

Evolution toward Lower Doses of Postmenopausal Estrogen Therapy

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The clinical use of estrogens to treat menopausal symptoms was first described nearly 80 years ago.¹ In the early 1940s oral estrogen formulations for postmenopausal hormonal therapy (HT) became available and, since that time, doses of estrogen in HT have been continually decreasing.² Until the mid-1970s daily doses of conjugated equine estrogens (CEE) as high as 1.25 mg or 2.5 mg were commonly used,³ thereafter transitioning to 0.625 mg/day as the standard dose.⁴ Use of the lowest clinically effective dose of HT for relief of menopause-related symptoms and for prevention of osteoporosis is now recommended. Low-dose estrogen therapy (ET) is currently defined as a dose of oral CEE of ≤ 0.45 mg/d, oral estradiol ≤ 0.5 mg/d, transdermal estradiol ≤ 0.025 mg/d, or the equivalent. Today, tablet formulations containing as little as 0.3 mg of CEE and 0.5 mg of 17β -estradiol (E_2) are available for once-daily dosing. These lower doses of estrogen are increasingly being recommended for relief of menopausal symptoms,^{5,6} as well as for prevention of osteoporosis in postmenopausal women.⁷

Even before the discontinuation of the Women's Health Initiative (WHI) hormone therapy trials,^{8,9} strong interest in the safety and efficacy of lower doses of ET and estrogen-plus-progestin therapy (EPT) was evident.^{3,4,10,11} The initial WHI results highlighted the need for and, in all likelihood, accelerated the adoption of lower ET/EPT doses in clinical practice.⁶ In 2002 the initial results reported from the WHI indicated that 5 years of standard-dose EPT decreased a woman's risk of fracture but increased her risk for coronary

heart disease, stroke, venous thromboembolism (VTE) and breast cancer.^{8,12} As is now well known, the EPT trial was stopped prematurely and the overall risks of ET/EPT were said to outweigh the benefits in all postmenopausal women. However, the WHI study population was, on average, more than 63 years of age at the time of study enrollment and hormone initiation, raising the question as to whether the WHI results can or should be generalized to all women.¹³⁻¹⁵ The results from the ET trial of the WHI⁹ and more recent age-stratified

analyses from the EPT trial^{12,16,17} provide good evidence that the risk-benefit profile of standard-dose ET and EPT is significantly more favorable in younger postmenopausal women—ie, those who initiate ET/EPT within a few years following their final menstrual period—than that observed in the overall WHI study population.^{15,18}

Regardless of these recent reassuring findings about standard-dose ET/EPT, use of the lowest effective dose of any medication remains an important tenet of clinical practice and is a worthwhile goal in the treatment of the postmenopausal patient.⁶ Consistent with this goal, current guidelines around the world unanimously recommend the use of the lowest effective dose of ET/EPT.^{7,19-21}

The purpose of this article is to review the efficacy and safety data from recent trials on low-dose ET/EPT regimens, and to put this evidence into context for clinicians who treat women transitioning into menopause and beyond, hopefully reassuring both clinicians and patients that currently available preparations afford a favorable benefit-to-risk profile for women who seek menopausal symptom relief and prevention of bone loss.

Low-Dose Regimens

Accumulating evidence demonstrates the improved tolerability of low-dose systemic ET/EPT, and its efficacy in relieving menopausal vasomotor and

vulvovaginal symptoms and preventing postmenopausal bone loss.^{2,5,6,22,23} In recent years a variety of low-dose estrogen options in two dosage forms—oral tablets and transdermal patches—have been introduced.^{2,22} The low-dose formulations available

in the US are summarized in the Table below, along with their indications.^{24–43} Newer lower-dose options include oral estradiol (E₂) 0.45–0.5 mg per day, transdermal E₂ patches that deliver 0.014 mg or 0.025 mg per day, and an estradiol gel that

delivers 0.0125 mg per day. The 0.014-mg transdermal formulation of E₂, however, is currently approved only for prevention of postmenopausal osteoporosis and not for relief of vasomotor or vulvovaginal symptoms of menopause,⁴⁰ while estrogen gel is

Table. Low-Dose Formulations of Estrogens and Estrogen-Progestin Combinations Available in the US

