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 17\(\beta\)-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 17\(\beta\)-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 17\(\beta\)-estradiol, 5 trials: pooled weighted mean difference, –16.8; 95% CI, –23.4 to –10.2; transdermal 17\(\beta\)-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 17\(\beta\)-estradiol have consistent and comparable effects on treatment of menopausal hot flashes and may have similar short-term adverse effects.

**See also p 1621.**

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man carcinogens. The US Preventive Services Task Force as well as professional organizations 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, 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. 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 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. 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, 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 defects, thrombosis, cardiovascular
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, 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. 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 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.

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. Funnel plots were constructed and indicated no evidence of publication bias, although they are a crude estimate and were limited by the small numbers of eligible studies.

RESULTS

Head-to-Head Comparisons

Four trials compared estrogen preparations head-to-head, including 1 trial of CEE compared with oral 17β-estradiol and 3 trials comparing oral CEE with transdermal 17β-estradiol (TABLE 1 and TABLE 2). Women enrolled in these trials had hot flashes at baseline, and all trials reported
### Table 2. Main Outcomes of Trials of 17β-Estradiol Compared With Conjugated Equine Estrogen (CEE)

<table>
<thead>
<tr>
<th>Source</th>
<th>Main Outcomes/Results</th>
<th>Withdrawals Due to Adverse Effects</th>
<th>Total Withdrawals</th>
<th>Main Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Archer et al,20 1992</td>
<td>Reduction in frequency of vasomotor events (80%-95% estrogen, 66% placebo); all agents significantly different from placebo (P&lt;.05), no differences between agents</td>
<td>9</td>
<td>21</td>
<td>Incidence of possible drug-related adverse experiences ranged from 20% (placebo, 1-mg/d estradiol, 0.625-mg/d CEE) to 55% (2-mg/d estradiol, 1.25-mg/d CEE) with no significant differences between groups</td>
</tr>
<tr>
<td>Good et al,11 1999</td>
<td>Reduction of hot flashes by 90% for both agents, no differences at comparable doses</td>
<td>16</td>
<td>47</td>
<td>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)</td>
</tr>
<tr>
<td>Gordon et al,21 1995 (study 2)</td>
<td>Reduction in mean weekly hot flashes in all groups (63%-78%), no differences between agents</td>
<td>32 (15 0.05-mg/d estradiol, 10 0.1-mg/d estradiol, and 7 CEE)</td>
<td>64</td>
<td>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&lt;.05)</td>
</tr>
<tr>
<td>Studd et al,22 1995</td>
<td>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</td>
<td>Not reported</td>
<td>Not reported</td>
<td>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</td>
</tr>
</tbody>
</table>

### Table 3. Trials of Oral 17β-Estradiol

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

Abbreviation: CCT, combined continuous therapy.

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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, and 1 was excluded because data were provided in graphic form. 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. In a 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). 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. Trials were conducted predominantly in the United States or western Europe and recruited participants from general pri-

