Commonly Used Types of Postmenopausal Estrogen for Treatment of Hot Flashes

Scientific Review

Heidi D. Nelson, MD, MPH

Context Recommendations for postmenopausal hormone therapy have changed since the Women's Health Initiative indicated that estrogen was harmful for use in disease prevention; however, treatment of menopausal symptoms with low-dose estrogen remains an approved indication for use.

Objective To compare the short-term efficacy and adverse effects of 2 commonly used estrogens, conjugated equine estrogen (CEE) and 17β-estradiol, for reducing menopausal hot flashes by systematically reviewing randomized controlled trials.

Data Sources MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and Cochrane Controlled Trials Registry were searched from the database start dates to July 2003 using database-specific key words. Reference lists of published articles, experts, and pharmaceutical manufacturers were also consulted.

Study Selection English-language abstracts of double-blind, randomized, placebo-controlled trials and systematic evidence reviews of oral CEE and oral and transdermal 17β-estradiol, and treatment of menopausal hot flashes and their adverse effects.

Data Extraction Study design, population characteristics, eligibility criteria, interventions, withdrawals, adverse effects, and results for each outcome. Study quality was assessed using predefined criteria based on parameters developed with the US Preventive Services Task Force and the UK National Health Services Centre.

Data Synthesis A total of 32 trials including 4 head-to-head comparisons met inclusion criteria; 14 trials met criteria for meta-analysis. All estrogen agents significantly reduced the weekly number of hot flashes compared with placebo (CEE, 1 trial: mean change, –19.1; 95% confidence interval [CI], –33.0 to –5.1; oral 17β-estradiol, 5 trials: pooled weighted mean difference, –16.8; 95% CI, –23.4 to –10.2; transdermal 17β-estradiol, 6 trials: pooled weighted mean difference, –22.4; 95% CI, –35.9 to –10.4); differences between agents were not significant. Breast tenderness and atypical vaginal bleeding were the most frequently reported adverse effects among estrogen users. The influence of progestin or progesterone use, cyclic and continuous regimens, and differences in adverse effects could not be determined.

Conclusion Conjugated equine estrogen and 17β-estradiol have consistent and comparable effects on treatment of menopausal hot flashes and may have similar short-term adverse effects.

JAMA. 2004;291:1610-1620 www.jama.com

ESTROGEN WAS APPROVED AS A hormone supplement in the 1940s to treat menopausal symptoms. During the ensuing years, observational studies indicated additional health benefits for estrogen users such as prevention of chronic diseases like cardiovascular disease and osteoporosis.[1] A national survey conducted in 1995 indicated that 37% of women aged 50 years or older were using estrogen for multiple purposes.[2]

Estrogen use has decreased since 2002[3,4] when the results of the Women's Health Initiative (WHI), the first large randomized controlled trial of estrogen for prevention of disease, released its findings contradicting previous beliefs about cardiovascular benefits.[5] In this study, women using conjugated equine estrogen (CEE) and medroxyprogesterone acetate had significantly increased risks of coronary heart disease events, strokes, and breast cancer than women taking placebo.[5] The US Food and Drug Administration recently ordered estrogen safety warnings on product labels referring to WHI findings and altered approved indications for its use.[6,7] Package inserts indicate that treatment of menopausal symptoms remains an indication for estrogen use, although now physicians are advised to use the smallest effective dose for the shortest duration possible.[7] The National Institutes of Health added steroidal estrogens to its list of known hu-

See also p 1621.

CME available online at www.jama.com

Author Affiliations: Oregon Evidence-based Practice Center, Department of Medical Informatics and Clinical Epidemiology, and Department of Medicine, Oregon Health and Science University, Portland.
Corresponding Author: Heidi D. Nelson, MD, MPH, Oregon Health and Science University, Mail Code BICC 504, 3181 SW Sam Jackson Park Rd, Portland, OR 97239 (nelsonh@ohsu.edu).

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015

man carcinogens.[8] The US Preventive Services Task Force[9] as well as professional organizations[10] updated their recommendations and now advise against using estrogen for prevention of chronic conditions. Recently the estrogen-only treatment group of the WHI was stopped due to increased incidence of strokes (http://www.nhlbi.nih.gov/whi/#estrogen).

Several estrogen preparations are available for symptom management, including oral, transdermal, and topical forms. There is interest in comparing different estrogen agents because of concerns about CEE reported in the WHI study. Differences between agents and routes have been described,[11] although it is not known if these differences result in important clinical effects. Treatment with transdermal 17β-estradiol provides higher estradiol levels than corresponding doses of CEE that provide higher levels of estrone and estrone sulfate.[11] This difference reflects the hormonal compositions of the different drugs as well as the consequences of the hepatic first-pass metabolism effect with oral use.

Recent trials[1,12] indicate that when estrogen is combined with a progestin or progesterone, the risks of endometrial hypertrophy and endometrial cancer are comparable with placebo. Both agents can be combined into 1 daily pill, although other regimens using separate estrogen and progestin or progesterone pills taken together or distributed cyclically over a month are also used. The effect of progestin or progesterone on other clinical outcomes, such as cardiovascular disease, is not clear.

The purpose of this review was to compare the efficacy and safety of the most commonly used estrogen preparations for reducing menopausal hot flashes. Trials of oral CEE and oral and transdermal 17β-estradiol were focused on because they are commonly used in the United States and our preliminary search of the literature indicated few published trials of other forms. Our preliminary review also indicated that trials of estrogen for treatment of other menopausal symptoms, such as quality-of-life, mood changes, and vaginal atrophy, varied widely in methodological approaches and outcome measures precluding a quantitative analysis of results.

METHODS

MEDLINE (1966 to July 2003), EMBASE (1980 to July 2003), the Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Registry (2003, issue 1), and reference lists of published articles, including a recently published systematic review listed in the Cochrane database, were searched for trials.[13,14] Citations were obtained from pharmaceutical manufacturers and experts. All citations were imported into an electronic database (EndNote 6.0; Thomson ISI ResearchSoft, Carlsbad, Calif).

The English-language, double-blind, randomized, placebo-controlled trials and systematic evidence reviews of oral CEE and oral and transdermal 17β-estradiol, and treatment of menopausal hot flashes and flushes were included. Included studies were at least 3 months in duration and compared one estrogen preparation with another estrogen or placebo with or without concomitant use of progestin or progesterone administered as cyclic or continuous regimens. Progestin or progesterone preparations were not separately considered.

Study participants included women experiencing menopause who were recruited from health care settings or the general population. When available, data were considered separately for women with natural or surgical menopause (oophorectomy), and for women in perimenopausal or postmenopausal periods. Perimenopausal women were considered as those women transitioning through natural menopause who had irregular menstrual periods within the last 12 months. Postmenopausal women were those women with surgical oophorectomy, or natural menopause and amenorrhea for more than 12 months. Differences based on patient characteristics, such as age, race, comorbidities, and early oophorectomy (<45 years) or premature menopause (<35 years), were also considered. Studies of women with major intercurrent disease were excluded as where those with previous estrogen use within 1 month of commencement of the study due to carry-over effects.