Estrogen type	Dose per day	Products available	Menopause-associated indication(s) ⁱ
Oral estrogens			
Conjugated equine estrogens (CEE) ⁱⁱ	0.3 mg and 0.45 mg	Premarin®; Prempro® (also contains a low-dose progestin [1.5 mg medroxyprogesterone])	<ul style="list-style-type: none"> • Treatment of mild to severe vasomotor symptoms • Prevention of osteoporosis • Treatment of vaginal and vulvar atrophy (0.45-mg dose)
Synthetic conjugated estrogens (SCE)	0.3 mg and 0.45 mg	Cenestin® (SCE-A), ⁱⁱⁱ Enjuvia® (SCE-B) ^{iv}	<ul style="list-style-type: none"> • Treatment of mild to severe vasomotor symptoms • Treatment of vaginal and vulvar atrophy
Oral estradiol (E ₂) (17β-estradiol)	0.45 mg or 0.5 mg depending on product	Activella® (also contains a low-dose progestin [0.1 mg norethindrone]), Estrace, ^{ov} Femtrace®	<ul style="list-style-type: none"> • Treatment of mild to severe vasomotor symptoms • Prevention of osteoporosis
Ethinyl estradiol (EE ₂)	2.5 mcg	Femhrt® (also contains a progestin [norethindrone])	<ul style="list-style-type: none"> • Treatment of mild to severe vasomotor symptoms • Prevention of osteoporosis
Esterified estrogens	0.3 mg and 0.45 mg	Menest® ^{vi}	<ul style="list-style-type: none"> • Vaginal and vulvar atrophy (0.3 mg) • Treatment of moderate to severe vasomotor symptoms (doses of 0.45 mg and higher recommended)
Transdermal estrogens			
E ₂ patch	To deliver 0.025 mg/day	Alora®, Climara®, Vivelle®, Vivelle-Dot®	<ul style="list-style-type: none"> • Treatment of mild to severe vasomotor symptoms • Treatment of vaginal and vulvar atrophy • Prevention of osteoporosis
	To deliver 0.014 mg/day	Menostar®	<ul style="list-style-type: none"> • Prevention of osteoporosis
E ₂ gel	To deliver 0.025 mg/d	Elestrin™	<ul style="list-style-type: none"> • Treatment of moderate to severe vasomotor symptoms
	To deliver 0.003, 0.009, or 0.027 mg/d	Divigel® ^{vii}	<ul style="list-style-type: none"> • Treatment of moderate to severe vasomotor symptoms
E ₂ spray	To deliver 0.021 mg/d	Evamist™ ^{viii}	<ul style="list-style-type: none"> • Treatment of moderate to severe vasomotor symptoms

ⁱIndications apply to the general type of estrogen listed, but within each class, specific indications may vary by product and dose. Consult each product's prescribing information for approved indication and dosing information.

ⁱⁱCEEs contain a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin. Whereas the 0.45-mg dose is indicated for treatment of vulvar atrophy, the 0.3-mg dose [or higher] may be used for treatment of vasomotor symptoms or for prevention of osteoporosis. {Wyeth, 2006 74998 /id}

ⁱⁱⁱSCE-A contains a mixture of nine synthetic estrogenic substances: sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17β-estradiol sulfate. The 0.3-mg dose of SCE-A is indicated for treatment of vaginal and vulvar atrophy, whereas the 0.45-mg dose (or higher) of SCE-A is indicated for treatment of mild to severe vasomotor symptoms. {Duramed Pharmaceuticals, 2004 58556 /id}

^{iv}SCE-B contains a mixture of ten synthetic estrogenic substances: sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate, sodium 17β-estradiol sulfate, and sodium Δ8,9-dehydroestrone sulfate. {Enjuvia PI, Duramed}

^vHigher doses (1–2 mg) are recommended in the Estrace prescribing information for treatment of vasomotor, vaginal, and vulvar symptoms {Estrace PI, Warner-Chilcott}

^{vi}A mixture of sodium estrone sulfate (~75–85%) and sodium equilin sulfate (~6–15%) {Menest PI, Monarch}

^{vii}Ackerman R, Hedrick R, Lambrecht L. Efficacy of 3 doses of estradiol gel 0.1% in the treatment of vasomotor symptoms and vulvar vaginal atrophy. Poster presented at the 18th Annual Meeting of The North American Menopause Society, October 3–6, 2007; Dallas, TX.

