/day (Vivelle)	Norethidrone acetate:140, 250, 400 microgm/day days 15-28	DB RCT	12 weeks	Mean number of hot flashes per day, mean intensity of hot flashes and sweating: sig reductions for all outcomes for all Rx regimens compared to placebo (p<0.001).

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 1. Trials of estrogen with hot flash/flush outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial	Main outcomes/results
Shulman, 2002	293 in 3 groups	Symptomatic women with 7 or more moderate to severe hot flashes/day for 1 week; with and without a uterus; mean age 51-52 (44-68); US	NR	E2: 0.045 mg/day	Levonorgestrel: 0.03, 0.04 mg/day	DB RCT	12 weeks	Mean decrease from baseline in daily number of hot flashes: 9 and 10 for E2 groups, 5 for placebo (p<0.001).
Speroff 1996	324 in 7 groups	Postmenopausal women with hysterectomy with hot flashes; Mean age 49; US	324/324	E2: 0.02 mg/day (different delivery systems)	None	DB RCT	12 weeks	Hot flash frequency: 84% decrease in Rx groups sig lower than in placebo group.
Utian 1999	196 in 4 groups	Postmenopausal women with symptoms; Mean age 50; US	124/196	E2: 0.025, 0.05, 0.1 mg/day (Esclim)	None	DB RCT	12 weeks	Frequency of moderate to severe vasomotor symptoms: sig reduced compared with placebo (p<0.05).
van Holst 2000	186 in 2 groups	Postmenopausal women with symptoms; Mean age 53; Germany	186/186	E2: 0.05 mg/day (Fem 7)	None	DB RCT	12 weeks	Changes in Kupperman index: declined in both groups, sig lower in Rx group (27.6 to 11.2 for Rx, 27.9 to 16 for placebo, p=0.0006); mean hot flashes: sig lower in Rx group (44.3 to 11.8 in Rx, 41.4 to 19.4 in placebo, p=0.0025).
van Holst 2002	179 in 3 groups	Postmenopausal with symptoms; Mean age 53; Germany	0/179	E2: 0.05 mg/day (Fem 7 and Fem 7 Combi)	Levonorgestrel patch: 10 microgm/day	DB RCT	12 weeks	Changes in Kupperman index: sig lower in Rx group (26.3 to 9.5 in Rx group, 27.1 to 15.9 for placebo, p=0.0001); number of hot flashes: sig lower for Rx group.

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 1. Trials of estrogen with hot flash/flush outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial	Main outcomes/results
Wiklund, 1993	242 in 2 groups	Symptomatic postmenopausal women age 45-65; Mean age 52-53; Sweden	0/242	E2: 0.05 mg/day	None	DB RCT	12 weeks	Mean change from baseline for vasomotor symptoms score and Kupperman index stat sig reduced compared to placebo (p<0.0001).
Vaginal E2								
Speroff, 2003	333 in 3 groups	Postmenopausal women with at least 7 moderate to severe hot flushes per day or an average of at least 56 moderate to severe vasomotor symptoms per week for 2 weeks. Mean age 51.7 (range 29-85)	165/333	intravaginal ring delivering the equivalent of E2 50 mcg or 100 mcg per day; placebo vaginal ring	2.5 mg per day oral norethindrone or 10 mg per day oral medroxyprogesterone acetate for 14 days after removal of the vaginal ring.	DB RCT	13 weeks	Percentage reduction from baseline in number of moderate to severe vasomotor symptoms per week at 13 weeks: E2 50 mcg vs E2 100 mcg vs placebo: 79.9% vs 90.6% vs 49.1% (p<0.05 vs placebo for both E2 groups)
Oral E2V								
Blumel 1994*	50 in 2 groups	Post and perimenopausal women hospital workers; 68% had baseline vasomotor symptoms; Mean age 52.6 (37-66); Chile	NR	E2V: 2 mg/day	MPA 2.5 mg/day (CCT)	DB RCT	6 months	Vasomotor severity score (0-3), number with hot flashes, number with moderate to severe hot flashes: improvement in both Rx and placebo groups over time, sig better response with Rx group.
Jensen P 1987*	76 in 2 groups	Post and perimenopausal women; 89% had hot flashes at baseline; Mean age 49.8; Denmark	0/76	E2V: 2 mg/day days 1-21	Cyproterone acetate 1 mg/day days 12-21 (cyclic)	DB RCT	2 years	Number with hot flashes: sig reduction for Rx group (93% to 22%), no sig change for placebo (87% to 77%).

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 1. Trials of estrogen with hot flash/flush outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial	Main outcomes/results
Marslew 1992*	50 in 2 groups	Post and perimenopausal women; 90% had hot flashes at baseline; Mean age 51 (45-54); Denmark	0/50	E2V: 2 mg/day	Cyproterone acetate 1 mg/day (CCT)	DB RCT	2 years	Number with hot flashes: sig reduction for both Rx groups (28 to 8), no sig change in placebo group (20 to 17); sig reduction in Kupperman score for Rx groups (-70), no sig change for placebo (-16).
Oral CEE								
Baumgardner 1978*	160 in 4 groups	Post and perimenopausal women in US gyn practices with "moderate to severe" hot flashes; Age not reported	58/156	CEE: 1.25 mg/day for 21/28 days	None	DB RCT	24 weeks	Number of subjects with moderate to severe hot flashes: sig decrease for Rx group (results provided in graphs); women with TAHBSO also had sig relief compared to placebo.
Campbell 1976*	68 in 2 groups	Post and perimenopausal women in menopause clinic; most had vasomotor symptoms; age NR; London, UK	NR	CEE: 1.25 mg/day for 21/28 days	None	DB RCT cross-over	12 months	Hot flash rating: improved mean scores with CEE compared to placebo.
Carranza-Lira 2001 Brief report	75 in 5 groups	Healthy postmenopausal women with hot flashes; Age not reported; Mexico	15/15 in CEE group	CEE: 0.625 mg/day	None	DB RCT	3 months	Number, severity, and duration of hot flashes; if insomnia and sweating accompanied hot flashes: all sig decreased in CEE group compared to placebo.
Coope 1975*	66 in 2 groups	Post and perimenopausal women from semi-rural general practice; some with depression; Mean age 52 (40-61); UK	NR	CEE: 1.25 mg/day for 21/28 days	None	DB RCT cross-over	6 months	Number with hot flashes: 10 women with complete relief of hot flashes in CEE group, 4 in placebo (p=0.78); results become sig when only women with hot flashes at baseline were evaluated (p=0.04).

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 1. Trials of estrogen with hot flash/flush outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial	Main outcomes/results
Greendale 1998*	875 in 5 groups	Postmenopausal women from several populations (PEPI trial); 52.5% had vasomotor symptoms at baseline; Mean age 56.1 (45-64); USA	279/875	CEE: 0.625 mg/day alone and with MPA (CCT and cyclic)	MPA: 10 mg/day days 1-12 (cyclic), 2.5 mg/day (CCT); micronized progesterone 100 mg/day days 1-	DB RCT	3 years	Number with any vasomotor symptoms: sig reduced among all Rx groups compared with placebo, no diff between Rx groups.
Utian 2001	2,673 in 8 groups	Healthy postmenopausal women; Mean age 53; US	0/2,673	CEE: 0.625, 0.45, 0.3 mg/day; combined and unopposed regimens	MPA 1.5, 2.5 mg/day (CCT)	DB RCT	1 year	Mean daily number and severity of hot flashes: sig reduced for all Rx groups compared to placebo; dose-response relationship.
Oral estropipate								
Coope 1981*	66 in 2 groups	Post and perimenopausal women from semi-rural general practice with depression; Mean age 48 (40-60); UK	19/55	Estropipate: 1.5 mg/day for 21/28 days	None	DB RCT cross-over	14 months	Hot flash frequency/week: both Rx and placebo groups improved, Rx improved sig more than placebo ($p<0.05$).

*Included in Cochrane review (MacLennan, 2000)

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Comparisons								
Oral CEE compared with transdermal E2								
Castelo-Branco 1992*	99	Postmenopausal; 4 groups Age NR Barcelona, Spain	NR	CEE: 0.625 mg/day; E2: 0.05 mg/day; calcium NR	MPA: 2.5 mg/day (all treatment groups)	Open	1	BMD: Lumbar spine (percent change). Baseline comparisons: All treatment groups had increases in BMD. CEE CCT group (+4.4%, p<0.05); E2 transdermal (+7.1%, p<0.01); CEE cyclic (+1.3%, NS); Placebo (-1.5%, p<0.05). Between group comparisons: CEE CCT vs. placebo (p<0.05) ; E2
Castelo-Branco 1993*	118	Postmenopausal with hysterectomy; 4 groups Age NR Barcelona, Spain	118/118	CEE: 0.625 mg/day; E2: 0.05 mg/day; calcium NR	MPA: 2.5 mg/day (all treatment groups)	Unclear	1	BMD: Lumbar Spine (percent change). Baseline comparisons: All treatment groups had increases in BMD. CEE cyclic (+1.8%, NS); CEE CCT group (+2.8%, p<0.05); E2 transdermal (+2.8%, p<0.05); Placebo (-1.5%, p<0.05). Between group comparisons: CEE CCT vs. placebo (p<0.05) ; E2
Oral E2V compared with transdermal E2								
Marslew 1991*	73	Healthy women average 0.5-3 years after menopause Mean age 51 (45-54 years) Glostrup, Denmark	NR	E2: 1.5 mg/day (12 days); E2V: 2 mg/day (11 days); calcium NR	DG: 150 micrograms/day cyclic; MPA: 10 mg/day cyclic	Blind	2	BMD: Lumbar spine, forearm (mean gain or loss). Differences between groups: No significant differences between Rx groups at any site. Placebo vs. Rx groups 7% in the forearm and 8.5% in the spine (p<0.001). Placebo group had a mean loss of 5-7% in the forearm and 4% in the spine (p<0.001).

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Placebo Comparisons								
Oral E2								
Abrahamsen 1997*	95	Women 6 months to 2 years after menopause; 2 groups Mean age, 52.5 Denmark (2 yrs of followup to The Danish Osteoporosis Prevention Study)	0/95	E2: 2 mg/day (22 days), 1 mg/day (6 days); calcium NR	MPA: 1 mg/day (10 days)	Open	2	BMD: Lumbar/spine, forearm, femur Baseline comparisons: All treatment groups showed increases in BMD and placebo showed a decrease. At 2 years: lumbar and forearm BMD were significantly increased for the treatment group compared to placebo. Mean + SD: placebo, lumbar: 0.98+ 0.150; treatment: 1.060 + 0.16 (p = 0.01); placebo, forearm: 0.610 + 0.050; treatment: 0.650 + 0.040 (p=0.01); femur BMD NS.
Cheng 2002	80	Healthy 50-57 yrs; < 5 yrs after menopause 4 groups Finland	NR	E2: 2 mg/day; calcium NR	NETA: 1 mg/day CCT	Blind	1	BMD: Femur, tibia Increase in BMD for treatment group; decrease or maintenance for placebo group. Proximal femur BMD was significantly greater in the Rx group compared to the placebo at 12 months (326 vs. 293 mg/cm, p<0.05). Similar trend was seen with the tibia shaft. No differences in mid femur or proximal femur.
Christiansen 1990*	40	Postmenopausal Mean age 65 Denmark	NR	E2: 2 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	NETA: 1 mg/day CCT	Blind	1	BMD: Spine and forearm BMD was increased in all groups compared to placebo, forearm and spine (8%), proximal forearm (3%), (p<0.05). Placebo remained the same or decreased, NS.
Ettinger 1992*	51	Women more than 6 months after menopause Mean age 51 (40-58 years) Kaiser Permanente San Francisco	NR	E2: 0.5, 1.0, or 2.0 mg/day + Ca 1500 mg/day; placebo: Ca 1500 mg/day	None	Blind	1.5	BMD: Lumbar spine Within group differences showed increase in E2 groups, NS for placebo. All 3 estrogen groups had a statistically significant increase compared to placebo (p<0.001). An increase of 0.3% in 0.5 mg group; 1.8% in 1.0 mg group; 2.5% in 2 mg group.