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Main Outcomes/Results</th>
<th>Withdrawals Due to Adverse Effects</th>
<th>Total Withdrawals</th>
<th>Main Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baerug et al, 1998</td>
<td>Reduction in mean hot flash frequency and severity; significantly different from placebo; no differences between progestin groups</td>
<td>5</td>
<td>11</td>
<td>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</td>
</tr>
<tr>
<td>Bech et al, 1998</td>
<td>Reduction in hot flash severity (Kupperman Index scores: estradiol, 3-3.7; placebo, 9; P &lt; .01); no difference between CCT and cyclic regimens</td>
<td>Not reported</td>
<td>20</td>
<td>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</td>
</tr>
<tr>
<td>Chung et al, 1996</td>
<td>No significant differences between estradiol and placebo for vasomotor severity score, number with hot flashes, and number with moderate to severe hot flashes</td>
<td>Not reported</td>
<td>17</td>
<td>Headache and dizziness reported; no differences between groups</td>
</tr>
<tr>
<td>Conard et al, 1995</td>
<td>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</td>
<td>4</td>
<td>13</td>
<td>1 Withdrawal from estradiol group for atypical bleeding</td>
</tr>
<tr>
<td>Derman et al, 1995</td>
<td>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</td>
<td>6</td>
<td>35</td>
<td>Withdrawals from estradiol group for atypical bleeding, weight change, palpitations; from placebo group for lack of effect (data not reported)</td>
</tr>
<tr>
<td>Freedman and Blacker, 2002</td>
<td>Reduction in hot flash frequency significantly different from placebo (determined by laboratory measures rather than self-report)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Notelovitz et al, 2000</td>
<td>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 &lt; .001); the 0.25-mg group was not different than placebo (25%)</td>
<td>26 (5 placebo, 21 estradiol, more in high-dose groups)</td>
<td>53</td>
<td>18 Withdrawals for atypical bleeding (11 from 2-mg group), breast tenderness reported in all groups with more reports in higher dose groups</td>
</tr>
<tr>
<td>Notelovitz and Mattox, 2000</td>
<td>Reduction in mean number of hot flashes from baseline (83% 1-mg/d group, 66% 0.5-mg/d group), significantly different from placebo</td>
<td>Not reported</td>
<td>23</td>
<td>Atypical bleeding reported in estradiol groups with 1 case of endometrial cancer; headaches and abdominal pain reported in all groups</td>
</tr>
<tr>
<td>Vikhlyaeva et al, 1997 (English abstract)</td>
<td>Improvement on Kupperman Index score for estradiol group vs placebo (P = .01)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

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.20 When reported, women in placebo groups also had improvement of 28 trials.

Three trials included concomitant progesterone agents.† Studies that compared groups using estrogen alone with groups using estrogen with progesterin 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 (TABLE 5 and TABLE 6).21,32-41 Three trials included concomitant progesterin or progesterone (cyclic norethindrone acetate, continuous cyclic levonorgestrel, and levonorgestrel 10 µg/d).23,34,35,40

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 progesterin or progesterone (cyclic norethindrone acetate, continuous transdermal levonorgestrel).23,34,35,40

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 progesterin or progesterone use (cyclic and continuous