Outcome measures included hot flashes or flushes defined as any otherwise unexplained sensation of flushing or sweating experienced by the woman being studied. Although the term *flash* indicates a prodromal phase and *flush* the vasomotor dilation phase, they are combined herein because they were reported inconsistently among the trials. Hot flashes were measured in many ways in the estrogen trials. Most commonly, study participants recorded the number of episodes over a day or week period, and changes indicated treatment responses. Other trials used measures such as percentage of participants experiencing symptoms or severity of symptoms. A cumulative symptom score, the Kupperman Index,[15] was used in some studies to classify the severity and intensity of hot flashes as well as various other menopausal symptoms. However, the use of the score is controversial because it has not been validated. Studies were included if they measured frequency, severity, presence vs absence, or a combination measure of frequency and severity as either primary or secondary outcomes at baseline, 3 months, and/or end of study.

Outcomes were determined by the differences in hot flashes measured at baseline compared with the end of the study. Treatment effects were defined as the differences in outcomes between the estrogen and placebo groups, or second estrogen group for head-to-head comparisons, at the end of the study. For crossover trials, only results from the end of the first phase were used because of the potential carry-over effect.

Adverse effects were also evaluated such as withdrawals from the study, atypical bleeding, endometrial hypertrophy, nausea and vomiting, breast tenderness, headaches, weight changes, dizziness, thrombosis, cardiovascular

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015

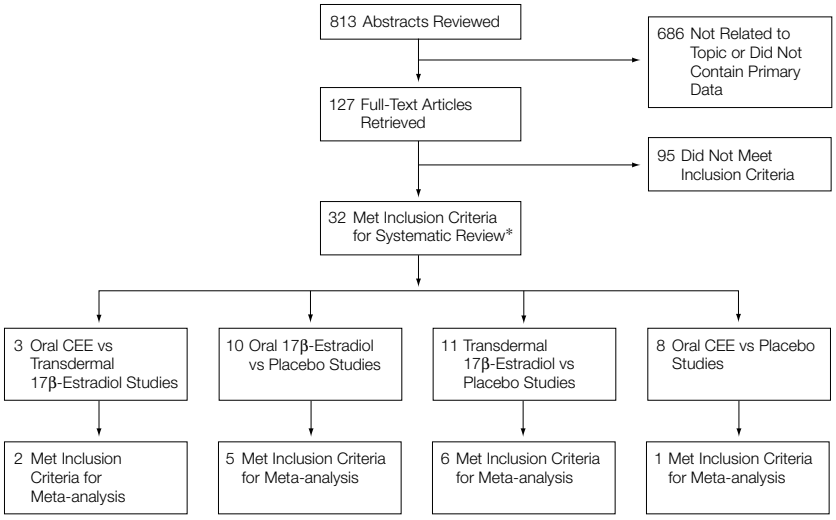
events, rash and pruritus, cholecystitis, effects on the liver, and other adverse effects, if reported.

From each trial, study design, population characteristics, eligibility criteria, interventions (estrogen type, form, dose and duration, use of progestin or progesterone, cyclic or continuous regimen), comparisons, numbers enrolled and lost to follow-up, method of outcome ascertainment, results for each outcome, and adverse effects were assessed. Intention-to-treat results were recorded if available.

For trials not included in the published Cochrane review,[13,14] the internal validity (quality) was assessed using predefined criteria based on those developed by the US Preventive Services Task Force and the UK National Health Services Centre.[16-18] Only trials of good or fair quality were included. All trials included in the Cochrane review were of at least fair quality by these criteria and were not rated in this review. 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 (menopausal women with hot flash symptoms seeking treatment), and whether the treatment received by the control group was reasonably representative of standard practice. The funding source was also recorded. Overall quality ratings for individual studies were based on ratings of the internal and external validity of each trial.

A meta-analysis was conducted of trials reporting hot flash outcomes to provide a more precise and standard measure of treatment effect. Trials that presented data on frequency of hot flash outcomes after treatment in numerical format and provided standard deviations met criteria for the meta-analysis (FIGURE 1). DerSimonian-Laird weighted mean differences in mean weekly number of hot flashes 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 by using StatsDirect statistical software version 1.9.14.[19] Funnel plots were constructed and indicated no evidence of publication bias, although they are a crude estimate and were limited by the small numbers of eligible studies.

Figure 1. Search and Selection of Trials for Meta-analysis



CEE indicates conjugated equine estrogen.
*Includes 2 studies from Archer et al.[20]

RESULTS

Head-to-Head Comparisons

Four trials compared estrogen preparations head-to-head, including 1 trial of CEE compared with oral 17β-estradiol[20] and 3 trials comparing oral CEE with transdermal 17β-estradiol[11,21,22] (TABLE 1 and TABLE 2). Women enrolled in these trials had hot flashes at baseline, and all trials reported

Table 1. Trials of 17β-Estradiol Compared With Conjugated Equine Estrogen (CEE)

Source	No. of Patients	Sample	Type, Dose, and Regimen: Estrogen	Type, Dose, and Regimen: Progestin	Length of Trial, wk
Archer et al,[20] 1992	128 (5 groups), including placebo	≥5 Vasomotor symptoms per day; mean age, 51 y (range, 40-60 y); United States	Oral estradiol: 1, 2 mg/d CEE: 0.625, 1.25 mg/d	None	12
Good et al,[11] 1999	321 (4 groups)	≥60 Hot flashes per week; mean age, 50-51 y; United States	Transdermal estradiol: 0.05, 0.1 mg/d CEE: 0.625, 1.25 mg/d	None	12
Gordon et al,[21] 1995 (study 2)	390 (3 groups)	With symptoms; mean age, 51 y (range, 26-73 y); United States	Transdermal estradiol: 0.05, 0.1 mg/d CEE: 0.625 mg/d	None	11
Studd et al,[22] 1995	214 (2 groups)	≥21 Hot flashes per week; mean age, approximately 52 y (range, 38-65 y); United States	Transdermal estradiol: 0.05 mg/d CEE: 0.625 mg/d	Dydrogesterone: 20 mg/d (days 16-28)	12

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015

Table 2. Main Outcomes of Trials of 17β-Estradiol Compared With Conjugated Equine Estrogen (CEE)