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Gambacciani 1995*	60	Postmenopausal with hysterectomy Mean age 49	60/60	E2: 2 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	None	Open	1	BMD: Lumbar spine, forearm, total body No significant modification in radial bone density in E2 groups-trend toward increase. Decrease for placebo. No difference between E2 dose groups.
Lees 2001	595	Healthy, at least 6 months postmenopause Mean age 55 (44-65 years) Canada and UK	0/595	E2: 1 or 2 mg/day; Canadian group encouraged to take 500 mg/day Ca	Dydrogesterone: 5, 10 or 20 mg/day cyclic	Blind	2	BMD: Lumbar spine, proximal femur, femoral neck, Ward's triangle Within group: E2 1 mg or 2 mg had increased BMD of LS +5.2-6.7% ($p<0.001$) from baseline. Femoral neck was similar. Placebo (-1.9% BMD). Between group: E2 2 mg group showed a significantly greater increase in lumbar BMD than the E2 1 mg group at 24 months ($p<0.001$). All groups vs placebo at all sites were significant ($p<0.001$).
Mosekilde 2000	1,006	Postmenopausal women recruited by mailed questionnaire Mean age 48 (45-58 years) Denmark	NR	E2: 1-2 mg/day; calcium NR	NETA: cyclic 1 mg/day 10 days (intact uterus); CCT 1 mg/day (without uterus)	Open	5	Fractures: Vertebral, forearm, hip BMD: Lumbar spine, femoral neck, forearm Within group: Hip BMD declined after 5 yrs in control group and remained stable ($p<0.01$) in treatment groups ($p=0.20$). Overall fracture risk was NS (RR=0.82, 95% CI 0.53-1.29). Forearm fracture risk was reduced (RR=0.45, 95% CI 0.22-0.90).
Munk-Jensen 1988*	151	Women average 15 months after menopause Denmark	NR	E2: 2 mg/day CCT vs. cyclic; calcium NR	NETA: 1 mg/day	Blind	1	BMD: Lumbar spine, forearm Within group: All groups significantly different than baseline. Between group: Treatment group had an increase (6%) in lumbar spine and in distal forearm (3.5%) ($p<0.01$) compared to placebo. No difference in bone gain between the treatment groups.
Resch 1990*	31	Postmenopausal osteoporotic women with spine fractures Age NR Austria	NR	E2: 2 mg/day cyclic + Ca 500 mg/day; placebo: Ca 500 mg/day	NETA: 1 mg/day CCT	Blind	1	BMD: Forearm Within group: At 12 months, BMD showed an increase (8%) in treatment group ($p<0.02$), no significant change in the control group. Between group: NR

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Riis 1988*	49	Healthy, postmenopausal 0.5 to 3 yrs Mean age 50 (45-54 years) Denmark	NR	E2: 2 mg/day CCT; calcium NR	NETA: 1 mg/day CCT	Blind	2	BMD: Lumbar spine, forearm Within group: Rx: Significant increases of 1-2% in proximal forearm at 12 months; spine BMD increased by 5% (P<0.01) at 24 months. Placebo: Significant decreases of 4-7% over 2 yrs. Between group: Difference between BMD for placebo and treatment were highly significant at all sites.
Transdermal E2								
Adami 1989*	34	Women 2-4 years after menopause, 2 groups Age NR Verona, Italy	NR	E2: 0.5 mg day + Ca 1200 mg/day + vitamin D 600-800 units/day; placebo: Ca 1200 mg/day + vitamin D 600-800 units/day	MPA: 10 mg/day (12 days)	Open	1.5	BMD: Forearm 4.3% increase in treatment group (p<0.01) 3.5% decrease in control group (p<0.01).
Alexandersen 1999*	68	2 groups postmenopausal women Mean age 65 half osteoporotic, half osteopenic Denmark	NR	E2: 0.05 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	Oral NETA: 1 mg/day	Blind	2	BMD: Lumbar spine, forearm, hip, femoral neck Fracture: Vertebral, nonvertebral (overall RR: 2.78 [0.12 - 65.09])* Within group: Rx group had a 4.0% increase in spinal BMD; 0% increase in placebo group (no sign level given).
Arrenrecht 2002	160	Postmenopausal with hysterectomy Mean age 53 Netherlands	160/160	E2: 0.05, 0.1 mg/day; calcium NR	None		2	BMD: Lumbar spine, wrist, hip Between group: BMD lumbar spine in E2-0.1 group differed by 7.7% (5.8-9.5%) (p<0.0001) compared to placebo.
Cagnacci 1991*	40	1 - 3 years after menopause Mean age 53.5 Italy	NR	E2: 0.050 mg/day cyclic; calcium NR	After 6 months, MPA 5 mg/day cyclic	Unclear	2	BMD: Forearm Within group: Significant increase in BMD, maximum value at 6 months (+4.3% p<0.02) Between group: Significantly higher than placebo (p<0.05) at 24 months

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Cooper 1999		Women 1-6 years after menopause 4 groups Denmark	NR	E2:.025,.050, 0.075 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	MPA: 20 mg/day cyclic	Blind	2	BMD: lumbar spine, femoral neck and total hip BMD lumbar spine increased significantly in all 3 E2 groups (4.7%, 7.3%, 8.7% respectively)
Filipponi 1995*	124	Early postmenopausal Italy	T: 7/42 C: 3/40	E2: 0.05 mg/day + Ca 1200-1500 mg/day; placebo: Ca 1200-1500 mg/day	MPA: 20 mg/day cyclic	Open	2	BMD: Lumbar spine Between group: Percent change in BMD at 24 months for the treatment (-0.14) and control (-7.3) groups were significant ($p<0.0005$).
Gonnelli 1997*	90	Osteoporotic women 2 or more years after menopause Mean age 56 (46-66 years) Siena, Italy	NR	E2: 0.05 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	MPA: 10 mg/day cyclic	Open	2	BMD: Lumbar spine Within group: E2 BMD showed increase ($p<0.001$) compared to baseline.
Hesley 1998*	91	Surgically menopausal Mean age 48 Rochester, MN	NR	E2: 0.025, 0.05, and 0.1 mg/day; calcium NR	None	Blind	2	BMD: Lumbar spine, forearm Within group: Spine BMD increased 3% in 6 months for 0.1 mg group; 1.2% in 0.05 group. Between group: All treatment groups were different from placebo at 2 years ($p<0.001$).
Lufkin 1992*	75	Postmenopausal women with pre-existing vertebral fractures 2 groups; Mean age 65.5 Mayo Clinic and La Crosse, WI	17/36 treatment; 14/30 placebo	E2: 0.1 mg/day (1-21 days) + Ca 800 mg/day; placebo: Ca 800 mg/day	MPA: 10 mg/day, 10 days cyclic	Blind	1	BMD: Lumbar spine, hip, radius Fractures: vertebral Between group: Lumbar spine 5.3 compared to 0.2 ($p=0.007$); hip 7.6 compared to 2.1 ($p=0.03$), radius 1.0 compared to -2.6 ($p<0.001$), compared to placebo. Vertebral fracture: RR= 0.39; 95% CI 0.16-0.9; lower risk in CEE group; Wells Review reports weighted RR= 0.66; 95% CI 0.41-1.07.

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
McKeever 2000	261	Healthy women average 32 months after menopause Mean age 52 Multicenter, US	161/261	E2: 0.025, 0.0375, 0.05, 0.1 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	MPA: 2.5 mg/day CCT non-hysterectomized women	Open	2	BMD: Lumbar spine and femoral neck Percentage change from baseline in BMD of lumbar spine (0.1 and 0.05 mg, p<0.001; 0.375 mg, p=0.024; 0.25 mg, p=0.002). Femoral neck (all p≤0.044).
Notelovitz, 200[illegible]	355 in 4 groups	Nonosteoporotic, postmenopausal women younger than age 70, who had a hysterectomy at least 12 months earlier.	355/355	E2: 0.025 mg/day, 0.05 mg/day, or 0.075 mg/day	None	RCT DB	2	Increase in lumbar BMD at 2 years: placebo: -0.59% E2 0.025 mg vs 0.05 mg vs 0.075 mg: 1.65% (p=0.0065 relative to placebo) vs 4.08% (p=0.0001) vs 4.82% (p=0.0001)
Perez-Jaraiz 1996*	104	Women 1-4 years after menopause 4 groups Mean age 49	24/104	E2: 0.05 mg/day; calcium NR	MPA: 10 mg/day for 10 days	Open	1	BMD: Total body E2 group showed significant differences when compared to controls on total body BMD (-2.14% vs -0.14% in the E2 group, p<0.05).
Rubinacci, 2003	124 in 2 groups	Postmenopausal women with intact uterus younger than age 70, at least 4 years past menopause. Mean age 56.8	0/124	E2: 0.025 mg/day	norethisterone acetate 0.125 mg/day	RCT DB	2	Mean percentage change from baseline in BMD at 24 months: (E2 vs placebo) femoral neck: 1.6% vs -0.9% (p=0.0006) trochanter: 3.2% vs -0.4% (p<0.0001) Ward's triangle: 5.0% vs -0.7% (p=0.0008) intertrochanteric region: 2.0% vs -0.5% (p<0.0001) total hip: 2.2% vs -0.7% (p<0.0001)
Oral E2V								
Doren 1995*	280	Early postmenopausal 3 groups Mean age 54 Germany	64/210	E2V: 2 mg/day + Ca 1000 mg/day; E2: 2 mg/day + Ca 1000 mg/day;	NETA: 5 mg/day cyclic; 1 mg/day CCT	Open	2	BMD: Lumbar spine and hip E2 CCT increased BMD (p=0.001); E2V and control, NS. E2 CCT group had increased BMD at 2 yrs compared to control (+17%) (p=0.01). E2V group; NS. No fractures were reported during study.

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Heikkinen 1997*	78	Women 0.5-3 years after menopause 3 groups mean age 53 (49-55 years) Northern Finland	78/78 ovaries removed	E2V: 2 mg/day; calcium NR	MPA: 2 mg/day cyclic	Blind	2	BMD: Femoral neck, lumbar spine, femur Compared with placebo, both estrogen groups had increased BMD: spine (p<0.001); femoral neck (p<0.001) and femur (0.05).
Isaia 1989*	57	Postmenopausal 2 groups: 1 ovariectomized; 1 within 6 months of natural menopause Mean age 44	NR	E2V: 2 mg/day cyclic; calcium NR	MPA: 10 mg/day for 40 days	Open	1	BMD: Lumbar spine BMD was significantly higher in ovariectomized treated groups compared to untreated (p<0.05 after 6 months; p<0.005 after 9 and 12 months). BMD also significant in natural menopause group after 6 months (p<0.005).
Komulainen 1997*	464	Postmenopausal 16-24 months after menopause Mean age 53 (44-79 years) Finland (subgroup of the OSTPRE Study)	NR	Group 1: E2V 2 mg/day cyclic; Group 2: vit D 300 IU day + Ca 500 mg/day; Group 3: T1 + T2; placebo: Ca 500 mg/day	T1 & T3: CPA 1 mg/day cyclic	Open	2.5	BMD: Lumbar and femoral neck Fractures: non-vertebral Within group: At 2.5 yrs, compared to baseline, lumbar spine BMD increased 1.8% in the E2V group (p<0.001) and 1.4% in the E2V + Vit D group, and decreased 3.7% in placebo group (p<0.001). Placebo and vit D only group showed a significant decrease in femoral neck BMD from baseline (p<0.001). Between group: Both treatment groups were significantly different than the placebo group. Fracture: Estimated risk for nonvertebral fractures in the E2V group, RR=0.29, 95% CI 0.10 - 0.90; in the E2V + vit D group, RR=0.44 95% CI 0.17-1.15.
Marslew 1992*	62	Healthy women average 5-3 years after menopause 3 groups Mean age 55 (38-64 years)	NR	E2V: 2 mg/day CCT or cyclic; calcium NR	Cyproterone acetate (1 mg/day) or levonorgestrel (75 microgrm/day)	Blind	2	BMD: Lumbar spine, forearm, calcaneus BMD in the spine increased by 3-4% in E2 groups, decreased 2% in placebo. In the forearm, E2 groups had no change in BMD when the placebo group decreased 6%

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Oral CEE								
Agnusdei 1990*	24	Postmenopausal with osteoporosis or osteopenia 2 groups Mean age 57.5 Italy	NR	CEE: 0.625 mg/day (days 1-20) + Ca 800-1200 mg/day; placebo: Ca 800-1200 mg/day	MPA: cyclic 5 mg/day	Open	1	BMD: Lumbar spine, femoral neck Within group: Placebo had a decrease in BMD at 12 months (p<0.01). Between group: HT group showed increased lumbar spine BMD at 12 months (p<0.01) compared to placebo. Femoral neck BMD remained the same for treatment, decreased for placebo (p<0.05).
Agnusdei 1995*	83	Women 6 months - 2 years after menopause Mean age 50 Siena, Italy	NR	CEE: 0.3 mg/day CCT and cyclic;Ca 1000/day; placebo: Ca 1000 mg/day	MPA 10 mg/day, 15 days every 3 months.	Blind	1	BMD: Distal forearm Within group: Placebo had a decrease in BMD (1.7%); estrogen only group maintained bone; group with CEE plus MPA had an increase in BMD at 1 year (+5.6% p<0.01). Between group: All groups were different than placebo (P<0.05).
Aloia 1994*	118	3 groups of women 6 months - 6 years after menopause, three groups Long Island, NY	0/118	CEE: 0.625 mg + CA: 1700 mg/day + vitamin D 400 IU /day Ca 1700 mg/day + vitamin D 400 IU /day Placebo:	MPA: cyclic 10 mg/day (days16-25)	Open	3	BMD: Lumbar spine, femur, radius Between group: Compared with placebo, femoral neck BMD was greater for the CEE and calcium group (-0.8%/y; p=0.03).
Cauley, 2003	16,608 in 2 groups	Postmenopausal women with an intact uterus ages 50-79. Mean age 63 (sd 7.10) 40 US centers	0/16,608	CEE: 0.625 mg/day	medroxyprogesterone acetate 2.5 mg/day	RCT DB	5.6 (average)	Fracture: 8.6% in HRT group vs 11.1% in placebo group had a fracture during 5.6 years followup (hazard ratio 0.76; 95% CI 0.69-0.83). Hip fracture hazard ratio 0.67 (95% CI 0.47-0.96) BMD at year 3: Total Hip: increased 3.7% in HRT group vs 0.14% increase in placebo group (p<0.001)