^{viii}Buster JE, Koltun WD, Pascual ML, et al. Low-dose estradiol spray to treat vasomotor symptoms: a randomized controlled trial. *Obstet Gynecol* 2008;111:1343–51.

indicated only for relief of vasomotor symptoms.⁴² Doses of oral CEE (0.3 mg/d), oral E₂ (0.5 mg/d) and transdermal E₂ (0.025 mg/d) are generally considered equivalent, as are doses of oral E₂ (0.25 mg/d) and transdermal E₂ (0.014 mg/d). Differences in common dosing paradigms, as well as the ongoing dialogue about what constitutes a minimally effective dose of HT,¹⁹ can lead to some confusion and inconsistencies regarding low-dose definitions. In fact, as pointed out by Ettinger⁴ nearly a decade ago, the assumption that there exists a single dose of estrogen that will relieve all menopausal symptoms and prevent bone loss is probably incorrect. Rather, a continuum of positive changes with regard to symptoms and bone density is to be expected, with no threshold minimal dose, as was once believed.⁴

Using lower estrogen doses has the added benefit of allowing the use of reduced progestin doses to protect the endometrium in nonhysterectomized women.^{5,11,44,45} Several combination EPT products are available. Low-dose oral CEE 0.45 mg/d or 0.3 mg/d has been combined with low-dose medroxyprogesterone acetate (MPA) 1.5 mg per day; low-dose oral E₂ 0.5 mg/d is currently available in combination with low-dose norethindrone acetate (NETA) 0.1 mg for once-daily dosing. A low-dose transdermal combination patch is not yet commercially available.

Efficacy of Low-Dose Estrogens

Low doses of estrogen have been found to be extremely effective. There may, however, be a time lag of a few weeks before efficacy is evident (when compared with standard doses). A variety of preparations is available.

Vasomotor symptoms. Low ET/EPT doses have been shown to effectively reduce the number and severity of hot flashes. A review of studies comparing

low-dose estrogens to placebo found that hot flashes experienced by patients in active treatment groups were reduced by an average of 65%.⁴⁶ Low-dose regimens of oral CEE 0.45 mg/d and 0.3 mg/d with MPA 1.5 mg/d have been reported to relieve vasomotor symptoms as effectively as standard-dose CEE+MPA. Unopposed low-dose CEE formulations are also effective but show a slight dose-related effect in treating vasomotor symptoms.⁴⁷ Another study evaluating the effects of three different transdermal doses of unopposed E₂ (0.025 mg [low], 0.05 mg [standard] and 0.1 mg [high] per day) in highly symptomatic menopausal women (mean age, 50.4 years) demonstrated that low-dose and higher-dose transdermal E₂ were similar in their ability to effectively reduce the number of vasomotor symptoms. A slight dose-related trend to reduce severe symptoms by 60%,

67% and 75% was observed in the low-, standard- and high-dose arms, respectively.⁴⁸ Another study reported that low-dose estradiol gel delivering 0.0125 or 0.0375 mg/d effectively relieved hot flashes compared with placebo, but the reduction in the daily number of hot flashes was slightly greater with the 0.0375-mg/d dose.⁴²

One recent study evaluated the efficacy of two low-dose oral estrogen formulations in a relatively young population of postmenopausal women (n = 577) between 44 and 65 years of age (mean age, 55.5 years), each with an intact uterus.⁴⁹ Compared with placebo, a rapid, statistically significant decrease in the frequency and severity of hot flashes was achieved by week 3 in women receiving 0.5 mg oral 17 β -estradiol + 0.1 mg NETA or 0.5 mg 17 β -estradiol + 0.25 mg NETA (Figure 1). This effect was followed by further improvement that

