

Drug Class Review
on
Estrogen
for Treatment of Menopausal Symptoms and Prevention of
Low Bone Density & Fractures

Final Report

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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.

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
 - a. Reducing symptoms of menopause: hot flashes/flushes, sleep disturbances/night sweats, mood changes (depression), urogenital atrophy, sexual function, and quality-of-life measures?
 - b. Preventing low bone density and fractures?

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

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, bisphosphonates).

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). Subcommittee members were invited to provide additional citations. 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).

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.

1a. 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 Table 2 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
<i>Head-to-head comparisons</i>					
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	1	1
Vaginal estrogen creams	NA	NA	NA	3	NA
<i>Placebo comparisons</i>					
Estradiol (E2)					
Oral	10	0	1	0	2
Transdermal	11	3	1	4	4
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 Table 2 include all measures of hot flashes.

Head-to-head comparisons. Five trials compared estrogen preparations head-to-head including a trial of CEE compared to oral E2,¹² oral E2 compared to E2V,¹³ and three trials comparing CEE to transdermal E2,^{14, 15} (Table 2). 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,^{14, 15} 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).

Dose-response trends were demonstrated in trials that tested multiple doses with higher doses corresponding to bigger treatment effects.^{12, 14} Too few dose comparisons were conducted between estrogens to determine if differences exist.

Placebo comparisons. Thirty-one randomized controlled trials comparing an eligible estrogen preparation with placebo met criteria for this review (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.
- 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 Table 2.
- 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.

Nine of ten trials of oral E2 demonstrated statistically significant improvements in hot flash frequency and/or severity compared to placebo.¹⁶⁻²⁴ The one trial that reported no difference between groups was conducted in Chinese women in Hong Kong after oophorectomy.²⁵ 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.¹⁶ Six trials included concomitant progestin/progesterone use (continuous and cyclic norethidrone acetate [NETA], cyclic norgestrel).^{16-19, 21, 24}

Three trials of E2V reported statistically significant improvements in hot flash frequency and/or severity compared to placebo.²⁶⁻²⁸ 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.²⁹⁻³⁴ 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.^{33, 34} 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.³⁴

One trial of estropipate indicated statistically significant improvements in hot flash frequency compared to placebo.³⁵ 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.^{14, 36-44} Two trials included concomitant progestin/progesterone (cyclic NETA, continuous transdermal levonorgestrel).^{39, 42}

Meta-analysis. Of ten trials of oral E2 compared to placebo, five met criteria for the meta-analysis.^{16, 18-20, 24} 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)].^{16, 18, 19, 24} Trials were excluded from analysis because they did not provide data on frequency of hot flashes^{17, 21, 25} or did not provide standard deviations.^{22, 23}

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.²⁶⁻²⁸

Of six trials of CEE compared to placebo, one met criteria for the meta-analysis.³² 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,^{31, 33} provided data in a graph form,²⁹ or did not provide standard deviations.^{29, 30, 34}

One trial of estropipate compared to placebo was identified from the search and met inclusion criteria.³⁵ 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.^{14, 36, 38, 40-42} 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.⁴² Trials were excluded because data was provided in a graph form,^{39, 43} and the trials did not provide standard deviations.^{23, 43}

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.⁴⁵ Another trial of transdermal E2 indicated significant improvement in sleep quality, sleep onset, and decreased nocturnal restlessness and awakenings compared to placebo.⁴⁶ 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.^{36, 38}

Mood Changes

Eight trials of estrogen reporting mood outcomes met eligibility criteria including one trial comparing E2 and E2V,¹³ one of oral E2,¹⁷ one of transdermal E2⁴⁷ compared to placebo, and five of CEE compared to placebo.^{33, 48-50}

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.¹⁷ 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).⁴⁷ 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.⁴⁸ Another trial of psychologically well-adjusted women reported significant improvement on the Beck Depression Inventory with CEE ($p<0.05$).⁴⁹ 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.⁵⁰ In the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI), women on CEE did not differ from those on placebo for anxiety and affective symptoms.³³ 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.³⁰

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.⁵¹ 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 cream⁵² and a trial of the E2 tablet and CEE cream.⁵³

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.⁵⁴ 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.⁴⁴ Another trial of transdermal E2 indicated improvement in vaginal dryness, but not dyspareunia, frequent urination, dysuria, stress incontinence, and nocturia, compared to placebo.⁵⁵ Another trial comparing transdermal E2 and placebo indicated no differences between groups for symptoms of vaginal discomfort, loss of libido, and incontinence.⁴¹

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.³⁰ 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.⁵⁶

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.⁵⁷ Two trials of oral E2 reported improvements on Green and Beck scores¹⁹ and on the General Health Questionnaire.¹⁷ 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.^{44, 55, 58} 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.⁵⁹ 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.⁵⁰ One trial of esterified estrogens reported improvement in the Quality of Life Menopause Scale compared to placebo.⁶⁰

1b. 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 3, trials are described in Table 4, and quality ratings in Appendix F. Characteristics of the trials include:

- Three trials with bone density outcomes compared estrogens head-to-head.
- 51 trials with bone density outcomes compared an estrogen preparation to placebo.
- 11 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.

