Drug Class Review
on
Hormone Therapy for Postmenopausal Women or Women in the Menopausal Transition Stage

Final Report
Update #3

October 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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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, and cholecystitis). Estrogen was approved as a hormone supplement in the 1940's 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] More recent US national data indicate that hormone use in postmenopausal women has declined following publicity about the potential harms of postmenopausal estrogen use.[2]

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.[3] This difference reflects the hormonal compositions of the different drugs as well as the consequences of hepatic first-pass metabolism effect with oral use. It is not known if these differences result in important clinical effects.

Recent research and current practices dictate that systemically administered estrogen is 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, or taken separately, concurrently, or sequentially over a monthly cycle.

The current FDA approved indications for postmenopausal estrogen include treatment of menopausal symptoms and prevention of low bone density and fractures. When prescribing solely for the prevention of postmenopausal osteoporosis, FDA recommends that therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.

The FDA added health warnings to its label including new data on health harms from the Women's Health Initiative (WHI) trial published in July 2002[4] and the WHI Memory Study (WHIMS) published in 2003.[5] 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.[6] 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 was to compare the efficacy and adverse effects of different estrogens. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest. These questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review (DERP) Project. The participating organizations of DERP were responsible for ensuring

that the scope of the review reflected the populations, drugs, and outcome measures of interest to clinicians and patients. The participating organizations approved the following key questions to guide this updated review:

1. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for reducing symptoms of menopause: hot flashes/flushes, sleep disturbances/night sweats, mood changes (depression), urogenital atrophy, sexual function, and quality-of-life measures?

2. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for preventing low bone density and fractures?

3. What is the comparative safety of different hormone therapy preparations for short-term use (<5 years)?

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

5. Are there subgroups of patients based on demographics, other medications, co-morbidities, length of use, or initiation of use relative to onset of menopause, for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

- Study participants include women recruited from any health care setting or a population-based sample experiencing menopause. When possible, data are considered separately for women with natural versus surgical menopause (oophorectomy) and for postmenopausal women versus women in the menopausal transition stage.
- Women in the menopausal transition stage are those transitioning through natural menopause who have 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.

Interventions

Interventions include oral and transdermal estrogen monotherapy or estrogen plus progestin/progesterone preparations listed below for all symptoms, bone density and fracture outcomes, and vaginal tablet or cream for urogenital atrophy, administered as sequential or continuous regimens. Included products are shown in Table 1.

Table 1. Included estrogen products

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Oral estrogens			
17b Estradiol	Estradiol (generic) Estrace	0.5, 1, 2 mg 0.5, 1, 2 mg	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar or vaginal atrophy, topical vaginal products should be considered. 3. Treatment of Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 5. Treatment of advanced androgen dependant carcinoma of the prostrate (for palliation only). 6. Prevention of osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
Estradiol acetate	Femtrace	0.45, 0.9, 1.8 mg	Treatment of moderate to severe vasomotor symptoms associated with the menopause.
Esterified estrogens	Menest Neo-Estrone	0.3, 0.625, 1.25, 2.5 mg 0.3, 0.625, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Atrophic vaginitis. 3. Kraurosis Vulvae. 4. Female hypogonadism. 5. Female castration. 6. Primary ovarian failure. 7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 8. Prostatic carcinoma-palliative therapy of advanced disease.
Estropipate	Estropipate (generic) Ogen Ortho-est	0.75, 1.5, 3 mg 0.75, 1.5, 3 mg 0.75, 1.5 mg	1. Signs and symptoms of naturally occurring or surgically induced estrogen deficiency states associated with menopausal and post-menopausal symptoms, e.g., hot flashes, sleep disturbances and urogenital atrophy. 2. Osteoporosis induced by estrogen deficiency states in conjunction with other pertinent measures.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Conjugated equine estrogens (CEE)	Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. 5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only). 6. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.
Synthetic conjugated estrogens	Cenestin Enjuvia C.E.S Congest PMS-Conjugated	0.3, 0.45, 0.625, 0.9, 1.25 mg 0.625, 1.25 mg 0.3, 0.625, 0.9, 1.25 0.3, 0.625, 0.9, 1.25, 2.5 mg 0.3, 0.625, 0.9, 1.25 mg	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause: 0.45mg, 0.625mg, 0.9mg, 1.25mg 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 0.3 mg
Estrogen-progestin combinations			
CEE, medroxyprogesterone	Prempro Premplus Premphase	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5 mg 2.5/0.625 mg, 5/0.625 mg 0.625 mg CEE, 5.0 mg progesterone	1. Treatment of moderate to severe symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
17b-estradiol, norgestimate	Ortho-Prefest	1 mg estradiol/0.9 mg norgestimate	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
17-b estradiol, norethindrone acetate	Activella	1 mg estradiol/0.5 mg norethindrone acetate	1.0 mg/0.5mg and 0.5mg/0.1mg 1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. 1.0mg/0.5mg 3. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
17b-estradiol, drospirenone	Angeliq	1.0 mg estradiol, 0.5 mg drospirenone	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Ethinyl estradiol, norethindrone acetate	FemHRT	5 mcg ethinyl estradiol/1 mg norethindrone acetate	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis. Non-estrogen medications should be carefully considered.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
Transdermal estrogens			
17b-estradiol matrix patch	Alora Climara Esclim Vivelle Vivelle-Dot Menostar Estradot Oesclim 17-b estradiol (generic)	0.025, 0.05, 0.075, 0.1 mg/d 0.025, 0.05, 0.06, 0.075, 0.1 mg/d 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d 0.05, 0.1 mg/d 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d 14 mcg/d 25, 37.5, 50, 75, 100 µg/d 25, 50 µg/day 25, 50, 100 µg/d 0.1, 0.05 mg/d	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.
17b-estradiol reservoir patch	Estraderm	0.025, 0.0375, 0.05, 0.075, 0.1 mg/d	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. 4. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risks of osteoporosis and non-estrogen medications should be carefully considered.
17b-estradiol, norethindrone acetate patch	Combi-Patch Estalis Estalis Sequi Estracomb	0.05 mg estradiol/0.14 mg norethindrone, 0.05/0.25 mg 140 µg norethindrone acetate/50 µg estradiol-17β per day, 250/50 µg/day 0.05 mg estrogen twice/week (Vivelle 50 patch) for 2 weeks, then 9 or 16 cm^2 Estalis patch twice/week for 2 weeks 0.05 mg estrogen twice/week for 2 weeks, then 0.05 mg estrogen +	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. 3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

Included Estrogen Products			
Drug	**Trade names**	**Available strengths**	**FDA-approved indications**
		0.25 mg progesterone for 2 weeks	
17b-estradiol, levonorgestrel patch	Climara Pro	0.045 mg estradiol/0.015 mg levonorgestrel	Treatment of moderate to severe vasomotor symptoms associated with menopause
17b-estradiol transdermal gel	EstroGel Elestrin Divigel	1.25 g (0.75 mg estradiol) 0.87 g (0.52 mg estradiol) 0.25, 0.5, 1.0 g (0.25, 0.5, 1.0 mg estradiol)	1. Treatment of moderate to severe vasomotor symptoms associated with menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Estradiol hemihydrate topical emulsion	Estrasorb	1.74 g (0.5 mg estradiol)	Estrasorb is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause**.**
Topical products			
17b-estradiol vaginal cream	Estrace vaginal cream	0.1 mg estrogen/g	Treatment of vulvar and vaginal atrophy.
CEE cream	Premarin vaginal cream	0.625 mg estrogen/g	Treatment of atrophic vaginitis and kraurosis vulvae.
Esterified estrogen cream	Neo-Estrone vaginal cream	1 mg estrogen/g	1. Treatment of menopausal and post menopausal symptoms. 2. Should be prescribed with an appropriate dosage of a progestin for women with intact uteri to prevent endometrial hyperplasia/carcinoma.
17-b estradiol intravaginal ring	Femring Estring	0.05 mg estradiol, 0.1 mg/d 2 mg (7.5 µg estradiol/day)	1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. 2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
Estradiol hemihydrate vaginal tablet	Vagifem	25 µg	Treatment of atrophic vaginitis.

Effectiveness Outcomes

- Hot flashes or flushes defined as any otherwise unexplained sensation of flushing/sweating experienced by the woman being studied. Studies will be 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 the end of the study.
- 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.

Safety Outcomes

- 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 (including relationship to estradiol levels)
- Cardiovascular events
- Rash and pruritus
- Cholecystitis
- Effects on the liver

For long-term use

- Cardiovascular events
- Breast cancer
- Thrombosis
- Cholecystitis
- Ovarian cancer
- Endometrial cancer

Study Designs

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

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Registry (2007, Issue 1), MEDLINE (1966 through March Week 1, 2007), Embase (1980 through April, 2004), PreMEDLINE (through March Week 1, 2007), reference lists of review articles, and dossiers submitted by pharmaceutical companies (see Appendix A for complete search strategies). All citations were imported into an electronic database (EndNote 9.0).

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). Systematic reviews were included if they conducted literature searches in 2004 or later.

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,[7, 8] we assessed the internal validity (quality) based on the pre-defined criteria listed in Appendix C. These criteria are based on those developed by the U.S. Preventive Services Task Force and the Center for Reviews and Dissemination (UK).[9-11]

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 appeared 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.[8]

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.

Overall quality ratings for individual studies 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 precision of the relevant studies and their estimates of effect.

Data Synthesis

Treatment effects were defined as the difference in outcomes between the estrogen and placebo groups, or between estrogen groups for head-to-head comparisons. For crossover trials, only results from the end of the first phase were used because of the potential for carry-over effects.

We conducted a meta-analysis of trials reporting hot flash or flush outcomes in order to provide a more precise and more broadly applicable 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.[12] Funnel plots were constructed to examine the possible existence of small study bias, although this approach is subject to significant limitations.[13]

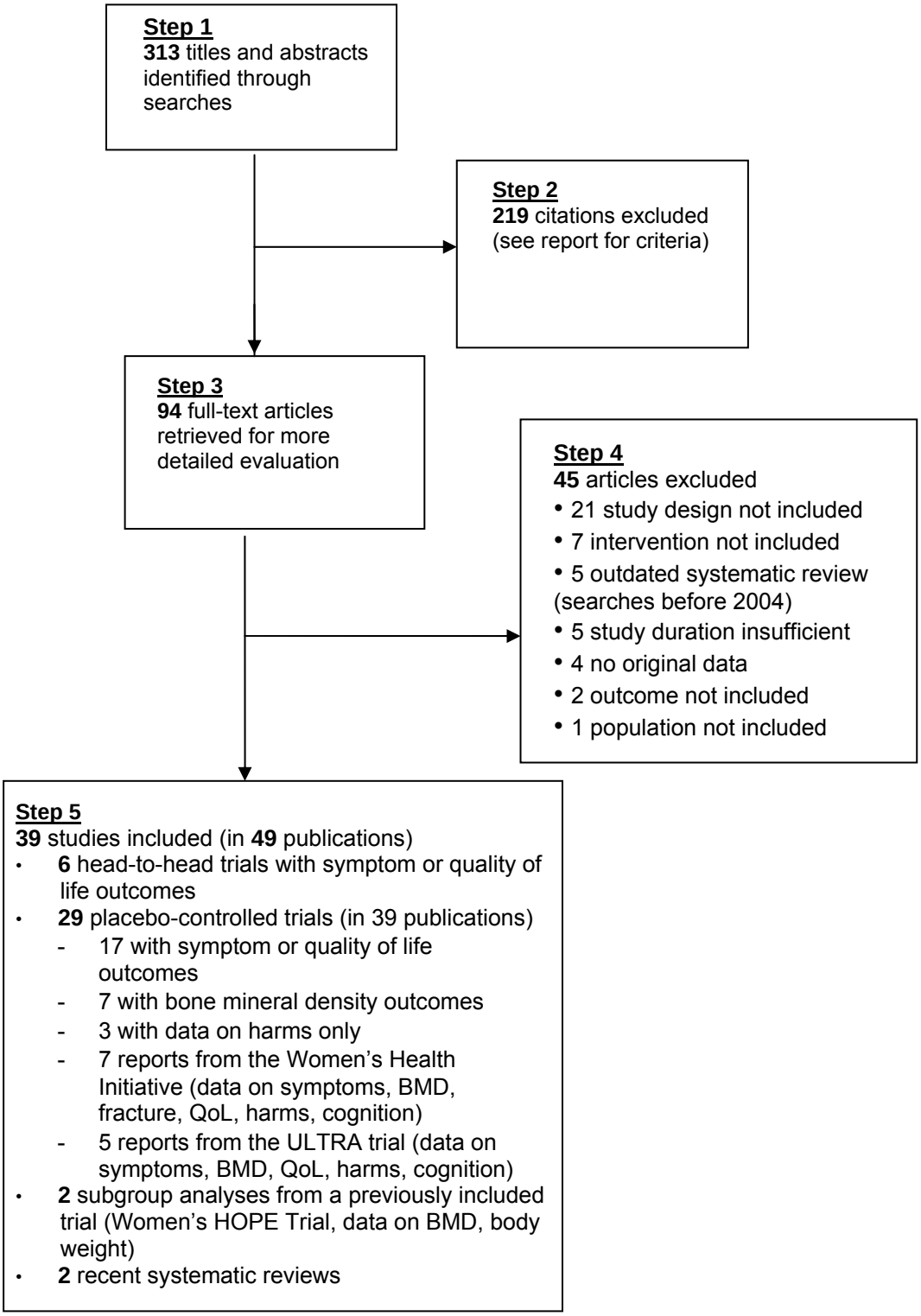
RESULTS

Overview

Prior to Update #3, electronic searches identified 1,426 citations: 94 from the Cochrane Library, 735 from MEDLINE, 479 from Embase, 28 from hand searching of reference lists, 58 from pharmaceutical company submissions, and 32 from PreMEDLINE.

Results of literature searches for Update #3 are shown in Figure 1. Forty-four new studies were included: 6 head-to-head trials with hot flash or other symptom outcomes, 16 placebo-controlled trials with hot flash or other symptom outcomes, 9 placebo controlled trials with bone mineral density outcomes, 4 placebo-controlled trials with data about harms, 7 reports from the Women's Health Initiative, and 2 recent systematic reviews. Dossiers were submitted by one pharmaceutical company (Wyeth, for Prempro, Premarin, and Premarin Vaginal Cream), but these dossiers did not contain any new studies not previously identified.

Figure 1. Results of literature search for Update #3



Key Question 1. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage for reducing symptoms?

Numbers of included studies are summarized in Table 2. Additional data on these trials are provided in Evidence Tables 1 (head-to-head trials) and 2 (placebo-controlled trials), and quality scores are provided in Appendix E. Quality ratings of studies added for Update #3 are shown in Appendix G.

Table 2. 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 synthetic estrogen (CEE) vs. oral estradiol (E2)	1	0	1	0	0
Conjugated equine estrogen (CEE) vs. oral estradiol (E2)	2	0	0	1	0
Oral estradiol (E2) vs. estradiol valerate (E2V)	2	1	1	0	1
Conjugated equine estrogen (CEE) vs. transdermal estradiol (E2)	4	0	0	3	2
Vaginal estrogen creams	0	0	0	3	NA
E2 intravaginal ring vs. oral E2	1	0	0	0	1
E2 intravaginal ring vs. E2 vaginal tablet	0	0	0	1	1
Placebo comparisons					
Estradiol (E2) Oral Transdermal Intravaginal ring	 16 13 1	 0 5 0	 2 4 0	 1 5 0	 8 8 0
Estradiol valerate (E2V)	4	1	1	0	1
Ethinyl estradiol	2	0	0	0	0
Conjugated equine estrogen (CEE)	8	3	7	3	2
Conjugated synthetic estrogens	1	0	0	0	0
Esterified estrogen (EE)	0	0	0	0	1
Estropipate	1	0	0	0	0

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 reported in many ways in the included studies. 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,[14] was used in some studies to classify the severity of menopausal symptoms. This index 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 are the most important symptom in the index. The use of this score is controversial, however, as it has not been validated.