Source	Main Outcomes/Results	Withdrawals Due to Adverse Effects	Total Withdrawals	Main Adverse Effects
Archer et al,[20] 1992	Reduction in frequency of vasomotor events (80%-95% estrogen, 66% placebo); all agents significantly different from placebo ($P<.05$), no differences between agents	9	21	Incidence of possible drug-related adverse experiences ranged from 20% (placebo, 1-mg/d estradiol, 0.625-mg/d CEE) to 35% (2-mg/d estradiol, 1.25-mg/d CEE) with no significant differences between groups Breast tenderness common among higher doses (30% 1.25-mg/d CEE and 22% 2-mg/d estradiol)
Good et al,[11] 1999	Reduction of hot flashes by 90% for both agents, no differences at comparable doses	16	47	Breakthrough bleeding, breast tenderness (3%-4% low doses, 11%-12% high doses), headaches, rash, and pruritus No differences between agents except for breakthrough bleeding with higher doses (4% estradiol, 10% CEE)
Gordon et al,[21] 1995 (study 2)	Reduction in mean weekly hot flashes in all groups (63%-78%), no differences between agents	32 (15 0.05-mg/d estradiol, 10 0.1-mg/d estradiol, and 7 CEE)	64	Application-site reactions were most common (6% withdrew), breast pain and vaginal bleeding were more common in 0.1-mg/d estradiol group than in other groups ($P<.05$)
Studd et al,[22] 1995	Reduction in mean number of hot flashes per day (estradiol, from 7.1 to 0.9 per day; CEE, from 6.7 to 0.5 per day), no differences between agents	Not reported	Not reported	Headache (8 in each group), abdominal pain (4 in each group), nausea (5 in estradiol, 6 in CEE), breast pain (6 in estradiol), weight gain (3 in CEE), and depression (3 in CEE); total events: 11 in estradiol and 6 in CEE groups

Table 3. Trials of Oral 17β-Estradiol

Source	No. of Patients	Sample	Type, Dose, and Regimen: Estrogen	Type, Dose, and Regimen: Progestin	Length of Trial
Baerug et al,[23] 1998	119 (3 groups)	Moderate to severe symptoms; mean age, 51 y (range, 45-61 y); Norway	1 mg/d (CCT)	Norethindrone acetate: 0.25, 0.5 mg/d (CCT)	12 wk
Bech et al,[24] 1998	151 (3 groups)	From community; age not reported; Denmark	2 mg/d (CCT) or 2 mg/d for days 1-22, then 1 mg/d for days 23-28 (cyclic)	Norethindrone acetate: 1 mg/d (CCT) or days 13-22 (cyclic)	1 y
Chung et al,[25] 1996	100 (2 groups)	With oophorectomy (66% had vasomotor symptoms); mean age, 44 y; Hong Kong	2 mg/d	None	1 y
Conard et al,[26] 1995	57 (3 groups)	From hospital clinics (93% with moderate to severe symptoms); mean age, 52 y (range, 44-61 y); Paris, France	1, 1.5 mg/d for days 1-24 (cyclic)	Nomegestrol acetate: 2.5, 3.75 mg/d for days 11-24 (cyclic)	12 wk
Derman et al,[27] 1995	82 (2 groups)	≥20 Vasomotor events per week; mean age, 50 y (range, 40-60 y); United States	2 mg/d for days 1-22, 1 mg/d for days 23-28 (cyclic)	Norethindrone acetate: 1 mg/d for days 13-22 (cyclic)	16 wk
Freedman and Blacker,[28] 2002	24 (2 groups)	≥5 Hot flashes per day in university setting; mean age, 52 y; United States	1 mg/d	None	12 wk
Notelovitz et al,[29] 2000	333 (5 groups)	Moderate or severe hot flashes; mean age, 51 y (range, 40-60 y); United States	0.25, 0.5, 1, 2 mg/d	None	12 wk
Notelovitz and Mattox,[30] 2000	145 (3 groups)	≥8 Hot flashes per day; mean age, 49 y (range, 28-63 y); United States	0.5, 1 mg/d	None	12 wk
Vikhlyaeva et al,[31] 1997 (English abstract)	64 (2 groups)	Perimenopausal, moderate to severe symptoms; age range, 39-56 y; Moscow, Russia	2 mg/d for days 1-22, 1 mg/d for days 23-28 (cyclic)	Norethindrone acetate: 1 mg/d for days 13-22 (cyclic)	24 wk

Abbreviation: CCT, combined continuous therapy.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015

Table 4. Main Outcomes of Oral 17β-Estradiol Trials

Source	Main Outcomes/Results	Withdrawals Due to Adverse Effects	Total Withdrawals	Main Adverse Effects
Baerug et al,[23] 1998	Reduction in mean hot flash frequency and severity; significantly different from placebo; no differences between progestin groups Women in early (3-12 mo amenorrhea) as well as late menopause (>12 mo amenorrhea) had similar benefit	5	11	Higher rates of atypical bleeding for estradiol than placebo; estradiol group had 1 withdrawal each for breast tenderness, edema, emotional lability; placebo group had 1 withdrawal each for nausea and headache
Bech et al,[24] 1998	Reduction in hot flash severity (Kupperman Index scores: estradiol, 3-3.7; placebo, 9; $P<.01$); no difference between CCT and cyclic regimens	Not reported	20	Estradiol groups had 4 withdrawals for atypical bleeding, 1 for weight change, 2 for nausea; placebo group had 2 withdrawals for nausea; more reports of breast tenderness in estradiol groups
Chung et al,[25] 1996	No significant differences between estradiol and placebo for vasomotor severity score, number with hot flashes, and number with moderate to severe hot flashes	Not reported	17	Headache and dizziness reported, no differences between groups
Conard et al,[26] 1995	Reduction in daily hot flash frequency, vasomotor severity score, number with hot flashes among all groups; significantly different from placebo; no difference between estradiol groups	4	13	1 Withdrawal from estradiol group for atypical bleeding
Derman et al,[27] 1995	Reduction in hot flash frequency (estradiol from 7 to 1.3 per day, placebo from 6 to 4.2 per day; significant difference); significant differences between estradiol and placebo for Kupperman Index, Greene, and Beck scores	6	35	Withdrawals from estradiol group for atypical bleeding, weight change, palpitations; from placebo group for lack of effect (data not reported)
Freedman and Blacker,[28] 2002	Reduction in hot flash frequency significantly different from placebo (determined by laboratory measures rather than self-report)	Not reported	Not reported	Not reported
Notelovitz et al,[29] 2000	Proportions of women with adequate relief of hot flashes for 0.5-mg (61%), 1-mg (71%), and 2-mg groups (89%) were higher than the placebo group (25%, $P<.001$); the 0.25-mg group was not different than placebo (25%)	26 (5 placebo, 21 estradiol, more in high-dose groups)	53	18 Withdrawals for atypical bleeding (11 from 2-mg group), breast tenderness reported in all groups with more reports in higher dose groups
Notelovitz and Mattox,[30] 2000	Reduction in mean number of hot flashes from baseline (83% 1-mg/d group, 66% 0.5-mg/d group), significantly different from placebo	Not reported	23	Atypical bleeding reported in estradiol groups with 1 case of endometrial cancer; headaches and abdominal pain reported in all groups
Vikhlyaeva et al,[31] 1997 (English abstract)	Improvement on Kupperman Index score for estradiol group vs placebo ($P = .01$)	Not reported	Not reported	Not reported

Abbreviation: CCT, combined continuous therapy.

improved number, severity of hot flashes, or both for all of the estrogen treatment groups. There were no statistically significant differences in treatment effects in any of the head-to-head estrogen comparisons in any of the trials.