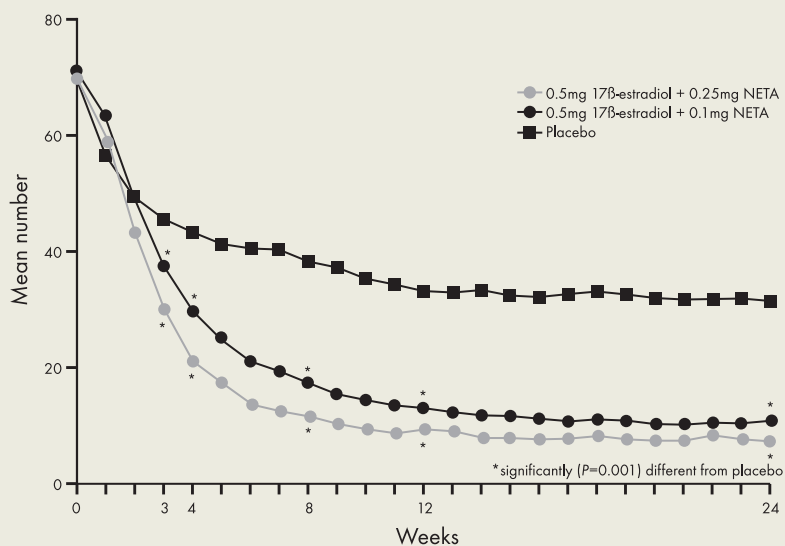


Figure 1. Effects of low-dose oral E₂ on moderate to severe vasomotor symptoms, compared to placebo. Number of moderate to severe hot flashes per week in patients receiving 0.5 mg 17 β -estradiol + 0.25 mg NETA (●), 0.5 mg 17 β -estradiol + 0.1 mg NETA (●), or placebo (■).

Data reproduced from Panay N, et al. Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief. *Climacteric* 2007 10:120-131. Reprinted with permission of Taylor & Francis, Ltd. (www.tandf.co.uk/journals).

continued throughout the 24-week study.⁴⁹ Previous studies of unopposed oral 17 β -estradiol had suggested that the 0.5-mg dose provided relief only after 8 weeks;^{50,51} addition of NETA (either 0.1 or 0.25 mg) to low-dose 17 β -estradiol appears to significantly enhance vasomotor symptom relief.⁴⁹ The finding that the addition of a progestin enhances the vasomotor response to low-dose oral estrogen was also reported in the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study, which evaluated the efficacy of lower doses of CEE (0.3 or 0.45 mg/d) with or without MPA 1.5 mg/d.⁴⁷

Another recent study evaluated the impact of two different transdermal formulations of E₂ among patients with moderate-to-severe menopausal symptoms.⁵² In this trial, 425 women received transdermal 0.023 mg/d E₂ (low-dose E₂) with 0.0075 mg/d levonorgestrel, transdermal 0.014 mg/d E₂ or placebo for 12 weeks. Results indicated that lower doses of transdermal E₂ significantly reduced the number and severity of vasomotor symptoms, compared with placebo. However, treatment response rates were significantly greater in the E₂/levonorgestrel group, indicating that some women may require higher E₂ doses for vasomotor symptom relief or that there may be an enhanced effect with the addition of a progestin.

Vulvovaginal atrophy. As with vasomotor symptom relief, low estrogen doses have been shown to effectively reduce vaginal atrophy. Utian and colleagues⁴⁷ reported results from the subset of postmenopausal women (n = 241) who had participated in the Women's HOPE study and were treated with low-dose oral CEE with or without MPA. The women recruited into the HOPE study were healthy and relatively young (45–65 years of age). The mean age of the

efficacy-evaluable population for low-dose HT was 52.4 years. Younger postmenopausal women are, in general, a population with a low baseline incidence of urogenital menopausal symptoms; nevertheless, in this population, low-dose CEE with or without MPA was shown to improve the vaginal maturation index (VMI) comparably to standard-dose therapy with CEE/MPA 0.625/2.5 mg. Calculated from the proportion of vaginal superficial cells relative to parabasal and intermediate cells from a vaginal wall smear, some investigators have argued that the VMI is not, however, correlated with symptoms associated with vaginal atrophy.^{53,54}

Low-dose oral 0.5 mg 17 β -estradiol with either 0.1 mg or 0.25 mg NETA resulted in a reduction in vaginal dryness scores compared with placebo, also in relatively young postmenopausal women.⁴⁹ In addition, the VMI value and pH were significantly improved in the low EPT groups versus those receiving placebo at weeks 12 and 24. Johnson and colleagues investigated the uterine effects of unopposed low-dose transdermal estradiol (14 mcg per day) over 2 years in non-hysterectomized women 60–80 years of age (mean age, 67 years).⁵⁵ A significantly greater maturation of vaginal epithelial cells, compared with placebo, was observed in this population.⁵⁵ However, transdermal E₂ 14 mcg is not currently indicated for relief of vaginal symptoms and further study will be needed to ascertain any vulvovaginal benefit.