Head-to-head comparisons reporting hot flash/flush outcomes

Twelve trials compared estrogen preparations head-to-head (Table 3, Evidence Table 1). Five trials compared different oral preparations, including one trial of CEE compared to oral E2,[15] one trial of CEE compared to E2 acetate and micronized E2,[16] two trials of oral E2 compared to E2V (one rated poor quality),[17, 18] and one trial of conjugated synthetic estrogen compared to E2.[19] In three trials, the type of progestin was different in different estrogen treatment groups;[17-19] two trials used unopposed oral estrogen preparations.[15, 19] Symptoms improved from baseline for all treatment groups in these trials, but none found one oral estrogen preparation to be superior to another.

Five trials compared oral CEE to transdermal E2 (gel or patch).[3, 20-23] One of these was rated poor quality[22] and the others were fair. All trials reported improved number and/or severity of hot flashes for all of the estrogen treatment groups compared to placebo or baseline. The poor quality trial found more patients had improvement in vasomotor symptoms at one year with E2 transdermal gel or patch than with oral CEE at one year.[22] However, because of flaws in the study's design (high withdrawal rate, no intention-to-treat analysis, patients not masked), these results are not reliable. There were no statistically significant differences in treatment effects in any of the head-to-head estrogen comparisons in any of the other trials. Two trials were combined in a meta-analysis,[20, 21] and one excluded because data was provided in graph form.[3] 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 mg 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.[24] A fair quality trial of postmenopausal women with symptoms of vaginal atrophy compared an E2 vaginal ring with an E2 vaginal tablet.[25] There were no significant differences between treatments on self-reported vaginal symptoms at week 4, or on investigator-assessed vaginal signs at week 48. Urogenital quality of life was improved for both groups at week 48, but there were no differences between groups. Hot flashes were not assessed in this study.

Dose-response trends were demonstrated in three trials, with higher doses corresponding to bigger treatment effects.[15, 20, 24] In the intravaginal E2 ring trial, a dose response pattern was seen at 12 weeks, but not at 24 weeks.[24] Too few dose comparisons were conducted between estrogens to determine if differences exist.

Table 3. Head-to-head trials with hot flash/flush or other symptom outcomes

Study/Year (Quality)	Study design; Sample size; Duration of followup	Population characteristics	Interventions	Main outcomes/results
Oral estrogens				
Archer 1992 (Not assessed)	Double-blind; N=128 in 5 groups; 12 weeks	Post and perimenopausal women with 5 or more vasomotor symptoms/day; Mean age 50.6 (40-60); Uterine status NR	CEE: 0.625, 1.25 mg/day E2: 1, 2 mg/day	Mean % change in daily frequency of vasomotor events: All significantly different from placebo, but no differences between groups.
Utian 2005 (Fair)	Double-blind; N=249; 12 weeks	Postmenopausal women with moderate or severe vasomotor symptoms (MSVS); Mean age 52.8 yrs (SD 6.7); 50.4% hysterectomy	E2 acetate: 0.9 mg Micronized E2: 1 mg CEE: 0.625 mg	NSD between treatment groups in mean percent reduction in number of weekly MSVS or severity of MSVS at week 4 or 12. Estradiol group had improvement in dyspareunia and worsening of urinary urgency scores at 12 weeks; no differences between treatments on other urogenital symptom scores. NSD between groups on investigator-assessed vaginal atrophy.
Oral estrogen/progestin combinations				
Odmark 2004 (Fair)	Double-blind; N=249; 1 year	Postmenopausal, with symptoms or ongoing HT; Mean age 55.9 yrs (SE 0.28); HRT naïve 89/246 (36%); 0/249 hysterectomy	CE: 0.625 mg/5 mg medroxyprogesterone acetate (MPA) qd E2: 2 mg/1 mg norethisterone acetate (NETA) qd	Improvement in symptom "sweating" during first 6 months in both treatment groups (p<0.001); subsequent deterioration comparing 6th and 13th cycle in estradiol group (p<0.01); no deterioration in CE group. Breast tenderness worse in estradiol group (p<0.001). Otherwise, no significant differences between treatment groups on well-being variables.
Pornel 2005 (Poor)	Double-blind; N=1219; 1 year (+ 1 year extension)	Postmenopausal, with average 3 hot flashes/day during a period of seven days; 52.6 yrs (SD 4.5); 0/1219 hysterectomy	E2: 1 mg (days 1 -14) followed by 1 mg + 0.125 mg or 0.25 mg trimegestone (days 15-28) E2V: 1 mg (days 1-16) followed by 1 mg + 1 mg norethisterone (days 17-28)	Hot flushes: Mean daily number decreased from cycle 1 in both treatment groups; NSD between groups at cycle 13. Night sweats: Significant improvement from baseline in both groups Kupperman index: Significant improvement from baseline in both groups; NSD between groups; mean total score higher at most time points for E2V than for estradiol, indicating slightly better improvement with estradiol. Fewer sleep disorders in estradiol group than E2V at cycles 3, 4, and 5 only (p=0.02). No differences between groups on other psycho functional disturbances or quality-of-life responses.

Study/Year (Quality)	Study design; Sample size; Duration of followup	Population characteristics	Interventions	Main outcomes/results
Saure 2000 (Fair)	Double-blind crossover; N=376 in 2 groups; 12 weeks	Perimenopausal women with symptoms; Mean age 49; Denmark 0/376 hysterectomy	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	Hot flashes, night sweats: decreased in both Rx groups; no difference between groups.
Oral CEE compared with transdermal estradiol				
Good 1999 (Fair)	Double-blind; N=321 in 4 groups; 3 months	Postmenopausal women with 60 or more hot flashes per week; Mean age 50-51; 147/321 hysterectomy	E2: 0.05, 0.1 mg/day CEE 0.625, 1.25 mg/day	Reduction of hot flashes by 90% for both Rx; no significant differences between Rx at comparable doses; data provided in graphs.
Gordon 2005 (Fair)	Double-blind; N=604 in 6 groups; 11 weeks	Postmenopausal women with symptoms; Mean age approx. 50 (25-74); 382/604 hysterectomy	E2: 0.05, 0.1 mg/day (Climara) CEE: 0.625 mg/day oral	Number and severity of hot flashes: all groups decreased, Rx groups had Significant decline compared to placebo (67-72% decrease, p<0.05); no significant difference between Rx groups but some dose-response trends for 2 doses of E2.
Akhila 2006 (Poor)	Blinding NR; N=116; 1 year	Postmenopausal, with symptoms; Age and uterine status NR	CEE: 0.625 mg/day E2 percutaneous gel E2 Transdermal patch All three groups received MPA 2.5 mg orally every day in presence of uterus or with history of endometriosis	Vasomotor symptoms: no significant differences between groups on % of patients with complete symptom improvement at one month % of patients with complete symptom improvement; one year followup. Vasomotor symptoms (N=75) 62% oral CEE; 95% E2 gel; 100% E2 patch oral CEE vs E2 gel: p=0.023 E2 gel vs E2 patch: p>0.05 oral CEE vs E2 patch: p=0.0025
Serrano 2006 (Fair)	Open label; N=226; 1 year	Postmenopausal women willing to initiate HRT for menopausal symptom relief; 52.5 yrs; 0/226 hysterectomy	CEE 0.625 mg/day and placebo CEE 0.625 mg/day and fenretinide 100 mg/bid Transdermal E2 50 µg/day released by a weekly patch and placebo Transdermal E2 50 µg/day released by a weekly patch and fenretinide 100 mg/bid	MENQOL mean score (SD) at 12 months: Reductions from baseline statistically significant in all domains, but in multiple regression the only significant variable was time; no other effect achieved statistical significance, indicating that the type of hormonal treatment or administration of fenretinide did not affect improvement. P-value for CEE vs E2: 0.287.
Studd 1995 (Fair)	RCT; N=214 in 2 groups; 12 weeks	Postmenopausal women with symptoms (at least 21 hot flashes per week); Mean age approx. 52 (40-65); 1% hysterectomy	E2: 0.05 mg/day (Menorest); CEE: 0.625 mg/day Dydrogesterone: 10 mg/day days 16-28	Mean number of hot flashes per day: Significant decrease from baseline in both Rx groups (E2 7.1 to 0.9 per day, CEE 6.7 to 0.5 per day), no significant differences between groups.

Study/Year (Quality)	Study design; Sample size; Duration of followup	Population characteristics	Interventions	Main outcomes/results
Vaginal E2 compared with oral E2				
Al-Azzawi, 2003 Buckler et al, 2003 (Good)	Double-blind Multi-center; N=159 in 2 groups; 24 weeks	Postmenopausal women younger than age 65 with 20 or more hot flushes/night sweats per week; Mean age 51 (31-63); 71/159 hysterectomy	Vaginal E2: vaginal ring releasing 50 mg/day Oral E2: 1 mg/day Norethisterone 1 mg/day for last 12 days of each 28-day cycle	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 From Buckler 2003: Significant improvement from baseline in total Greene Climacteric Scale scores in both treatment groups at 12 and 24 weeks, no between-group differences.
E2 vaginal ring compared with E2 vaginal tablet				
Weisberg 2005 (Fair)	Open label; N=185; 1 year	Postmenopausal, with significant symptoms or objective signs of urogenital atrophy; Mean age 57.9 years; 0/185 hysterectomy	Estring vaginal ring containing 2 mg micronized E2 Vagifem Muco adhesive tablet containing 25 µg E2	Investigator rated pelvic floor strength not changed by either treatment. No significant differences between treatments on self-reported vaginal symptoms at week 4 No significant differences between treatments on vaginal signs on inspection at week 48 Improvement in urogenital quality of life was statistically significant at 48 weeks for both groups, with no difference between treatments

Placebo-controlled trials reporting hot flash/flush outcomes

Thirty-six RCTs comparing an eligible estrogen preparation with placebo met criteria for this review through Update #2 (Evidence Table 2). Among 16 new trials added for Update #3, 13 (in 15 publications) were rated fair quality,[26-39] 1 was fair to poor,[40] and 2 (in 3 publications) were rated poor.[41-43]

Summary

- Trials were conducted predominantly in the U.S. or Western 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 that "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 60's; most trials reported mean ages in the early 50's.
- 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 2.
- All estrogen preparations generally improved vasomotor symptoms among symptomatic women compared to placebo.
- Women in placebo groups usually also had an improvement in symptoms, as 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.
- Data on the effects of estrogen preparations on sleep were sparse and inconsistent.
- Studies reporting health-related quality of life reported conflicting results.
- In the WHI, CEE-only and CEE/MPA study, vasomotor symptoms improved; the small improvement in sleep was not likely clinically significant and health-related quality of life was not different from placebo at 3-year follow-up.

Eleven of twelve trials of oral E2 demonstrated statistically significant improvements in hot flash frequency and/or severity compared to placebo.[44-54] The one trial that reported no difference between groups was conducted in Chinese women in Hong Kong after oophorectomy.[55] 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.[44] Eight trials included concomitant progestin/progesterone use (continuous and cyclic norethindrone acetate,[56] cyclic nomegestrol).[44-47, 49, 52-54]

Three trials of E2V reported statistically significant improvements in hot flash frequency and/or severity compared to placebo.[57-59] 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.[60-65] 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.[64, 65] 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.[65]

A 12-week trial of synthetic conjugated estrogens B compared with placebo in 281 US women included three doses of conjugated estrogen (0.3 mg, 0.625 mg, 1.25 mg/day). Significant reduction in frequency of hot flashes occurred at all dosage strengths compared with

placebo (-72%, -85%, -87%, -47% for 0.3 mg, 0.625 mg, 1.25 mg, and placebo, respectively) but a dose-response relationship was not reported.[66] This study was rated fair quality. Adequate randomization and allocation concealment methods were used, intention-to-treat results are not reported, but only 5 patients were excluded from the analysis. A relatively high number of women discontinued treatment (19% for 0.3 mg, 15% for 0.625 mg, 17% for 1.25 mg, and 24% for placebo), but discontinuation rates were not significantly different between groups. Percent reductions differed from placebo ($P<0.05$) at 4, 8, and 12 weeks for all dosage strengths. Dose-response relationship was not reported.

One trial of estropipate indicated statistically significant improvements in hot flash frequency compared to placebo.[67] 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.[20, 68-76] Two trials included concomitant progestin/progesterone (cyclic NETA, continuous transdermal levonorgestrel).[71, 74]

There is one fair quality placebo-controlled trial of a transdermal vaginal ring releasing E2 for treatment of vasomotor symptoms.[77] 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).

For Update #3, we identified eight new fair-quality studies (in 11 publications) which examined symptoms (Table 4).[27, 28, 30, 33-39, 78] An additional two studies (in three publications) were rated poor quality.[41-43] All of the new studies focused on postmenopausal women except one which examined a mix of postmenopausal women and women in the menopausal transition(Newton 2006). This latter study did not examine these two population subgroups separately. The number of flushes and/or the severity of symptoms decreased in all fair-quality studies of oral estrogen preparations: estradiol acetate,[37] conjugated equine estrogen,[34, 35] estradiol with norethisterone,[28] oral estradiol with drospirenone,[36] and ethinyl estradiol with norethindrone.[38] Transdermal estradiol 50mcg/day with norethindrone acetate decreased hot flashes compared to placebo,[33] as did transdermal estradiol with oral tibolone (not available in the US),[27] whereas the UltraLow Transdermal estRogen Assessment trial (ULTRA) (n=417) did not demonstrate an improvement in postmenopausal symptoms among older, asymptomatic women compared with placebo at 2-year follow-up.[78]

Table 4. Placebo-controlled trials reporting symptoms or quality of life outcomes (new for Update #3)