Of 3 trials comparing oral CEE with transdermal 17β-estradiol, 2 were combined in a meta-analysis,[21,22] and 1 was excluded because data were provided in graphic form.[11] The pooled weighted mean difference in hot flashes was not significantly different between 17β-estradiol and CEE treatment groups, thereby favoring neither agent (–0.3; 95% confidence interval [CI], –3.4 to 2.7).

Dose-response trends were demonstrated in trials that tested multiple doses with higher doses corresponding to bigger treatment effects; however, these did not reach statistical significance.[20,21] In 1 study, patients using CEE at 0.625 mg/d had a reduction of mean daily frequency of hot flashes by 80%, and patients using CEE at 1.25 mg/d had a reduction of 95% ($P=.06$).[20] Too few dose comparisons were conducted between estrogen agents to determine if differences exist at various doses.

Placebo Comparisons

Twenty-eight randomized controlled trials comparing CEE or 17β-estradiol with placebo met criteria for this review.[20,21,23-48] Trials were conducted predominantly in the United States or western Europe and recruited participants from general pri-

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015

Table 5. Trials of Transdermal 17β-Estradiol

Source	No. of Patients	Sample	Type, Dose, and Regimen: Estrogen	Type, Dose, and Regimen: Progestin	Length of Trial, wk
Bacchi-Modena et al,[32] 1997	109 (2 groups)	≥7 Hot flashes per day; mean age, 52 y (range, 39-61 y); Italy	0.05 mg/d	None	12
de Aloysio et al,[33] 2000	156 (3 groups)	≥5 Hot flashes per day; mean age, 53-54 y; Italy	0.025, 0.0375 mg/d	None	12
de Vrijer et al,[34] 2000	254 (3 groups)	≥7 Hot flashes per day; mean age, 52 y (range, 40-64 y); the Netherlands	0.05, 0.1 mg/d	None	12
Gordon et al,[21] 1995 (study 1)	214 (3 groups)	With symptoms; mean age, approximately 52 y (range, 25-74 y); United States	0.05, 0.1 mg/d	None	11
Notelovitz et al,[35] 2000	220 (2 groups)	≥8 Hot flashes per day; mean age, approximately 53 y; United States	0.05 mg/d (cyclic)	Norethindrone acetate: 140, 250, 400 μg/d for days 15-28 (cyclic)	12
Shulman et al,[36] 2002	293 (3 groups)	≥7 Moderate to severe hot flashes per day; mean age, 51-52 y (range, 44-68 y); United States	0.045 mg/d (CCT)	Levonorgestrel patch: 30, 40 μg/d (CCT)	12
Speroff et al,[37] 1996	324 (7 groups)	With hysterectomy and hot flashes; mean age, 49 y; United States	0.02 mg/d	None	12
Utian et al,[38] 1999	196 (4 groups)	With symptoms; mean age, 50 y; United States	0.025, 0.05, 0.1 mg/d	None	12
von Holst and Salbach,[39] 2000	186 (2 groups)	With symptoms; mean age, 53 y; Germany	0.05 mg/d	None	12
von Holst and Salbach,[40] 2002	179 (3 groups)	With symptoms; mean age, 53 y; Germany	0.05 mg/d (CCT)	Levonorgestrel patch: 10 μg/d (CCT)	12
Wiklund et al,[41] 1993	242 (2 groups)	With symptoms; mean age, 53 y (range, 45-65 y); Sweden	0.05 mg/d	None	12

Abbreviation: CCT, combined continuous therapy.

mary care or gynecology practices. Trials enrolled patients with mean age approximately 50 years (range, 25-88 years) and included from 24 to 2763 patients in 1 to 8 comparison groups.

Inclusion criteria varied among studies from most or a percentage of participants with baseline symptoms to a specified level of symptoms, such as "5 or more vasomotor symptoms per day." Trials often enrolled both perimenopausal and postmenopausal women but did not separate them in the analysis-limiting comparisons. Hysterectomy status was clearly reported if inclusion criteria called for women either with or without hysterectomy.[37] For trials including both women with and without hysterectomies, data were not separately reported and comparisons could not be made. No trial specifically addressed treatment in women with premature ovarian failure. Reporting of concurrent medications, comorbidities, or other potential confounders was minimal, and inclusion criteria generally focused on healthy symptomatic women.

Different outcomes were reported and lack of standardization limited comparisons. Frequency of hot flashes was the most common measure reported in 19 of 28 trials.* When reported, women in placebo groups also had improvement of symptoms from baseline by as much as 66%.[20] Ten trials included estrogen combined with various progestin or progesterone agents.† Studies that compared groups using estrogen alone with groups using estrogen with progestin or progesterone found no differences in treatment effects.[24,47,48]

Nine of 10 trials of oral 17β-estradiol demonstrated statistically significant improvements in hot flash frequency, severity, or both compared with placebo (Tables 1 and 2, TABLE 3, and TABLE 4).[20,23,24,26-31] The 1 trial that reported no difference between groups was conducted in Chinese women in Hong Kong after oophorectomy.[25] Approximately 66% of women in this trial had vasomotor symptoms at baseline and 23% to 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 similar benefit.[23] Five trials included concomitant progestin or progesterone use (continuous and cyclic norethindrone acetate, cyclic nomegestrol).[23,24,26,27,31]

All 11 trials of transdermal 17β-estradiol reported statistically significant improvements in hot flash frequency, severity, or both compared with placebo (TABLE 5 and TABLE 6).[21,32-41] Three trials included concomitant progestin or progesterone (cyclic norethindrone acetate, continuous transdermal levonorgestrel).[35,36,40]

All 8 trials of oral CEE reported statistically significant improvements in hot flash frequency, severity, or both compared with placebo (Table 1, TABLE 7 and TABLE 8).[20,42-48] Three trials included treatment groups with concomitant progestin or progesterone use (cyclic and continuous

*References 20, 21, 23, 25-28, 30, 32-40, 45, 48.
†References 23, 24, 26, 27, 31, 35, 36, 40, 47, 48.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015