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Civitelli 1988*	21	Postmenopausal osteoporotic Mean age 55 Siena, Italy	NR	CEE: 1.25 mg/day + Ca 800-1000 mg/day; placebo: Ca 800-1000 mg/day	None	Blind	1	BMD: Lumbar spine, femoral shaft Within group: Femoral shaft BMC increase +2.6%; Lumbar spine BMD increases in treatment group (+8.3%, p<0.05). Between group: Treatment group different than placebo.
Civitelli, 2002	135 in 2 groups	Women postmenopausal for at least 1 year with no moderate or advanced periodontal disease. Mean age ERT group 60.0 (sd 5.5) placebo group 58.1 (sd 6.8); p=0.07	49/135	CEE: 0.625 mg/day	medroxy-progesterone acetate 2.5 mg/day	RCT DB	3	BMD: Femoral neck HRT vs placebo 2.39% difference in increase from baseline (p=0.02) Total femur HRT vs placebo 3.37% difference in increase from baseline (p<0.001) Trochanter HRT vs placebo 3.42% difference in increase from baseline (p<0.001) Lumbar spine HRT vs placebo 0.84% difference in increase from baseline (p=0.39)
Gallagher 1991*	81	Postmenopausal Mean age 52 Omaha, Nebraska and Salt Lake City, Utah	NR	CEE: 0.625 mg/day; progestin only; CEE 0.3 mg/day + progestin; All subjects: Ca 1000 mg/day	NETA: 2, 10 mg/day cyclic	Blind	2	BMD: Lumbar spine, forearm Within group: All groups showed a significant change. Between group: All Rx groups differed from placebo. CEE groups had 0.3 mg increase in spine and decrease in radial BMD (p<0.05). CEE + progestin had no change (p<0.01).
Gambacciani 1997*	80	Postmenopausal Age 40-49 Pisa, Italy	NR	CEE: 0.3 mg/day All subjects: Ca 500 mg/day	None	Unclear	2	BMD: Lumbar spine Within group: All Rx groups showed a significant decrease in BMD after 12, 18, and 24 months (p<0.001). Between group: When compared with control or CEE alone, CEE had a greater LS BMD increase (p<0.05).

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Genant 1982*	37	Women with hysterectomies Mean age 42 (24-49 years) San Fran., CA	37/37	CEE: 0.15, 0.30, 0.45, 0.625 mg/day; calcium NR	None	Blind	2	BMD: Lumbar spine Within group: CEE 0.15, 0.3 and 0.45 mg/day NS from baseline. CEE 0.625 mg/day maintained axial and peripheral bone mass but were not significant.
Greenspan 1998*	425	Postmenopausal Age greater than 45 years; spine BMD 2 SD below normal Multicenter US	425/425	CEE: 0.625 mg/day; calcium NR	None	Blind	2	BMD: Lumbar spine, femoral neck, total hip Vertebral fracture Within and between group: BMD increased (p<0.001) vs baseline & placebo (+6.0%, +3.4%, +2.6%). Vertebral fracture: RR = 0.70, 95% CI 0.06 - 7.55 (Wells Review 2002)*
Hosking 1998*	1609 total; (CEE group 110, placebo 502)	Menopausal for at least 6 months Mean age 53 (45-59 years) 4 study centers in USA and UK	0 in treatment group; NR in placebo group	US group: CEE 0.625 mg/day; UK: E2 1 to 2 mg/day calcium NR	US: MPA 5 mg/day CCT UK: NETA 1 mg/day cyclic	Open	4	BMD: Lumbar spine, forearm, hip Non-vertebral fractures Within group: Hip and spine BMD differed significantly from placebo in US Rx groups. Nonvertebral fracture: RR=0.98, 95% CI 0.29, 3.34; NS*.
Hulley 1998*	2763	Postmenopausal with coronary disease Mean age 67 (44-79 years) USA	0/2763	CEE: 0.625 mg/day; calcium NR	MPA: 2.5 mg/day CCT	Blind	4	Fractures: Hip, other, and any Hip: 1.10 (0.49-2.50) Other: 0.93 (0.73-1.20) Any: 0.95 (0.75-1.24) No differences between groups.
Hulley 2002 (HERS II)	2763	Postmenopausal with coronary disease Mean age 67 (44-79 years) 20 US Clinical centers	0/2763	CEE: 0.625 day; calcium NR	MPA: 2.5 mg/day CCT	Blind	4 (3 of follow-up)	Fractures: Hip, other, any Any fracture (RR=1.04, 95% CI .87-1.25) not statistically significant

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Leung 1999	105	Women 2 years after menopause; 3 groups Mean age 48 Age 45+ Hong Kong, China	NR	CEE: 0.625, 0.3 mg/day; calcium NR	MPA: 5 mg/day (if uterus present) cyclic	Unclear	1	BMD: Lumbar spine and femoral neck Within group: Lumbar spine and femoral neck BMD maintained at 1 yr in 0.625 mg/day group; for control and CEE 0.3 group, a decrease was seen. Between group: CEE 0.625 mg/day showed LS BMD was different vs. placebo ($p<0.01$); not for femoral neck. CEE 0.3 mg/day NS for spine or femoral neck.
Lindsay 1984*	150	Women 18-20 months after menopause Mean age 49 New York, NY	62% overall	CEE: 0.15, 0.3, 0.625, 1.25 mg/day; calcium NR	None	Blind	2	BMD: Metacarpal CEE at 0.625 and 1.25 mg/day showed protection of BMD, less loss than placebo and lower doses
Lindsay 1990*	50	Women approximately 13 years past menopause with osteoporosis 2 groups	11/50	CEE: 0.625 mg/day + 1500 mg Ca/day; placebo: 1500 mg Ca/day	MPA: 5 or 10 mg/day cyclic (if uterus present)	Open	2	BMD: Lumbar spine, femoral neck Lumbar bone mass increased significantly ($p<0.01$) and was significantly greater in estrogen group ($p<0.05$)
Lindsay 2002	822	Women within 4 years of menopause 8 groups Mean age 51.6 (40-65 years) HOPE trial	822/822	CEE: 0.625, 0.45, 1.5, 0.3 mg/day + Ca 600 mg/day; placebo: Ca 600 mg/day	MPA: 2.5, 1.5 mg/day CCT		2	BMD: Spine, total hip Within group: All treatment groups had significant gains from baseline ($p<0.001$) for spine and hip BMD. Between group: All Rx groups different than placebo. CEE 0.625 had an increase in spine BMD compared to the CEE 0 .3 group (CEE 0.45 was borderline significant).
Meschia 1993*	95	Women 1.5-10 years after menopause 4 groups Mean age 51 Milan, Italy	NR	CEE: 1.25 mg/day; calcium NR	MPA: 10 mg/day cyclic	Open	2	BMD: Lumbar spine Within group: CEE group showed an increase in BMD of 0.823 to 0.867 ($p<0.01$); placebo group had a decrease in BMD of 0.83 to 0.771 ($p<0.001$). Between group: Rx group differed from placebo (significance level NR).

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Mizunuma 1997*	52	Postmenopausal 4 groups Mean age 55 Japan	4/52	CEE: 0.3 and 0.625 mg/day; calcium NR	MPA: 2.5 mg/day CCT	Open	2	BMD: Lumbar spine, femoral neck Lumbar spine BMD significantly higher in all CEE groups CEE alone: 8.52% (4.61-12.4%); CEE 0.625 + MPA: 7.4% (0.60-14.2%); CEE 0.31 + MPA: 3.2% (0.61-5.84%) (p<0.05)
PEPI 1996*	875	Healthy postmenopausal 5 groups Mean age 56 (45-65 years) 7 US clinical sites	159/875	T1: CEE 0.625 mg/day only; T2 - T 3: CEE 0.625 mg/day + progestin; calcium NR	T2: MPA 10 mg/day cyclic, 12 days T3: MPA 2.5 mg/day daily T4: MP (micronized) 200 mg/day 12 days	Blind	3	BMD: Lumbar spine, hip Fractures: spine, wrist, hip Within group: CEE groups had an average increase of 1.7% hip BMD compared to average decrease of 1.7% in placebo (p<0.05) Between group: At 3 months, CEE plus MPA CCT regimen showed greater increase in spinal BMD (5%) then those assigned to other regimens (3.8%, p<0.05). No difference in number of fractures between groups.*
Recker 1977*	60	Healthy postmenopausal 3 groups Mean age 51 Omaha, Nebraska	NR	CEE: 0.625 mg/day; Ca 2600 mg/day	MPA: 5 mg/day cyclic	Open	2	BMD: Forearm Between group: CEE group showed significant difference in metacarpal thickness from baseline and significant difference compared to placebo (0.00154 mean rate of loss CEE) (0.0124 mean rate of loss placebo)
Recker 1999	128	Women over 65 years with low BMD (no previous fractures) recruited by university center; 2 groups; mean age, 73 treatment; 74 controls Omaha,	NR	CEE: 0.3 mg day + Ca 1000 mg/day + vitamin D 75 nmol/L/day; placebo: Ca 1000 mg/day + vitamin D 75 nmol/L/day	MPA: 2.5 mg/day CCT	Blind	3.5	BMD: Spine, hip, forearm At three years, spinal BMD increased significantly in the estrogen group compared to baseline and to placebo (ranged from 3.5% - 5.2%; p<0.001). Significant increases were also found in forearm bone density (p<0.01). No significant losses in spine BMD in placebo group with calcium + vit D.

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Rosen 1997*	236	Postmenopausal women Mean age 51 Diet of 800-120 mg Ca day Clinical research sites throughout the US	NR	CEE: 0.625 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	MPA: 2.5 mg/day CCT, 5 mg/day cyclic	Blind	1	BMD: Lumbar spine, femoral neck At 12 months, BMD increased in CEE group at both spine (+2.5%; p<0.0001) and femoral neck (+1.0%; p<0.05). In the calcium group, BMD decreased at the spine and hip (-1.1%; p< 0.01). Between group differences not reported.
Villareal 2001	67	Frail women aged 75 years of older Mean age 82 St. Louis, MO	22/45 treatment; 6/22 control	CEE: 0.625 mg/day + Ca 1200 mg/day	MPA: 5 mg/day cyclic	Blind	9 months	BMD: Lumbar spine, proximal femur, and hip BMD was greater in all sites for the treatment group compared to placebo. The adherent Rx group showed greater increases in lumbar spine BMD than placebo (mean change, 4.3% vs 0.4%; between group difference,) and total hip (mean change, 1.7% vs -0.1%; between group difference).
Rossouw 2002 WHI	16,608	Postmenopausal for at least 6 months Mean age 63.3 (50 years or older) 40 clinical centers in the US	248/8506 treatment; 183/8102 control	CEE: 0.625 mg/day; calcium NR	MPA: 2.5 mg/day	Blind	5.2	Fracture: Hip, vertebral.. Hip fracture was decreased in the treatment group when compared with placebo 0.66 (0.33 - 1.33); 106 cases. Vertebral and other osteoporotic fractures were significantly lower in the treatment group (RR=0.66, 95% CI 0.32-1.34; RR=0.7, 95% CI 0.63-0.94), respectively. Total fractures: RR=0.76, 95% CI 0.63 -0.92.
Wimalawansa 1998*	72	Postmenopausal with osteoporosis attending bone clinics Mean age 64.9 (58-72 years) UK	0/72	CEE: 0.625 mg/day + Ca 1000 mg/day + vit D 400 units/day; placebo: Ca 1000 mg/day + vit D 400 units/day	norgestrel: 150 micrograms/day cyclic	Open	4	BMD: Lumbar spine, hip Fractures: Vertebral, nonvertebral Rx group showed greater BMD when compared to the control group for both lumbar spine and total hip at 4 yrs (7%, p<0.001 and 4.8%, p<0.01, respectively). Ca + vit D group lost BMD from baseline for the lumbar spine and total hip at 4 yrs (2.5% and 4.4%, p<0.01, respectively). Those on no treatment showed a significant loss of bone compared to CEE and Ca groups (p<0.05). No difference in fracture rates was found. Vertebral RR=0.49, 95% CI 0.09 - 1.80; non-vertebral RR=1.00, 95% CI 0.07 - 14.79*.