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Main Outcomes/Results</th>
<th>Withdrawals Due to Adverse Effects</th>
<th>Total Withdrawals</th>
<th>Main Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacchi-Modena et al.97, 1997</td>
<td>Reduction in mean number of moderate to severe hot flashes per 24 h (~8 from baseline for estradiol and ~4 for placebo, <em>P</em> &lt; .001); improvement in Kupperman Index score (~18 for estradiol and ~9 for placebo, <em>P</em> &lt; .001)</td>
<td>2</td>
<td>11</td>
<td>Atypical bleeding reported in 15% estradiol and 13% placebo, breast tenderness in 28% estradiol and 27% placebo, skin reactions in 30% estradiol and 30% placebo groups</td>
</tr>
<tr>
<td>de Aloysio et al.98, 2000</td>
<td>Reduction in number of hot flashes (83%-84% in estradiol and 58% in placebo groups, <em>P</em> &lt; .05)</td>
<td>3</td>
<td>20</td>
<td>Atypical bleeding reported in all groups (1 withdrew from 0.0575-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 16% estradiol and 8% placebo groups</td>
</tr>
<tr>
<td>de Vrijer et al.99, 2000</td>
<td>Reduction in mean number of moderate to severe hot flashes per 24 h similar for both estradiol groups, significantly different from placebo (~5 to ~5.2 for estradiol and ~5.3 for placebo, <em>P</em> &lt; .001); Kupperman Index score and night sweats also significantly decreased for both estradiol groups vs placebo</td>
<td>18</td>
<td>Not reported</td>
<td>5 Withdraw 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 group; skin reactions reported in both estradiol and placebo groups</td>
</tr>
<tr>
<td>Gordon et al.100, 1995 (study 1)</td>
<td>Reduction in mean weekly hot flashes in all groups (67% 0.05-mg estradiol, 72% 0.1-mg estradiol, 16% placebo; <em>P</em> &lt; .05)</td>
<td>22</td>
<td>50</td>
<td>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 (<em>P</em> &lt; .05); application-site reactions were the most common adverse experience (8% withdrew), other adverse events reported include vaginal bleeding, breast pain, depression, and dizziness</td>
</tr>
<tr>
<td>Notelovitz et al.101, 2000</td>
<td>Reduction in mean number of hot flashes per day, mean intensity of hot flashes, and sweating all significantly different from placebo (<em>P</em> &lt; .001)</td>
<td>6</td>
<td>12</td>
<td>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</td>
</tr>
<tr>
<td>Shulman et al.102, 2002</td>
<td>Reduction in daily number of hot flashes from baseline (9 and 10 for estradiol groups, 5 for placebo; <em>P</em> &lt; .001)</td>
<td>11 Estradiol, 6 placebo</td>
<td>42</td>
<td>4 Withdraw 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)</td>
</tr>
<tr>
<td>Speroff et al.103, 1996</td>
<td>Reduction in hot flash frequency (84% for estradiol group), significantly different from placebo</td>
<td>18</td>
<td>63</td>
<td>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)</td>
</tr>
<tr>
<td>Utian et al.104, 1999</td>
<td>Reduction in frequency of moderate to severe vasomotor symptoms significantly different from placebo (<em>P</em> &lt; .05)</td>
<td>7</td>
<td>20</td>
<td>4 Withdraw 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, 25% 0.05-mg estradiol, and 58% 0.10-mg estradiol</td>
</tr>
<tr>
<td>von Holst and Sabbach,105, 2000</td>
<td>Reduction in mean hot flashes (44 to 12 in estradiol, 41 to 19 in placebo; <em>P</em> = .003); improvement in Kupperman Index score (27.6 to 11.2 for estradiol, 27.9 to 16 for placebo; <em>P</em> &lt; .001)</td>
<td>9 Estradiol, 7 placebo</td>
<td>Not reported</td>
<td>4 From estradiol group had breast tenderness; 7 had skin reactions (4 estradiol, 3 placebo)</td>
</tr>
<tr>
<td>von Holst and Sabbach,106, 2002</td>
<td>Reduction in number of hot flashes in estradiol group significantly lower than placebo; improvement in Kupperman Index score (28.8 to 9.5 in estradiol, 27.1 to 16.9 in placebo; <em>P</em> &lt; .001)</td>
<td>8</td>
<td>31</td>
<td>Headaches and skin reactions were reported in all groups</td>
</tr>
<tr>
<td>Windlund et al.107, 1993</td>
<td>Mean change from baseline for vasomotor symptoms score, Kupperman Index score reduced vs placebo (<em>P</em> &lt; .001)</td>
<td>Not reported</td>
<td>18</td>
<td>Atypical bleeding in 8% placebo and 13% estradiol groups; some withdrawals in estradiol group due to headache and skin reactions</td>
</tr>
</tbody>
</table>
**Table 7. Trials of Conjugated Equine Estrogen**