Table 6. Main Outcomes of Transdermal 17β-Estradiol Trials

Source	Main Outcomes/Results	Withdrawals Due to Adverse Effects	Total Withdrawals	Main Adverse Effects
Bacchi-Modena et al,[32] 1997	Reduction in mean number of moderate to severe hot flashes per 24 h (–8 from baseline for estradiol and –4 for placebo, $P<.001$); improvement in Kupperman Index score (–18 for estradiol and –9 for placebo, $P<.001$)	2	11	Atypical bleeding reported in 15% estradiol and 13% placebo, breast tenderness in 28% estradiol and 27% placebo, skin reactions in 30% estradiol and 20% placebo groups
de Aloysio et al,[33] 2000	Reduction in number of hot flashes (83%-84% in estradiol and 58% in placebo groups, $P<.05$)	3	20	Atypical bleeding reported in all groups (1 withdrew from 0.0375-mg estradiol group), breast tenderness in 10% placebo and 40% to 43% estradiol groups (1 withdrew from 0.025-mg estradiol group), headache reported in all groups, 1 withdrew due to skin reactions in estradiol group, overall events were 10% estradiol and 8% placebo groups
de Vrijer et al,[34] 2000	Reduction in mean number of moderate to severe hot flashes per 24 h similar for both estradiol groups, significantly different from placebo (–5 to –5.3 for estradiol and –0.3 for placebo, $P<.001$); Kupperman Index score and night sweats also significantly decreased for both estradiol groups vs placebo	18	Not reported	5 Withdrew in 0.1-mg estradiol group from atypical bleeding; 5 cases of endometrial hypertrophy and 1 case of endometrial cancer in estradiol groups; breast tenderness reported in 11% placebo, 26% 0.05-mg estradiol, and 61% 0.1-mg estradiol groups; headache, dizziness, edema, and sleep disturbances reported in estradiol groups; skin reactions reported in both estradiol and placebo groups
Gordon et al,[21] 1995 (study 1)	Reduction in mean weekly hot flashes in all groups (67% 0.05-mg estradiol, 72% 0.1-mg estradiol, 18% placebo; $P<.05$)	22	50	Highest withdrawal rates were in placebo (30%) and 0.05-mg estradiol groups (26%) vs 0.1-mg estradiol group (13%) because of inadequate therapeutic response ($P<.05$); application-site reactions were the most common adverse experience (8% withdrew), other adverse events reported include vaginal bleeding, breast pain, depression, and dizziness
Notelovitz et al,[35] 2000	Reduction in mean number of hot flashes per day, mean intensity of hot flashes, and sweating all significantly different from placebo ($P<.001$)	6	12	Atypical bleeding reported in estradiol groups; overall adverse events were reported in 79% of placebo and 83%-90% of estradiol groups; all withdrawals for adverse effects were in the estradiol group
Shulman et al,[36] 2002	Reduction in daily number of hot flashes from baseline (9 and 10 for estradiol groups, 5 for placebo; $P<.001$)	11 Estradiol, 6 placebo	42	4 Withdrew from estradiol group for atypical bleeding; breast tenderness reported in 12 (estradiol) and 2 (placebo); headache reported in 10 patients in estradiol group; weight change in 8 (estradiol) and 1 (placebo); skin reactions led to 6 withdrawals (3 estradiol and 3 placebo)
Speroff et al,[37] 1996	Reduction in hot flash frequency (84% for estradiol group), significantly different from placebo	18	63	Breast tenderness reported in 6%-14% in estradiol and 3% in placebo groups, headache was most frequently reported effect (16% estradiol, 20% placebo), 9 withdrew for skin reactions (4 estradiol, 5 placebo)
Utian et al,[38] 1999	Reduction in frequency of moderate to severe vasomotor symptoms significantly different from placebo ($P<.05$)	7	20	4 Withdrew from estradiol groups for atypical bleeding; 32%-57% in estradiol and 10% in placebo groups reported spotting; breast tenderness was most common symptom in estradiol groups (23%-45%); 5%-11% in all groups had skin reactions; overall effects were 11% placebo, 31% 0.025-mg estradiol, 55% 0.05-mg estradiol, and 58% 0.10-mg estradiol
von Holst and Salbach,[39] 2000	Reduction in mean hot flashes (44 to 12 in estradiol, 41 to 19 in placebo; $P = .003$); improvement in Kupperman Index score (27.6 to 11.2 for estradiol, 27.9 to 16 for placebo; $P<.001$)	9 Estradiol, 7 placebo	Not reported	4 From estradiol group had breast tenderness; 7 had skin reactions (4 estradiol, 3 placebo)
von Holst and Salbach,[40] 2002	Reduction in number of hot flashes in estradiol group significantly lower than placebo; improvement in Kupperman Index score (26.3 to 9.5 in estradiol, 27.1 to 15.9 in placebo; $P<.001$)	8	31	Heachaches and skin reactions were reported in all groups
Wiklund et al,[41] 1993	Mean change from baseline for vasomotor symptoms score, Kupperman Index score reduced vs placebo ($P<.001$)	Not reported	18	Atypical bleeding in 8% placebo and 13% estradiol groups; some withdrawals in estradiol group due to headache and skin reactions

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015

Table 7. Trials of Conjugated Equine Estrogen

Source	No. of Patients	Sample	Type, Dose, Regimen: Estrogen	Type, Dose, Regimen: Progestin	Length of Trial
Barnabei et al,[42] 2002	2763 (2 groups)	Participants in HERS trial; 16% with hot flashes; mean age, 67 y (range, 55-88 y); United States	0.625 mg/d (CCT)	Medroxyprogesterone acetate: 2.5 mg/d (CCT)	4 y
Baumgardner et al,[43] 1978	79 (2 groups)	Gynecology practices; moderate to severe hot flashes; age, not reported; United States	1.25 mg/d for 21 days per mo	None	24 wk
Campbell,[44] 1976	56 (2 groups)	Menopause clinic; most had vasomotor symptoms; age, not reported; London, England	1.25 mg/d for 21 days per mo	None	6 mo
Carranza-Lira and Cortes-Fuentes,[45] 2001	75 (5 groups)	With hot flashes; age, not reported; Mexico	0.625 mg/d	None	12 wk
Coope et al,[46] 1975	30 (2 groups)	Semirural general practice; some had depression; mean age, 52 y (range, 40-61 y); England	1.25 mg/d for 21 days per mo	None	3 mo
Greendale et al,[47] 1998	875 (5 groups)	Participants in PEPI trial; 53% had vasomotor symptoms; mean age, 56 y (range, 45-64 y); United States	0.625 mg/d (CCT and cyclic)	Medroxyprogesterone acetate: 10 mg/d for days 1-12 (cyclic), 2.5 mg/d (CCT); micronized progesterone 100 mg/d for days 1-12 (cyclic)	3 y
Utian et al,[48] 2001	2673 (8 groups)	Postmenopausal; mean age, 53 y; United States	0.625, 0.45, 0.3 mg/d (CCT and unopposed regimens)	Medroxyprogesterone acetate: 1.5, 2.5 mg/d (CCT)	1 y

Abbreviations: CCT, combined continuous therapy; HERS, The Heart and Estrogen/Progestin Replacement Study; PEPI, Postmenopausal Estrogen/Progestin Intervention.