Study/Year (Quality)	Study Design; Sample size; Duration of followup	Population Characteristics; Mean age; Uterine status	Interventions	Main outcomes/results	Conclusions
Oral estradiol					
Almeida, 2006 (Fair)	Double-blind; N=115; 20 wks	Postmenopausal; 73.7 yrs; Previous use of HRT 37.6 %, 100% hysterectomy	0.5 mg estradiol during the initial 2 wks, 1 mg during wks 3 and 4, 2 mg from wks 5 to 16, and again 1 and 0.5 mg during the remaining 4 wks (2 wks each, respectively)	Mean change from baseline to end of study, estradiol vs. placebo Beck Depression Inventory score: -1.5 vs. -1.3, NS Beck Anxiety Inventory: -0.8 vs. 0.4, NS SF-36 Score: -0.7 vs. -2.7, NS CAMCOG: 3.2 vs. 2.6, NS	NSD between groups on mood, cognition, or quality of life outcomes
Speroff, 2006 (Fair)	Double-blind Multicenter Study 1: N=289 Study 2: N=221; 12 wks	Postmenopausal; Study 1: 53.4 yrs; 124/289 hysterectomy Study 2: 52.2 yrs; 130/221 hysterectomy	Study 1: oral estradiol acetate 0.9 mg, oral estradiol acetate 1.8 mg, or placebo Study 2: oral estradiol acetate 0.45 mg or placebo	Study 1: ↓mean vasomotor symptom severity score (VSSS) from baseline to week 12, 1.8mg vs. 0.9 mg vs. placebo p<0.001 vs. p<0.001 vs. placebo Relative ↓number of vasomotor symptoms: 77.8% in EA 0.9 mg, 91% in 1.8 mg EA and 45.6% with placebo; o<0.001 for treatment groups vs. placebo Vaginal atrophy: reduction in investigator-assessed vaginal atrophy, dryness, friability for both EA groups vs. placebo (p<0.05) Study 2: mean change in VSSS baseline to week 12, 0.45 mg vs. placebo p<0.001	Oral estradiol acetate decreased mean number of symptoms and symptom severity after 12 wks of treatment compared to placebo.
Oral conjugated equine estrogen					
Dayal, 2005 (Fair)	Single center; N=32; 12 wks	Postmenopausal 56.6 yrs; Uterine status not reported	DHEA 50 mg CEE 0.625 mg DHEA 50 mg + CEE 0.625 mg placebo	No significant change from baseline to follow-up in CEE group on measures of mood, anxiety, sleep and quality of life	CEE did not improve mood or quality of life at 12-week follow-up.
Gambacciani, 2005 (Poor)	Single center; N=60 12 wks	Postmenopausal 53y Uterine status NR	CEE 0.3 mg qd + 2.5mg MPA CEE 0.3 mg qd + 100 mg natural micronized progesterone Calcium 1000 mg qd (control group)	Vasomotor, somatic, anxiety, psychological, depression, sexual scores of Green's climacteric scale: improvement in all scores both progesterone groups vs calcium group (p<0.05) Sleep and hot flash scores improved in CEE +progesterone vs calcium	CEE + either MPA or micronized progesterone improve menopausal,sleep, and mood symptoms. CEE+micronized progesterone improved sleep

Study/Year (Quality)	Study Design; Sample size; Duration of followup	Population Characteristics; Mean age; Uterine status	Interventions	Main outcomes/results	Conclusions
				(p=0.05); CEE+micronized progesterone improved sleep more than CEE+MPA (p=0.05)	more than CEE+MPA.
Reddy, 2006 (Fair)	Single center; N=60; 12 wks	Postmenopausal; 52 yrs; Uterine status not reported	0.625 mg conjugated estrogen 400 mg starting dose, titrated to 2,400 mg gabapentin placebo	Conjugated estrogen vs. placebo % of baseline hot flush composite score (severity and frequency): 23% vs. 46% (p<0.016)	CEE significantly reduces a composite score of hot flushes.
Oral estradiol and progesterone					
Crisafulli, 2004 (Fair)	Double-blind; N=115; 1 year	Postmenopausal; 51.7 yrs; 0/90 hysterectomy	1 mg/day 17β-estradiol/norethisterone acetate 54 mg/day genistein placebo	Mean % change in daily flush score as compared with placebo 3 months: -53% (p<0.001) 6 months: -56% (p<0.001) 12 months: -54% (p<0.001)	The frequency of hot flushes decreased significantly with estradiol/norethisterone acetate vs. placebo and remained suppressed at 12 months.
Schurmann, 2004 (Fair)	Double-blind Multicenter; N=225; 16 wks	Postmenopausal; 53.6 yrs; 0/225 hysterectomy	1 mg E2/1 mg drospirenone 1 mg E2/2 mg drospirenone 1 mg E2/3 mg drospirenone placebo	Relative change number hot flushes (%) 1 mg estradiol/1 mg drospirenone vs. 1 mg estradiol/2 mg drospirenone vs. 1 mg estradiol/3 mg drospirenone vs. placebo (p vs. placebo): -85.6 (p<0.001) vs. -88.0 (p<0.001) vs.-84.5 (p<0.001) vs.-47.0	Estradiol with drospirenone significantly decreased the frequency of hot flushes compared to placebo.
Oral estradiol valerate and progesterone					
Heinrich, 2005 Wolf 2005 (Poor)	Single center; N=51; 24 wks	Postmenopausal 64.1 yrs; Time since treatment with gonadal hormones 13.5 (SD 1.5) yrs; 100% hysterectomy	2 mg estradiol valerate 2 mg estradiol valerate + 100 mg progesterone (not available in the US) placebo	NSD between groups on measures of mood, well-being, menopausal symptoms, sleep quality, or depressive symptoms. Mean change in cognitive tests, E2V vs. E2V/Prog vs. placebo Paragraph recall delayed: 1.29 vs. 0.9 vs. 1.69, p=0 .90 Digit span forwards: -0.09 vs. 0.9 vs. -0.15, p=0.14 Block span forwards: -0.84 vs. 0.1 vs. 0.61, p=0.16 Verbal Fluency (Categories): 1.5 vs. -2 vs. -0.69, p=0.90	Estradiol valerate with micronized progesterone did not improve mood, well-being, symptoms, or sleep compared with placebo. NSD between groups in mean change in cognitive tests

Study/Year (Quality)	Study Design; Sample size; Duration of followup	Population Characteristics; Mean age; Uterine status	Interventions	Main outcomes/results	Conclusions
Oral conjugated equine estrogen and progesterone					
Greenspan, 2005 (Fair)	Single center; N=373; 3 yrs	Postmenopausal; 71.3 (SD 5.2) yrs; 35% hysterectomy	0.625 mg CEE 0.625 mg CEE + 2.5 mg medroxyprogesterone placebo	Self-reported functional assessment tests at 3 yrs, CEE vs. placebo Instrumental Activities of Daily Living test: -0.2 (SD 0.8) vs. -0.2 (SD 1.1); mean difference: 0.1 (-0.1 to 0.3); p=0.49 Physical Activity Scale of the Elderly -25 (SD 54) vs. -22 (SD 59); mean difference -3 (-15 to 8); p=0.30 Folstein Mini-Mental State Exam at 3 yrs, CEE vs. placebo: NSD	NSD between groups on self-reported functional assessment tests or Folstein Mini-Mental State Exam at 3 yrs.
Newton, 2006 HALT trial (Fair)	Single center; N=351; 1 year	52% menopausal transition vs. 48% postmenopausal; 52.2 (SD 2.4) yrs; 38/351 hysterectomy	0.625 mg CEE (+ 2.5 mg medroxyprogesterone acetate for hysterectomy patients only)160 mg qd black cohosh multibotanical + soy diet counseling placebo	12 month data: CEE vs. placebo (adjusted means) Change in vasomotor symptom frequency: -3.76 (-5.76 to -1.76; p<0.001) Change in vasomotor symptom intensity: 0.05 (-0.15 to 0.26; p=0.63) Difference in Wiklund Vasomotor Symptom Subscale score: -1.77 (-2.79 to -0.75; p<0.001)	CEE + MPA was effective in decreasing vasomotor symptom frequency, but not symptom intensity.
Ethinyl estradiol and norethindrone acetate					
Speroff, 2000 (Fair) 2 studies, differing dosages and F/U interval Symons, 2000 (vaginal bleeding)	2 studies, single center; Study 1: 219, 16 wks Study 2: 266, 12 wks	Postmenopausal Study 1: 90.5% Caucasian 8.3% black 1.2% other; 51.7 yrs Study 2: 88.8% Caucasian 7.5% black 3.7% other; 50.9 yrs	Study 1: norethindrone acetate/ethinyl estradiol 0.2mg/1mcg, 0.5mg/2.5mcg, 1mg/5mcg or 1mg/10mcg or placebo/day Study 2: norethindrone acetate/ethinyl estradiol 0.5mg/2.5mcg, 1mg/5mcg or 1mg/10mcg or placebo/day	Study 1: mean change in hot flushes from baseline to week 16, NA/EE 0.5mg/2.5mcg compared with placebo -30.0 (-73.7%), p<0.05; responder rate: greater than 75% improvement from baseline 63.4% vs. 27.9%, p=0.002 Study 2: mean change hot flushes, baseline to week 12, NA/EE 0.5mg/2.5mcg vs. placebo -63.8 (-82.2%), p<0.001; mean change from baseline in intensity score -1.30 vs. -0.67, p=0.001 Vaginal bleeding: increased with dosage and was greater than placebo (no statistics); maximal week 4, decreased over time	Norethindrone acetate and estradiol significantly decreased hot flash severity. Vaginal bleeding risk was higher with higher dosages, but the risk decreased over time.

Study/Year (Quality)	Study Design; Sample size; Duration of followup	Population Characteristics; Mean age; Uterine status	Interventions	Main outcomes/results	Conclusions
Transdermal estradiol					
Baksu, 2005 (Fair)	Double-blind; N=75; 6 months	Postmenopausal Age NR; 100% hysterectomy	Tibolone 2.5mg/day continuously (not available in US) transdermal estradiol 3.9mg/week placebo oral qd	Change in mean scores E2 vs. Placebo Hamilton Depression Rating Scale:-8.4 vs. -0.7 (p<0.05) Hamilton Anxiety Rating Scale (0-56): -12.5 vs. -0.7 (p<0.05) Kupperman's Scale (0-51): -14.7 vs. -1.9 (p<0.05)	Transdermal estradiol significantly improved depression and menopausal total symptom scores.
Joffe, 2006 (Fair)	Double-blind; N=52; 12 wks	Menopausal transition or postmenopausal; 51.0 yrs; 2/52 hysterectomy	Estradiol 0.05mg/day patch placebo patch	Estrogen vs. placebo California Verbal Learning Test: immediate verbal recall: 0.6 vs. 2.6, NS Wechsler Memory Scale-Revised: 1.9 vs. 1.0, NS Wechsler Memory Scale-Revised: 0.2 vs. 0.2, NS	NSD between groups on measures of cognition.
Schiff, 2005 (Fair-Poor)	Crossover single center; N=24; 24 wks (12 wks each arm)	Postmenopausal; 71 yrs; 100% hysterectomy	50 ug/day transdermal estradiol transdermal placebo	Mean depression score (Brief Assessment Scale Depression Cards) estradiol 1.05 (SD 1.41) vs. placebo 1.55 (SD 1.47); p=0.05 Cognitive assessment improved in 1 of 5 tests vs placebo (p=0.05)	Depression score improved with transdermal estradiol vs placebo. One of 5 measures of cognitive function improved.
Yaffe, 2006 Diem, 2006 Waetjen, 2005 ULTRA (Fair)	Multicenter (clinics); N=417; 2 yrs	Postmenopausal; 67 yrs (SD 5); 0/417 hysterectomy	14 ug/day transdermal estradiol transdermal placebo	NSD between groups in Modified Mini Mental Status Examination, SF-36, or incontinence at 2 yrs NSD in proportion reporting postmenopausal symptoms (hot flashes, vaginal dryness, trouble sleeping)	Low dose transdermal estradiol did not improve menopausal symptoms, urinary incontinence, or cognitive function at 2 yrs.
Transdermal estradiol and progesterone					
Levine, 2005 (Trial 2 only) (Fair)	Double-blind; N=226; 12 wks	Postmenopausal; 52.5 yrs; 0/226 hysterectomy	Combined patch with E2 50mcg/day and norethindrone acetate (140, 250 or 400 mcg/day) or placebo	Pre-post difference, treatment vs. placebo: Hot flashes: 8.96 (SD=3.3) vs. 5.42(SD=3.6), p<0.0001 WHI Insomnia rating scale: 4.79 (SD=5.0) vs. 2.97 (SD=3.8), p=0.035	A transdermal patch with estradiol and norethindrone significantly improved hot flashes and insomnia.

Abbreviations: CAMCOG=the Cambridge cognitive examination for mental disorders of the elderly, CEE=conjugated equine estrogens, EA=estradiol acetate, EE= ethinyl estradiol, E2=estradiol, HALT=herbal alternatives for menopause trial, HRT=hormone replacement therapy, MPA= medroxyprogesterone acetate, N=sample size, NSD=no significant difference, NR=not reported, Prog=progesterone, QD=daily, SD=standard deviation, ULTRA=ultra-low dose transdermal estrogen assessment, WHI-Women's health initiative, Wks=weeks, Yrs=years

Women's Health Initiative Hormone Replacement Study

The Women's Health Initiative (WHI), begun in 1993, was designed to examine major causes of morbidity and mortality in postmenopausal women (Tables 5 and 6). Details of hormone replacement studies from the WHI are shown in and Evidence Tables 3 (outcomes) and 4 (quality assessment). It encompasses two large, randomized, controlled, double-blind studies of estrogen therapy in postmenopausal women. In addition, there is a dietary trial and a calcium and vitamin D supplementation trial.[79] Women between the ages of 50 and 79 years were recruited form 40 clinical centers in the U.S. The WHI estrogen plus progesterone trial randomized 16,608 postmenopausal women with an intact uterus assigned to 0.625 mg of conjugated equine estrogen (CEE) plus 2.5 mg medroxy progesterone acetate (MPA) (Prempro, Wyeth) or to placebo.[4] This trial was stopped early due to an unfavorable global risk-benefit profile at 5.2 years, rather than the planned 8.5 years of duration.[4] The WHI CEE-only trial involved 10,739 women who had had a hysterectomy. This study was also stopped early (at 6.8 years) due to a lack of overall health benefit and an increased risk of stroke similar to that seen in the estrogen-only trial.[80]

Barnabei and colleagues[81] reported that women with an intact uterus and moderate-to-severe hot flashes, night sweats, or vaginal or genital dryness at baseline who took CEE and MPA had improvements in these symptoms, as well as improvements in joint pain and stiffness ($p<0.001$ for each of these outcomes) at 1-year follow-up. Women who were younger, thinner, and closer to the menopause experienced more relief of hot flushes and night sweats. Among women asymptomatic at baseline, treatment-related beneficial effects included prevention of hot flushes ($p<0.001$), night sweats ($p=0.003$), and vaginal or genital dryness ($p<0.001$) and reduction in the incidence of new musculoskeletal symptoms ($p<0.001$).

A subgroup (8.6% of randomized population, oversampled for minorities) of women was examined at 3-year follow-up.[81] Among women who had moderate-to-severe symptoms at baseline, there were no significant differences between treatment groups for hot flashes or for various genital and musculoskeletal symptoms. Among women who were asymptomatic at baseline, vasomotor symptoms were not prevented, but these women were less likely to report vaginal or genital dryness and joint pain or stiffness than women on placebo.

The WHI was a good-quality study with high follow-up rates for most outcomes, intention-to-treat analyses, and baseline comparability of treatment groups. Adherence rates were low, however. In the CEE/MPA study, 42% of the treatment group and 38% of the placebo group stopped taking the study drug during the follow-up period.[4] In the estrogen-only study, 54% stopped the study medication.[80]

Data informing the question of the applicability of the study to broad U.S. population are reported by Stefanick and colleagues.[82] The hormone replacement therapy study of the WHI involved a very large and diverse cohort: over 16,000 women in the estrogen/progesterone study and over 10,000 in the estrogen-alone cohort. The ethnic distribution of participants was similar to that of the U.S. census for women aged 50 to 79 years.

There were important differences between study participants and the general U.S. population, however.[82] Family household income and percentage with a college degree were higher in the study population than among general populations. The WHI hormone therapy participants contained fewer smokers and fewer women reporting no leisure time physical activity each week. There were more obese women in the study and the average intake of dietary calcium was above average. Study participants also appeared to be at fairly low risk for

coronary heart disease, including low rates of hypertension, diabetes, and elevated cholesterol requiring drug therapy.