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

**Table 8. Main Outcomes of Conjugated Equine Estrogen Trials**

<table>
<thead>
<tr>
<th>Source</th>
<th>Main Outcomes/Results</th>
<th>Withdrawals Due to Adverse Effects</th>
<th>Total Withdrawals</th>
<th>Main Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnabei et al,42 2002</td>
<td>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&lt;.001)</td>
<td>Not reported Not reported</td>
<td>Reports of breast symptoms (40% after first year in CEE group, 9% in placebo; P&lt;.001); uterine bleeding (31%) and spotting (33%) among women in CEE group; weight gain and edema in both groups</td>
<td></td>
</tr>
<tr>
<td>Baumgardner et al,43 1978</td>
<td>Reduction in number of patients with moderate to severe hot flashes in CEE groups, significantly different from placebo</td>
<td>Not reported Not reported</td>
<td>1 Withdraw from CEE group for nausea, additional withdrawals for edema and visual symptoms (no differences between groups), and lack of effect in placebo group</td>
<td></td>
</tr>
<tr>
<td>Campbell,44 1976</td>
<td>Improved mean scores on hot flash rating scale with CEE, significantly different from placebo</td>
<td>Not reported</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Carranza-Lira and Cortes-Fuentes,45 2001</td>
<td>Reduction in number, severity, and duration of hot flashes and if insomnia and sweating accompanied hot flashes for CEE group, significantly different from placebo</td>
<td>Not reported Not reported Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coope et al,46 1975</td>
<td>Reduction in number of patients with hot flashes among those with hot flashes at baseline (P = .04)</td>
<td>Not reported</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Greendale et al,47 1998</td>
<td>Reduction in number of patients with any vasomotor symptom in all CEE groups, significantly different from placebo, no difference between CEE groups</td>
<td>127 210</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Utian et al,48 2001</td>
<td>Reduction in mean daily number and severity of hot flashes in all CEE groups, significantly different from placebo</td>
<td>221 521</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CCT, combined continuous therapy; HERS, The Heart and Estrogen/Progestin Replacement Study; PEPI, Postmenopausal Estrogen/Progestin Intervention.
medroxyprogesterone acetate, cyclic micronized progesterone). 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). 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 –1.68 per week (95% CI, –2.34 to –1.02) compared with placebo (Figure 2). Combining only the 4 trials that included 17β-estradiol and progesterin or progesterone did not significantly change results (pooled weighted mean difference, –1.91; 95% CI, –2.96 to –0.86).23,26,27,31 Trials were excluded from analysis because they did not provide data on frequency of hot flashes21,25 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 progesterin or progesterone and results were not significantly different from the other studies.45 Trials were excluded because they did not provide data on frequency of hot flashes22,49 provided data in graphic form,23,35,38 or did not provide standard deviations.20,36

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,22,45,47 provided data in graphic form,45 or did not provide standard deviations.20,30,34,36

**Comparative Safety**

All but 5 trials 21,23,42,47,48 were less than 1 year in duration and only 3 trials enrolled more than 500 participants.52,47,48 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, cholesterolysis, 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.50 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.30,33 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.21,32,33,38-41,49,50 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.

2References 11, 20, 23, 24, 26, 27, 33, 34, 37-39, 42, 47-49.
3References 11, 21-24, 26, 29, 30, 33, 34, 36, 38, 41, 42.

Figure 2. Trials of Oral 17β-Estradiol

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted Mean Difference (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baerug et al.23, 1998</td>
<td></td>
</tr>
<tr>
<td>Conard et al.20, 1995</td>
<td></td>
</tr>
<tr>
<td>Derman et al.27, 1997</td>
<td></td>
</tr>
<tr>
<td>Freedman and Blacker.20, 2002*</td>
<td></td>
</tr>
<tr>
<td>Velyan et al.21, 1997</td>
<td></td>
</tr>
</tbody>
</table>

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 progesterin, with the exception of this study, which used 17β-estradiol alone.

Figure 3. Trials of Transdermal 17β-Estradiol

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted Mean Difference (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacchi-Morena et al.20, 1997</td>
<td></td>
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<tr>
<td>de Vrese et al.19, 2000</td>
<td></td>
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<tr>
<td>Gordon et al.18, 1996</td>
<td></td>
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<tr>
<td>Speroff et al.37, 1996</td>
<td></td>
</tr>
<tr>
<td>von Holst and Salbach.36, 2000*</td>
<td></td>
</tr>
<tr>
<td>van Holst and Salbach.40, 2002*</td>
<td></td>
</tr>
</tbody>
</table>

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 –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 progesterin.

**Postmenopausal Estrogen for Treatment of Hot Flashes**

April 7, 2004—Vol 291, No. 13 (Reprinted)
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.3 This trial was designed as a primary prevention trial and enrolled more than 16,000 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 cancer53 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 thrombosis57 and 2 trials reported 1 case each of endometrial cancer in 17β-estradiol users30,34; 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 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.

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REFERENCES

POSTMENOPAUSAL ESTROGEN FOR TREATMENT OF HOT FLUSHES