Table 8. Main Outcomes of Conjugated Equine Estrogen Trials

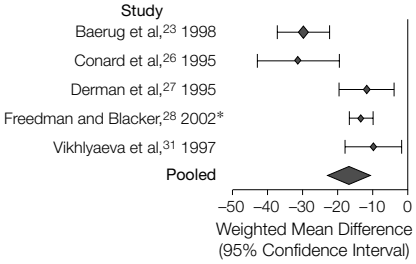
Source	Main Outcomes/Results	Withdrawals Due to Adverse Effects	Total Withdrawals	Main Adverse Effects
Barnabei et al,[42] 2002	After the first year, reduction in the proportion with hot flashes in CEE group (12% marked improvement, 73% some improvement for CEE group, 2% marked improvement, 46% some improvement for placebo; $P<.001$)	Not reported	Not reported	Reports of breast symptoms (40% after first year in CEE group, 9% in placebo; $P<.001$); uterine bleeding (31%) and spotting (33%) among women in CEE group; weight gain and edema in both groups
Baumgardner et al,[43] 1978	Reduction in number of patients with moderate to severe hot flashes in CEE groups, significantly different from placebo	Not reported	Not reported	1 Withdrew from CEE group for nausea, additional withdrawals for edema and visual symptoms (no differences between groups), and lack of effect in placebo group
Campbell,[44] 1976	Improved mean scores on hot flash rating scale with CEE, significantly different from placebo	Not reported	7	Atypical bleeding was increased in the CEE group, breast tenderness reported for both groups (13% CEE, 10% placebo), other symptoms described but did not differ between groups
Carranza-Lira and Cortes-Fuentes,[45] 2001	Reduction in number, severity, and duration of hot flashes and if insomnia and sweating accompanied hot flashes for CEE group, significantly different from placebo	Not reported	Not reported	Not reported
Coope et al,[46] 1975	Reduction in number of patients with hot flashes among those with hot flashes at baseline ($P = .04$)	Not reported	5	Withdrawal bleeding in majority of perimenopausal women but no breakthrough bleeding, reports of breast tenderness and weight changes but did not differ between groups
Greendale et al,[47] 1998	Reduction in number of patients with any vasomotor symptom in all CEE groups, significantly different from placebo, no difference between CEE groups	127	210	Breast tenderness was more common with combined regimens than estrogen alone or placebo groups, 2 cases of deep vein thrombosis in estrogen only group, 1 case of superficial phlebitis in combined group
Utian et al,[48] 2001	Reduction in mean daily number and severity of hot flashes in all CEE groups, significantly different from placebo	221	521	Breast tenderness was the most commonly reported effect (15% overall), more common in combined than in estrogen-alone groups (13%-25% vs 7%-12%), also reports of leg cramps in CEE groups

Abbreviation: CEE, conjugated equine estrogen.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015

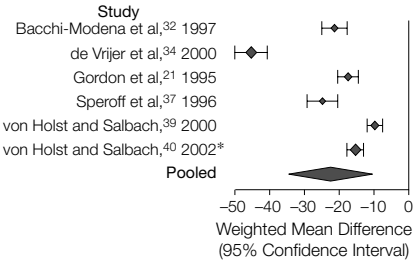
Figure 2. Trials of Oral 17β-Estradiol



All trials indicate a significant decrease in weekly number of hot flashes compared with placebo. The pooled weighted mean difference in weekly hot flashes compared with placebo was –16.8 (95% confidence interval, –23.4 to –10.2). Data marker sizes correlate with study sample sizes.

*All trials include oral 17β-estradiol and progestin, with the exception of this study, which used 17β-estradiol alone.

Figure 3. Trials of Transdermal 17β-Estradiol



All trials indicate a significant decrease in weekly number of hot flashes compared with placebo. The pooled weighted mean difference in weekly hot flashes compared with placebo was –22.4 (95% confidence interval, –35.9 to –10.4). Data marker sizes correlate with study sample sizes.

*All trials include transdermal 17β-estradiol alone, with the exception of this study, which used transdermal 17β-estradiol and progestin.

medroxyprogesterone acetate, cyclic micronized progesterone).[42,47,48] One trial compared 3 doses of CEE alone (0.3, 0.45, and 0.625 mg/d) and reported bigger treatment effects with 0.625 mg than 0.45 mg or 0.3 mg ($P<.05$).[48] Differences between estrogen doses were not found in patients provided with CEE (0.3, 0.45, and 0.625 mg/d) and continuous medroxyprogesterone acetate (1.5 or 2.5 mg/d) in this trial.[48]

Meta-analysis

Of 10 trials of oral 17β-estradiol compared with placebo, 5 met criteria for the meta-analysis.[23,26-28,31] The pooled weighted mean difference in hot flashes was –16.8 per week (95% CI, –23.4 to –10.2) compared with placebo (FIGURE 2). Combining only the 4 trials that included 17β-estradiol and progestin or progesterone did not significantly change results (pooled weighted mean difference, –19.1; 95% CI, –29.6 to –8.6).[23,26,27,31] Trials were excluded from analysis because they did not provide data on frequency of hot flashes[24,25] or did not provide standard deviations.[20,29,30]

Of 11 trials of transdermal 17β-estradiol compared with placebo, 6 met criteria for the meta-analysis.[21,32,34,37,39,40] The pooled weighted mean difference in hot flashes for these trials was –22.4 per week (95% CI, –35.9 to –10.4) compared with placebo (FIGURE 3). Only 1 trial included 17β-estradiol and progestin or progesterone and results were not significantly different from the other studies.[40] Trials were excluded because they did not provide data on frequency of hot flashes,[32,41] provided data in graphic form,[33,35,38] or did not provide standard deviations.[36,38]

Of 8 trials of CEE compared with placebo, 1 met criteria for the meta-analysis.[46] This trial reported a mean reduction of –19.1 hot flashes per week (95% CI, –33.0 to –5.1) after treatment compared with placebo. The other 7 trials were excluded from analysis because they did not provide data on frequency of hot flashes,[42,45,47] provided data in graphic form,[43] or did not provide standard deviations.[20,43,44,48]

Comparative Safety

All but 5 trials[24,25,42,47,48] were less than 1 year in duration and only 3 trials enrolled more than 500 participants.[42,47,48] Studies reported multiple specific adverse effects, including atypical bleeding and endometrial hypertrophy, nausea and vomiting, breast tenderness, headache, weight change, dizziness, venous thromboembolic events, cardiovascular events, rash and pruritus, cholecystitis, liver effects, and other adverse events. These outcomes were reported unevenly across studies and could not be combined in summary statistics.

Head-to-head comparison trials lacked data to determine the relative adverse effects of different estrogens. One trial of CEE and oral 17β-estradiol reported that the incidence of possible drug-related adverse experiences ranged from 20% in placebo, 1-mg/d 17β-estradiol, and 0.625-mg/d CEE groups to 35% in 2-mg/d 17β-estradiol and 1.25-mg/d CEE groups with no statistically significant differences between groups.[20] Among trials with placebo groups, comparisons between types of estrogens could not be made with the data provided.

A 4-year trial with 875 patients reported 2 cases of deep vein thrombosis among CEE users,[47] otherwise no cardiovascular events were reported in the trials. Breast tenderness‡ and vaginal bleeding§ were the most commonly reported adverse effects among estrogen users in the trials. Two trials each reported 1 case of endometrial cancer in an 17β-estradiol user.[30,34] Bleeding and breast tenderness were more frequent among patients with higher vs lower doses of estrogen regardless of the type of estrogen in some trials.[11,20,21] Adverse skin reactions were most common among women using transdermal forms of 17β-estradiol or placebo.[21,32-35,38-41,49,50] Withdrawals from placebo groups due to lack of treatment effect were also reported.[27,43]

Study Quality Assessment

Trials included in this review used similar methodology and met criteria for at least a fair quality score for internal and external validity. In several studies, it was not apparent whether quality criterion, such as use of intention-to-treat analysis, was met because it was not reported in the publication. The most common problem with the studies was differential loss to follow-up and it was unclear if comparable groups were maintained. Most studies were either funded by industry or the funding source was not reported.