In addition, there are important differences between the populations of the estrogen-only study (post hysterectomy)[80] and the estrogen/medroxyprogesterone study (intact uterus).[82] The estrogen-only study subjects were at higher risk for coronary heart disease, were more obese and less active, and had a slightly higher incidence of pre-existing cardiovascular disease than the estrogen/progesterone study subjects.[82] It is not possible to determine if the differences between the two study groups is due to uterine status, and data are not available to determine if demographic and other characteristics vary between women with and without a uterus.[82]

Table 5. Women's Health Initiative hormone replacement studies

Study	Intervention; uterine status	Sample size; follow-up; period (years)	Primary endpoint: efficacy or safety	Other endpoints	Conclusions
Cardiovascular outcomes					
CEE + MPA					
Rossouw, 2002 (prior review)	CEE 0.625 + MPA 2.5 mg qd; Intact uterus	Total N: 16,608 CEE: 8506 Placebo: 8102 Average F/U: 5.2 (stopped early due to concerns regarding increased breast cancer and some increase in CHD, stroke, and PE)	CHD events: HR 1.29 (95% CI, 1.02-1.63) CHD deaths: HR 1.18 (95% CI, 0.70 - 1.97) Global index (earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer, colorectal cancer, hip fracture, death due to other causes): HR 1.15 (95% CI,1.03 - 1.28) Safety: Invasive breast cancer: HR 1.26 (95% CI, 1.00 - 1.59) Total deaths: HR 0.98 (95% CI, 0.82 - 1.18)	Strokes: HR 1.41 (95% CI, 1.07 - 1.85) Venous thromboembolic disease: HR 2.11 (95% CI, 1.58 - 2.82) Colorectal cancer: HR 0.63 (95% CI, 0.43 - 0.92) Total fractures: HR 0.76 (95% CI, 0.69 - 0.89) Hip fractures: HR 0.66 (95% CI, 0.45-0.98)	After mean follow-up of 5.2 years, CEE/MPA increased CHD events, invasive breast cancer, stroke, and PE. The incidence of colorectal cancer and hip and vertebral fractures were decreased. Total mortality and endometrial cancer did not differ significantly between groups.

	Study	Intervention; uterine status	Sample size; follow-up; period (years)	Primary endpoint: efficacy or safety	Other endpoints	Conclusions
CEE						
	Anderson, 2004	CEE 0.625 mg qd; Hysterectomy	Total: 10,739CEE: 5,310 Placebo: 5,429; Average F/U: 6.8 (range 5.7 to 10.7y); Study stopped early at 6.8y as concern about ↑ risk of stroke and lack of cardioprotective effect	Incidence per 10,000 person-years CHD events: CEE 49, placebo 54 (p>0.05); HR 0.91 (95% CI, 0.75-1.12) Total CVD events: CEE 225, placebo 201; HR 1.12 (95% CI, 1.01 - 1.24) Global index of health risks and benefits: HR 1.01 (95% CI, 0.91-1.12) Safety: Invasive breast cancer: CEE 26, placebo 33 (p=0.06); HR 0.77 (95% CI, 0.59 - 1.10) Total mortality: HR 1.04 (95% CI, 0.88 - 1.22)	Incidence per 10,000 person-years: Hip fractures: CEE 11, placebo 17 (p=0.01), HR 0.61 (95% CI, 0.41 - 0.91) Total osteoporotic fractures: CEE 139, placebo 195 (p<0.001), HR 0.70 (95% CI, 0.63 - 0.79) Stroke: CEE 44, placebo 32 (p=0.007); HR 1.39 (95% CI, 1.10 - 1.77) VTE (DVT and PE): CEE 28, placebo 21 (p>0.05); HR 1.33 (95% CI, 0.99-1.79) Colorectal cancer: HR 1.08 (95% CI, 0.75 - 1.55)	CEE in women with a hysterectomy increases the risk of stroke, reduces the risk of hip and other fractures, and does not significantly affect CHD event rates or overall mortality. There was a nonsignificant reduction in breast cancer.

Study	Intervention; uterine status	Sample size; follow-up; period (years)	Primary endpoint: efficacy or safety	Other endpoints	Conclusions
Symptoms					
Barnabei, 2005	CEE 0.625 + MPA 2.5 mg; qdIntact uterus	Total: 16,608F/U 5.6	Relief/improvement of symptoms at 1y: Symptomatic at baseline: Hot flashes, night sweats, breast tenderness, vaginal/genital dryness, joint pain/stiffness: improved (p<0.05) Vaginal/genital discharge, irritation/itching, headaches, mood swings, extremity swelling: NSD Asymptomatic at baseline: Similar findings (p<0.05) Safety: Vaginal bleeding: most frequently reported treatment effect in CEE+MPA (42.5% and 51.0% at 6w and 6m); placebo < 5% throughout study	Weight 1y: higher proportion lost weight with CEE+MPA than placebo (no statistics) Breast tenderness, vaginal irritation and discharge, headaches: increased (p<0.05) Mood swings, extremity swelling: NSD	At 1 year follow-up, CEE+ MPA decreased hot flushes/night sweats and musculoskeletal symptoms. Breast tenderness and vaginal discharge increased in asymptomatic women. At 3-year follow-up, there was NSD in hot flushes/night sweats and musculoskeletal symptoms between groups; vaginal or genital dryness decreased among asymptomatic women.
Bone					
CEE+MPA					
Cauley, 2003 (prior review)	CEE 0.625 + MPA 2.5 mg qd; Intact uterus	Total N: 16,608; Patients with BMD measurements: 1024 F/U 5.6 (average)	F/U average 5.6y Total fractures: CEE+MPA 8.6%, placebo 11.1%; HR.76 (95% CI, 0.69-0.83) Hip fracture: HR 0.67 (95% CI, 0.47-0.96)	BMD at 3y: Total hip: increased 3.7% in CEE+MPA vs. 0.14% increase in placebo (p<0.001)	CEE+MPA increases BMD and reduces the risk of fractures in healthy postmenopausal women, regardless of fracture risk.

	Study	Intervention; uterine status	Sample size; follow-up; period (years)	Primary endpoint: efficacy or safety	Other endpoints	Conclusions
CEE						
	Jackson, 2006 (Update of Anderson, 2004)	CEE 0.625 mg qd; Hysterectomy	Total N: 10,739I: 5310C: 5429; F/U: mean 7.1y	Hip fracture: HR 0.65 (95% CI, 0.45-0.94)Total fracture: HR 0.71 (95% CI, 0.64-0.80) BMD lumbar spine (n=938): CEE increase 7.1%, placebo increase 1.9% (p<0.0001)		CEE in hysterectomized women reduces fractures and increases BMD, largely independent of fracture risk.
Health-related quality of life						
CEE + MPA						
	Hays, 2003 (prior review)	CEE 0.625 + MPA 2.5 mg qd; Intact uterus	CEE+MPA: 8,506 Placebo: 8,102; F/U: 1y	HRQL (SF-36, 8 subscales) 1 y: CEE+MPA > placebo for physical function, bodily pain, sleep disturbance (all p<0.001) 3 y: NSD between CEE+MPA and placebo (9% subsample)	Subgroup analyses: no significant interactions between baseline age, race, BMI, symptoms and outcomes Age 50-59: same findings as main study Moderate-to-severe vasomotor symptoms at baseline: same findings as main study	CEE+MPA did not have a clinically significant effect on HRQL in postmenopausal women.
CEE						
	Brunner, 2005	CEE 0.625 mg qd; Hysterectomy	I: 5310 C: 5429; F/U: 1 and 3 y	1y: Sleep disturbance: positive effect CEE vs. placebo (absolute effect 2%) (p<0.001) SF-36: negative effect of CEE on social functioning (p=0.003); NSD other measures 3y: NSD any HRQL measure (8.6% subsample)	Global QOL rating: NSD in distributions of scores between CEE and placebo	CEE did not improve HRQL to a clinically significant degree at up to 3-y follow-up.

Study	Intervention; uterine status	Sample size; follow-up; period (years)	Primary endpoint: efficacy or safety	Other endpoints	Conclusions
Cognition and dementia					
CEE + MPA					
Rapp, 2003 **WHIMS**	CEE 0.625 + MPA 2.5 mg qd; Intact uterus	Total N: 4,532; F/U mean 4.2 (range, 0.9 - 6.4)	Safety: Rates of change in 3MSE (global cognitive function): Both groups increased over the first 4y, then decreased; Y3 and Y4 scores for placebo > CEE (p<0.05); NSD Y5 and Y6	Strokes: NSD between groups (p=0.62) Probable dementia: CEE 40, placebo 21 (p=0.01)	CEE offers no benefit for global cognitive function or no negative effect.
Schumaker, 2003 **WHIMS**	CEE 0.625 + MPA 2.5 mg qd; Intact uterus	Total N: 4,532; F/U mean: 4.05y (SD 1.19)	Safety: incidence probable dementia: CEE + MPA vs. placebo: HR 2.05 (95% CI, 1.21-3.48) (p=0.01)	Mild cognitive impairment: CEE + MPA vs. placebo: HR 1.07 (95% CI, 0.74-1.55) Probable dementia or mild cognitive impairment: CEE vs. placebo: HR 1.37 (95% CI, 0.99 - 1.89)	CEE + MPA increased the risk for probable dementia in postmenopausal women ≥ 65y and did not prevent mild cognitive impairment
Resnick, 2006, 2004 **WHISCA**	CEE 0.625 + MPA 2.5 mg qd; Intact uterus	Total N: 1,416; Mean F/U: 1.35 Study started 3y after WHI randomization	Safety: Verbal memory: CEE negative impact vs. placebo (p<0.01) Figural memory: CEE positive impact vs. placebo (p=0.012) Other cognitive domains, affect, depressive symptoms: NSD		CEE + MPA effect on cognitive function varies across cognitive domains in women over 65y.

	Study	Intervention; uterine status	Sample size; follow-up; period (years)	Primary endpoint: efficacy or safety	Other endpoints	Conclusions
CEE						
	Espeland, 2004 **WHIMS**	CEE 0.625 mg qd; Hysterectomy	CEE: 1,387Placebo: 1,421Mean; F/U: 5.4y	Safety: Rates of change in 3MSE (global cognitive function): Both groups increased over the first 4y, then decreased; NSD between groups for each year Overall mean 3MSE score: placebo slightly higher than CEE (p=0.04)	Largest declines in scores occurred more frequently in CEE than placebo: relative risk of decline of 10 units in 3MSE with CEE vs. placebo: 1.47 (95% CI, 1.04 - 2.07)	Global cognitive function decreased with CEE compared to placebo during follow-up of 5.4 years. This adverse effect was more pronounced among women with lower cognitive function at baseline.
	Schumaker 2004 **WHIMS**	CEE 0.625 + MPA 2.5 mg qd or CEE 0.625 mg qd	CEE alone: 2,947 Pooled data (CEE alone and CEE+MPA): 7,479; F/U CEE alone: 5.21y (SD 1.73) F/U Pooled data: 4.05y (SD 1.19)	Safety: Incidence of probable dementia: CEE alone: HR 1.49 (95% CI, 0.83 - 2.66) Pooled data: HR 2.05 (95% CI, 1.21 - 3.48) NSD between CEE alone CEE+MPA (p=0.11)	Mild cognitive impairment: CEE alone: HR 1.34 (95% CI, 0.95 - 1.89) Pooled data: HR 1.25 (95% CI, 0.97 - 1.60)	CEE does not reduce dementia or mild cognitive impairment incidence.

Abbreviations: BMI= body mass index (kg/m2), BMD=bone mineral density, CVD=cardiovascular disease, CEE=conjugated equine estrogens, C=control, CI=confidence interval, CHD=coronary heart disease, DVT=deep vein thrombosis, F/U=follow-up, HR=hazard ratio, HRQL=health-related quality of life, HT=hormone therapy, I=intervention, MPA= medroxyprogesterone acetate, MSE=mini-mental state examinations, MI=myocardial infarction, N=sample size, NSD=no significant difference, NR=not reported, p=patients, PE=pulmonary embolism, qd=daily, QOL= quality of life, SD=standard deviation, VTE=Venous thromboembolism, WHI=the women's health initiative, WHIMS=the women's health initiative memory study, WHISCA= the women's health initiative study of cognitive aging, y=year

Table 6. Women's Health Initiative: Summary of benefits

Outcome	CEE+MPA (5.2y)	CEE alone (6.8y)
Vasomotor symptoms	↓ 1y, NSD 3y	Not reported
HRQL	No clinically significant differences, 1 and 3y	No clinically significant differences, 1 and 3y
Total fractures	↓	↓
BMD	↑	↑

Meta-analysis of placebo-controlled trials examining symptoms

Of 12 trials of oral E2 compared to placebo for treatment of hot flashes, five met criteria for the meta-analysis.[44, 46-48, 52] 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).[44, 46, 47, 52] Trials were excluded from analysis if they did not provide data on frequency of hot flashes[45, 49, 53-55, 83] or did not provide standard deviations.[50, 51]

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.[57-59]

Of six trials of CEE compared to placebo, one met criteria for the meta-analysis.[63] This trial reported a mean reduction of -19.1 (95% CI: -33.0, -5.1) of hot flashes per week after treatment compared to placebo. The other five trials were excluded from analysis if they did not provide data on frequency of hot flashes,[62, 64] provided data in a graph form,[60] or did not provide standard deviations.[60, 61, 65]

One trial of estropipate compared to placebo was identified from the search and met inclusion criteria.[67] 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.[20, 68, 70, 72-74] 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.[74] Trials were excluded if data was provided in a graph form[71, 75] or the trials did not provide standard deviations.[51, 75]

In Update #3, we were unable to obtain a pooled estimate of effect for any outcome, including hot flashes/flushes (the most frequently reported outcome in our review) as there was marked heterogeneity of relevant outcomes measures, including vasomotor composite scores, mean number of flashes/flushes per week, mean change in number of flashes/flushes, and percentage improved. In addition, very few studies reported measures of dispersion (standard deviation or standard error). We therefore used a qualitative approach to synthesis of these data.

Comparison with Cochrane meta-analysis

The results of this 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.[8] 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 month's 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.[84] Sleep disturbances were measured along with other quality-of-life measures in a subset of 1511 women enrolled in the WHI.[85] At one year of follow-up 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.[86] 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.[68, 70]

A head-to-head trial of an intravaginal ring delivering E2 compared with oral E2[24] 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.

The WHI reported night sweats, as noted above under the section Hot Flashes/Flushes.[81] For Update #3, four new studies were identified. A small, fair-quality trial of postmenopausal women taking oral conjugated equine estrogens did not find significant improvement in sleep symptoms[29] and a study of transdermal estradiol found an improvement in sleep at 12 weeks (p=0.046).[33] Two other studies were of poor quality.[41, 42]

Mood changes

Nine trials of estrogen reporting mood outcomes met eligibility criteria, including one trial comparing E2 and E2V,[17] one of oral E2 compared to placebo,[45] two of transdermal E2 compared to placebo,[87, 88] and five of CEE compared to placebo.[34,64, 89-91]

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.[17] At the end of treatment, symptoms were reduced to 52% in the E2 group compared to 44% in the E2V group (p=0.039).