*Included in Wells Review, 2002.

Evidence Table 2. Trials of estrogen with bone density and/or fracture outcomes (continued)

Study/Year	N	Population	Hysterectomy (#/n)	Estrogen type; dose; regimen	Progestin type; dose; regimen	Type of Trial	Length of Trial (years)	Main outcomes/results
Oral esterified estrogen								
Genant 1997*	406	Women 6 months - 4 years after menopause Mean age 52 29 centers US	128/406	Esterified estrogens: 0.3, 0.625, 1.25 mg day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	None	Blind	2	BMD: Lumbar spine, hip Within and between group: All doses of estrogen showed greater BMD at all sites compared with baseline and placebo ($p<0.05$). LS was greater with 1.25 mg Rx group, than the 0.3 or 0.625 mg Rx groups.

*Included in Wells Review, 2002.

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials

					Withdrawals due to specific adverse effects		
Study/Year	**Estrogen type; dose; regimen**	**Progestin type; dose; regimen**	**Withdrawals**	**Withdrawals due to adverse effects**	**Atypical bleeding & endometrial hypertrophy**	**Nausea & vomiting**	**Breast tenderness**
Head-to-head comparisions							
Oral estrogens							
Archer, 1992*	CEE: 0.625, 1.25 mg/day; E2: 1, 2 mg/day	None	21/128	9	NR	Few at baseline, no trends during study.	Increased with higher doses; 78% with 2 mg/day E2 and 70% with 1.25 mg/day CEE had no discomfort.
Saure, 2000	E2: 1.5 mg/day for 24 days; E2V: 2 mg/day for 21 days	Desogestrel: 0.15 mg/day for 12 days/mo with E2; MPA: 10 mg/day for 10 days/mo with E2V	59/376	35	3 in E2V; 4 in E2	None	2 in each group
Oral CEE compared with transdermal E2							
Good, 1999	E2: 0.05 or 0.1 mg/day; CEE 0.625 or 1.25 mg/day	None	NR	NR	Breakthrough bleeding: 3.8% with E2, 10.1% CEE; wthdls NR	NR	Dose related: 12% E2, 11% CEE high dose; 3% E2, 4% CEE low dose; wthdls NR
Gordon, 1995	E2: 0.05, 0.1 mg/day (Climera); CEE: 0.625 mg/day oral	None	71/603	54	12 in E2 0.05mg, 22 in E2 0.1 mg, 5 in CEE; wthdls NR	NR	17 in E2 0.05mg, 55 in E2 0.1 mg, 18 in CEE; wthdls NR
Studd, 1995	E2: 0.05 mg/day (Menorest); CEE: 0.625 mg/day	Dydrogesterone: 10 mg/day days 16-28	NR	NR	NR	NR	NR

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Head-to-head comparisions								
Oral estrogens								
Archer, 1992*	Most reported at baseline; decreased in all groups during study.	NR	NR	NR	Reports for 2/25 placebo, 1/102 Rx.	NR	NR	Incidence of possible drug-related adverse experiences ranged from 20% placebo, E2 1 mg, CEE 0.625 mg to 35% E2 2 mg and CEE 1.25 mg; no stat sig differences between groups.
Saure, 2000	3 in each group	None	2 in E2; 3 in E2V	None	1 in E2	None	None	Also abdominal pain (1 in E2), depression (2 in each group), edema (1 in each group), feeling unwell (1 in each group), psychiatric changes (1 in E2), fluid retension (1 in E2V).
Oral CEE compared with transdermal E2								
Good, 1999	Most common adverse reaction; wthdls NR	NR	NR	NR	6 E2, 4 CEE	NR	NR	No differences between groups except for breakthrough bleeding with higher doses.
Gordon, 1995	Most common adverse reaction; wthdls NR	NR	NR	NR	41 due to site reactions	NR	NR	No differences between Rx groups except for uterine bleeding; much lower rates in placebo group.
Studd, 1995	NR	NR	NR	NR	91% with no pruritis.	NR	NR	Most common symptoms: E2 headache (8), abdominal pain (4), nausea (5), breast pain (6); CEE headache (8), abdominal pain (4), nausea (6), weight gain (3) depression (3); wthdls not reported.

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to adverse effects	Withdrawals due to specific adverse effects: Atypical bleeding & endometrial hypertrophy	Withdrawals due to specific adverse effects: Nausea & vomiting	Withdrawals due to specific adverse effects: Breast tenderness
Vaginal E2 compared with oral E2							
Al-Azzawi, 2003	vaginal E2: vaginal ring releasing 50 mcg/day. Oral E2: 1 mg/day	Norethisterone 1 mg/day for last 12 days of each 28-day cycle.	39/159	19	1 endometrial hyperplasia in oral E2 group (withdrew after switching to vaginal ring).	17 vaginal ring, 11 oral (NS); withdrawals not reported	28 vaginal ring, 14 oral (NS); withdrawals not reported
Placebo Comparisons							
Oral E2							
Baerug, 1998*	E2: 1 mg/day	NETA: 0.25, 0.5 mg/day (CCT)	11/119	5	Higher rates of bleeding for E2 compared to placebo; no difference in incidence of severe bleeding.	One wthdl from placebo group.	One wthdl from E2 group.
Bech, 1998*	E2: 2 mg/day (CCT), 2 mg/day days 1-12, then 1 mg/day days 23-28 (cyclic)	NETA: 1 mg/day (CCT & cyclic)	46/151	20	Four wthdls from E2, none from placebo.	2 wthdls from cyclic group, 2 placebo group, none CCT.	Significantly more frequent in E2 groups.
Chung, 1996*	E2: 2 mg/day	None	17/100	NR	NR	NR	NR
Conard, 1995*	E2: 1, 1.5 mg/day days 1-24	Nomegestrol acetate: 2.5, 3.75 days 11-24 (cyclic)	7/57	4	One wthdl from E2 group.	NR	Increased in E2 group (31.6% vs 5.3%, p=0.04); 2 wthdls in E2 group.
Derman, 1995*	E2: 2 mg/day days 1-12, 1 mg/day days 23-28	NETA 1 mg/day days 13-22 (cyclic)	35/82	6	Some wthdls in E2 group (number not given).	NR	NR

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Vaginal E2 compared with oral E2								
Al-Azzawi, 2003	49 vaginal ring, 35 oral (NS); withdrawals not reported	NR	13 vaginal ring, 10 oral (NS); withdrawals not reported	NR	NR	NR	NR	No significant differences between groups in frequency of most common adverse events.
Placebo Comparisons								
Oral E2								
Baerug, 1998*	One wthdl from placebo group.	NR	NR	NR	NR	NR	NR	Additional wthdls for edema and emotional lability.
Bech, 1998*	NR	One wthdl in cyclic group.	NR	NR	NR	None	None	Few reports of edema in all groups.
Chung, 1996*	No differences between groups.	NR	No differences between groups.	NR	NR	NR	NR	NR
Conard, 1995*	NR	None	NR	NR	NR	NR	NR	Also abdominal pain and metorrhagia.
Derman, 1995*	NR	wthdls from Rx group (number not given)	NR	NR	NR	NR	NR	Also palpitations in Rx group, lack of effect in placebo group.

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

					Withdrawals due to specific adverse effects		
Study/Year	**Estrogen type; dose; regimen**	**Progestin type; dose; regimen**	**Withdrawals**	**Withdrawals due to adverse effects**	**Atypical bleeding & endometrial hypertrophy**	**Nausea & vomiting**	**Breast tenderness**
Freedman, 2002	E2: 1 mg/day	None	NR	NR	NR	NR	NR
Gelfand 2003	E2: 1 mg/day	norgestimate 90 mcg/day for 3 days on, 3 days off.	5/119	6 (including open-label phase)	3	5 in E2, 0 in placebo; withdrawals not reported	8 in E2, 3 in placebo; withdrawals not reported
Jensen J, 1983*	E2: 1, 2, 4 mg/day days 1-12, 1, 2, 4 mg/day days 13-22, 1 mg/day days 23-28; estriol: 1, 2 mg/day days 1-22, 0.5 mg/day days 23-28.	NETA 1 mg/day days 13-22 (cyclic)	13/100	4	Increased regular and irregular bleeding in E2 groups compared to placebo; some wthdls (number not given).	wthdls (number not given)	Wthdls (number not given).
Notelovitz, 2000a	E2: 0.25, 0.5, 1, 2 mg/day	None	53/333	26 (5 placebo, 21 E2, more in higher dose groups)	18 (11 from 2 mg group).	NR	Reported in all groups, highest with higher doses.
Notelovitz, 2000b	E2: 0.5, 1 mg/day	None	NR	NR	Reported in E2 groups, more with higher dose; 1 with cancer from E2 1 mg group.	NR	NR
Viklyleva, 1997;* English abstract	E2: 2 mg/day days 1-22, 1 mg/day days 23-28	NETA: 1 mg/day days 13-22 (cyclic)	4/64	NR	Regular bleeding with E2, no excessive bleeding.	NR	NR
Yang, 2002	E2: 2 mg/day	norethisterone acetate 1 mg/day	16/56	NR	10 E2, 0 placebo; withdrawals not reported	NR	6 E2, 0 placebo

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Freedman, 2002	NR	NR	NR	NR	NR	NR	NR	Also wthdls due to lack of effect in placebo group.
Gelfand 2003	5 in E2, 9 in placebo; withdrawals not reported	3 in E2, 3 in placebo; withdrawals not reported	NR	NR	NR	NR	NR	
Jensen J, 1983*	NR	No differences between groups.	NR	NR	NR	NR	NR	Also nervousness, depression, rectal cancer, bronchitis; groups not specified.
Notelovitz, 2000a	NR	NR	NR	NR	NR	NR	NR	NR
Notelovitz, 2000b	Reported in all groups by 10-15%.	NR	NR	NR	NR	NR	NR	Also reports of abdominal pain in all groups.
Viklyleva, 1997;* English abstract	Reduced in Rx group.	NR	No differences between groups.	NR	NR	NR	NR	NR
Yang, 2002	NR	2 E2, 1 placebo	NR	NR	None	NR	NR	

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

					Withdrawals due to specific adverse effects		
Study/Year	**Estrogen type; dose; regimen**	**Progestin type; dose; regimen**	**Withdrawals**	**Withdrawals due to adverse effects**	**Atypical bleeding & endometrial hypertrophy**	**Nausea & vomiting**	**Breast tenderness**
Transdermal E2							
Bacchi-Modena, 1997	E2: 0.05 mg/day	None	NR	NR	Reported 15% E2, 13% placebo.	NR	Reported in 28% E2, 27% placebo.
De Aloysio, 2000	E2: 0.025, 0.0375 mg/day	None	NR	2 (E2 0.025); 1 (E2 0.0375)	1 wthdl (E2 0.375); reports in all groups.	NR	10% placebo; 40-43% E2 groups; 1 wthdl in E2 0.025.
de Vrijer, 1999	E2: 0.05, 0.10 mg/day	None	NR	18/245	5 wthdls in E2 0.10; 5 cases of hypertrophy in E2 groups; 1 case cancer.	NR	1 wthdl E2 0.10; reported in 11% placebo, 26% E2 0.05, 61% E2 0.10.
Gordon, 1995	E2: 0.05, 0.1 mg/day; CEE: 0.625 mg/day oral	None	71/603	54	12 in E2 0.05mg, 22 in E2 0.1 mg, 5 in CEE; wthdls NR	NR	17 in E2 0.05mg, 55 in E2 0.1 mg, 18 in CEE; wthdls NR
Notelovitz, 2000c	E2: 0.05 mg/day	Norethidrone acetate: 140, 250, 400 mg/day, 15-28	NR	6 in E2 groups	Reported in E2 groups.	NR	Reported in E2.
Shulman, 2002	E2: 0.045 mg/day	Levonorgestrel: 0.03, 0.04 mg/day	NR	11 E2, 6 placebo	4 wthdls E2	NR	Reported in 12 E2, 2 placebo.
Speroff, 1996	E2: 0.02 mg/day	None	63	18/63	NR	NR	Reported in 6-14% E2, 3% placebo.
Utian, 1999	E2: 0.025, 0.05, 0.1 mg/day	None	NR	3	3 wthdls in E2 groups; hyperplasia in 19 E2 groups (1 with atypia); 32-57% spotting in E2, 10% placebo.	NR	Most common symptom in E2 groups (23-45% E2, 45 placebo).