Table 3. Number of studies of estrogens with bone density or fracture outcomes

	Total	Bone Density	Fractures
<i>Head-to-head comparisons</i>			
CEE and transdermal E2	2	2	0
Transdermal E2 and estradiol valerate (E2V)	1	1	0
<i>Placebo comparisons</i>			
Estradiol (E2)	10	10	1
Oral	11	11	2
Transdermal			
Estradiol valerate (E2V)	5	5	1
Conjugated equine estrogen (CEE)	24	21	7
Conjugated synthetic estrogen	0	0	0
Esterified estrogen (EE)	1	1	0
Estropipate	0	0	0

Bone Density

Head-to-head comparisons. Three head-to-head trials compared different estrogen preparations including two trials of CEE compared to transdermal E2,^{61, 62} and one trial of transdermal E2 compared to estradiol valerate.⁶³

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).^{61, 62} 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%, $p < 0.01$).⁶¹ 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.⁶²

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.⁶³ Both groups significantly gained bone density compared to placebo, and no significant differences between groups were found at any site.

Placebo comparisons. Forty-eight 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 Table 4. 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 1,600; trials ranged from 1 to 5 years in duration.
- 26 trials of estradiol in three forms were included: 10 trials of oral E2, 11 trials of transdermal E2, and 5 trials of E2V.
- 21 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.⁶⁴⁻⁷¹ 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.⁷² Another trial reported a trend in E2 groups towards increased bone density, however statistical significance was not reached for between group comparisons.⁷³

All 11 trials of transdermal E2 reported statistically significant improvements in bone density compared to placebo.⁷⁴⁻⁸⁴ Only two trials did not use concomitant progestin/progesterone.^{76, 81}

Five trials of E2V with concomitant progestin/progesterone reported bone density outcomes.^{63, 85-88} Four of the five trials noted improvement in treatment groups compared to placebo.^{63, 85-87} and one did not.⁸⁸

Twenty-one trials evaluated the effect of CEE on bone density outcomes.⁸⁹⁻¹⁰⁹ All trials reported significant within group changes in bone density at multiple sites for various doses with higher doses showing greater changes. Some trials reported that doses lower than 0.625 mg were less effective in maintaining or increasing bone density.^{90, 95, 99-101}

One study of esterified estrogen and bone density met criteria for this review.¹¹⁰ 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.¹¹⁰

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.¹¹¹⁻¹²⁵ 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 (Table 4). Seven were included^{75, 82, 87, 96, 97, 109, 126} in a recent Cochrane meta-analysis,⁵ while three were not because they were recently published.^{3, 69, 127}

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).⁶⁹ Both studies of transdermal E2 indicated no significant improvement in vertebral^{75, 82} and non-vertebral fractures.⁷⁵ 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.⁸⁷

Seven studies examined CEE preparations.^{3, 96, 97, 104, 109, 126, 127} 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.

Comparison with Cochrane meta-analysis. Seven studies^{75, 82, 87, 96, 97, 109, 126} 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.⁶⁹ 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.^{75, 87, 97, 109, 126}
 - One study indicated a statistically significant relative risk reduction for nonvertebral fractures with estrogen use.⁸⁷
 - Three of the other studies had a risk reduction that was not statistically significant,^{75, 97, 126} and the other had a RR of 1.0.¹⁰⁹
- When all studies were pooled, there was a nonsignificant reduction in nonvertebral fractures (RR=0.87; 95% CI: 0.71, 1.08).

2a. 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 Table 5 for trials of hot flashes and Table 6 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 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, 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).^{127, 128} In HERS, risks remained elevated for thromboembolic 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.¹²⁹

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).¹²⁷ 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).¹³⁰

2b. 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, 127, 128}

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).¹²⁸

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).¹³¹ 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.^{127, 129} 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).¹²⁷ 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).¹³¹ 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.

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).¹²⁷ The Nurse's Health Study also reported an increased risk with long-term use (RR=2.5; 95% CI: 2.0, 2.9).¹³⁰ 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, 127} Other studies of unopposed estrogen have indicated increased endometrial cancer for a woman

with a uterus.¹³² Observational studies of estrogen imply an increased risk for ovarian cancer^{133,}
¹³⁴ while others do not.¹³⁵

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

Elderly

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 but will be forthcoming for the WHI. 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 nonwhite participants of the WHI could provide comparative data when this analysis is published.

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 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 7.

Table 7. 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: results will be more widely generalizable when the WHI data are stratified by age, race, and risk groups.
5. Are there subgroups of patients for which one medication or preparation is more effective or associated with fewer adverse effects?	Not Available		

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. Comparison of results for these

women with women of different age groups, racial or ethnic groups, co-morbidities and risk factors are not possible.

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