

Hormone therapy for menopausal vasomotor symptoms

➡ Given our available (better) options for treating hot flashes, can we reduce our use of medroxyprogesterone acetate?



Robert L. Barbieri, MD
Editor in Chief, OBG MANAGEMENT
Chair, Obstetrics and Gynecology
Brigham and Women's Hospital, Boston, Massachusetts
Kate Macy Ladd Professor of Obstetrics,
Gynecology and Reproductive Biology
Harvard Medical School, Boston

Estrogen therapy is highly effective in the treatment of hot flashes among postmenopausal women. For postmenopausal women with a uterus, estrogen treatment for hot flashes is almost always combined with a progestin to reduce the risk of endometrial polyps, hyperplasia, and cancer. For instance, in the Postmenopausal Estrogen/Progestin Interventions Trial, 62% of the women with a uterus treated with conjugated equine estrogen (CEE) 0.625 mg daily without a progestin developed endometrial hyperplasia.¹

In the United States, the most commonly prescribed progestin for hormone therapy has been medroxyprogesterone acetate (MPA; Provera). However, data from the Women's Health Initiative (WHI) trials indicate that MPA, when combined with CEE, may have adverse health effects among postmenopausal women.

Let's examine the WHI data

Among women 50 to 59 years of age with a uterus, the combination of CEE plus MPA was associated with a trend toward an increased risk of breast

cancer, coronary heart disease, and myocardial infarction.² In contrast, among women 50 to 59 years of age without a uterus, CEE monotherapy was associated with a trend toward a decreased risk of invasive breast cancer, coronary heart disease, and myocardial infarction (TABLE 1, page 13).

Among women 50 to 79 years of age with a uterus, the combination of CEE plus MPA was associated with a significantly increased risk of breast cancer (hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.01–1.53; $P = .04$).² In contrast, among women 50 to 79 years of age without a uterus, CEE monotherapy was associated with a trend toward a decreased risk of breast cancer (HR, 0.79; 95% CI, 0.61–1.02, $P = .07$).²

When the analysis was limited to women consistently adherent to their CEE monotherapy, the estrogen treatment significantly decreased the risk of invasive breast cancer (HR, 0.67; 95% CI, 0.47–0.97; $P = .03$).³

The addition of MPA to CEE appears to reverse some of the health benefits of CEE monotherapy, although the biological mechanisms

are unclear. This observation should prompt us to explore alternative and novel treatments of vasomotor symptoms that do not utilize MPA. Some options for MPA-free hormone therapy include:

- transdermal estradiol plus micronized progesterone
- CEE plus a levonorgestrel-releasing intrauterine system
- bazedoxifene plus CEE.

In addition, nonhormonal treatment of hot flashes is an option, with selective serotonin reuptake inhibitors (SSRIs).

MPA-free hormone therapy for hot flashes

Estrogen plus micronized progesterone

When using an estrogen plus progestin regimen to treat hot flashes, many experts favor a combination of low-dose transdermal estradiol and oral micronized progesterone (Prometrium). This combination is believed by some experts to result in a lower risk of venous thromboembolism, stroke, cardiovascular disease, and breast cancer

CONTINUED ON PAGE 13

TABLE 1 Women’s Health Initiative randomized clinical trials²

Disease	Trial 1: CEE plus MPA versus placebo*		Trial 2: CEE versus placebo [†]	
	Hazard ratio [‡]	95% CI	Hazard ratio [‡]	95% CI
Invasive breast cancer	1.21	0.81–1.80	0.82	0.50–1.34
Coronary heart disease	1.34	0.82–2.19	0.60	0.35–1.04
Total myocardial infarction	1.32	0.77–2.25	0.55	0.31–1.00
Coronary heart bypass graft or percutaneous coronary intervention	1.03	0.63–1.68	0.56	0.35–0.88

Abbreviations: CEE, conjugated equine estrogen; CI, confidence interval; MPA, medroxyprogesterone acetate.

*Trial 1: For postmenopausal women with a uterus: CEE (0.625 mg daily) plus MPA (2.5 mg daily) versus placebo.

[†]Trial 2: For women without a uterus: CEE (0.625 mg daily) vs placebo.

[‡]Hazard ratio of hormone treatment versus placebo.

than an estrogen-MPA combination.⁴⁻⁷

When prescribing transdermal estradiol plus oral micronized progesterone for a woman within 1 to 2 years of her last menses, a cyclic regimen can help reduce episodes of irregular, unscheduled uterine bleeding. I often use this cyclic regimen: transdermal estradiol 0.0375 mg plus cyclic oral micronized progesterone 200 mg prior to bedtime for calendar days 1 to 12.

When using transdermal estradiol plus oral micronized progesterone in a woman more than 2 years from her last menses, a continuous regimen is often prescribed. I often use this continuous regimen: transdermal estradiol 0.0375 mg plus continuous oral micronized progesterone 100 mg daily prior to bedtime.

Estrogen plus a levonorgestrel-releasing intrauterine system

The levonorgestrel intrauterine system (LNG-IUS; 20 µg daily; Mirena) is frequently used in Europe to protect the endometrium against the adverse effects of estrogen therapy in postmenopausal women. In a meta-analysis of five clinical trials involving postmenopausal women, the

LNG-IUS provided excellent protection against endometrial hyperplasia, compared with MPA.⁸

One caution about using the LNG-IUS system with estrogen in postmenopausal women is that an observational study of all women with breast cancer in Finland from 1995 through 2007 reported a significantly increased risk of breast cancer among postmenopausal women using an LNG-IUS compared with women who did not use hormones or used only estrogen because they had a hysterectomy (TABLE 2, page 14).⁹ This study was not a randomized clinical trial and patients at higher baseline risk for breast cancer, including women with a high body mass index, may have been preferentially treated with an LNG-IUS. More information is needed to better understand the relationship between the LNG-IUS and breast cancer in postmenopausal women.