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Transdermal E2								
Bacchi-Modena, 1997	Reported in all groups.	None	NR	NR	Reported in 30% E2, 20% placebo.	NR	NR	Also reports of abdominal pain; no changes in blood pressure.
De Aloysio, 2000	Reported in all groups.	None	NR	NR	1 wthdl E2.	NR	None	Overall systemic events: 10% E2 groups, 8% placebo.
de Vrijer, 1999	1 wthdl E2 0.10.	NR	Reported in E2 group.	NR	3 wthdls E2, 2 placebo.	NR	NR	Other wthdls: edema (1 E2), sleep disturbances (1 E2), anxiety/mood (2 placebo), leg hematoma (1 placebo).
Gordon, 1995	Most common adverse reaction; wthdls NR	NR	NR	NR	41 due to site reactions	NR	NR	No differences between Rx groups except for uterine bleeding; much lower rates in placebo group.
Notelovitz, 2000c	NR	NR	NR	NR	Reported in 4-7% E2, 1-10% placebo.	NR	NR	Overall events: 79% placebo, 83-90% E2.
Shulman, 2002	Reported in 10 E2.	Reported in 8 E2, 1 placebo.	NR	NR	3 wthdls E2, 3 placebo.	NR	NR	Also abdominal and back pain, edema, mood in all groups, flatulence in E2.
Speroff, 1996	Most frequently reported: 20% placebo, 16% E2.	NR	NR	NR	9 wthdls (5 placebo, 4 E2).	NR	NR	NR
Utian, 1999	NR	NR	NR	NR	5-11% in all groups.	NR	NR	Overall: 11% placebo, 31% E2 0.025, 55% E2 0.05, 58% E2 0.10.

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

					Withdrawals due to specific adverse effects		
Study/Year	**Estrogen type; dose; regimen**	**Progestin type; dose; regimen**	**Withdrawals**	**Withdrawals due to adverse effects**	**Atypical bleeding & endometrial hypertrophy**	**Nausea & vomiting**	**Breast tenderness**
van Holst, 2000	E2: 0.05 mg/day	None	NR	18 (9 E2, 7 placebo)	NR	NR	4 wthdls in E2 group.
van Holst, 2002	E2: 0.050 mg/day	Levonorgestrel patch: 10 microgm/day	NR	NR	NR	None	NR
Wiklund, 1993	E2: 0.05 mg/day	None	NR	NR	8% placebo, 15% E2 (NS difference).	NR	NR
Oral E2V							
Blumel, 1994*	E2V: 2 mg/day	MPA 2.5 mg/day (CCT)	2/50	2	No difference at 3 months, significantly more in E2V group (12/25) than placebo group (3/23) at 6 months.	NR	At 3 months, 7/25 in E2V group reported symptom, 3/23 of placebo; at 6 months, 1/25 E2V, 0/23 placebo.
Jensen P, 1987*	E2V: 2 mg/day days 1-21	Cyproterone acetate 1 mg/day days 12-21 (cyclic)	19/76	NR	NR	NR	NR
Marslew, 1992*	E2V: 2 mg/day	Cyproterone acetate 1 mg/day (CCT)	11/50	NR	Three in E2V withdrew due to regular bleeding.	NR	Increased in E2V group.
Oral CEE							
Baumgardner, 1978*	CEE: 1.25 mg/day for 21/28 days	None	23/160	23	No differences between groups.	One wthdl from CEE group.	Few reports, no differences between groups.

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
van Holst, 2000	NR	None	NR	NR	4 wthdls E2, 3 placebo.	NR	None	No blood pressure changes.
van Holst, 2002	Reported in both groups.	None	NR	NR	Erythema & edema in both groups.	NR	NR	No blood pressure changes; general gastrointestinal symptoms in both groups.
Wiklund, 1993	NR	NR	NR	NR	NR	NR	NR	NR
Oral E2V								
Blumel, 1994*	Improvement for Rx group compared to placebo (p=0.05).	NR	No differences between groups.	NR	NR	NR	NR	NR
Jensen P, 1987*	NR	One wthdl due to weight gain.	NR	NR	NR	NR	NR	Wthdls due to varicose veins.
Marslew, 1992*	NR	NR	NR	NR	NR	NR	NR	More reports in Rx group but not specified.
Oral CEE								
Baumgardner, 1978*	Few reports, no differences between groups.	No significant weight gain.	Few reports, no differences between groups.	None	None	NR	NR	Additional wthdls due to edema and visual symptoms (no difference between groups), lack of effect in placebo group.

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

					Withdrawals due to specific adverse effects		
Study/Year	**Estrogen type; dose; regimen**	**Progestin type; dose; regimen**	**Withdrawals**	**Withdrawals due to adverse effects**	**Atypical bleeding & endometrial hypertrophy**	**Nausea & vomiting**	**Breast tenderness**
Campbell, 1976*	CEE: 1.25 mg/day for 21/28 days	None	7/68	NR	Increased in CEE group.	7% during CEE phase, 3% during placebo.	13% during CEE phase, 10% during placebo.
Carranza-Lira, 2001; Brief report	CEE: 0.625 mg/day	None	NR	NR	NR	NR	NR
Coope, 1975*	CEE: 1.25 mg/day for 21/28 days	None	5/35	NR	Wthdl bleeding in majority of perimenopausal women, no breakthrough bleeding.	Two reported in placebo group.	Two reported in placebo, 1 in CEE group.
Greendale, 1998*	CEE: 0.625 mg/day alone and with MPA (CCT and cyclic)	MPA: 10 mg/day days 1-12 (cyclic), 2.5 mg/day (CCT); micronized progesterone 100 mg/day days 1-12 (cyclic)	210/875	127	NR	NR	More common with E + P compared to E alone or placebo.

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Campbell, 1976*	Nonsignificant improvement during Rx phase.	No differences between groups.	NR	None	NR	NR	NR	Most common adverse events were leg cramps, breast tenderness, limb pains, fluid retention, eye irritation, nasea, vaginal discharge; all slightly higher during Rx phase but not significantly different.
Carranza-Lira, 2001; Brief report	NR	NR	NR	NR	NR	NR	NR	NR
Coope, 1975*	One reported in Rx group.	Reports of 4 with more than 3 kg weight gain, 2 in placebo, 2 in Rx group.	NR	NR	NR	NR	NR	Other reports of urinary infections, increased blood pressure, nasal stuffiness (groups not specified).
Greendale, 1998*	If HA at baseline, E only group had less, if no HA at baseline, E only group more likely to get.	E + P group more likley to lose weight.	NR	Two cases of DVT in E only group, one case of superficial phlebitis in E + P group.	NR	NR	NR	Reports of joint pain, depression, lack of effect.

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

					Withdrawals due to specific adverse effects		
Study/Year	**Estrogen type; dose; regimen**	**Progestin type; dose; regimen**	**Withdrawals**	**Withdrawals due to adverse effects**	**Atypical bleeding & endometrial hypertrophy**	**Nausea & vomiting**	**Breast tenderness**
Utian, 2001	CEE: 0.625, 0.45, 0.3 mg/day; combined and unopposed regimens	MPA 1.5, 2.5 mg/day (CCT)	521 (19%)	221 (8% overall, highest in 0.625 group)	Most common in CEE 0.625 groups (6-14%); 2% in low dose CEE, none in placebo.	NR	Most commonly reported effect (15% overall), more in combined than in unopposed groups (13-25% vs 7-12%).
Oral estropipate							
Coope, 1981*	Estropipate: 1.5 mg/day for 21/28 days	None	11/66	NR	Wthdl bleeding in majority of women, 1/36 with breakthrough bleeding.	NR	One in Rx group.
Vaginal E2							
Speroff, 2003	vaginal E2 delivering the equivalent of 50 mcg or 100 mcg per day; placebo vaginal ring	2.5 mg per day oral norethindrone or 10 mg per day oral medroxyprogesterone acetate for 14 days after removal of the vaginal ring.	54/333 (16.2%) Discontinuation rates lower in E2 50 mcg (p=0.007) and E2 100 mcg (p=0.001) groups than placebo.	NR- discontinuation rates due to adverse events were significantly lower in the E2 groups than placebo.	6.6% intermenstrual bleeding (withdrawals not reported)	NR	6.3% (withdrawals not reported)

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Tabe 3. Adverse effects reported in hot flash/flush trials (continued)

	Withdrawals due to specific adverse effects							
Study/Year	**Headache**	**Weight change**	**Dizziness**	**VTE**	**Rash & pruritis**	**Chole-cystitis**	**Liver effects**	**Other**
Utian, 2001	NR	NR	NR	NR	NR	NR	NR	Also reported leg cramps in CEE groups.
Oral estropipate								
Coope, 1981*	NR	NR	NR	One with small vein thrombosis.	NR	NR	NR	Also reports of fluid retension and LV failure in Rx group; 2 with severe depression in Rx group. Two deaths (recurrent gastic cancer, epileptic seizure).
Vaginal E2								
Speroff, 2003	8.7% (withdrawals not reported)	NR	NR	NR	NR	NR	NR	vaginal candidiasis 6.6% (withdrawals not reported)

*Included in Cochrane review (MacLennan, 2000)
wthdls=withdrawals

Evidence Table 4. Adverse effects reported in bone density and fracture trials

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to specific adverse effects		
				Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Head to Head Comparisons						
Oral CEE compared with transdermal E2						
Castelo-Branco, 1992	CEE: 0.625 mg/day; E2: 0.05 mg/day; calcium NR	MPA: 2.5 mg/day (all treatment groups)	15	Bleeding: CEE cont 2; Endometrial hyperplasia: transdermal E2 4, CEE cyclic, 3	NR	NR
Castelo-Branco, 1993	CEE: 0.625 mg/day; E2: 0.05 mg/day; calcium NR	MPA: 2.5 mg/day (all treatment groups)	12	NR	NR	1
Oral E2V compared with transdermal E2						
Marslew, 1991	E2: 1.5 mg/day (12 days); E2V: 2 mg/day (11 days); calcium NR	DG: 150 micrograms/day cyclic; MPA: 10 mg/day cyclic	16 12 in treatment 4 in placebo 78% completed	4	NR	NR
Placebo Comparisons						
Oral E2						
Abrahamsen, 1997	E2: 2 mg/day (22 days), 1 mg/day (6 days); calcium NR	MPA: 1 mg/day (10 days)	NR	NR	NR	NR
Cheng, 2002	E2: 2 mg/day; calcium NR	NETA: 1 mg/day CCT	E2 15 placebo 15	NR	NR	NR
Ettinger, 1992	E2: 0.5, 1.0, or 2.0 mg/day micronized + Ca 1500 mg/day; placebo: Ca 1500 mg/day	None	41 (65%) completed follow-up	5 due to bleeding	NR	NR
Gambacciani, 1995	E2: 2 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	None	9	NR	NR	2

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

	Withdrawals due to specific adverse effects								
Study/Year	Headache	Weight change	Dizziness	VTE	CVD events	Rash & pruritis	Chole-cystitis	Liver effects	Other
Head to Head Comparisons									
Oral CEEcompared with transdermal E2									
Castelo-Branco, 1992	NR	NR	NR	NR	NR	Transdermal E2: 4	NR	NR	Poor relief of hot flashes: CEE cyclic 2 withdrawals; transdermal E2 1 withdrawal
Castelo-Branco, 1993	NR	NR	NR	NR	NR	4	NR	NR	3 withdrew due to hot flashes 3 incorrect use of medicine
E2Vcompared with transdermal E2									
Marslew, 1991	3	1	NR	NR	NR	NR	NR	NR	Withdrawal: 6 personal reasons, lack of time, moved
Placebo Comparisons									
Oral E2									
Abrahamsen, 1997	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cheng, 2002	NR	NR	NR	NR	NR	NR	NR	NR	Lack of time or interest; Health concerns; Poor compliance for pill regimen (n=6); Side effects
Ettinger, 1992	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gambacciani, 1995	1	NR	NR	NR	NR	NR	NR	NR	NR

