Postmenopausal Estrogen for Treatment of Hot Flashes
Clinical Applications

Heidi D. Nelson, MD, MPH

Use of postmenopausal estrogen has changed since the release of the first results from the Women’s Health Initiative in 2002. Professional organizations, the US Food and Drug Administration, and the US Preventive Services Task Force have issued new recommendations against use of estrogen and progestin or progesterone for prevention of chronic conditions. This article applies the current state of evidence for postmenopausal estrogen use to management decisions in 2 clinical scenarios: initiating therapy in a perimenopausal woman with hot flashes and discontinuing estrogen use in a long-term user.

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Patient 1: Initiating Therapy in a Perimenopausal Woman With Hot Flashes

A 49-year-old woman seeks the advice of her physician on how to manage hot flashes. She has been having irregular menstrual periods during the past 6 months and has had increasingly frequent episodes of hot flashes that wake her from sleep at least weekly. She has no other major health problems as determined by her history, recent physical examination, and routine laboratory test results. Her primary sources of information about menopause have been the popular press and discussions with friends.

Although this woman’s hot flashes are currently increasing in frequency, she may find it helpful to know that an estimated 30% to 50% of women have improved hot flashes within several months, and hot flashes resolve in most women within 4 to 5 years. Many women can tolerate their menopausal symptoms if they are mild and transient; however, the nature, frequency, severity, and duration of symptoms vary widely among individuals. In a study of menopausal women, more than half of respondents reported that symptoms other than hot flashes, such as sleep disturbance and genitourinary symptoms, strongly influenced their decision making about initiating hormone therapy. All menopausal symptoms should be addressed and included in a management plan, if indicated.

Algorithms guiding a decision-making process for menopausal symptoms are available; however, they are not evidence-based and have not been subjected to trials demonstrating effectiveness. Additional evaluations, including hormone tests, are usually not needed.

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See also p 1610.
needed to evaluate menopause, although follicle-stimulating hormone levels may be helpful to sort out symptoms in a woman who has undergone hysterectomy without removal of her ovaries. In such patients, the inability of uterine bleeding as a marker makes the distinction of perimenopause and menopause more difficult. Women and physicians must identify individual benefits and harms of interventions based on the woman’s experiences, her personal preferences, and relevant evidence and then develop a management plan through a shared decision-making process. Women have previously expressed dissatisfaction with the decision-making process with physicians regarding menopause, although the opinion of physicians is also important to their decisions. A woman is the best judge of what symptoms are present and tolerable and what management strategies and outcomes are acceptable for her. Improved patient education and communication may enhance this process.

Interest has grown for use of dietary supplements containing isoflavones from soy or red clover to treat hot flashes, and these remedies are being used as alternatives to estrogen. Evidence for improvement of hot flashes is based on a large number of randomized controlled trials of symptomatic women in their late 40s and early 50s. Improvement in sleep disturbances and urogenital atrophy is supported by a fewer number of randomized controlled trials reporting a variety of measures. Studies of improvement in mood are suggestive of benefit, but study methods and outcome measures vary, rendering results inconclusive. Data from the WHI, a large randomized controlled prevention trial of conjugated equine estrogen (CEE) and medroxyprogesterone acetate, indicate improved vasomotor symptoms among women aged 50 to 54 years who were randomized to estrogen. These women also reported small improvements in sleep disturbances but not improvements in other quality-of-life outcomes, such as fatigue, bodily pain, and depression, among others.

Osteoporosis prevention is another potential benefit of postmenopausal estrogen use. Randomized controlled trials of estrogen indicate improved bone density for estrogen users, including women in early menopause. The WHI analysis indicated reduced total fractures among estrogen users aged 50 to 54 years (hazard ratio [HR], 0.68; unadjusted 95% confidence interval [CI], 0.49-0.93) but not among women aged 55 to 59 years (HR, 0.91; 95% CI, 0.71-1.16). An analysis of the subgroup of women in the WHI with menopausal symptoms has not been published. The role of estrogen or other medications in preventing osteoporosis in women without low bone density is controversial, because the long-term benefits and adverse effects of this strategy are not known. Use of nonestrogen agents, such as bisphosphonates, to treat established osteoporosis is supported by randomized controlled trials and is recommended as the first choice.