Bone. Preventing the loss of bone mineral density (BMD) is a key factor in influencing many women's decisions about whether to initiate or continue ET/EPT.⁵⁶ Given the trend to use lower and lower doses of estrogen, it is important to understand if low-dose ET/EPT's effects on BMD are comparable to those of standard-dose

ET/EPT. Genant and colleagues¹¹ studied the effects of unopposed low (0.3 mg per day) and standard doses (0.625 and 1.25 mg per day) of oral esterified estrogens compared with placebo in four groups of postmenopausal women (n = 406; mean age, 51.1 to 51.9) for 2 years. All doses produced significant increases in BMD of the lumbar spine compared with baseline and with placebo at 6, 12, 18 and 24 months. Changes in BMD appeared to be related to plasma estradiol concentrations.¹¹ Mean plasma levels of estradiol >90 pmol/L (24.5 pg/mL), which were achieved with all three doses, were associated with significant increases in spinal BMD. Of historical note, plasma estradiol concentrations of at least 180 pmol/L (49 pg/mL) were previously believed to be necessary to prevent vertebral bone loss.^{57,58} In a more recent, 2-year, randomized clinical trial, low doses (0.3 mg and 0.45 mg) of oral CEE alone and CEE+MPA (1.5 mg and 2.5 mg) effectively increased BMD and total bone mineral content and reduced markers of bone turnover in postmenopausal women (mean age, 51.6 years).⁵⁹ Positive effects of 0.3 mg CEE with 2.5 mg MPA on spinal BMD were also found in postmenopausal women >65 years of age with low bone mass.⁶⁰ Low doses of oral 17 β -estradiol (0.25 and 0.50 mg per day) reduced bone turnover in healthy women >65 years to a similar degree to that seen with standard-dose therapy (1.0 mg per day).⁶¹ Another 3-year randomized study in a healthy population of women >65 years (n = 83) confirmed that oral 17 β -estradiol in doses of 0.25 mg/day increased BMD of the hip, spine and total body, and reduced bone turnover compared with placebo (n = 84). In this study, women also received calcium supplementation, and those with an intact uterus (61%) also received 100 mg/day

of oral micronized progesterone for 2-week periods every 6 months. No differences in BMD measures were noted between women who did or did not receive a progestin.⁶² Transdermal 17 β -estradiol 0.025 mg/d, alone or with 0.125 mg/d NETA, also has been shown to effectively prevent postmenopausal bone loss.^{63,64} Moreover, data demonstrating that the transder-

mal E₂ patch delivering 0.014 mg/day prevents osteoporosis (Figure 2)⁶⁵ support the FDA approval of the only indication for this product.⁴⁰

Collectively, these studies contrast with data from the Continuous Hormones as Replacement Therapy (CHART) study, which found that lower doses of oral ethinyl estradiol (EE₂) (1–2.5 mcg per day) with NETA

(0.2–0.5 mg per day) plus calcium supplementation failed to increase BMD relative to baseline after 2 years in women whose mean age was 51.9 years.⁶⁶ Higher doses of oral EE₂ (5–10 mcg) plus NETA (1 mg) produced a dose-related significant increase in BMD that was not present with unopposed EE₂ treatment.⁶⁶

Except for the CHART study, the bulk of available evidence suggests that both low doses (1 and 2.5 mg/d) of ET/EPT were superior to no treatment with regard to prevention of bone loss. Regardless of the ET/EPT regimen chosen, supplementation with 1,200–1,500 mg of oral calcium per day is recommended for postmenopausal women age 51 and over.⁷ This degree of calcium intake reportedly augments the antiresorptive effects of estrogen by up to 100%.⁶⁷ The American College of Obstetricians and Gynecologists also recommends adequate vitamin D consumption (400 to 800 IU daily).⁷

Other potential benefits. Several studies have examined other potential beneficial effects of these lower-dose ET and EPT regimens. For example, in the study of vasomotor symptoms conducted by Panay and colleagues,⁴⁹ low-dose oral E₂ (0.5 mg/d) with NETA (0.1 or 0.25 mg/d) was associated with significantly less difficulty sleeping than placebo, as measured by the Greene Climacteric Scale. However, Kenny and colleagues⁶⁸ found no effects of low-dose oral E₂ (0.25 mg/d) compared with placebo on skeletal muscle mass, physical functioning and body fat in women 65 years of age or older who were treated for 3 years.