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to specific adverse effects: Atypical bleeding & endometrial hypertrophy	Withdrawals due to specific adverse effects: Nausea & vomiting	Withdrawals due to specific adverse effects: Breast tenderness
Lees, 2001	E2: 1 or 2 mg/day Canadian group encouraged to take 500 mg/day Ca	Dydrogesterone: 5, 10 or 20 mg/day cyclic	117	34 (6%) all in E2 group	NR	E2 2mg: 36% E2 1mg: 24% P: 12% Breast tenderness: worse with E2 2
Mosekilde, 2000	E2: 1-2 mg/day; calcium NR	NETA: cyclic 1 mg/day 10 days (intact uterus); CCT 1 mg/day (without uterus)	89% completed study	NR	NR	NR
Munk-Jensen, 1988	E2: 2 mg/day CCT vs. cyclic; calcium NR	NETA: 1 mg/day	86% completed (130)	3 E2 0 placebo	NR	2 E2 0 placebo
Resch, 1990	E2: 2 mg/day cyclic + Ca 500 mg/day; placebo: Ca 500 mg/day	NETA: 1 mg/day CCT	E2: 6 placebo: 7	E2: 4	None	None
Riis, 1988	E2: 2 mg/day CCT; calcium NR	NETA: 1 mg/day CCT	E2: 3 placebo: 3	E2: 1	None	None
Transdermal E2						
Adami, 1989	E2: 50 mg day + Ca 1200 mg/day + vitamin D 600-800 units/day; placebo: Ca 1200 mg/day + vitamin D 600-800 units/day	MPA: 10 mg/day (12 days)	None	NR	NR	NR
Alexandersen, 1999	E2: 50 microgm/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	Oral NETA: 1 mg/day	5 had poor compliance; 68/100 completed study	2	Reported	Reported

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

	Withdrawals due to specific adverse effects								
Study/Year	Headache	Weight change	Dizziness	VTE	CVD events	Rash & pruritis	Chole-cystitis	Liver effects	Other
Lees, 2001	NR	NR	NR	NR	NR	NR	NR	NR	83 withdrawals due to 'other adverse events;" 11% in placebo, 62% in treatment groups. Nausea, abdominal pain were expected at greater than 10%. 13 fractures during the study: placebo: 3 (3%), E2:10 (4%).
Mosekilde, 2000	NR	NR	NR	NR	NR	NR	NR	NR	NR
Munk-Jensen, 1988	NR	1 E2	NR	NR	NR	NR	NR	NR	Breast cancer: treatment 2, placebo 0; Confusion: treatment 0, placebo1; Cancer: treatment 3, placebo 0; Private reasons: 10; Technical errors: treatment 22, placebo 16; Paresthesia: treatment 1, placebo, 0
Resch, 1990	None	None	None	T: 1	None	None	None	None	E2: 1 transitory ischemic attack placebo: 7 lack of interest
Riis, 1988	None	None	None	None	None	None	None	None	E2: 2 lack of time placebo: 1 edema of legs & fingers 2 hot flashes
Transdermal E2									
Adami, 1989	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alexandersen, 1999	NR	Reported	NR	NR	2	NR	NR	NR	Mood changes reported

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to specific adverse effects		
				Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Arrenrecht, 2002	E2: 50, 100 microgm/day; calcium NR	None	E2: 39	NR	NR	5 (9%)
Cagnacci, 1991	E2: 50 microgm/day cyclic; calcium NR	After 6 months, MPA 5 mg/day cyclic	NR	NR	NR	NR
Cooper, 1999	E2: 25, 50, 75 micrograms/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	MPA: 20 mg/day cyclic	74-80% compliance in groups; 14% withdrew due to adverse events	NR	NR	37% reported symptoms
Filipponi, 1995	E2: 0.05 mg/day + Ca 1200-1500 mg/day; placebo: Ca 1200-1500 mg/day	MPA: 20 mg/day cyclic	92 of 124 completed study E2: 9 (21%) placebo: 12 (30%)	NR	NR	NR
Gonnelli, 1997	E2: 0.05 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	MPA: 10 mg/day cyclic	9	1	NR	NR
Hesley, 1998	E2: 0.025, 0.05, and 0.01 mg/day; calcium NR	None	NR	NR	NR	NR
Lufkin, 1992	E2: 0.1 mg/day (1-21 days) + Ca 800 mg/day; placebo: Ca 800 mg/day	MPA: 10 mg/day, 10 days cyclic	9 total; 3 in E2 group; Over 50% of E2 group talked of adverse events	8% E2 group	NR	56% of E2 group
McKeever, 2000	E2: 0.025, 0.0375, 0.05, 0.1 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	MPA: 2.5 mg/day CCT non-hysterectomized women	27 withdrew	34 reports	NR	43 reports

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

	Withdrawals due to specific adverse effects								
Study/Year	Headache	Weight change	Dizziness	VTE	CVD events	Rash & pruritis	Chole-cystitis	Liver effects	Other
Arrenrecht, 2002	12 complaints	NR	NR	NR	NR	5 (9%) in E2	NR	NR	E2: 7 Edema (complaints) 4 hot flashes (withdrawal) 6 subject choice (withdrawal)
Cagnacci, 1991	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cooper, 1999	Reported	NR	NR	NR	NR	Reported	NR	NR	Back pain; flu syndrome
Filipponi, 1995	NR	NR	NR	NR	NR	E2: 3	NR	NR	E2: 2 fear of side effects (cancer); 2 loss to followup placebo: 5 dissatisfied with results; 3 had hot flashes; 4 loss to followup
Gonnelli, 1997	NR	NR	NR	NR	NR	2	NR	NR	5 withdrawals for personal reasons; 1 withdrawal for side effects
Hesley, 1998	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lufkin, 1992	NR	NR	NR	NR	NR	2 E2	NR	NR	1 withdrawal for no reason
McKeever, 2000	3	NR	NR	1	NR	Reported	NR	NR	1 depression

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to specific adverse effects		
				Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Notelovitz, 2002	E2: 0.025 mg/day, 0.05 mg/day, or 0.075 mg/day	None	159/355	NR	NR	14.6% E2 0.025 mg/day, 17.8% E2 0.05 mg/day, 34.8% E2 0.075 mg/day, 8% placebo; withdrawals not reported
Perez-Jaraiz, 1996	E2: 50 microgm/day; calcium NR	MPA: 10 mg/day for 10 days	NR	NR	NR	NR
Rubinacci, 2003	E2: 0.025 mg/day	norethisterone acetate 0.125 mg/day	32/124	36% of E2 and 24% of placebo had some bleeding; withdrawals not reported. Endometrial thickness increased by an average of 0.45 mm in E2, decreased by 0.18 mm in placebo; withdrawals not reported.	NR	36.7% E2, 22.2% placebo; withdrawals not reported
Oral E2V						
Doren, 1995	E2V: 2 mg/day + Ca 1000 mg/day; E2: 2 mg/day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	NETA: 5 mg/day cyclic; 1 mg/day CCT	NR	E2V: 24% -reason for discontinuing of drug	NR	2

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

	Withdrawals due to specific adverse effects								
Study/Year	Headache	Weight change	Dizziness	VTE	CVD events	Rash & pruritis	Chole-cystitis	Liver effects	Other
Notelovitz, 2002	11.2% E2 0.025 mg/day, 8.9% E2 0.05 mg/day, 5.6% E2 0.075 mg/day, 12.6% placebo; withdrawals not reported	NR	NR	NR	NR	application-site reactions 9% in E2, 0 placebo			1 case of breast cancer in E2 0.025 mg/day and 0.075 mg/day group.
Perez-Jaraiz, 1996	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rubinacci, 2003	5% E2, 6.3% placebo; withdrawals not reported	NR	NR	NR	NR	erythema 9% E2, 14% placebo	NR	NR	2 cases of breast cancer in E2 group, one after 12 months and the other after 24 months.
Oral E2V									
Doren, 1995	NR	2	NR	NR	NR	NR	NR	NR	10 (missed appointments or misc.)

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to specific adverse effects: Atypical bleeding & endometrial hypertrophy	Withdrawals due to specific adverse effects: Nausea & vomiting	Withdrawals due to specific adverse effects: Breast tenderness
Heikkinen, 1997	E2V: 2 mg/day; calcium NR	MPA: 2 mg/day cyclic	8 in E2V	2	NR	Reported
Isaia, 1989	E2V: 2 mg/day cyclic; calcium NR	MPA: 10 mg/day for 40 days	NR	NR	NR	NR
Komulainen, 1997	T1: E2V 2 mg/day cyclic; T2: vit D 300 IU day + Ca 500 mg/day; T3: T1 + T2; placebo: Ca 500 mg/day	T1 & T3: CPA 1 mg/day cyclic	73: 55 from HT groups 84% completed study/99% compliance	17	None	None
Marslew, 1992	E2V: 2 mg/day CCT or cyclic; calcium NR	Cyproterone acetate (1 mg/day) or levonorgestrel (75 microgrm/day)	13: 12 in HT 1 in placebo	4	NR	NR
Oral CEE						
Agnusdei, 1990	CEE: 0.625 mg/day (days 1-20) + Ca 800-1200 mg/day; placebo: Ca 800-1200 mg/day	MPA: cyclic 5 mg/day	NR	NR	NR	NR
Agnusdei, 1995	T1: CEE 0.3 mg/day alone; T2: CEE 0.3 mg/day + progestin; placebo: Ca carbonate 1000 mg/day; All subjects: Ca carbonate 1000/day	All patients, 10 mg/day MPA 15 days every 3 months.	27 (33%): 19 for personal reasons, 8 for adverse effects	3 with endometrial modification	5	NR
Aloia, 1994	T1: CEE 0.65 mg + CA 1700 mg/day + vitamin D 400 IU /day T2: CA 1700 mg/day + vitamin D 400 IU /day; P: vitamin D 400 IU /day	MPA: cyclic 10 mg/day (days16-25)	17: 6 due to disease; 5 wanted change in HT; 3 no reason given	NR	1	2

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

	Withdrawals due to specific adverse effects								
Study/Year	Headache	Weight change	Dizziness	VTE	CVD events	Rash & pruritis	Chole-cystitis	Liver effects	Other
Heikkinen, 1997	NR	NR	NR	1	NR	NR	NR	NR	4 Hot flashes 1 Psychiatric syptoms 1 Personal reasons 1 Breast cancer 1 Death
Isaia, 1989	NR	NR	NR	NR	NR	NR	NR	NR	NR
Komulainen, 1997	12	None	None	None	None	None	None	None	6 withdrawals from diagonisis of osteoporosis; 3 withdrawal disruptions in medication adherence
Marslew, 1992	2	1	NR	NR	NR	NR	NR	NR	4 withdrawal due to anxiety, unrelated illness
Oral CEE									
Agnusdei, 1990	NR	NR	NR	NR	NR	NR	NR	NR	NR
Agnusdei, 1995	NR	NR	NR	NR	NR	3 cases	NR	NR	NR
Aloia, 1994	2	2	NR	NR	NR	NR	NR	NR	2 mood, 1 cramps, 1 libido, 1 eructation, 1 constipation

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to specific adverse effects		
				Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Cauley, 2003	CEE: 0.625 mg/day	medroxy-progesterone acetate 2.5 mg/day	541/16608	NR	NR	NR
Civitelli, 1988	CEE: 1.25 mg/day + Ca 800-1000 mg/day; placebo: Ca 800-1000 mg/day	None	NR	NR	NR	NR
Civitelli, 2002	CEE: 0.625 mg/day	medroxy-progesterone acetate 2.5 mg/day	49/135 (45% placebo, 28% CEE)	vaginal bleeding 2 CEE, 3 placebo; endometrial cancer 1 CEE, 0 placebo.	none	none
Gallagher, 1991	T1: CEE 0 .625 mg/day; T2: progestin only; T3: CEE 0.3 mg/day + progestin; All subjects: Ca 1000 mg/day; placebo: Ca 1000 mg/day	NETA: 2, 10 mg/day cyclic	16	2 bleeding	NR	NR
Gambacciani, 1997	CEE: 0.3 mg/day; All subjects: Ca 500 mg/day	None	7: 4 poor compliance	NR	NR	1
Genant, 1982	CEE: 0.15, 0.30, 0.45, 0.60 mg/day; calcium NR	None	NR	NR	NR	NR
Greenspan, 1998	CEE: 0.625 mg/day; calcium NR	None	NR	NR	NR	NR
Hosking, 1998	US group: CEE 0.625 mg/day cyclic; UK: E2 1 to 2 mg/day cyclic; calcium NR	US: MPA 5 mg/day CCT UK: NETA 1 mg/day cyclic	NR Compliance to regimen was >75%	99 complaints	51%	None

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

	Withdrawals due to specific adverse effects								
Study/Year	Headache	Weight change	Dizziness	VTE	CVD events	Rash & pruritis	Chole-cystitis	Liver effects	Other
Cauley, 2003	NR	NR	NR	NR	NR	NR	NR	NR	
Civitelli, 1988	NR	NR	NR	NR	NR	NR	NR	NR	NR
Civitelli, 2002	at least 1 (combined with other events in "other" category)	none	none	none	none	none	none	none	1 withdrawal in CEE group due to breast cancer, 0 placebo; 1 withdrawal in placebo group due to ankle fracture, 0 CEE; 1 withdrawal in placebo group due to excessive decrease in BMD, 0 CEE.
Gallagher, 1991	NR	NR	NR	NR	NR	NR	NR	NR	2 hot flashes
Gambacciani, 1997	NR	NR	NR	NR	NR	NR	NR	NR	1 menopausal symptoms
Genant, 1982	NR	NR	NR	NR	NR	NR	NR	NR	NR
Greenspan, 1998	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hosking, 1998	None	None	None	None	14%	28%	None	None	Nervous system, psychiatric 33%