In placebo-controlled trials, one study that randomized early postmenopausal women to oral E2 reported significantly improved scores after one year 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.[45]

One trial of transdermal E2 enrolled 50 women meeting DSM-IV criteria for major depressive disorder (26 women), dysthymic disorder (11 women), or minor depressive disorder (13 women).[87] 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). Another trial of 87 women diagnosed with major depression, dysthymia, or minor depression compared changes in Hamilton Depression Scale (HAM-D) and Center for Epidemiologic Studies Depression Scale (CESD) scores after 8 weeks of treatment with low dose transdermal E2 (0.1 mg per day) or placebo. Both groups had improvements in depressive symptoms and the differences between placebo and E2 were not significant.[88]

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.[89] Another trial of psychologically well-adjusted women reported significant improvement on the Beck Depression Inventory with CEE ($p<0.05$).[90] 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.[91] In the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI), women on CEE did not differ from those on placebo for anxiety and affective symptoms.[64] 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.[61]

For Update #3, a small fair-poor quality study[40] found no significant differences between treatment with transdermal estradiol and placebo for depressive symptoms measured with the BASDEC (brief assessment scale depression cards). In a poor-quality study, Heinrich and colleagues[42] found no significant effects of treatment with estradiol on mood or depression, both measured with self-administered, German questionnaires.

Urogenital symptoms and 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.[3] 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.[92] 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[93] and a trial of the E2 tablet and CEE cream.[94]

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.[24] 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[77] 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.[95] 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.[76] Another trial of transdermal E2 indicated improvement in vaginal dryness, but not dyspareunia, frequent urination, dysuria, stress incontinence, and nocturia, compared to placebo.[96] Another trial comparing transdermal E2 and placebo indicated no differences between groups for symptoms of vaginal discomfort, loss of libido, and incontinence.[73]

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[97] and the other a poster presentation.[98] 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.[61] The HERS trial found that women with at least one episode of incontinence per week at baseline who received CEE/MPA had worsening incontinence after approximately 4 years of follow up compared to women taking placebo.[99]

The WHI reported on genital symptoms, as noted above under the section 'Hot flashes/flushes'.[81]

In Update #3, the ULTRA study found no differences between treatment with low-dose transdermal estradiol on vaginal dryness[30] or on urinary incontinence.[39] There was a reduction in

investigator-assessed vaginal atrophy, dryness, and friability for estradiol acetate compared with placebo ($p<0.05$) in a large, fair-quality study.[37]

A Cochrane systematic review compared efficacy and safety of intra-vaginal estrogen preparations (creams, pessaries, tablets, and estradiol-releasing ring) for the relief of symptoms of vaginal atrophy (vaginal dryness, itching, discomfort, and painful sexual intercourse).[100] Overall, the author concluded that the preparations appear to be equally effective for the symptoms of vaginal atrophy. CEE cream caused more side effects compared to estradiol tablets (uterine bleeding, breast pain, and perineal pain) or estradiol vaginal ring (endometrial overstimulation). For the comparison of the estradiol ring to CEE vaginal cream, there was no difference between groups in patient assessment of vaginal dryness or withdrawals due to adverse events, but there was more improvement in pruritis with the ring. For the comparison of estradiol ring versus estradiol tablet, vaginal dryness was improved more with tablets, but there was no difference between groups in genital pruritis or withdrawals due to adverse events. Symptom improvement was similar for tablet versus cream, but there were fewer withdrawals due to adverse effects with tablets compared with cream. There was no difference among all treatment comparisons for dysuria, nocturia, urgency, urge incontinence, participant symptom improvement in dryness, soreness, and irritation, loss of libido, and vaginitis.

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.[101] A trial comparing oral E2 and intravaginal ring E2 found significant improvement on the Greene Climacteric Scale among both treatment groups but no between-group differences.[102]

Six placebo-controlled trials of oral E2[45 44, 47, 52-54] and one trial of E2V[59] reported significant improvements compared with placebo on various quality-of-life scales, including Kupperman index, Greene climacteric score, and General Health Questionnaire. One trial of oral E2 conducted in HRT-naive women in Thailand observed no difference in mean Greene score improvement compared with placebo after 12 months of treatment.[83] A trial of low-dose oral E2 (1 mg per day)[103] reported significant improvement from baseline at 6 and 12 weeks on six of nine domains of the Women's Health Questionnaire (vasomotor symptoms, sexual behavior, depressed mood, somatic symptoms, anxiety/fear, and sleep problems). There was no difference between control and treatment groups on the memory concentration, menstrual symptoms, and attractiveness items of the scale.

Seven 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, and psychological general well-being index.[68, 70, 73, 74, 76, 96, 104] 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.[105]

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 that use of CEE had little effect.[91] One trial found a significant decrease in Kupperman's index among women treated with E2V compared with placebo.[59] A trial of

esterified estrogens reported improvement in the Quality of Life Menopause Scale compared to placebo.[106]

Health-related quality of life (HRQL) measures were collected on a subgroup of women enrolled in the WHI randomized to CEE plus MPA or to placebo (n=16,608).[85] 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 1-year follow-up, there were small but statistically significant positive effects of CEE/MPA on physical functioning (0.8 units on a 100-point scale), bodily pain (1.9 points on a 100-point scale), and sleep disturbance (0.4 units on a 20-point scale) compared with placebo. There were no differences from placebo in any other HRQL measure and by 3 years of follow-up (n=1511) there were no significant differences from placebo on any HRQL measure. Subgroup analyses detected no statistically significant interactions between baseline age, race, ethnicity, body mass index, or menopausal symptoms and HRQL. In a *post hoc* analysis of women 50 to 54 years of age who reported moderate-to-severe vasomotor symptoms at baseline, there was a positive effect on sleep disturbance, but no effect on other HRQL measures, despite significant improvement in vasomotor symptoms.

HRQL was also examined in the WHI estrogen-only study (n=10,739).[107] At 1-year follow-up, there was a small positive effect of CEE on sleep disturbance (0.4 on a 20-point scale, $p<0.001$) and a negative effect on social functioning (1.3 on a 100-point scale, $p=0.003$). At 1-year follow-up of women who had moderate-to-severe vasomotor symptoms at baseline, 72.4% of the CEE group no longer reported these symptoms, compared to 55.6% of the placebo group ($p<0.001$). In a subsample (n=1,189) examined at 3-year follow-up there were no significant differences in any HRQL measure between treatment groups.

For Update #3, none of the three new studies reporting HRQL or related outcomes showed significant effects between the treatment and placebo groups. The ULTRA study of low-dose transdermal estrogen[78] reported no significant improvements in the SF-36 subscales of physical and mental function. The findings of Dayal and colleagues[29] were similar in that conjugated equine estrogen did not improve vitality, general health status, or quality of life at 12-week follow-up. A third study of women over 70 years randomized to oral estradiol or placebo also did not report significant changes in a "SF-36 score."[26]

Key Question 2. What is the comparative effectiveness of different hormone therapy preparations when used by postmenopausal women or women in the menopausal transition stage 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 7 below; trials are described in Evidence Tables 5 (head-to-head trials) and 6 (placebo-controlled trials), and quality ratings are presented in Appendix F. Quality ratings of studies added for Update #3 are shown in Appendix G.

Table 7. Number of studies of estrogens with bone density or fracture outcomes

	Total	Bone Density	Fractures
Head-to-head comparisons			
CEE and transdermal estradiol (E2)	3	3	0
Transdermal estradiol (E2) and estradiol valerate (E2V)	1	1	0
Placebo comparisons			
Estradiol (E2) Oral Transdermal	 16 15	 16 15	 1 2
Estradiol valerate (E2V)	5	5	1
Conjugated equine estrogen (CEE)	29	26	8
Conjugated synthetic estrogen	1	1	0
Esterified estrogen (EE)	1	1	0
Estropipate	0	0	0

Characteristics of the trials included:

- Three trials with bone density outcomes compared estrogens head-to-head.
- 68 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.
- X-rays verified all fracture outcomes.
- 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

We identified no new head-to-head trials with bone density or fracture outcomes in this update. Four head-to-head trials compared different estrogen preparations, including three trials of CEE compared to transdermal E2,[108-110] and one trial of transdermal E2 compared to estradiol valerate (Table 8 and Evidence Table 5).[111]

Table 8. Head-to-head trials with bone density outcomes

Study/year	Study design	Population characteristics	Interventions	Main outcomes/results
Oral CEE compared with transdermal E2				
Castelo-Branco, 1992	Open label N=99 1 year	Postmenopausal Age NR Uterine status not reported	CEE: 0.625 mg/day; E2: 0.05 mg/day; calcium NR MPA: 2.5 mg/day (all treatment groups)	BMD: Lumbar spine (percent change from baseline). 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 transdermal vs. placebo (p<0.01).
Oral CEE compared oral E2				
Castelo-Branco, 1993	Blinding unclear N=118 1 year	Postmenopausal with hysterectomy Age NR	CEE: 0.625 mg/day; E2: 0.05 mg/day; calcium NR MPA: 2.5 mg/day (all treatment groups)	BMD: Lumbar Spine (percent change from baseline). 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 transdermal vs. placebo (p<0.05).
Davas, 2003	Blinding unclear N=173 1 year	Postmenopausal women with menopausal symptoms and BMD T score <-1 SD Mean age 50.7 (46-60) years Uterine status not reported	CEE: 0.625 mg/day; E2: 0.05 mg twice weekly; CEE+AL: 0.625 mg/day + alendronate 10mg/day; E2+AL: 0.05 mg twice weekly + alendronate: 10mg/day; Calcium: 1000 mg/day (all treatment groups) MPA: 5 mg/day (all treatment groups)	BMD: Lumbar spine (mean increase from baseline): All treatment groups had increases in BMD. Increases in BMD did not differ significantly between CEE and E2 groups, alone or with alendronate. Hormone therapy plus alendronate increased BMD significantly more than HT alone, and significantly more so among osteoporotic women compared with osteopenic women.
Oral E2V compared with transdermal E2				
Marslew, 1991	Double-blind N=73 2 years	Postmenopausal Mean age 51 (45-54 years) Uterine status not reported	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	BMD: Lumbar spine, forearm (mean gain or loss). No significant differences between treatment groups at any site. Placebo vs. treatment 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).

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).[108, 109] 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%, $p<0.01$).[108] 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.[109]

A third trial comparing oral CEE (0.625 mg/day) with transdermal E2 (0.05 mg twice weekly) further evaluated the addition of alendronate (10mg/day) to each form of estrogen treatment. Increases in bone mineral density (BMD) occurred in all treatment groups after one year, and the increases did not differ significantly between the CEE and E2 groups. The addition of alendronate to either form of hormone therapy increased BMD significantly more than did hormone therapy alone.[110]

One study of 73 healthy postmenopausal women age 45 to 54 years compared the effects of oral E2 and E2V on forearm and spinal BMD.[111] Both groups significantly gained bone density compared to placebo, and no significant differences between groups were found at any site.

Placebo comparisons

Sixty-four RCTs comparing an eligible estrogen preparation with placebo and reporting BMD outcome data met criteria for this review. These studies are described in Evidence Table 6. New studies added for Update #3 are shown in Table 9.

Characteristics of the trials include:

- Trials were conducted predominantly in the U.S. or Western Europe and most often recruited participants from general or gynecology practices.
- Both prevention and treatment trials were included and a broad patient population was provided 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 was not separately reported so comparisons could not 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.
- 36 trials of estradiol in three forms were included: 16 trials of oral E2, 15 trials of transdermal E2, and 5 trials of E2V.
- 26 trials of CEE and one trial of esterified estrogen were included.
- One trial of conjugated synthetic estrogen plus medroxyprogesterone was 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.

Table 9. Placebo controlled trials with bone density outcomes (new for Update #3)

Study/year (quality)	Study Design; Number; Duration	Population characteristics	Interventions	Main outcomes/results
Oral estrogens				
Conjugated equine estrogen				
Reid, 2004 (Fair)	Double-blind Multicenter; N=619; 3 years	Postmenopausal; Age: 53; 100% hysterectomy	CEE 0.625 mg raloxifene 60mg raloxifene 150mg placebo	Lumbar spine BMD: placebo: mean loss amounting to 2% (p<.05) CEE: gain of 4.6% (p<.001) raloxifene groups: maintenance of BMD Total Hip BMD: placebo: loss of 1.3% (p<.05) CEE: gain of 3.0% (p<.001) raloxifene groups: maintenance of BMD. (similar patterns of response were seen in the subregions of the proximal femur)
Oral estrogen/progestin combinations				
Estradiol combinations				
Arrenbrecht, 2004 (Poor)	Blind Multicenter; N=146; 1 year	Postmenopausal; Mean age 55 (44-65), BMI (kg/m2) -26; 0/146 hysterectomy	Continuous oral Estradiol 1mg/day plus intermittent norgestimate 90µg per day (3 of 6 days) for 1 year	Mean % change in lumbar spine BMD over 1 year (primary outcome): E2 (N=62): +2.40% placebo (N=55): -1.40 difference between groups 3.82% (p<0.0001) Also significant differences between groups at other sites (trochanter, intertrochanter, Ward's triangle, femoral neck, and total hip)
Greenwald, 2005 (Fair-Poor)	Double-blind Multicenter (17 centers); N=327; 2 years	Postmenopausal; Mean age 53 years (range 45 to 62); 0/327 hysterectomy	E2 0.25 mg; E2 0.5; E2 1mg; E2 1mg/NETA 0.25mg, E2 1mg/NETA 0.5mg, or E2 2mg/NETA 1mg; placebo for 26 months	Mean % change in lumbar spine BMD from baseline to 2 years (95% CI); p vs. placebo: placebo: -2.3 (-3.3 to -1.3) E2 0.25 mg: 0.4 (-0.6 to 1.4); p=0.0019 E2 0.5 mg: 2.3 (1.1 to 3.4); p<0.0001 E2 1 mg: 2.7 (1.6 to 3.7); p<0.0001 E2 1 mg/NETA 0.25 mg: 3.5 (2.5 to 4.7); p<0.0001 E2 1 mg/NETA 0.5 mg: 3.8 (2.8 to 4.9); p<0.0001 E2 2 mg/NETA 1 mg: 5.0 (4.0 to 5.9); p<0.0001
Liu, 2005 (Fair)	Double-blind Multicenter; N=132; 2 years	Less than 5 years from menopause; Mean age 52.5; Uterine status not reported	E2- 1mg/day; E2 -1mg/day + MPA 10mg/day; placebo Micronized progesterone (P4) 300mg/day; MPA 10mg/day NET 1mg/day	Mean % change from baseline in spine BMD: E2 treatment alone or E2 + MPA increased BMD from 2% to 4% (p<0.05) MPA, P4, or placebo groups had a trend towards a -2% to -4% decrease. With NET treatment, BMD did not change significantly from baseline and was not statistically different from placebo. Femoral neck: No change from baseline in placebo group. Trend for increased BMD in E2 or E2 + MPA groups, but not significant All 3 progestin treatments were similar to placebo