This woman has no known contraindications to using estrogen, including undiagnosed abnormal genital bleeding, current or previous venous or arterial thrombotic events, breast cancer, other estrogen-sensitive cancers, or liver dysfunction or disease. Estrogen can cause breast tenderness, vaginal bleeding, headaches, nausea, weight change, and other symptoms in some women. Estrogen users in the WHI underwent more procedures to evaluate vaginal bleeding than the placebo group (endometrial biopsies, 33.4% vs 5.7%, P<.001; transvaginal uterine ultrasounds, 12.8% vs 4.1%, P<.001), although cases of endometrial cancer were not higher (27 vs 31 cases; rate, 0.06% per person-year) in estrogen users. Estrogen use increases risks for cholecystitis and thromboembolic events, coronary artery disease, and stroke. Risk for cholecystitis was elevated by 40% to 80% in studies that did not specifically evaluate risk in symptomatic women in early menopause. Risk for thromboembolic events was increased approximately 3-fold in the first year of use and 2-fold in subsequent years in a number of studies with women from wide age ranges. In the WHI, a subgroup of estrogen users aged 50 to 59 years with hot flashes at baseline did not have significantly increased risks for coronary heart disease events (nonfatal myocardial infarction and death due to coronary heart disease) or stroke compared with placebo, and there were few events in both groups (coronary heart disease events: 21 estrogen users, 17 placebo users; stroke: 13 estrogen users, 5 placebo users). Studies do not support increased breast cancer incidence with fewer than 4 or 5 years of use.
Table. Potential Adverse Effects With Estrogen Use in the Women’s Health Initiative

<table>
<thead>
<tr>
<th>Potential Adverse Effect</th>
<th>Risk With Estrogen Use, Hazard Ratio (95% CI)</th>
<th>Estimated No. of Events per 10,000 Women per Year Due to Estrogen Use</th>
<th>Duration Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease events†</td>
<td></td>
<td></td>
<td>Highest risk during the first year, continued risk after the first year that decreases after 6 years</td>
</tr>
<tr>
<td>Total</td>
<td>1.24 (1.00-1.54)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Women with symptoms (aged 50-59 y)</td>
<td>1.16*</td>
<td>0-3</td>
<td></td>
</tr>
<tr>
<td>Strokes†</td>
<td></td>
<td></td>
<td>Increased risk after 2 years</td>
</tr>
<tr>
<td>Total</td>
<td>1.31 (1.02-1.68)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Women with symptoms</td>
<td>1.37 (0.84-2.23)</td>
<td>0-7</td>
<td></td>
</tr>
<tr>
<td>Thromboembolic events†</td>
<td></td>
<td></td>
<td>Highest risk during first year, continued risk after the first year</td>
</tr>
<tr>
<td>Total</td>
<td>2.11 (1.26-3.55)</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>During first year</td>
<td>3.60*</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Breast cancer cases†</td>
<td>1.24 (1.01-1.54)</td>
<td>8</td>
<td>Increased risk after 4 years</td>
</tr>
<tr>
<td>Cholecystitis cases††</td>
<td>1.8 (1.6-2.0)</td>
<td>25</td>
<td>Increased risk with increased duration</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*95% CI not given.
†Cholecystitis has not yet been reported for the Women’s Health Initiative, and data are based on relative risks from the Nurses’ Health Study.46

Although several types of estrogen are approved in the United States, oral CEE is the most commonly used despite a decline in use after the results of the WHI were released (from 63% of total estrogen prescriptions in 2001 to 50% in 2003).35 Other oral estrogens comprised 34% of estrogen prescriptions in 2003, transdermal estrogens comprised 11%, and vaginal estrogens comprised 6%.36 Trial data indicate that CEE and oral and transdermal 17β-estradiol have similar effectiveness in treating hot flashes.37 Limited numbers of trials of other estrogens indicate effectiveness also,35-38 but few provide direct comparisons among agents.39 Data about adverse effects are inconsistently collected across trials and are difficult to compare among agents.