With regard to health-related quality of life (QoL), a 2-year study of a lower-dose transdermal patch delivering 0.014 mg/d E₂ versus placebo in 417 older postmenopausal women (60–80 years, mean age, 66.8) revealed

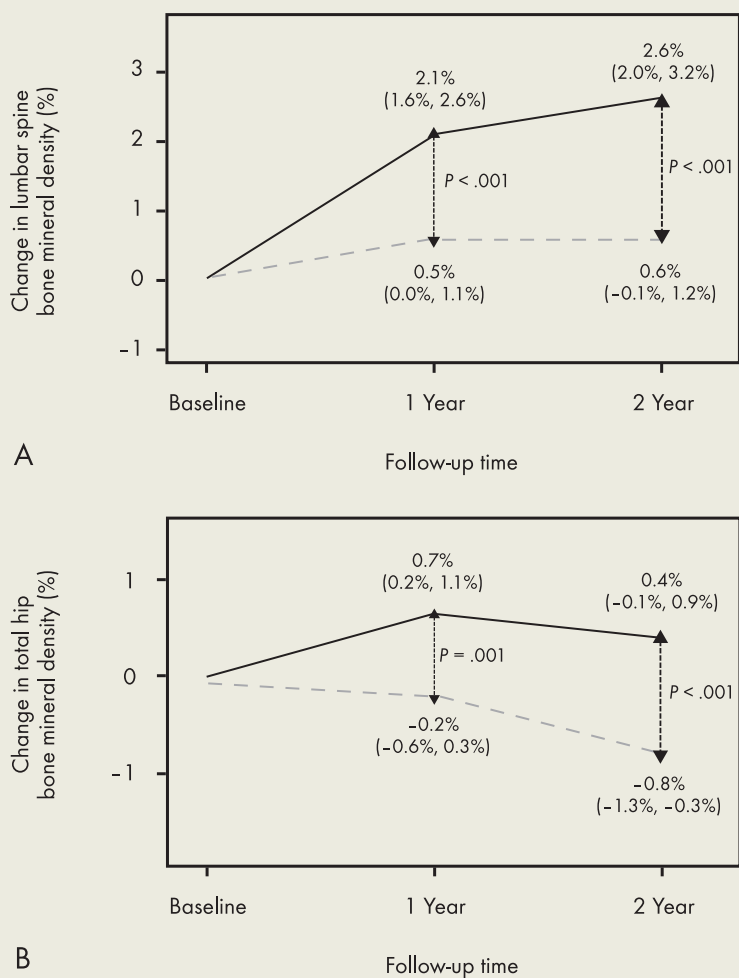


Figure 2. Effects of ultra-low dose transdermal E₂ on BMD, compared with placebo. (A) Changes from baseline in mean lumbar spine BMD measurements over time. (B) Changes from baseline in mean total hip BMD measurements over time in patients receiving ultra-low dose transdermal E₂ (0.014 mg/d).

Solid line = estradiol; dashed line = placebo.

Reproduced with permission from Ettinger B, et al. Effects of ultra low-dose transdermal estradiol on bone mineral density: a randomized clinical trial. *Obstet Gynecol* 2004;104:443-51.

no statistically significant differences in cognitive test scores or on the 36-Item Short-Form General Health Survey, suggesting neither benefit nor detriment on cognitive function or in health-related QoL over 2 years of treatment.⁶⁹ A recent smaller study (n = 57) of older women (mean age, 76 years) randomly assigned to 0.25 mg oral E₂ or placebo for 3 years also reported no effects of ET on cognition (beneficial or detrimental) or on measures of depression.⁷⁰

Side Effects and Safety

Endometrial safety is an important issue even with lower doses of estrogen. The use of lower doses has led to different and lower regimens of progestins for endometrial protection.