Study/year (quality)	Study Design; Number; Duration	Population characteristics	Interventions	Main outcomes/results
Warming, 2004 Denmark (Fair-Poor)	Double-blind; N=240; 2 years	Postmenopausal; 0/240 hysterectomy	E2 1 mg + 1mg drospirenone, E2 1 mg + 2mg drospirenone E2 1 mg + 3mg drospirenone placebo	Difference between HRT and placebo after 2 years: Spine: 7% (p<0.001) Hip: 4% (p<0.001) Total body: 3% (p<0.001)
Conjugated equine estrogen combinations				
Greenspan, 2003 (Fair-good)	Double-blind single center; N=373; 3 years	Postmenopausal, over age 65; 34% had osteoporosis. Mean age: 71.5 130/373 hysterectomy	CEE 0.625mg with or without medroxyprogesterone 2.5mg/day and alendronate 10mg daily, both agents, or placebo	Total hip BMD (after 3 years): mean (SD) increase of 4.2% (3.8) with alendronate, increase of 3.0% (4.9) with HRT, increase 5.9% (3.8) with HRT + ALN HRT + ALN vs. HRT alone (p<.001) HRT + ALN vs. ALN (p<.01) Maintenance of BMD in the placebo group. Lateral lumbar spine: increase 11.8% (6.8) with HRT + ALN vs. HRT, (p<.001) After 12 months and for the remainder of the study, % change in total hip BMD was significantly greater in each of the 3 active treatment groups than in the placebo group (p<.001). At 36 months, combination therapy had a significantly greater increase in total hip BMD than those on either ALN or HRT alone (p<.01).
Conjugated synthetic estrogen combination				
Lindsay, 2005 Utian, 2004 Women's HOPE substudy (Good)	Double-blind Multicenter; N=822; 2 years	Postmenopausal Mean age 51.6 (40-65) 0/822 hysterectomy	Conjugated estrogens (CE) 0.625 mg, CE 0.625 mg/medroxyprogesterone acetate (MPA) 2.5, CE 0.45, CE 0.45/MPA 2.5, CE 0.45/MPA 1.5, CE 0.3, CE 0.3/MPA 1.5 mg or placebo for 2 years	% of patients who did not lose >2% of spine BMD at 24 months: CE 0.45 or CE 0.625 with or without a progestin: between 87.7% and 93.3% CE 0.3mg: 83% CE 0.3/MP 1.5 mg: 73.6% <10% in all HT groups who did not lose >2% at 12 months lost >2% at 24 months. Placebo: 30%; 27% who did not lose >2% in 12 months lost >2% at 24 months. % of patients who did not lose >2% of hip BMD at 24 months: Active treatment group: 81.4% to 94.4% Less than 8% of women who did not lose >2% at 12 months lost >2% at 24 months. Placebo: 55.4%; 14.3% who did not lose >2% in 12 months lost >2% at 24 months.
Transdermal estrogens				
Estradiol patch				
Ettinger, 2004 (Fair)	Double-blind Multicenter; N=417; 2 years	Postmenopausal; age 60-80 years, Mean 67 ±5 years; 0/417 hysterectomy	estradiol patch releasing 0.014 mg per day (replaced once/week) placebo	Lumbar spine BMD: Increased 2.6% at 2 years with E2 compared to 0.6% in placebo. Between group difference at 2 years: 2.1% (95% CI 1.3-2.8, p=.001). TOTAL HIP: At 2 years, the difference between E2 and placebo was 1.2% (95% CI 0.6-1.8, p <.001).

Study/year (quality)	Study Design; Number; Duration	Population characteristics	Interventions	Main outcomes/results
Estradiol patch/levonorgestrel				
Warming, 2005 (Fair-Poor)	Double-blind Multicenter; N=212; 2 years	Postmenopausal, osteopenic; Mean Age: 54± 3.0; weight 67.0 ±9.7 kg; 0/212 hysterectomy	45 micrograms estradiol combined with 30 (n=69) or 40 microgram levonorgestrel daily (n=72) or placebo (n=71)	Difference in BMD, HRT vs. placebo group Lumbar spine L2-L4: 8% (p<0.001) Left hip: 6% (p<0.001) Total body: 3% (p<0.001) Response in BMD at all sites was similar in the two HRT groups with no dose-related effect of levonorgestrel.

Fourteen of 16 studies of oral E2 demonstrated statistically significant improvements in bone density compared with placebo.[83, 112-124] 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.[125] Another trial reported a trend in E2 groups towards increased bone density, however statistical significance was not reached for between group comparisons.[126]

All 15 trials of transdermal E2 reported statistically significant improvements in bone density compared to placebo.[127-139] Only three trials did not use concomitant progestin/progesterone.[129, 134, 138, 140, 141]

Five trials of E2V with concomitant progestin/progesterone reported bone density outcomes.[111, 142-145] Four of the five trials noted improvement in treatment groups compared to placebo,[111, 142-144] and one did not.[145]

Twenty-six trials evaluated the effect of CEE on bone density outcomes.[146-171] All trials reported significant within-group changes in bone density at multiple sites for various doses with higher doses showing greater changes. In a good-quality trial comparing combination treatment with CEE (with or without medroxyprogesterone) plus alendronate to either treatment alone, patients on combination therapy had a significantly greater increase in total hip BMD than those on either ALN or HRT alone after 3 years (p<.01).[170, 171] In one small (N=135) trial,[151] 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% 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.[147, 154, 158-160] A more recent substudy of the Women's HOPE trial found that most women on lower doses of CE with or without medroxyprogesterone (0.625, CE 0.625/MPA 2.5, CE 0.45, CE 0.45/MPA 2.5, CE 0.45/MPA 1.5, CE 0.3, CE 0.3/MPA 1.5) had less continued bone loss over 2 years than women randomized to placebo (See Table 9).[172]

The WHI study of CEE plus MPA[149] demonstrated consistent positive effects on BMD: hip BMD increased a mean of 1.7% and 3.7% by year 3, compared with a loss of 0.44% at year 1 and 0.14% improvement in the placebo group (p<0.001). Similar improvements were found in the lumbar spine. In subjects with 6-year follow-up BMD data (n=443), the percentage increase in lumbar spine BMD was 7.5% in the CEE plus MPA group compared with 2.6% in the placebo group. The CEE-only study of the WHI produced modest but consistent positive effects on bone mineral density.[173]

One study of esterified estrogen[174] examined dosages of 0.3, 0.625, and 1.25 mg daily, and all doses showed statistically significant increases in lumbar spine and total hip bone density compared to placebo ($p<0.05$). The 1.25 mg/day dose was significantly more effective in increasing bone density at the lumbar spine than the lower doses.[174]

Effect of discontinuation of estrogen on bone density

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.[175, 176] Both studies found the rate of bone loss after stopping estrogen was similar to that of women who did not receive estrogen treatment, as described below.

A follow-up study from the PEPI trial[175] 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.[176] 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 other meta-analyses

A Cochrane review and meta-analysis published in 2002 on estrogen and bone density and fractures was reviewed for this report.[7] Fifteen of the trials included in the Cochrane review did not meet inclusion criteria for this review because they used ineligible estrogen preparations.[177-191]

Results of the Cochrane meta-analysis included:

- 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% at the forearm, and 2.0% at the femoral neck.

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

Another meta-analysis, published in 2003,[192] similarly found that different estrogen preparations, including CEE, oral and transdermal E2, E2V, and EE, were equally effective in the maintenance or gain of BMD at the lumbar spine and hip. This study was restricted to placebo-controlled trials of at least 2 year's duration and enrollment of at least 60 subjects. Although the study did not report a systematic assessment of the quality of the trials selected for review, the number of dropouts in each trial and use of intention-to-treat results were assessed. The 2-year mean changes in lumbar spine BMD (weighted for the ratio of sample size/dropouts) are summarized as follows:

- 7.6% (range 1.5% to 13.4%) for CEE;
- 7.2% (range -1.5% to 20.0%) for oral E2, E2V, EE, and estrone sulphate;
- 7.5% (range 3.4% to 14.4%) for non-oral estrogens.

Fractures

Head-to-head comparisons

No head-to-head trials were found.

Placebo comparisons

We identified 11 studies of estrogen that included outcome data on fractures (Evidence Table 6). Seven were included[128, 135, 144, 155, 156, 168, 193] in a recent Cochrane meta-analysis,[7] and the remainder were more recently published.[4, 117, 149, 194]

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 for overall fractures (RR=0.82; 95% CI: 0.53, 1.29).[117] Both studies of transdermal E2 indicated no significant improvement in vertebral[128, 135] and non-vertebral fractures.[128] 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.[144]

Seven studies examined CEE preparations.[4, 155, 156, 163, 168, 193, 194] Although some of these studies showed a trend toward reduction of fractures at various sites in the treatment groups, only the WHI showed a significant result.[4] When compared with the placebo group, total fractures for women on CEE were significantly reduced (HR=0.76; CI: 0.69, 0.85).[4] Risks were also reduced for site-specific fractures of the hip and vertebra, although confidence intervals adjusted for multiple comparisons included 1.0.

In a more recent update of fracture data from the WHI[149] with average follow-up of 5.6 years, 8.6% of women in the CEE plus MPA group compared with 11.1% in the placebo group

had a fracture at any site (HR 0.76; 95% CI, 0.69-0.83) and CEE plus MPA reduced the risk of hip fracture by 33% (HR 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.

The WHI study of CEE use in women post hysterectomy[80] also reported a decrease in total fracture rates at mean follow-up interval of 6.8 years (HR 0.70, 95% CI, 0.63-0.79, 95% CI adjusted for multiple comparisons 0.59-0.83) ($p<0.001$). Hip fractures and clinical vertebral fractures were also decreased, although 95% confidence intervals adjusted for multiple comparisons overlapped a HR of 1.0 [hip fractures HR: 0.61 (adjusted 95% CI, 0.33 – 1.11); vertebral fractures HR 0.62 (adjusted 95% CI, 0.34-1.13)]. Additional data on fractures recorded through the study termination (average 7.1 years of follow-up)[173] also showed a reduction in incident fractures at the hip, spine, and wrist. These positive effects occurred largely irrespective of baseline risk factors for osteoporosis or fracture. The global index of overall health risks and benefits was balanced, however, with no evidence of overall benefit or risk noted even for women in the highest tertile of risk for fracture.

Comparison with Cochrane meta-analysis

Seven studies[128, 135, 144, 155, 156, 168, 193] reporting fracture outcomes were included in a Cochrane review published in 2002.[7] Two trials indicating significant fracture risk reduction, including the WHI, were not included because they were published after the Cochrane analysis.[117] Findings included:

- 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).[131, 151 ,164, 188]
- Five studies measured the effect of estrogen on nonvertebral fractures.[128, 144, 156, 168, 193]
    - One study indicated a statistically significant relative risk reduction for nonvertebral fractures with estrogen use.[144]
    - Three of the other studies had a risk reduction that was not statistically significant[128, 156, 193] and the other had a RR of 1.0.[168]
- When all studies were pooled, there was a nonsignificant reduction in nonvertebral fractures (RR=0.87; 95% CI: 0.71, 1.08).

Key Question 3. What is the comparative safety of different hormone therapy preparations for short-term use (<5 years)?

Summary points

- Breast tenderness and vaginal bleeding increase with all estrogen preparations.
- In the few studies reporting on endometrial hyperplasia, no cases were identified with estrogen treatment.
- The incidence of venous thrombosis was not increased in a large study of healthy women given estradiol and norethisterone.

- 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.
- The WHI CEE+MPA study reported an increased rate of vaginal bleeding, breast tenderness, headaches or migraines, and vaginal or genital discharge than women in the placebo group at 1-year follow-up in women asymptomatic at baseline.
- Cognitive function was not significantly affected in four fair-quality studies with follow-up between 12 weeks and 3 years.

Head-to-head trials

Adverse events reported in short-term head-to-head trials of different estrogen preparations are shown in Evidence Tables 7 (trials with symptom outcomes) and 8 (trials with bone outcomes). 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.[15]

Most head-to-head trials reported similar rates of specific adverse events and withdrawals due to adverse events between treatment groups, with a few exceptions. In one trial, a significantly greater incidence of breast tenderness was found in women randomized to oral E2 2 mg plus NETA versus CE 5 mg plus MPA, and more women in the E2/NETA group withdrew from the trial during the first 3 months (17.1% vs. 4.1%; $p<0.001$).[19] A trial of a vaginal ring releasing E2 compared with an E2 vaginal tablet found more withdrawals in the vaginal ring group, mainly occurring during the first 3 months of treatment and due to abdominal discomfort, lower back pain, and slippage of the ring.[25] 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.[24]

Placebo-controlled trials

Withdrawals due to adverse effects and withdrawals due to specific adverse effects in placebo controlled trials are summarized in Evidence Table 9 for trials of hot flashes and Evidence Table 10 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 pruritus, cholecystitis, liver effects, and others including breast cancer and additional problems. These outcomes were reported unevenly across studies and could not be combined in summary statistics.

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; 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.

In Update #3, among placebo-controlled trials examining efficacy/effectiveness of estrogen projects on symptoms, five studies reported harms.[31, 34-36, 38] All efficacy trials with bone density outcomes reported some information on harms. We identified an additional four studies which reported adverse effects without reporting efficacy or effectiveness (Evidence Tables 9 and 10).[195-198]

Oral estrogen/progesterone regimens increased vaginal spotting and atypical vaginal bleeding compared with placebo.[31, 34, 38, 121, 122, 141, 170, 198, 199] Withdrawal rates due to vaginal bleeding specific to treatment group were not reported in most studies, however. In a trial of BMD outcomes, 18% of women taking E2 1 mg plus intermittent norgestimate withdrew due to uterine bleeding.[121] A study of estradiol/drospirenone reported one woman with severe bleeding requiring hysterectomy, revealing adenomyosis and leiomyomata.[36] Langer and colleagues[198] reported no cases of endometrial hyperplasia in the treatment or placebo group; one case of endometrial cancer occurred in the placebo group.

In the ULTRA study[196] of low-dose unopposed transdermal estradiol (14 ug per day), vaginal bleeding occurred at year 1 in 5-6% of participants in both groups. Rates in year 2 were also similar (between-group p-value 0.03). Focal atypical endometrial hyperplasia developed in 1/188 women in treatment group and in 0/177 in the placebo group. One adenosarcoma of the uterus developed in the treatment group and none with placebo.

Breast tenderness was reported significantly more frequently with conjugated equine estrogen with medroxyprogesterone than with placebo.[170, 171] Headache[34] and dizziness or disorientation[31, 34] were reported at similar rates between estrogen users and the placebo group, as was the percentage of study subjects gaining weight.[31] Greenspan and colleagues[31] reported that the incidence of venous thromboembolic disease, endometrial and colon cancer, hospitalizations, myocardial infarction, and clinical fractures was similar between subjects receiving conjugated equine estrogen with medroxyprogesterone and placebo. Speroff and colleagues[38] reported that rates of headache, breast tenderness, vaginal bleeding, and palpitations were evenly distributed between treatment with ethinyl estradiol/norethindrone acetate and placebo (n=266). In a small study (n=40), similar rates of unspecified gastrointestinal adverse effects and headache were reported between the group using CEE and the placebo group (no statistics provided).[35]

In the WHI (see Table 11, summary table), vaginal bleeding was frequent among the CEE plus MPA treatment group,[81] occurring in 42.5% and 51.0% of subjects in the first 6 weeks and 6 months of the trial, respectively. At year 5, 13.0% of the treatment group reported bleeding. In contrast, reports of bleeding never exceeded 8% in the placebo group. Among women asymptomatic at baseline, the treatment group also reported more breast tenderness at 1-year follow-up (CEE+MPA 9.3%, placebo 2.4%, p=0.026), particularly among thinner or older women and those further from menopause. This group also reported more vaginal discharge (CEE+MPA 4.1%, placebo 1.0%, p<0.001), more headaches or migraines (p=0.003), but less vaginal dryness (p<0.001).[81]

In Update #3, six new trials were identified which examined the effects of hormone therapy on cognitive function with follow-up between 12 weeks and 3 years,[26, 31, 32, 40, 43, 78] all demonstrating no differences between groups at up to 2-year followup. The fair-quality ULTRA trial[78] found no significant differences at 2-year follow-up between treatment with low-dose transdermal estradiol and placebo for multiple measures of cognitive function: Mini Mental

State Exam, logical memory, Brief Visual Spatial Memory Test, memory and recall of words, and verbal fluency. Similar negative results were found in a small, fair-quality study of estradiol patch.[32] In the fair quality study (n=373), the Folstein Mini-mental State Examination did not differ between the hormone replacement group (conjugated equine estrogen with or without progesterone depending on uterine status) and placebo at 3-year follow-up. Self-reported function and physical activity levels also did not differ significantly between groups.[31] Almeida and colleagues[26] also did not find significant differences between treatment with oral estradiol and placebo for a battery of cognitive tests among women 70 years of age and older. A poor-quality study did not find differences between treatment group for multiple measures of cognitive function either.[43] A fair-poor quality study reported improvement in 1 of 5 measures of cognitive function at 12-week follow-up (p=0.05).[40]

Key Question 4. What is the comparative safety of different hormone therapy preparations for long-term use (5 or more years)?