Progestin-free hormone treatment, bazedoxifene plus CEE

The main reason for adding a progestin to estrogen therapy for vasomotor symptoms in postmenopausal

women with a uterus is to prevent estrogen-induced development of endometrial polyps, hyperplasia, and cancer. A major innovation in hormone therapy is the discovery that third-generation selective estrogen receptor modulators (SERMs), such as bazedoxifene (BZA), can prevent estrogen-induced development of endometrial polyps, hyperplasia, and cancer but do not interfere with the efficacy of estrogen in the treatment of vasomotor symptoms.

BZA is an estrogen agonist in bone and an estrogen antagonist in the endometrium.¹⁰⁻¹² The combination of BZA (20 mg daily) plus CEE (0.45 mg daily) (Duavee) is approved for the treatment of moderate to severe vasomotor symptoms and prevention of osteoporosis.¹³⁻¹⁵ Over 24 months of therapy, various doses of BZA plus CEE reduced reported daily hot flashes by 52% to 86%.¹⁶ In the same study, placebo treatment was associated with a 17% reduction in hot flashes.¹⁶

The main adverse effect of BZA/CEE is an increased risk of deep venous thrombosis. Therefore, BZA/CEE is contraindicated in women with a known thrombophilia or

TABLE 2 Relative risk of invasive breast cancer among postmenopausal women using various hormone therapy regimens⁹

Treatment	Cases	Controls	Odds ratio	95% CI	P value
No hormone therapy or <6 months of hormone therapy	5,473	17,956	1.00	Reference group	
Estradiol-only therapy	991	3,300	1.01	0.93–1.09	.88
LNG-IUS	329	708	1.53	1.33–1.75	.001
Estradiol plus LNG-IUS	287	473	2.07	1.78–2.41	.001

Abbreviations: CI, confidence interval; LNG-IUS, levonorgestrel intrauterine system.

a personal history of hormone-induced deep venous thrombosis. The effect of BZA/CEE on the risk of developing invasive breast cancer is not known; over 52 weeks of therapy it did not increase breast density on mammogram.^{17,18}

BZA/CEE is a remarkable advance in hormone therapy. It is progestin-free, uses estrogen to treat vasomotor symptoms, and uses BZA to protect the endometrium against estrogen-induced hyperplasia.

Nonhormone treatment of vasomotor symptoms

Paroxetine mesylate

For postmenopausal women with vasomotor symptoms who cannot take estrogen, SSRIs are modestly effective in reducing moderate to severe hot flashes. The US Food and Drug Administration recently approved paroxetine mesylate (Brisdelle) for the treatment of postmenopausal vasomotor symptoms. The approved dose is 7.5 mg daily taken at bedtime.

Data supporting the efficacy of paroxetine mesylate are available from two studies involving 1,184 menopausal women with vasomotor symptoms randomly assigned to receive paroxetine 7.5 mg daily or placebo for 12 weeks of treatment.¹⁹⁻²² In one of the two clinical trials,

women treated with paroxetine mesylate 7.5 mg daily had 5.6 fewer moderate to severe hot flashes daily after 12 weeks of treatment compared with 3.9 fewer hot flashes with placebo (median treatment difference, 1.7; $P < .001$).²¹

Paroxetine can block the metabolism of tamoxifen to its highly potent metabolite, endoxifen. Consequently, paroxetine may reduce the effectiveness of tamoxifen treatment for breast cancer and should be used with caution in postmenopausal women with breast cancer being treated with tamoxifen.

Escitalopram


Gynecologists are familiar with the use of venlafaxine, desvenlafaxine, clonidine, citalopram, sertraline, and fluoxetine for the treatment of postmenopausal hot flashes. Recently, escitalopram (Lexapro) at doses of 10 to 20 mg daily has been shown to be more effective than placebo in the treatment of hot flashes and sleep disturbances in postmenopausal women.^{23,24} In one trial of escitalopram 10 to 20 mg daily versus placebo in 205 postmenopausal women averaging 9.8 hot flashes daily at baseline, escitalopram and placebo reduced mean daily hot flashes by 4.6 and 3.2, respectively ($P < .001$), after 8 weeks of treatment.

In a meta-analysis of SSRIs for the treatment of hot flashes, data from a mixed-treatment comparison analysis indicated that the rank order from most to least effective therapy for hot flashes was: escitalopram > paroxetine > sertraline > citalopram > fluoxetine.²⁵ Venlafaxine and desvenlafaxine, two serotonin and norepinephrine reuptake inhibitors that are effective in the treatment of hot flashes, were not included in the mixed-treatment comparison.

Use of alternatives to MPA could mean fewer health risks for women on a wide scale

Substantial data indicate that MPA is not an optimal progestin to combine with estrogen for hormone therapy. Currently, many health insurance plans and Medicare use pharmacy management formularies that prioritize dispensing MPA for postmenopausal hormone therapy. Dispensing an alternative to MPA, such as micronized progesterone, often requires the patient to make a significant copayment.

Hopefully, health insurance companies, Medicare, and their affiliated pharmacy management administrators will soon stop their current policy of using financial

incentives to favor dispensing MPA when hormone therapy is prescribed because alternatives to MPA appear to be associated with fewer health risks for postmenopausal women. 



RBARBIERI@FRONTLINEMEDCOM.COM

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