‡References 11, 20, 23, 24, 26, 27, 33, 34, 37-39, 42, 47-49.
§References 11, 21-24, 26, 29, 30, 33, 34, 36, 38, 41, 42.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015

COMMENT

Trials included in this systematic review indicate that CEE and oral and transdermal 17β-estradiol are more effective than placebo in relieving menopausal hot flashes and available evidence does not indicate that one agent is more effective than another. A range of doses is effective, although a dose-response relationship was reported in a limited number of studies. Although data are limited, concomitant use of progestin or progesterone does not influence the effect of estrogen. Available trials do not allow additional comparisons between types of estrogens to determine the effects of cyclic and continuous regimens. There are too few trials of other types of estrogen than CEE and 17β-estradiol to evaluate their relative effectiveness.

These results are consistent with a Cochrane review and meta-analysis of trials of oral estrogens compared with placebo for treating menopausal hot flashes published before 2000.[14] Differences between types of estrogens were not determined in this review, although trials of 17β-estradiol and CEE predominated. Results indicated a 77% reduction in frequency and a significant reduction in severity of symptoms with oral estrogen compared with placebo.

Data from trials evaluated in this review do not allow comparisons of adverse effects because they were reported in incomplete and nonstandardized ways. The most comprehensive data about adverse effects of estrogen are reported in studies designed for purposes other than symptom treatment, such as the WHI.[5] This trial was designed as a primary prevention trial and enrolled more than 16000 women with a mean age of 63 years at study entry. After 5 years of continuous administration of 0.625-mg/d CEE and 2.5-mg/d medroxyprogesterone acetate, estrogen users had significantly increased coronary heart disease events,[51] strokes,[52] deep vein thrombotic events,[5] and breast cancer[53] compared with nonusers. The symptom treatment trials reviewed herein enrolled small numbers of patients for short periods and were inadequately designed to capture the important health outcomes reported by the WHI. One trial reported 2 CEE users with deep vein thrombosis[47] and 2 trials reported 1 case each of endometrial cancer in 17β-estradiol users[30,34]; otherwise, adverse effects included predominantly vaginal bleeding, breast tenderness, and other assorted nuisance symptoms. Although these adverse effects are important to individual women and may result in stopping use of estrogen, they are less serious health outcomes than those reported in the WHI. Available trial data do not prove that serious outcomes will not occur in younger short-term users but it is inconclusive.

Symptom treatment trials have other important limitations. Most trials enrolled white women in the United States or western Europe who were recruited through clinical practices. The few trials conducted in nonwhite women took place in countries where lifestyle factors substantially differ from those in the United States and could potentially influence outcomes. Trials usually included women ranging in age from 40 to 60 years old with a mean age of early 50s. Comparisons of results for these women with women of different age groups, racial or ethnic groups, comorbidities, and risk factors are not possible. No trials considered smokers, women at high risk for ovarian or breast cancer, or other risk factors and comorbidities separately. No trials compared women with early oophorectomy or premature menopause with women undergoing menopause at an older age.

This systematic review and meta-analysis of 32 treatment trials found that the use of CEE and oral and transdermal 17β-estradiol have consistent and comparable effects on treatment of hot flashes in menopausal women with symptoms and may have similar adverse effects. However, many issues remain unresolved by current trial data. Future trials could address these issues by providing a broader demographic sample of women, longer follow-up, larger numbers of patients, and more head-to-head comparisons of estrogens, progestins or progesterones, and other therapies (phytoestrogens, megestrol, clonidine, selective serotonin-reuptake inhibitors). Results of these trials would guide more individualized use of estrogen, including appropriate selection of treatment candidates, monitoring of treatment and adverse effects, and determining when and how to discontinue therapy.

Funding/Support: This study was conducted by the Oregon Evidence-based Practice Center under contract with the National Institute on Aging and Office of Research on Women's Health, National Institutes of Health, and the state of Oregon.

Acknowledgment: I thank Benjamin Chan, MS, for statistical support, and Peggy Nygren, MA, Miranda Norbraten, BA, and Christina Bougatsos, BS, for their contributions to this article.

REFERENCES

1. Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal hormone replacement therapy: scientific review. *JAMA.* 2002;288:872-881.

2. Keating N, Cleary P, Rossi A, et al. Use of hormone replacement therapy by postmenopausal women in the US. *Ann Intern Med.* 1999;130:545-553.

3. Austin PC, Mamdani MM, Tu K, Jaakkimainen L. Prescriptions for estrogen replacement therapy in Ontario before and after publication of the Women's Health Initiative Study. *JAMA.* 2003;289:3241-3242.

4. Hersch AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy. *JAMA.* 2004; 291:47-53.

5. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-333.

6. Stephenson J. FDA orders estrogen safety warnings: agency offers guidance for HRT use. *JAMA.* 2003; 289:537-538.

7. Wyeth Pharmaceuticals Web site. Available at: http://www.prempro.com/preinfo.html. Accessed March 3, 2004.

8. Vastag B. Some estrogens carcinogenic. *JAMA.* 2003;289:290.

9. US Preventive Services Task Force. Postmenopausal hormone replacement therapy to prevent chronic conditions: recommendations from the US Preventive Services Task Force. *Ann Intern Med.* 2002; 137:273-284.

10. The American College of Obstetricians and Gynecologists. Available at: http://www.acog.com. Accessed March 3, 2004.

11. Good WR, John VA, Ramirez M, Higgins JE. Comparison of Alora estradiol matrix transdermal delivery system with oral conjugated equine estrogen therapy in relieving menopausal symptoms. *Climacteric.* 1999; 2:29-36.

12. Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA.* 2003; 290:1739-1748.