Summary points

- In the WHI CEE/MPA study, coronary heart disease (CHD) events increased significantly, although CHD mortality did not at 5.2-year follow-up. In the WHI CEE-only study, CHD events were not increased.
- The risk of stroke and venous thromboembolism were increased in both the CEE-only and CEE/MPA WHI studies.
- The incidence of probable dementia increased in the WHI study of CEE/MPA, but not in the CEE-only study. Global cognitive function and mild cognitive impairment did not differ from placebo groups in either WHI study.
- No head-to-head studies were available that compared adverse effects of different estrogen preparations after 5 or more years of use.
- The WHI and HERS/HERS II studies provided the best evidence of long-term adverse effects for postmenopausal estrogen use and both used continuous regimens of CEE/MPA.[4, 194, 200]
- In the WHI CEE plus MPA study, a significant increase was noted in the hazard ratio (unadjusted for multiple comparisons) for cardiovascular events, stroke, venous thromboembolism, invasive breast cancer (p=0.05), and probable dementia. Rates of cardiovascular mortality were not increased
- In the WHI CEE-only study, a significant increase was noted in the hazard ratio (unadjusted for multiple comparisons) for stroke and venous thromboembolism. Rates of probable dementia, cardiovascular events or mortality, and invasive breast cancer were not increased.
- The WHI is the largest trial to evaluate the potential harms of postmenopausal estrogen use for both continuous CEE, MPA,[4] and CEE only among woman post hysterectomy (Table 10).[80] The WHI was designed as a primary prevention trial, not a trial of menopausal symptom treatment.

Table 10. Women's Health Initiative: Summary of the adverse effects

Outcome	CEE+MPA (5.2y)	CEE alone (6.8y)
Vaginal bleeding	↑ 1, 3y	Not applicable
Breast tenderness	↑ 1y	Not reported
CVD events	↑	NSD
CVD mortality	NSD	NSD
Stroke	↑	↑
Invasive breast cancer	↑ (p=0.05)	↓ (p=0.06)
Venous thromboembolism	↑	↑ (5.2y)
Mild cognitive impairment	NSD at 4y	NSD
Probable dementia	↑ at 4y	NSD

Cardiovascular events

The WHI demonstrated a statistically significant increase in coronary heart disease (CHD) events among users of CEE and MPA without known heart disease at a mean follow-up interval of 5.2 years (HR 1.29, 95% CI, 1.02, 1.63).[4] Mortality from coronary heart disease events was not elevated, however (HR 1.18, 95% CI, 0.70 – 1.97). Events occurred early in the trial and persisted throughout the 5.2-year follow-up period. No interaction was found for age, race, BMI, smoking status, blood pressure, diabetes, statin use, or the effect of CEE/MPA on CHD events. Absolute increases in coronary heart disease cases were estimated at 7 per 10,000 person-years. Among the small subgroup with established CHD at baseline (n=400), the HR was 1.29 (95% CI, 0.64 – 2.56) and was similar to the group without known CHD.

Among women in the WHI using CEE alone (post hysterectomy),[80] no significant effect on CHD rates was observed compared with placebo at a mean follow-up of 6.8 years (5 fewer events per 10,000 person-years with CEE, HR 0.91, 95% CI, 0.75 – 1.12). Total mortality was also not significantly different between treatment groups. Among women with prior myocardial infarction or revascularization procedures, the effect of CEE compared to placebo on CVD event rates did not differ from the effect among women without known CHD.

The WHI study examined a global index of risks and benefits which was defined for each subject as the time to the first event among the monitored outcomes, including CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, hip fractures, and death.[80] This measure was used to assess the overall balance of risks and benefits[4] and was balanced overall (HR 1.01, 95% CI 0.91 – 1.12). CEE did not affect total mortality or cause-specific mortality.[80]

The Heart and Estrogen progestin Replacement Study (HERS)[193] was a RCT of 2,763 women with a uterus comparing 0.625 mg CEE plus 2.5 mg MPA to placebo. All participants had documented coronary heart disease at randomization. The unadjusted relative hazard (HR)

for CHD events was not different from placebo (HR 1.00, 95% CI, 0.84 – 1.17) over the mean follow-up of 6.8 years.[200] In *post hoc* analyses, the HR for the first year of treatment was 1.52 (95% CI, 1.01 – 2.29), with lower rates in subsequent years.

Stroke

Risk for stroke was elevated in the WHI for CEE/MPA compared to placebo (HR 1.41, 95% CI, 0.97 – 1.85; adjusted 95% CI, 0.86 - 2.31)[4] and in 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 reported a significant increase in stroke risk (RR 1.12, 95% CI, 1.01 - 1.23).[201] Absolute increases in stroke are estimated at 8 per 10,000 person-years using WHI estimates.[4]

In the CEE-only WHI study[80] the risk for stroke was increased by 39% in the CEE group (p=0.007; HR 1.39, 95% CI, 1.10 - 1.77). The differences in cumulative hazards for stroke began to emerge early after randomization and persisted throughout the follow-up period (mean 6.8 years, range 5.7 to 10.7 years). A greater risk of stroke was estimated among study participants who complied with study medications, taking more than 80% of study drugs, compared to the intention-to-treat population.

Venous thromboembolism

Risk for venous thromboembolism (including both deep vein thrombosis and pulmonary embolism) were elevated with long-term use of CEE/MPA in the WHI (HR 2.11, 95% CI, 1.26 - 3.55).[4] Absolute increases in venous thromboembolic events are estimated at 18 per 10,000 using WHI estimates.[4] In the CEE-only WHI trial,[80] active treatment increased venous thromboembolic disease (p = 0.03, HR 1.47, 95% CI, 1.04 – 2.08; adjusted 95% CI, 0.87 – 2.47).

Venous thromboembolic events were elevated during the HERS study[193] with 4.1 years of follow-up (HR 2.66, 95% CI, 1.41 – 5.04), however, during follow-up to a mean of 6.8 years in HERS II, this elevated risk decreased (p-value for time trend =0.08). The overall risk for all 6.8 years was 1.08 (95% CI, 1.28 – 3.4).[194] A review and meta-analysis of studies of estrogen and venous thromboembolic events confirmed these findings, although studies with several different estrogen preparations were included and data were not stratified by preparation.[202]

The incidence of venous thrombosis was not increased in a large study (n=2016) with 1-year follow-up of healthy postmenopausal women treated with sequential estradiol and norethisterone acetate; the only three cases were in the placebo and non-treatment groups.[197] New or worsening urinary incontinence increased with CEE among post-hysterectomized women (n=619). At 3-year follow-up, rates were 7.0% with treatment and 1.3% with placebo (p<0.02).[195]

Breast cancer

The WHI of CEE/MPA reported increased risks for invasive breast cancer at 5.2 years of follow-up (HR 1.26; 95% CI, 1.00 - 1.59).[4] On the other hand, HERS/HERS II indicated no increase after 6.8 years (RR=1.27; 95% CI: 0.84, 1.94).[194] Mortality from breast cancer was not elevated in either of these studies.

This increased risk of breast cancer with estrogens in the WHI CEE/MPA trial is consistent with estimates based on a meta-analyses of other studies (RR 1.23 to 1.35).[201] Absolute increases in invasive breast cancer cases were estimated at 8 per 10,000 with CEE/MPA using WHI estimates.[4] Comparisons among estrogen preparations have not been conducted because of the limited data about types of preparations provided in the studies.

In the WHI study of CEE alone, the incidence of invasive breast cancer, the primary safety outcome for this trial, was decreased[80] over a mean follow-up duration of 6.8 years (HR 0.77, 95% CI, 0.59 – 1.01; 26 versus 33 cases per 10,000 person-years, p=0.06). This differential effect became apparent beginning in year 2.

A cohort study followed 3,175 French women, users (89% estrogen with progesterone) and non-users of estrogen, for 8.9 years for incidence of breast cancer.[203] 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.

Cognition and dementia

In the WHI Memory Study (WHIMS), an ancillary study to the WHI study, examined the effect of postmenopausal CEE with and without MPA on dementia and cognitive impairment in healthy women 65 years of age and older.[5, 204-208] The incidence of probable dementia among participants with an intact uterus taking CEE and MPA for mean duration 4 years (n=4532) was increased (HR 2.05, 95% CI, 1.21 – 3.48). Risk increased with age and with lower Mini Mental State exam scores at baseline.[5] Mild cognitive impairment was not significantly increased (HR 1.07, 95% CI, 0.74 – 1.55). Global cognitive function increased in both treatment and placebo groups for year 1 through 4 (likely due to a practice effect repeated testing) and then decreased in both groups with no significant differences between groups at year 5 and 6.[205] Mean rates of change in cognitive function over time did not vary significantly between treatment groups for age, education, race, BMI, diabetes, or use of aspirin when multiple comparisons were taken into account (significant p<0.003).[205]

The WHI Study of Cognitive Aging (WHISCA) was an ancillary study to the WHI and WHIMS[206] and started 3 years after WHI randomization. CEE/MPA appeared to have different effects on various cognitive domains in older women after 4.35 years of treatment, with a negative effect on verbal memory (p< 0.01) and a positive effect on figural memory (p=0.012). There were no significant differences between treatment and placebo for other cognitive domains, depressive symptoms, and affect.

In the CEE-only study of the WHI, the incidence of probable dementia was not significantly increased at mean follow-up of 5.2 years (HR 1.49, 95% CI, 0.83 – 2.66) and was not significantly different from rates with CEE/MPA.[207] Rates of mild cognitive impairment were also not significantly increased.[207] Similar to patterns in the CEE/MPA trial, global cognitive function increased for the first 4 years, then decreased, with no significant differences between treatment groups.[204] Subjects with lower baseline scores in cognitive function had the greatest decline in cognitive function (p<0.01).[204] The largest declines in scores occurred more frequently in CEE than in placebo, and the relative risk of decline of 10 units in the Mini Mental State exam with CEE compared to placebo was 1.47 (95% CI, 1.04 - 2.07).[204]

Cholecystitis

HERS/HERS II reported increased risks for biliary tract surgery among estrogen users with long-term use (mean follow-up of 6.8 years; RR=1.44; 95% CI: 1.10, 1.90).[194] The Nurse's

Health Study also reported an increased risk with long-term use (RR=2.5; 95% CI: 2.0, 2.9).[209] Data from this study also suggests that risk for cholecystitis increases with duration of estrogen use.

The HERS/HERS II trial reported increased risks for biliary tract surgery among estrogen users early in the study (RR 1.39 over the first 4.1 years, 95% CI, 1.00 - 1.93).[194] Follow-up of 6.8 years revealed an overall HR of 1.48 (95% CI, 1.12 – 1.95). This outcome 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).[209]

Ovarian cancer and endometrial cancer

The WHI and HERS/HERS II reported no increase in ovarian or endometrial cancer with CEE and MPA.[4, 194] Other studies of unopposed estrogen have indicated increased endometrial cancer for a woman with a uterus.[210] Observational studies of estrogen imply an increased risk for ovarian cancer [211, 212] while others do not.[213]

Systematic review

A recent Cochrane systematic review assessed the effect of long-term hormone therapy on mortality, heart disease, venous thromboembolism, stroke, transient ischemic attacks, breast cancer, colorectal cancer, ovarian cancer, endometrial cancer, gallbladder disease, cognitive function, dementia, fractures, and quality of life.[214] Searches were conducted through November 2004. Fifteen randomized controlled trials were included, but the WHI and HERS, the largest trials, contributed most of the data. This review concluded that combined continuous hormone therapy significantly increased the risk of both venous thromboembolism and coronary events after one year, stroke after 3 years, breast cancer after 5 years, and gallbladder disease. In women over age 65, the incidence of dementia was also increased. In younger women (age 50 to 59 years) taking either combined regimens or estrogen-only hormone therapy, there was an increased risk of venous thromboembolism, but the absolute risk was low.

Key Question 5. 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 50's. Data was 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,[149] 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. Younger post-menopausal women (50-54 years of age) who reported moderate-to-severe vasomotor symptoms at baseline were examined in the WHI CEE/MPA study[85] and there was a positive

effect on sleep disturbance, but no effect on other HRQL measures, despite significant improvement in vasomotor symptoms. These data were consistent with results in older women

For Update #3, several studies examined older women and results were similar to studies among younger women. A study of oral estradiol compared to placebo in women over 70 years with an intact uterus did not report significant changes in a "SF-36 score" or in cognitive function.[26] In a study of community-dwelling women 65 years of age and older, Greenspan and colleagues[31] reported no significant difference between treatment with CEE 0.625 mg with or without MPA (depending on uterine status) and placebo for self-reported functional assessment including instrumental activities of daily living at one year and cognitive function at 3 years. The ULTRA study examined the use of low-dose transdermal estradiol in women 60 to 80 years and found that active treatment did not improve menopausal symptoms, urinary incontinence, or cognitive function at 2 years.[30, 39, 78]

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 differences in lifestyle factors could influence outcomes. The WHI reported a subanalysis by race.[149] 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.

For Update #3, we identified no additional information on the effectiveness or harms in racial or ethnic groups.

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.[4, 149] 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.

In the WHI CEE/MPA study,[4] rates of CHD events were elevated to a similar degree in the small subgroup with established CHD at baseline (n=400) (HR 1.29, 95% CI, 0.64 – 2.56) compared to the main study group without known CHD.

In the WHIMS study,[5, 204-208] the increased incidence of probable dementia among participants taking CEE (+/-_ MPA) was positively related to increasing age and lower Mini Mental State exam scores at baseline.[5]

For Update #3, we identified no other additional information.

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.

For Update #3, we identified no additional information.

SUMMARY

Results of this review are summarized in Table 11.