Endometrial safety. Lower doses of oral or transdermal estrogen, when used with adequate doses of progestin, have an excellent endometrial safety profile.^{22,44,45,63,66} Some have suggested that women using low-dose estrogen may not require regular progestin or may safely take lower progestin doses⁵ because little-to-no endometrial stimulation is expected at these doses. The lack of uterine-related consequences of unopposed low-dose ET was demonstrated in a study of nonhysterectomized postmenopausal women (ages 60–80 years) receiving unopposed transdermal estradiol (14 mcg/d). Compared with placebo, women receiving transdermal ET had similar rates of endometrial hyperplasia, endometrial proliferation and vaginal bleeding over the course of 2 years of treatment.⁵⁵ Others, however, have observed an increased incidence of endometrial hyperplasia in younger nonhysterectomized women (ages 40 to 65 years) after 2 years of treatment with low-dose unopposed estrogen (CEE 0.3 and 0.45 mg/d);⁴⁵ thus, clinical practice guidelines still rec-

ommend the addition of progestin for women with an intact uterus.^{7,19,20}

Bleeding. Vaginal bleeding correlates with endometrial thickening,⁵⁵ and standard doses of estrogen produce irregular bleeding in many women, which is a major reason for poor compliance with therapy.^{10,11} By contrast, lower doses of estrogen are associated with higher rates of amenorrhea and a lower incidence of uterine bleeding compared with standard-dose therapy.^{10,22,48,50,61,66,71} A 0.3-mg dose of esterified estrogens in younger postmenopausal women produced minimal vaginal bleeding (ie, comparable to placebo), whereas higher doses (0.625 mg and 1.25 mg) resulted in more significant vaginal bleeding.¹¹ In the study of lower-dose transdermal E₂ (0.014 mg/d) on uterine and vaginal effects, conducted by Johnson and colleagues,⁵⁵ vaginal bleeding occurred in 12.4% of the treated group and in 8.6% of the placebo group; this difference was not statistically significant ($P = 0.3$). Eighty-nine percent of women treated with 0.5 mg 17 β -estradiol with 0.25 or 0.1 mg NETA were bleed-free by cycle 6 in a 6-month placebo-controlled study.⁴⁹

Breast tenderness. Lower doses of estrogen are associated with a lower incidence of breast tenderness, and this side effect of ET/EPT appears to be dose-related.^{22,50,61,66} Undesirable breast symptoms were similar to those seen with placebo in women receiving low-dose formulations of ET and EPT, including oral 0.5 mg 17 β -estradiol plus NETA (0.25 or 0.1 mg),⁴⁹ oral 0.25 mg 17 β -estradiol,⁶² oral 2.5 mcg ethinyl estradiol plus 0.5 mg NETA,²³ or transdermal 0.025 mg E₂.⁴⁰

Venous thromboembolism (VTE). An increased risk of VTE is well documented with standard-dose ET/EPT.^{8,9} Preliminary evidence suggests the possibility that lower ET/EPT doses may have a reduced impact on

risk of VTE versus standard-dose ET/EPT.^{72,73} In an analysis of pooled results from the Women's HOPE Study (n = 2,341) and the Menopause Study Group (n = 1,724), in which 1,662 women were using lower doses of oral CEE (0.3 or 0.45) with or without MPA 1.5 mg/d, investigators reported that the incidence of pulmonary embolism (PE) and deep vein thrombosis (DVT) was 0.56 per 1,000 patient years (95% CI, 0.19–1.78) and 0.28 (95% CI, 0.08–2.27), respectively, among estrogen-treated women.⁷³ In these trials, one case of PE occurred in a woman receiving CEE 0.45 mg/d, one case of PE occurred in a woman receiving CEE 0.625/MPA 5 mg/d, and one case of DVT occurred in a woman receiving CE 0.45/MPA 1.5 mg/d. Significantly larger studies are needed to clarify the risk of VTE with the use of low-dose versus standard-dose ET and EPT.