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to specific adverse effects		
				Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Hulley, 1998	CEE: 0.625 mg/day; Ca NR	MPA: 2.5 mg/day CCT	82% compliance	NR	NR	NR
Hulley, 2002 (HERS II)	CEE: 0.625 day Calcium NR	MPA: 2.5 mg/day CCT	NR	NR	NR	NR
Leung, 1999	CEE: 0.625, 0.3 mg/day; calcium NR	MPA: 5 mg/day (if uterus present) cyclic	13: 6 in 0.3 group; 5 in 0.625; 2 in control	Reported	Reported	Reported
Lindsay, 1984	CEE: 0.15, 0.3, 0.625, 1.25 mg/day; calcium NR	None	33 CEE	NR	NR	6
Lindsay, 1990	CEE: 0.625 mg/day + 1500 mg Ca/day; placebo: 1500 mg Ca/day	MPA: 5 or 10 mg/day cyclic (if uterus present)	10: 4 fractures 4 lost to follow-up 2 moved away	NR	NR	NR
Lindsay, 2002	CEE: 0.625, 0.45, 1.5, 0.3 mg/day + Ca 600 mg/day; placebo: Ca 600 mg/day	MPA: 2.5, 1.5 mg/day CCT	Adverse effects reported by 95% of subjects Drop outs: 8/94 (9%) placebo 103/655 (16%) treatment CEE	Reported in CEE groups ($p<0.05$)	NR	Reported in CEE groups ($p<0.05$)
Meschia, 1993*	CEE: 0.3 and 0.625 mg/day; calcium NR	MPA: 2.5 mg/day	24% year 1 45% year 2 Investigators say not due to CEE	NR	NR	NR
Mizunuma, 1997	CEE: 0.3 and 0.625 mg day calcium NR	2.5 mg MPA day MPA: 2.5 mg/day	3 in year 1 13 in year 2	6 vaginal bleeding (CEE group)	NR	NR

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

	Withdrawals due to specific adverse effects								
Study/Year	Headache	Weight change	Dizziness	VTE	CVD events	Rash & pruritis	Chole-cystitis	Liver effects	Other
Hulley, 1998	NR	NR	NR	Reported	Not significant between groups	NR	Reported	NR	VTE (2.89; 1.50-5.58). Cholecystitis (1.38; 1.00-1.92).
Hulley, 2002 (HERS II)	NR	NR	NR	Reported	NR	NR	NR	NR	VTE (2.08; 1.28-3.40). Biliary tract surgery (1.48; 1.12-1.95)
Leung, 1999	Reported	Reported	None	None	None	None	None	None	CEE: 4 withdrawals due to fear of side effects; 5 withdrawals due loss of fu; 2 felt they did not need the treatment. 2 in placebo group lost to fu.
Lindsay, 1984	NR	NR	NR	NR	NR	NR	NR	NR	12 withdrawals due to poor control of menopausal symptoms; 5 illness; 11 moved.
Lindsay, 1990	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lindsay, 2002	NR	NR	NR	NR	NR	NR	NR	NR	Vaginal dryness reported more with placebo ($p<0.05$)
Meschia, 1993	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mizunuma, 1997	NR	NR	NR	NR	NR	NR	NR	NR	CEE groups: 1 fear of cancer, 1 fatigue; placebo group: 2 loss of interest

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to specific adverse effects		
				Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
PEPI, 1996	T1: CEE 0.625 mg/day only; T2 - T 3: CEE 0.625 mg/day + progestin; calcium NR	T2: MPA 10 mg/day cyclic, 12 days T3: MPA 2.5 mg/day daily T4: MP (micronized) 200 mg/day 12 days	Compliance: At 36 months: Taking assigned medications: Combination CEE 78% CEE only 56% Placebo 74%	NR	NR	NR
Recker, 1977	CEE: 0.625 mg/day; Ca 2600 mg/day	MPA: 5 mg/day cyclic	NR	NR	NR	NR
Recker, 1999	CEE: 0.3 mg day + Ca 1000 mg/day + vitamin D 75 nmol/L/day; placebo: Ca 1000 mg/day + vitamin D 75 nmol/L/day	MPA: 2.5 mg/day CCT	CEE: 11 placebo: 10 complaints also listed	CEE: 31 compliants placebo: 1 complaint	None	CEE: 49 complaints placebo: 27 complaints
Rosen, 1997	CEE: 0.625 mg/day + Ca 500 mg/day; placebo: Ca 500 mg/day	MPA: 2.5 mg/day CCT, 5 mg/day cyclic	9; reasons not provided	NR	NR	NR
Villareal, 2001	CEE: 0.625 mg/day + Ca 1200 mg/day	MPA: 5 mg/day cyclic	CEE: 11, placebo: 2; 86% compliance in CEE group; 9 HT regimen changed due to adverse events; 141 eligible subjects	1 CEE	None	2 CEE
WHI, 2002	CEE: 0.625 mg/day; calcium NR	MPA: 2.5 mg/day CCT	583 (3.5%) lost to follow-up; CEE: 42% stopped treatment placebo: 38% stopped treatment	CEE: 248 hysterectomy placebo: 183 hysterectomy	NR	NR

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

	Withdrawals due to specific adverse effects								
Study/Year	Headache	Weight change	Dizziness	VTE	CVD events	Rash & pruritis	Chole-cystitis	Liver effects	Other
PEPI, 1996	NR	NR	NR	NR	NR	NR	NR	NR	NR
Recker, 1977	NR	NR	NR	NR	NR	NR	NR	NR	NR
Recker, 1999	None	None	None	None	None	None	None	None	Stroke: CEE 1, placebo 1; Hip fracture: placebo 1; Death: CEE 2, placebo 1; HT side effects: CEE 2, placebo 1; 17% of subjects had symptoms last more than 12 months.
Rosen, 1997	NR	NR	NR	NR	NR	NR	NR	NR	4 subjects moved away; CEE: 1 stopped taking treatment,1 removed by physician; placebo: 1 stopped taking treatment, 2 removed by physician
Villareal, 2001	None	None	None	None	None	None	None	None	CEE: 7 medical, unrelated to study;1 death due to car crash; placebo: 2 withdrew consent
WHI, 2002	NR	NR	NR	DVT: 167 cases PE: 101 cases	286 cases	NR	NR	NR	Breast cancer: 1.26 (1.00-1.59), 290 cases Stroke: 1.41 (0.86- 2.31), 212 cases Endometrial cancer: 0.83 (0.29-2.32), 47 cases

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

Study/Year	Estrogen type; dose; regimen	Progestin type; dose; regimen	Withdrawals	Withdrawals due to specific adverse effects		
				Atypical bleeding & endometrial hypertrophy	Nausea & vomiting	Breast tenderness
Wimalawansa, 1998	CEE: 0.625 mg/day + Ca 1000 mg/day + vit D 400 units/day; placebo: Ca 1000 mg/day + vit D 400 units/day	Norgestrel: 150 micrograms/day cyclic	CEE: 3 placebo: 3	NR	None	None
Oral esterified estrogen						
Genant, 1997	Esterified estrogens: 0.3, 0.625, 1.25 mg day + Ca 1000 mg/day; placebo: Ca 1000 mg/day	None	49 withdrawals 188 discontinued 94% compliance	Placebo = 3 HT: 0.3 mg=1 0.625 mg = 17	NR	NR

Evidence Table 4. Adverse effects reported in bone density and fracture trials (continued)

	Withdrawals due to specific adverse effects								
Study/Year	Headache	Weight change	Dizziness	VTE	CVD events	Rash & pruritis	Chole-cystitis	Liver effects	Other
Wimalawansa, 1998	None	None	None	None	None	None	None	None	Placebo: 1 withdrawal due to inability to take meds; 2 for other medical conditions; CEE: Some complaints about calcium supplementation, however did not result in withdrawals.
Oral esterified estrogen									
Genant, 1997	NR	NR	NR	NR	NR	NR	NR	NR	Adverse event 49

Appendix A. Literature search strategies

Menopausal Symptoms

1 DIENESTROL/ or dienestrol.mp.
2 exp ESTRADIOL/ or estradiol.mp.
3 exp ESTRONE/ or estrone.mp.
4 estropipate.mp.
5 exp Ethinyl Estradiol/ or ethinyl estradiol.mp.
6 quinestrol.mp. (175)
7 exp ESTROGENS/ or estrogens.mp.
8 estrogen vaginal cream.mp.
9 exp "Vaginal Creams, Foams and Jellies"/
10 7 and 9
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 10
12 limit 11 to randomized controlled trial
13 Randomized Controlled Trials/ or rct.mp.
14 11 and 13
15 12 or 14
16 limit 15 to (human and english language and yr=1980-2002)
17 (hotflash$ or hot flash$).mp.
18 exp Sleep/ or sleep disturb$.mp.
19 Sweating/ or night sweats.mp.
20 exp VASOMOTOR SYSTEM/ or vasomotor.mp.
21 exp Mood Disorders/ or mood changes.mp.
22 exp DEPRESSION/ or depression.mp.
23 exp Cognition/ or cognitive function$.mp.
24 urogenital atrophy.mp.
25 atrophy.tw. and exp urogenital system/
26 LIBIDO/ or libido.mp.
27 Quality of Life/ or quality of life.mp.
28 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29 16 and 28
30 from 29 keep 1-315

Bone Density and Fractures

1 DIENESTROL/ or dienestrol.mp.
2 exp ESTRADIOL/ or estradiol.mp.
3 exp ESTRONE/ or estrone.mp.
4 estropipate.mp.
5 exp Ethinyl Estradiol/ or ethinyl estradiol.mp.
6 quinestrol.mp.
7 exp ESTROGENS/ or estrogens.mp.
8 estrogen vaginal cream.mp.
9 exp "Vaginal Creams, Foams and Jellies"/
10 7 and 9
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 10
12 limit 11 to randomized controlled trial
13 Randomized Controlled Trials/ or rct.mp.
14 11 and 13
15 12 or 14
16 limit 15 to (human and english language and yr=1980-2002)
17 exp FRACTURES/ or fracture$.mp.
18 exp Bone Density/ or bone density.mp.
19 17 or 18
20 16 and 19
21 from 20 keep 1-259

Appendix B. Abbreviations and acronyms

BMC=Bone mineral content

BMD = Bone mineral density

Ca = Calcium

CCT = Combined continuous treatment regimen

CEE = Conjugated equine estrogen

Cyclic = Cyclic regimen

DB = Double blind

E2 = Estradiol

E2V=Estradiol valerate

EE= Esterified estrogen

IU = International Unit

MPA = Medroxyprogesterone acetate

NETA = Norethindrone acetate

NR = Not reported

P = Placebo group

RCT = Randomized controlled trial

Rx = Treatment group

SD = Standard deviation

TAHBSOO = Total abdominal hysterectomy with bilateral salpingo-oophorectomy

Appendix C. Quality criteria

For Controlled Trials:

Assessment of Internal Validity

To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination.