Table 11. Summary of the evidence by key question

Key Question	Quality of the evidence	Conclusions
1. What is the comparative efficacy of different hormone therapy preparations for reducing symptoms of menopause?	Fair: moderate to high drop-out rates.	**Placebo-controlled trials** Symptoms improve with estrogen +/- progesterone compared with placebo; low dose transdermal estrogen (1 trial) did not improve symptoms. Other outcomes: estrogen effect on vaginal dryness was inconsistent; data on sleep disturbance and mood were sparse and conflicting; health-related quality of life improved in some studies but not in the WHI at 3-year follow-up.
2. What is the comparative efficacy of different hormone therapy preparations for preventing low bone density and fractures?	Fair-good	Fair: small numbers in most studies, recruited from clinics. The majority of studies were 1 or 2 years in duration. In placebo-controlled and head-to-head trials, estrogen regimens increased BMD or slowed rate of bone loss, but differences among estrogen preparations were not found. In both the CEE-only and the CEE-progesterone studies of the WHI, total fractures decreased and bone mineral density increased at over 5-year follow-up. There are no head-to-head trials with fracture outcomes.
3. What is the comparative safety of different hormone therapy preparations for short-term use (<5 years)?	Fair	**Placebo-controlled trials** Estrogen preparations increased breast tenderness and vaginal bleeding. Endometrial hyperplasia did not occur in the few studies that examined this outcome.
4. What is the comparative safety of different hormone therapy preparations for long-term use (5 or more years)?	Fair: based on data from WHI and HERS/HERS II; moderate to high drop-out rates.	In the WHI, CEE/MPA increased CHD events in women without known CHD, but CHD mortality was not increased at 5.2-year follow-up. WHI, CEE-only and the HERS study did not find an increase in CHD events. Risk of stroke and venous thromboembolism were increased in the WHI with both CEE and CEE/MPA. Breast cancer was increased with CEE/MPA, but not in the HERS trial and not in the CEE-only study. The incidence of probable dementia increased with CEE/MPA usage, this effect was not seen with CEE only. Small studies examining cognitive function found no differences between estrogen treatment and placebo.
5. Are there subgroups of patients for which one medication or preparation is more effective or associated with fewer adverse effects?	Fair: based on data from WHI; moderate to high drop-out rates.	In the WHI (CEE and CEE/MPA) study, the positive effect of treatment on symptoms was similar in women 50-54 compared to older women. Women with and without CHD at baseline had a similar increase in risk of CHD events in the WHI CEE/MPA study.

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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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.
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)
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

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)
17 exp FRACTURES/ or fracture$.mp.
18 exp Bone Density/ or bone density.mp.
19 17 or 18
20 16 and 19

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 Buckler, 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

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 Buckler, 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

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
Jirapinyo et al, 2003	Yes; methods NR	Method NR	Mean Greene score slightly higher in E2 than placebo (20.1; SD 10.1 vs 17.9; SD 13.3)	Yes	Double-blind; methods NR	No; PP analysis excludes 30% randomized	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
Utian et al., 2004	Yes	Yes	Slight, non-significant racial variation among Rx groups	Yes	Double-blind	No (excludes 5 withdrawn after 1-day washout period)	Unclear

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

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
Jirapinyo et al, 2003	Attrition yes	16.7% withdrew in E2; 11.7% in placebo	Fair	Novo Nordisk Asia Pacific Pte Ltd.	Fair HRT-naïve women only
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
Utian et al., 2004	Attrition yes; Adherence yes	Discontinuations: Placebo: 24% 0.3 mg: 19% 0.625 mg: 15% 1.25 mg: 17% Discontinuation not sig. different between groups (P>0.05).	Fair	Endeavor Pharmaceuticals, Inc.	Fair

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?
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
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

Study Year	Reporting of attrition, contamination, etc?	Differential loss to followup or overall high loss to followup?	Quality Score	Funding source	External validity
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
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

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

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

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

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?
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
Davas, 2003	Yes, method NR	NR	Yes	Yes	NR	No	Unclear
Gambacciani, 2003	Yes	NR	Yes	Yes	Open-label	No	Unclear

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

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
Davas, 2003	Some	13 subjects dropped due to noncompliance, groups not specified.	Fair	NR	Poor
Gambacciani, 2003	Attrition yes	Control: 50% Rx: 30%	Poor: High loss to followup; treatment not blinded; 40% of controls withdrew for treatment of climacteric symptoms	NR	Poor

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?
Hulley, 2002 (HERS II)	Yes	Unclear	Yes	Yes	Double blind	Yes	Yes
Jirapinyo, 2003	Yes; methods NR	Yes; methods NR	Mean Greene score slightly higher in E2 than placebo (20.1 vs 17.9)	Yes	Double-blind; methods NR	No; PP analysis excludes 30% of randomized	Unclear
Lees, 2001	Yes	Unclear	Yes	Yes	Double blind	NR	Unclear

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

Study Year	Reporting of attrition, contamination, etc?	Differential loss to followup or overall high loss to followup?	Quality Score	Funding source	External validity
Hulley, 2002 (HERS II)	Some	7% lost to followup	Fair	Wyeth-Ayerst *	Fair
Jirapinyo, 2003	Attrition yes	16.7% withdrew in E2; 11.7% in placebo	Fair	Novo Nordisk Asia Pacific Pte Ltd.	Fair HRT-naïve women only
Lees, 2001	Some	Over 50% lost to followup - did not complete study	Fair/ Poor	Heart Disease and Diabetes Research Trust ∞	Fair

* 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.

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?
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
Prestwood, 2003	Yes, but method not reported	Method not reported	Physical activity in E2 significantly greater than placebo, otherwise similar	Yes	Double blind	Yes (Gaussian models used to account for missing data)	Yes
Recker, 1999	Yes	Yes	Slight variation	Yes	Double blind	Yes	Unclear

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

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
Prestwood, 2003	Attrition yes; adherence yes	E2: 29% discontinued Placebo: 36%	Fair	Claude Pepper Older Americans Independence Center/ General Clinical Research Center/ Paul Beeson Physician Faculty Scholars in Aging Research Program	Fair
Recker, 1999	Yes	P: 16% Rx: 20%	Fair	National Institutes of Health	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?
Villareal, 2001	Yes	Yes	Yes	Yes	Double blind	Yes	Yes
WHI, 2002	Yes	Yes	Yes	Yes	Double blind	Yes	Yes

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

Study Year	Reporting of attrition, contamination, etc?	Differential loss to followup or overall high loss to followup?	Quality Score	Funding source	External validity
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

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

Appendix G. Quality assessment of trials added for Update #3

Author	Year	Quality rating	Randomization method adequate?	Allocation concealment method adequate?	Groups similar at baseline?	Comments	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?
Akhila	2006	POOR	Method not described	Method not described	Yes		No	No	NR	No	No
Almeida	2006	FAIR	Yes	Yes	Yes		Yes	Yes	Yes	Unclear, reported as double blind	Yes
Arrenbrecht	2004	POOR	Method not described	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Baksu	2005	FAIR	Method not described	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Crisafulli	2004	FAIR	Yes	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Dayal	2005	FAIR	Yes	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Ettinger, Diem 2006	2004	FAIR	Yes	Method not described	No	Lumbar spine BMD lower in placebo group	Yes	Yes	Yes	Yes	Yes
Gambacciani	2005	POOR	Method not described	Method not described	Yes		Yes	Yes	NR	NR	NR

Appendix G. Quality assessment of trials added for Update #3

Author	Attrition reported?	Adherence reported?	Contamination reported?	Loss to followup differential or high?	Comments	Intention to treat analysis?	Comments	Post-randomization or post-enrollment exclusions?	Comments	Funding
Akhila	Yes	No	No	Yes		No	88/116 analyzed (75.9%)	Unable to determine		Not reported
Almeida	Yes	No	No	No		Yes	all analyzed, LOCF	No		Foundation
Arrenbrecht	Yes	No	No	Unable to determine		No	80.1% analyzed	Unable to determine		Not reported
Baksu	Yes	No	No	No		No	Completers only analyzed	Unable to determine		Not reported
Crisafulli	Yes	No	No	No		Yes		Unable to determine		Not reported
Dayal	Yes	No	No	No		Yes		Yes	8 women withdrew prior to receiving medication	Berlex
Ettinger, Diem 2006	Yes	No	No	No		Yes	LOCF	No		Berlex; one author holds a patent on the study drug
Gambacciani		No	No	Unable to determine		Unable to determine		Unable to determine		Not reported

Appendix G. Quality assessment of trials added for Update #3

Author	Year	Quality rating	Randomization method adequate?	Allocation concealment method adequate?	Groups similar at baseline?	Comments	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?
Greenspan (A)	2003	FAIR-GOOD	Yes	Yes	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Greenspan (B)	2005	FAIR	Yes	Method not described	Yes		Yes	Yes	Yes	Yes	Unclear, reported as double blind
Greenwald	2005	FAIR-POOR	Method not described	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Heikkinen	2004	POOR	Yes	Yes	Yes		Yes	Yes	No	No	No
Heinrich	2005	POOR	Not randomized	Not randomized	NR	Groups balanced for age, BMI and verbal IQ	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind

Appendix G. Quality assessment of trials added for Update #3

Author	Attrition reported?	Adherence reported?	Contamination reported?	Loss to followup differential or high?	Comments	Intention to treat analysis?	Comments	Post-randomization or post-enrollment exclusions?	Comments	Funding
Greenspan (A)	Yes	Yes	No	No		Yes		No		NIH, Merck, and Wyeth
Greenspan (B)	Yes	No	No	No		Yes		Yes	3 excluded for medical contraindication	NIH; Wyeth and Merck provided study medication
Greenwald	Yes	No	No	No		Yes	LOCF	Unable to determine		Novo Nordisk
Heikkinen	Yes	No	No	Unable to determine		No	316/464 analyzed (68.1%); Only completers and those without missing data were analyzed	Yes	52 women excluded because of missing data, poor quality of BMD scans, or presence of bone deformities	Schering AG
Heinrich	Yes	No	No	No		No	35/51 analyzed (68.6%), compliant subjects not analyzed	Yes	5/51 for noncompliance	Foundation

Appendix G. Quality assessment of trials added for Update #3

Author	Year	Quality rating	Randomization method adequate?	Allocation concealment method adequate?	Groups similar at baseline?	Comments	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?
Joffe	2006	FAIR	Method not described	Method not described	Yes		Yes	Yes	Yes	Yes	Yes
Levine	2005	FAIR	Method not described	Method not described	NR		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Liu	2005	FAIR	Method not described	Yes	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Newton	2006	FAIR	Yes	Yes	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Odmark	2004	FAIR	Yes	Method not described	Yes	lower DBP and higher BMI in starters vs switchers	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes

Appendix G. Quality assessment of trials added for Update #3

Author	Attrition reported?	Adherence reported?	Contamination reported?	Loss to followup differential or high?	Comments	Intention to treat analysis?	Comments	Post-randomization or post-enrollment exclusions?	Comments	Funding
Joffe	Yes	No	No	No		Yes		No		Pfizer; Berlex provided study medication
Levine	Yes	No	No	Unable to determine		Unable to determine	Unclear how many patients analyzed	Unable to determine		Not reported
Liu	Yes	Yes	No	Unable to determine		Yes		Unable to determine		NIH (National Institute of Aging)
Newton	Yes	Yes	No	No		Yes	95% analyzed at 3m, 92% at 12m	No		NIH
Odmark	Yes	No	No	No		No	symptom scores on 208/249 (83.5%)	Yes	1 excluded due to loss of diary card and rating scales; 2 never started treatment	Wyeth

Appendix G. Quality assessment of trials added for Update #3

Author	Year	Quality rating	Randomization method adequate?	Allocation concealment method adequate?	Groups similar at baseline?	Comments	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?
Pornel	2005	POOR	Method not described	Method not described	NR	Reported for efficacy evaluable population only	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Reddy	2006	FAIR	Yes	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes

Appendix G. Quality assessment of trials added for Update #3

Author	Attrition reported?	Adherence reported?	Contamination reported?	Loss to followup differential or high?	Comments	Intention to treat analysis?	Comments	Post-randomization or post-enrollment exclusions?	Comments	Funding
Pornel	Yes	Yes	No	Unable to determine		No	Report main outcome on 476/1143 patients only. Number in ITT population not reported	Unable to determine		Not reported
Reddy	Yes	Yes	No	No		Yes		Yes	2/60 for noncompliance	NIH; Pfizer provided gabapentin; one author has patent on gabapentin for hot flushes

Appendix G. Quality assessment of trials added for Update #3

Author	Year	Quality rating	Randomization method adequate?	Allocation concealment method adequate?	Groups similar at baseline?	Comments	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?
Reid	2004	FAIR	Method not described	Method not described	Yes		Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Schiff	2005	FAIR-POOR	Yes	Yes	NR		Yes	Yes	NR	NR	NR
Schurmann	2004	FAIR	Method not described	Method not described	NR		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Serrano	2006	FAIR	Yes	Yes	Yes		Yes	Yes	No	No	No
Speroff (A)	2006	FAIR	Yes	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes

Appendix G. Quality assessment of trials added for Update #3

Author	Attrition reported?	Adherence reported?	Contamination reported?	Loss to followup differential or high?	Comments	Intention to treat analysis?	Comments	Post-randomization or post-enrollment exclusions?	Comments	Funding
Reid	Yes	Yes	No	No	28/619 (4.5%)	Yes		Yes	6/619 (0.9%) patients never received study drug; additionally, 5.0% discontinued for protocol violation.	Lilly
Schiff	Yes	Yes	No	No		No	19/24 analyzed (79.2%)	Yes	2/24 excluded for lack of compliance	Merck
Schurmann	Yes	No	No	No		Yes		No		Schering
Serrano	Yes	No	No	No		No	184/226 (81.4%) analyzed	No		Susan G. Komen Foundation and Italian Foundation for Cancer Research
Speroff (A)	Yes	Yes	No	No		Yes	289/293 analyzed (98.6%)	No		Warner Chilcott

Appendix G. Quality assessment of trials added for Update #3

Author	Year	Quality rating	Randomization method adequate?	Allocation concealment method adequate?	Groups similar at baseline?	Comments	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?
Speroff (B)	2000	FAIR	Method not described	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Utian	2005	FAIR	Yes	Yes	No	fewer women in EA group had dyspareunia (27.6% vs 38% in estradiol and 36.6% in CEE groups)	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Warming (A)	2004	FAIR-POOR	Method not described	Yes	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind
Warming (B)	2005	FAIR	Method not described	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Weisberg	2005	FAIR	Yes	No	Yes		Yes	Yes	Partial (for some outcomes)	No	No
Wolf	2005	POOR	Not randomized	Not randomized	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind

Appendix G. Quality assessment of trials added for Update #3

Author	Attrition reported?	Adherence reported?	Contamination reported?	Loss to followup differential or high?	Comments	Intention to treat analysis?	Comments	Post-randomization or post-enrollment exclusions?	Comments	Funding
Speroff (B)	Yes	No	No	No		Unable to determine	Unclear how many analyzed	Unable to determine		
Utian	Yes	Yes	No	No		Yes		Yes	1 woman who never took study drug	Warner Chilcott
Warming (A)	Yes	No	No	No		No	Appears that only completers analyzed (180/240) (states ITT)	No		Not reported; one author from Wyeth
Warming (B)	Yes	No	No	No		Yes		Unable to determine	4% other Table 4	Not reported
Weisberg	Yes	Yes	No	Unable to determine		No	155/185 analyzed (83.8%)	Unable to determine		Pharmacia Upjohn
Wolf	Yes	No	No	No		No	35/51 analyzed = 69%	Yes		Governmen t

Appendix G. Quality assessment of trials added for Update #3

Author	Year	Quality rating	Randomization method adequate?	Allocation concealment method adequate?	Groups similar at baseline?	Comments	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?
Yaffe	2006	FAIR	Method not described	Method not described	Yes		Yes	Yes	Yes	Yes	Yes

Appendix G. Quality assessment of trials added for Update #3

Author	Attrition reported?	Adherence reported?	Contamination reported?	Loss to followup differential or high?	Comments	Intention to treat analysis?	Comments	Post-randomization or post-enrollment exclusions?	Comments	Funding
Yaffe	Yes	Yes	No	No		Yes	417 analyzed, but not clear how missing data handled	No		Berlex and National Institute on Aging