It has been suggested that the use of transdermal estrogen is associated with a lower risk of VTE, compared with oral estrogen.⁷⁴ The Estrogen and Thromboembolism Risk (ESTHER) Study evaluated the relative impact of transdermal and oral estrogen use on VTE risk, reporting that oral estrogen, but not transdermal estrogen, significantly increased VTE risk (OR for oral estrogen, 4.2; 95% CI, 1.5 to 11.6; OR for transdermal estrogen, 0.9; 95% CI, 0.4 to 2.1).⁷⁵ However, it should be noted that only 15% of transdermal estrogen users received doses >0.050 mg/d, a dose equivalent to an oral estradiol dose of 1.0 mg/d. In contrast, the mean dose of oral estradiol was 1.5 mg/d. Because the risk of VTE with estrogen use appears to be dose-related, it is conceivable that the increased risk observed with oral estrogen in ESTHER may not be entirely due to route of administration. Additional research on the impact of low-dose oral and transdermal ET/EPT is needed.

Stroke. Evidence from observational studies and from the ET and EPT arms of the WHI indicates that standard-dose estrogen use increases the risk of stroke.^{17,76,77} Few studies have evaluated the impact of lower doses of ET/EPT on the risk of stroke. Nonetheless, a report from the Nurses' Health Study found that the risk of stroke was related to the daily dose of estrogen.¹⁷ For example, women using CEE doses of 0.625 mg/d or higher had a significantly increased risk of stroke compared with women not using estrogen (RR for CE, 0.625 mg/d, 1.35; 95% CI, 1.08-1.68; RR for CE, ≥ 1.25 mg/d, 1.63; 95% CI, 1.18-2.26). In contrast, women using CEE 0.3 mg/d showed no increase in the risk of stroke (RR, 0.54; 95% CI, 0.28-1.06). Additional research is needed to determine the impact of route of administration on stroke risk.

Breast cancer. The WHI reported a small increased risk of breast cancer in women assigned to standard-dose EPT, but not among hysterectomized women using unopposed estrogen.^{8,9} The effect of lower estrogen and/or progestin doses on breast cancer risk in ET/EPT users is unclear, and there is currently little evidence that addresses this important clinical issue. However, investigators from the large, prospective Women's Health Study (from the US) reported that breast cancer risk increased with estrogen but not progestin dose, and that the relative risk for breast cancer with low-dose therapy was 0.87 (95% CI, 0.44-1.73).⁷⁸ Neither the Million Women Study,⁷⁹ which was conducted with a large cohort of British women, nor the Collaborative Group reanalysis⁸⁰ found an effect of estrogen dose on breast cancer risk. Although the impact of low-dose transdermal ET/EPT on breast cancer risk is unclear, most data indicate that standard-dose oral and transdermal estrogen

carry a similar risk of breast cancer.^{79,81} Recent evidence suggests that low-dose oral and transdermal ET/EPT have neutral effects on mammographic breast density,^{82,83} which has been suggested to be an intermediate phenotype for breast cancer.⁸⁴ Although a high mammographic density

The effect of lower estrogen and/or progestin doses on breast cancer risk in ET/EPT users is unclear, and there is currently little evidence that addresses this important clinical issue.

is a risk factor for breast cancer, changes in breast density with hormone use do not appear to increase breast cancer risk.^{85,86}

Cardiovascular disease. In general, changes in serum lipids are greater with standard versus low-dose oral estrogen,⁸⁷ although the clinical relevance of these changes has been challenged by the WHI findings of no cardioprotection with either ET or EPT use in the overall study population.^{8,9} Additional recent analyses from the WHI suggest a possible cardioprotective effect of ET/EPT in women who initiate treatment around the time of the menopause,^{16,88} but little is known about the impact of low-dose oral or transdermal regimens on cardiac outcomes.

Future Challenges

Ethnic differences in the occurrence and experience of menopausal symptoms have been documented.⁸⁹ Thus, an important limitation of studies conducted thus far is the relative lack of enrollment of women in minority populations compared with Caucasian women.^{10,47-49} Effects of low-dose ET/EPT preparations in different ethnic groups have not been well studied and need to be better addressed in the future. Research also is needed

to understand how lower doses of estrogens and/or progestins impact both potentially favorable and adverse cardiovascular outcomes.^{17,73}

Conclusions

Low-dose formulations of HT are increasingly becoming the first choice

for the initial management of menopausal symptoms. These regimens may be especially attractive for their established efficacy in relieving symptoms of menopause, as well as in prevention of bone loss. These data, together with the improved tolerability profile compared with that of standard-dose regimens, impart a favorable benefit-risk profile and suggest an important role for the lowest effective ET/EPT dose regimens in menopause and postmenopausal management. ■

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