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
    - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

Appendix D. Quality scores for trials in Cochrane review of hot flashes/flushes

Study/Year	Allocation	Treatment Blinding	Outcome Assessment	Baseline Equality	Losses to follow-up	Analysis Basis
Archer 1992	B	A	A	B	C	C
Baerug 1998	A	A	A	A	A	C
Baumgardner 1978	A	A	A	A	A	B
Bech 1998	B	A	A	C	C	C
Blumel 1994	A	A	A	A	A	C
Campbell 1976	B	B	A	B	C	C
Chung 1996	A	A	A	A	C	C
Conard 1995	A	B	A	A	C	C
Coope 1975	A	A	A	A	C	C
Coope 1981	A	A	A	A	C	C
Davidsen 1974	B	B	A	B	B	C
Dennerstein 1978	B	A	A	B	C	C
Derman 1995	A	A	A	A	C	A
Hagen 1982	B	B	A	A	C	C
Jensen J 1983	B	A	A	A	C	C
Jensen P 1987	B	B	A	A	C	C
Marslew 1992	A	A	A	A	C	C
Martin 1971	B	A	A	A	C	C
PEPI 1998	A	A	A	C	A	A
Paterson 1982a	A	A	A	A	C	C
Viklylaeva 1997	A	A	A	A	A	B

Appendix D. Quality scores for trials in Cochrane review of hot flashes/flushes (continued)

Cochrane Quality Assessment Criteria

Assessment	A	B	C
Allocation concealment	Adequate e.g. central randomization / allocation, sealed envelopes, etc.	Not reported/unclear	Inadequate
Treatment blinding	Statement that containers were identical, drugs were identical in appearance, etc.	Not reported/unclear	HRT and placebo not identical
Outcome assessment	Blinded, standardized assessment	Assessment procedures not stated	Assessment not blinded or standardized
Baseline equality of treatment groups	Groups balanced in terms of age, menopause status, and menopause symptoms	Balance not reported	Groups not balanced
Losses to follow-up (not including early cessation of therapy, followed up)	Losses of 10% or less	Not reported/unclear	Losses of more than10%
Basis for analysis	Intention-to-treat analysis	Unclear	Not intention-to-treat

Appendix E. Quality scores of reviewed hot flash/flush trials

Study Year	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Intention-to-treat analysis?	Maintenance of comparable groups?
Al-Azzawi, 2003	Yes	Yes	More oophorectomy in vaginal ring group (25% vs 21%)	Yes	Yes	Yes	Yes
Gelfand 2003	Yes	Not reported	More smokers in Prefest group (10.2% vs 1.7%); Months since LMP 30.6 prefest vs 34.2 placebo	Yes	Yes	Not clear- number randomized not reported	Not clear
Yang, 2002	Method not reported	Not reported	Yes	Yes	States double blind, but no details	No	Not clear
Speroff, 2003	Yes	Not reported	Yes	Yes	Yes	"Modified ITT analysis": 8/333 women did not provide postbaseline data, not included, but other withdrawals included in ITT analysis.	Not clear
Saure, 2000	Yes; methods NR	NR	Yes	Yes	Double-blind	NR	Unclear
Good, 1999	Yes; methods NR	NR	Yes	Yes	Double-blind	NR	Unclear

Appendix E. Quality scores of reviewed hot flash/flush trials (continued)

Study Year	Reporting of attrition, contamination, etc?	Differential loss to followup or overall high loss to followup?	Quality Score	Funding source	External validity
Al-Azzawi, 2003	Attrition yes	34/159 (21%) withdrew (by 12 weeks): 20.2% vaginal ring vs 22.7% oral E2	Good	Sponsored by Galen Holdings PLC.	Fair
Gelfand 2003	Attrition yes	3% of prefest and 5% of placebo withdrew	Fair	Supported by Janssen-Ortho	Fair
Yang, 2002	Only total withdrawals reported, not reported by group	28.6% withdrew, numbers in each group not given	Poor	Not reported.	Fair
Speroff, 2003	Attrition yes	16% withdrew: 12.4% in E2 vaginal ring 50 mcg, 9.8% in E2 vaginal ring 100 mcg, and 26.9% in placebo group withdrew (p=0.007 and p=0.001 vs placebo)	Fair	Supported by Waner Chilcott, a division of Galen Holdings. Authors have received speaking and consulting honoraria from the company. Author owns stock in the company.	Fair
Saure, 2000	Some	15% E2; 16% E2V	Fair	NR	Fair
Good, 1999	Some	15% overall	Fair	TheraTech Inc.	Fair

Appendix E. Quality scores of reviewed hot flash/flush trials (continued)

Study Year	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Intention-to-treat analysis?	Maintenance of comparable groups?
Gordon, 1995	Yes; methods NR	NR	Yes	Yes	Double-blind	Unclear	Unclear
Studd, 1995	Yes; methods NR	NR	Yes	Yes	Double-blind	Yes	Unclear
Freedman, 2002	Yes; methods NR	NR	Yes	Yes	Double-blind	NR	Unclear
Notelovitz, 2000a	Yes	Yes	Slight variation	Yes	Double-blind	Yes	Unclear
Notelovitz, 2000b	Yes; methods NR	NR	Slight variation	Yes	Double-blind	NR	Unclear
Utian, 2001	Yes	Yes	Yes	Yes	Double-blind	Yes	Unclear
Bacchi-Modena, 1997	Yes; methods NR	NR	Yes	Yes	Double-blind	Yes	Unclear
De Aloysio, 2000	Yes; methods NR	NR	Slight variation	Yes	Double-blind	Yes	Unclear
de Vrijer, 1999	Yes; methods NR	NR	Yes	Yes	Double-blind	Yes	Unclear

Appendix E. Quality scores of reviewed hot flash/flush trials (continued)

Study Year	Reporting of attrition, contamination, etc?	Differential loss to followup or overall high loss to followup?	Quality Score	Funding source	External validity
Gordon, 1995	Some	13-26% Rx; 30% placebo	Fair	3M	Fair
Studd, 1995	Some	16% overall	Fair	NR	Fair
Freedman, 2002	NR	NR	Fair	NIH	Fair
Notelovitz, 2000a	Some	Rx groups 11-21%; placebo 17%	Fair	Novo Nordisk	Fair
Notelovitz, 2000b	Some	16% overall	Fair	NR	Fair
Utian, 2001	Some	19% overall; 23% placebo; 30% 0.625 mg/day; 14-19% in other groups	Fair	Wyeth-Ayerst	Fair
Bacchi-Modena, 1997	Some	6% Rx; 15% placebo	Fair	NR	Fair
De Aloysio, 2000	Some	7% Rx; 25% placebo	Fair	NR	Fair
de Vrijer, 1999	Some	11% overall	Fair	NR	Fair

Appendix E. Quality scores of reviewed hot flash/flush trials (continued)

Study Year	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Intention-to-treat analysis?	Maintenance of comparable groups?
Notelovitz, 2000c	Yes; methods NR	NR	Yes	Yes	Double-blind	Yes	Unclear
Shulman, 2002	Yes	Yes	Yes except for smoking	Yes	Yes	Yes	Unclear
Speroff, 1996	Yes; methods NR	Yes	Described, data NR	Yes	Yes	Unclear	Unclear
van Holst, 2000	Yes; methods NR	NR	Described, data NR	Yes	Double-blind	Yes	Unclear
van Holst, 2002	Yes; methods NR	NR	Slight variation	Yes	Double-blind	Yes	Unclear
Utian, 1999	Yes; methods NR	Yes	Slight variation	Yes	Double-blind	Yes, data NR	Unclear
Wiklund, 1993	Yes; methods NR	NR	Yes	Yes	Unclear if double-blind	Yes	Yes, data NR

Appendix E. Quality scores of reviewed hot flash/flush trials (continued)

Study Year	Reporting of attrition, contamination, etc?	Differential loss to followup or overall high loss to followup?	Quality Score	Funding source	External validity
Notelovitz, 2000c	Some	5% overall (11 Rx, 1 placebo)	Fair	Rhone-Poulenc Rorer	Fair
Shulman, 2002	Some	3% overall	Fair	Berlex Labs	Fair
Speroff, 1996	Some	<20% Rx; 31% placebo	Fair	Park Davis	Fair
van Holst, 2000	Some	7% overall	Fair	NR	Fair
van Holst, 2002	Some	17% overall	Fair	NR	Fair
Utian, 1999	Some	10% overall (12 RX; 8 placebo)	Fair	Lab Fournier SA	Fair
Wiklund, 1993	Some	4% Rx; 8% placebo	Fair	NR	Fair

Appendix F. Quality scores of reviewed bone density and fracture trials

Study Year	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Intention-to-treat analysis?	Maintenance of comparable groups?
Rubinacci, 2003	Method not reported	Not reported	Mean FSH values slightly higher in E2 group; due mainly to very high value in one participant.	Yes	Yes	No	Not clear
Notelovitz, 2002	Method not reported	Not reported	Yes	Yes	Yes	Yes	Not clear
Civitelli, 2002	Method not reported	Not reported	Women in HRT arm 2 years older than placebo; number of years since menopause similar.	Yes	Yes	Not clear	Not clear
Cauley, 2003 (WHI)	Yes	Yes	Yes	Yes	Yes	Yes	Yes

*Some investigators were also funded by the following organizations during this study: Eli Lily, Merck, Pfizer, Proctor & Gamble Pharmaceuticals, Berlex, Abbott, Astra Zeneca, Bristol-Myers Squibb, Kos, and Ortho-McNeil Pharmaceuticals.

∞Some investigators were also funded by the following organizations during this study: Solvay Pharmaceuticals.

†Some investigators were also funded by the following organizations during this study: Merck, Pfizer, and Proctor & Gamble Pharmaceuticals.

Investigators given free medication for study subjects.

Appendix F. Quality scores of reviewed bone density and fracture trials (continued)

Study Year	Reporting of attrition, contamination, etc?	Differential loss to followup or overall high loss to followup?	Quality Score	Funding source	External validity
Rubinacci, 2003	Attrition yes	26% withdrew: 30% in E2 and 22% in placebo.	Poor- high followup, allocation concealment not described, high loss to followup	Supported by Novartis Pharma.	Fair
Notelovitz, 2002	Yes	High withdrawal rate: 44.8% withdrew overall; lost to followup: 9% E2 0.025 mg; 8% E2 0.05 mg; 12% E2 0.075 mg; 9% placebo.	Fair	Funded by Procter and Gamble Pharmaceuticals.	Fair
Civitelli, 2002	Attrition and adherence yes	At 12 months: 39% placebo vs 16% HRT dropped out. At 36 months, 45% placebo vs 28% HRT dropped out.	Fair	Supported by NIH; additional support from Wyeth-Ayerst Laboratories and Smith-Kline Beecham. First author owns stock in	Fair
Cauley, 2003 (WHI)	Yes	3.5% overall; 38% stopped medication; 'drop in' rate higher than expected	Fair	National Heart, Lung and Blood Institute #†	Fair

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Appendix F. Quality scores of reviewed bone density and fracture trials (continued)

Study Year	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Intention-to-treat analysis?	Maintenance of comparable groups?
Arrenrecht, 2002	Yes	Yes	Yes	Yes	Double blind	NR	Unclear
Cheng, 2002	Yes	Yes	Slight variation	Yes	Double blind	NR	Unclear
Cooper, 1999	Yes	Unclear	Yes	Yes	Double blind	Yes	Unclear
Hulley, 2002 (HERS II)	Yes	Unclear	Yes	Yes	Double blind	Yes	Yes
Lees, 2001	Yes	Unclear	Yes	Yes	Double blind	NR	Unclear

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Appendix F. Quality scores of reviewed bone density and fracture trials (continued)

Study Year	Reporting of attrition, contamination, etc?	Differential loss to followup or overall high loss to followup?	Quality Score	Funding source	External validity
Arrenrecht, 2002	Some	12% overall, slightly greater in Rx	Fair	NR	Fair
Cheng, 2002	Some	P: 25% Rx: 25% all groups, 13%	Fair	NR	Fair
Cooper, 1999	Yes	P: 17% Rx25: 13% Rx50: 13% Rx75: 19%	Fair	NR	Fair
Hulley, 2002 (HERS II)	Some	7% lost to followup	Fair	Wyeth-Ayerst*	Fair
Lees, 2001	Some	Over 50% lost to followup - did not complete study	Fair/ Poor	Heart Disease and Diabetes Research Trust∞	Fair

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Appendix F. Quality scores of reviewed bone density and fracture trials (continued)

Study Year	Random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Blinding: outcome assessors, care provider, patient?	Intention-to-treat analysis?	Maintenance of comparable groups?
Leung, 1999	Yes	Yes	Yes	Yes	Double blind	NR	Unclear
Lindsay, 2002	Yes	Unclear	Yes	Yes	Double blind	Yes	Unclear
Mosekilde, 2000	Yes	Unclear	Some variation	Yes	Not blinded	Yes	Unclear
Recker, 1999	Yes	Yes	Slight variation	Yes	Double blind	Yes	Unclear
Villareal, 2001	Yes	Yes	Yes	Yes	Double blind	Yes	Yes
WHI, 2002	Yes	Yes	Yes	Yes	Double blind	Yes	Yes

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Appendix F. Quality scores of reviewed bone density and fracture trials (continued)

Study Year	Reporting of attrition, contamination, etc?	Differential loss to followup or overall high loss to followup?	Quality Score	Funding source	External validity
Leung, 1999	Some	P: 12.4% Rx 1: 14% Rx 2: 17%	Fair	Queens Elizabeth Hospital Research Fund	Fair
Lindsay, 2002	Yes	P: 8% Rx: 16%	Good	Wyeth Research	Fair
Mosekilde, 2000	Yes	89% completed study	Fair/ Poor	Karen Elise Jensen Found./ Danish Med Res Council#	Fair
Recker, 1999	Yes	P: 16% Rx: 20%	Fair	National Institutes of Health	Fair
Villareal, 2001	Yes	P: 9% Rx: 24%	Fair	National Institutes of Health	Fair
WHI, 2002	Yes	3.5% overall; 38% stopped medication; 'drop in' rate higher than expected	Fair	National Heart, Lung and Blood Institute #†	Fair

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