©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015

13. Wells G, Tugwell P, Shea B, et al. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. *Endocr Rev.* 2002;23:529-539.
14. MacLennan A, Lester A, Moore V. Oral oestrogen replacement therapy versus placebo for hot flushes [Cochrane Review on CD-ROM]. Oxford, England: Cochrane Library, Update Software; 2002; issue 2.
15. Kupperman H, Wetchler B, Blatt M. Contemporary therapy of the menopausal syndrome. *JAMA.* 1959;111:1627-1637.
16. *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Those Carrying Out or Commissioning Reviews CRD Report Number 4.* 2nd ed. York, England: NHS Centre for Reviews and Dissemination; 2001.
17. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* 2001;20 (suppl 3):21-35.
18. Mulrow CD, Oxman A. *How to Conduct a Cochrane Systematic Review 3.0.2.* San Antonio, Tex: Cochrane Collaboration; 1997.
19. StatsDirect Statisical Software. Available at: http://www.statsdirect.com/. Accessed March 3, 2004.
20. Archer DR, Fischer LA, Rich D, et al. Estrace vs Premarin for treatment of menopausal symptoms: dosage comparison study. *Adv Ther.* 1992;9:21-31.
21. Gordon SF, Thompson KA, Ruoff GE, et al. Efficacy and safety of a seven-day, transdermal estradiol drug-delivery system: comparison with conjugated estrogens and placebo. *Int J Fertil Menopausal Stud.* 1995;40:126-134.
22. Studd JW, McCarthy K, Zamblera D, et al. Efficacy and tolerance of Menorest compared to Premarin in the treatment of postmenopausal women. *Maturitas.* 1995;22:105-114.
23. Baerug U, Winge T, Nordland G, et al. Do combinations of 1 mg estradiol and low doses of NETA effectively control menopausal symptoms? *Climacteric.* 1998;1:219-228.
24. Bech P, Munk-Jensen N, Obel EB, et al. Combined versus sequential hormonal replacement therapy: a double-blind, placebo-controlled study on quality of life-related outcome measures. *Psychother Psychosom.* 1998;67:259-265.
25. Chung TKH, Yip SK, Lam P, et al. A randomized, double-blind, placebo-controlled, crossover study on the effect of oral oestradiol on acute menopausal symptoms. *Maturitas.* 1996;25:115-123.
26. Conard J, Basdevant A, Thomas JL, et al. Cardiovascular risk factors and combined estrogen-progestin replacement therapy: a placebo-controlled study with nomegestrol acetate and estradiol. *Fertil Steril.* 1995;64:957-962.
27. Derman RJ, Dawood MY, Stone S. Quality of life during sequential hormone replacement therapy; a placebo-controlled study. *Int J Fertil Menopausal Stud.* 1995;40:73-78.
28. Freedman RR, Blacker CM. Estrogen raises the sweating threshold in postmenopausal women with hot flashes. *Fertil Steril.* 2002;77:487-490.
29. Notelovitz M, Lenihan JP, McDermott M, et al. Initial 17beta-estradiol dose for treating vasomotor symptoms. *Obstet Gynecol.* 2000;95:726-731.
30. Notelovitz M, Mattox JH. Suppression of vasomotor and vulvovaginal symptoms with continuous oral 17beta-estradiol. *Menopause.* 2000;7:310-317.
31. Vikhlyaeva E, Zaidiieva Y, Lobova T, et al. Trisequens in perimenopausal women with climacteric syndrome: a randomised double-blind trial. *J Akusherstvo i Ginecologia.* 1997;5:76-80.
32. Bacchi-Modena A, Bolis P, Campagnoli C, et al. Efficacy and tolerability of Estraderm MX, a new estradiol matrix patch. *Maturitas.* 1997;27:285-292.
33. de Aloysio D, Rovati LC, Giacovelli G, et al. Efficacy on climacteric symptoms and safety of low dose estradiol transdermal matrix patches. *Arzneimittelforschung.* 2000;50:293-300.
34. de Vrijer B, Snijders MP, Troostwijk AL, et al. Efficacy and tolerability of a new estradiol delivering matrix patch (Estraderm MX) in postmenopausal women. *Maturitas.* 2000;34:47-55.
35. Notelovitz M, Cassel D, Hille D, et al. Efficacy of continuous sequential transdermal estradiol and norethindrone acetate in relieving vasomotor symptoms associated with menopause. *Am J Obstet Gynecol.* 2000;182:7-12.
36. Shulman LP, Yankov V, Uhl K. Safety and efficacy of a continuous once-a-week 17beta-estradiol/levonorgestrel transdermal system and its effects on vasomotor symptoms and endometrial safety in postmenopausal women: the results of two multicenter, double-blind, randomized, controlled trials. *Menopause.* 2002;9:195-207.
37. Speroff L, Whitcomb RW, Kempfert NJ, et al. Efficacy and local tolerance of a low-dose, 7-day matrix estradiol transdermal system in the treatment of menopausal vasomotor symptoms. *Obstet Gynecol.* 1996;88:587-592.
38. Utian WH, Burry KA, Archer DF, et al. Efficacy and safety of low, standard, and high dosages of an estradiol transdermal system (Esclim) compared with placebo on vasomotor symptoms in highly symptomatic menopausal patients. *Am J Obstet Gynecol.* 1999; 181:71-79.
39. von Holst T, Salbach B. Efficacy and tolerability of a new 7-day transdermal estradiol patch versus placebo in hysterectomized women with postmenopausal complaints. *Maturitas.* 2000;34:143-153.
40. von Holst T, Salbach B. Efficacy of a new 7-day transdermal sequential estradiol/levonorgestrel patch in women. *Maturitas.* 2002;41:231-242.
41. Wiklund I, Karlberg J, Mattsson LA. Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: a double-blind placebo-controlled study. *Am J Obstet Gynecol.* 1993;168: 824-830.
42. Barnabei VM, Grady D, Stovall DW, et al. Menopausal symptoms in older women and the effects of treatment with hormone therapy. *Obstet Gynecol.* 2002;100:1209-1218.
43. Baumgardner SB, Condrea H, Daane TA, et al. Replacement estrogen therapy for menopausal vasomotor flushes: comparison of quinestrol and conjugated estrogens. *Obstet Gynecol.* 1978;51:445-452.
44. Campbell S. Double blind psychometric studies on the effects of natural estrogens on postmenopausal women. In: Campbell S, ed. *The Management of the Menopause and Post Menopausal Years.* Baltimore, Md: University Park Press; 1976.
45. Carranza-Lira S, Cortes-Fuentes E. Modification of vasomotor symptoms after various treatment modalities in the postmenopause. *Int J Gynaecol Obstet.* 2001;73:169-171.
46. Coope J, Thomson JM, Poller L. Effects of "natural oestrogen" replacement therapy on menopausal symptoms and blood clotting. *BMJ.* 1975;4:139-143.
47. Greendale GA, Reboussin BA, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet Gynecol.* 1998; 92:982-988.
48. Utian WH, Shoupe D, Bachmann G, et al. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril.* 2001;75: 1065-1079.
49. Shulman LP, Yankov V, Uhl K. Safety and efficacy of a continuous once-a-week 17beta-estradiol/levonorgestrel transdermal system and its effects on vasomotor symptoms and endometrial safety in postmenopausal women: the results of two multicenter, double-blind, randomized, controlled trials [published correction appears in *Menopause.* 2002;9: 385]. *Menopause.* 2002;9:195-207.
50. Speroff L, Rowan J, Symons J, et al. The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART study): a randomized controlled trial. *JAMA.* 1996;276:1397-1403.
51. Manson J, Hsia J, Johnson K, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med.* 2003;349:523-534.
52. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA.* 2003;289:2673-2684.
53. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA.* 2003;289:3243-3253.

 ©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 10/07/2015