A range of doses is available for most estrogen agents, and doses can be adjusted depending on improvement of symptoms and presence of adverse effects. Package inserts recommend starting at a low dose; for example, for oral CEE, begin at 0.3 mg/d.35 Although fertility decreases in perimenopause, contraceptive issues need to be addressed. Perimenopausal women with continuing menstrual cycles may require initiation of a low-dose estrogen oral contraceptive rather than a starting dose of CEE or 17β-estradiol, for example, to protect against unintended pregnancy.35,61 Estrogen is combined with a progestin or progestерone for a woman with a uterus to prevent endometrial hyperplasia and endometrial cancer23 and can be given on a daily or cyclic regimen. A woman taking menopausal estrogen should follow up periodically with her physician to assess her response, monitor adverse effects, reassess benefits and harms, and reexamine her need for estrogen. Dose and regimen adjustments may be required for optimal therapy. Trials discontinuing therapy or decreasing dose have been suggested after 2 to 3 years to help assess continued needs for estrogen.27

**Patient 2: Discontinuing Estrogen Use in a Long-term User**

A 61-year-old woman has been taking combined continuous estrogen for nearly 10 years and wants to discontinue its use. Use of estrogen was initially begun to control hot flashes, but she has continued to use it because of beliefs about potential cardiovascular and osteoporosis benefits. When the initial results of the WHI were released in 2002,31 she immediately stopped using it. Although she experienced frequent hot flashes initially, she understood that they were temporary and put up with them. After a couple of months of this, however, she resumed use because her symptoms interfered with her sleep and she started to feel depressed and generally not well. She has no major medical problems and uses no medications.

Prescribing data indicate that the number of dispensed prescriptions for monthly estrogen therapy in the United States decreased from 91 million in 2001 to 57 million in 2003, demonstrating a continuing downward trend since publication of the WHI 1 and Heart and Estrogen/Progestin Replacement Study II results in July 2002.34 This patient, and many more, determined that her risks outweighed the benefits of estrogen therapy, and she appropriately decided to stop use. However, she may have discontinued use of her estrogen too abruptly the first time and experienced withdrawal symptoms.

Her preferences are as important in planning to discontinue estrogen use as they are in initiating it. One option is to gradually taper her dose. This approach is based on clinical judgment, not evidence, but is similar to tapers of other medications. For women who stopped using postmenopausal estrogen, resuming use at a lower dose may relieve symptoms and start the taper, although some women may require a return to their original dose for symptom control. Once symptoms are relieved, doses can be decreased in a stepwise fashion by reducing the daily dose, reducing the number of days per week that estrogen is taken, or a combination.27 Individually tapering off the estrogen dose is important and some women will take longer than others and may require several weeks or months.
at each step. If the patient’s depression and feelings of ill health are substantial or continue after her hot flashes are controlled, a separate evaluation is needed. Postmenopausal estrogen is not a treatment for depression, and a selective serotonin reuptake inhibitor may be effective for both hot flashes and depression.24,25 Evidence of harms with continued use is relevant to this woman. Harms of continuing long-term therapy include a 2-fold increased risk of thromboembolic events4,46 and increases in risks for stroke and myocardial infarction.8,9 She has a 2.5-fold increased risk for cholecystitis with long-term use, a higher risk than for short-term use.46 Long-term use could increase her risk for breast cancer.51,53 She may have had some osteoporosis benefit with estrogen use42,43; however, it would be difficult to quantify this unless serial bone density test results had been obtained. Current evidence-based guidelines recommend screening for osteoporosis for all women aged 65 years or older and women aged 60 to 64 years with increased risk defined as low body weight and nonuse of estrogen.65,66 Women with previous fractures and other conditions related to osteoporosis, such as steroid use, require bone density monitoring outside screening guidelines. If she does not have these risk factors or other indications for bone densitometry, then performing bone densitometry before discontinuation of estrogen use at the age of 61 years is not warranted. She should be informed of recommendations to decrease her risk of postmenopausal osteoporosis by weight-bearing exercise and adequate calcium (1200 mg/d) and vitamin D intake.57 As with all patients changing or discontinuing therapy, she should be followed up periodically with her physician to assess her response, monitor adverse effects, reexamine her needs, and make adjustments.

Conclusion

Much attention has focused on the appropriate use of postmenopausal estrogen since the first reports from the WHI became available. As details of this trial are released, physicians and women are frequently challenged to determine how these data translate to practice. New evidence-based practice standards are emerging that clearly limit the role of postmenopausal estrogen use. However, for select symptomatic women, short-term use may have a favorable benefit-harm ratio.

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