INDIVIDUALIZING HRT WITH LOWER-DOSE REGIMENS: CLINICAL TRIAL REVIEW: MENOPAUSAL SYMPTOMS AND BLEEDING PROFILE

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INTRODUCTION

Despite the fact that all women in some way must face the short- and long-term health consequences of postmenopausal estrogen deficiency, many avoid hormone replacement therapy (HRT), primarily because of concerns related to safety and side effects. To date, clinicians have been limited in their ability to address these concerns through dosage adjustments due to a lack of adequate clinical data on the safety and effectiveness of lower-dose regimens. This is why the recent publications of the findings of the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) Study are so important. This study is the first large-scale, controlled clinical trial to demonstrate the efficacy and safety of lower-dose estrogen and estrogen/progestin regimens. More importantly, the efficacy and safety of lower-dose regimens were found comparable to those of the regimen most commonly prescribed today, with the added benefit of an improved bleeding profile. Based on the results of this trial, the sponsor has submitted a New Drug Application for conjugated equine estrogens (CEE) 0.45 mg/medroxyprogesterone actetate (MPA) 1.5 mg.

The focus of this review are the publications from the Women's HOPE Study on menopausal symptoms [1] and endometrial bleeding [2]. The results will be reviewed in the context of previous trials of lower-dose regimens and then discussed in terms of their application to clinical practice. Subsequent reviews will address the publications of the Women's HOPE Study data on endometrial safety [3] and metabolic profile [4] and the findings related to preservation of bone mass [5].

RATIONALE FOR LOWERING HRT DOSES

There are currently more than 33 million menopausal women in the US, a number that will grow to approximately 50 million by 2010 [6]. With an average life span of approximately 75 years [6] and an average age at menopause of 51.4 years [7] women spend about one third of their life beyond menopause. Therefore, lifestyle and pharmacologic interventions that maintain good health throughout this period are essential.

Although menopause is a normal part of aging, the decline in endogenous

estrogen level is associated with physiological changes that can produce a wide range of symptoms, physical and psychological changes, and potential long-term health consequences. The use of exogenous estrogen replacement for relief of menopausal symptoms and prevention of bone loss is supported by a considerable body of scientific evidence. Ongoing research is evaluating the potential benefits of estrogen replacement in other areas such as reduction of cardiovascular disease morbidity and mortality, improvements in cognition, cancer prevention, and others [7, 8].

Despite the known and potential short- and long-term health benefits of estrogen replacement therapy (ERT) or estrogen combined with a progestin (HRT), many women either do not start or discontinue treatment early [9–11] often due to concerns about safety and side effects, particularly endometrial bleeding [12, 13]. Adherence to HRT is especially poor when therapy is prescribed for prevention of osteoporosis in older women rather than for treatment of hot flushes in younger women [14–16].

Only 5–6% of menopausal women take HRT for more than 5 years [17].

Findings of previous lower-dose ERT/HRT studies

One way to encourage more women to initiate and continue ERT/HRT would be to improve the benefit/risk profile through reduction of side effects. Predictably, the question has been raised whether estrogen doses lower than those commonly prescribed would provide comparable efficacy while reducing the incidence of endometrial bleeding.

The most commonly prescribed oral estrogen replacement dose has decreased steadily over the past 50 years, from 1.25 mg conjugated estrogens per day or the equivalent in the 1950s and 1960s to 0.625 mg daily today [18]. The use of 0.625 mg conjugated estrogens or the equivalent as the standard replacement dose came about in large part as a result of both the identification of a link between unopposed estrogen therapy and endometrial cancer, and findings from 2 studies indicating that daily doses lower than 0.625 mg were inadequate for bone protection [19, 20]. However, use of lower estrogen doses has grown in popularity in the past decade [18] and the effectiveness of lower doses has been suggested by a number of small-scale clinical studies of vasomotor symptom relief [21, 22] maintenance of bone density [23–27] and reduction of cardiovascular risk and risk factors [23, 27–29].

Lower doses of estrogen have also been found to reduce the risk of endometrial hyperplasia [22, 23, 30]. Similarly rigorous evaluations of the effects of lower doses on breast cancer risk have not been conducted, although it is reasonable to expect that the dose of estrogen will play a role in promotion of breast neoplasms analogous to its dose-related promotion of endometrial cancer [18]. Studies also indicate that women who use lower than standard doses of estrogen are less likely to have unacceptable side effects such as bleeding [30] and breast tenderness [25, 26, 31].

The encouraging results of lower-dose studies pointed to the need for larger-scale, longer-duration controlled trials to more firmly establish the efficacy, safety, and tolerability of lower-dose estrogen and estrogen/progestin regimens. The Women's HOPE Study is the first study to meet this need.

Women's HOPE study: Study methodology and population [1]

The Women's HOPE Study was a 2-year randomized, double-blind, placebo-controlled, multi-center trial that evaluated the efficacy, safety, and tolerability of lower-dose CEE and CEE/MPA regimens. The first year basic study focused on menopausal symptoms (hot flushes and vaginal atrophy), endometrial histology, bleeding profile, and metabolic profile. A 2-year substudy examined the effects on bone density and turnover, and continued the evaluation of endometrial histology and metabolic profile.

The study included healthy, menopausal women, aged 40–65 years, who were assigned to receive either placebo or 1 of the following 7 treatment regimens:

CEE/MPA (mg)	CEE (mg)
0.625/2.5	0.625
0.45/2.5	0.45
0.45/1.5	
0.3/1.5	0.3

All women also received a daily calcium carbonate supplement (600 mg elemental calcium). Inclusion and exclusion criteria have been described in detail (please refer to Table 1 of Utian et al [1]). Notably, women had to have an intact uterus, no menses within the last year, and be within 20% of normal body weight range. Women were instructed to keep daily diary cards throughout the study to record the dates on which they took or missed taking study medication, episodes and severity of hot flushes, and episodes of vaginal bleeding or spotting.

The demographic and other baseline characteristics of the 2673 women included in the efficacy and safety analyses have been described in detail (please refer to Table 3 of Utian et al [1]). All variables were similar among the 8 treatment groups. Average age at study entry was 53.3 ± 4.9 years, average time since menopause was 4.7 ± 4.2 years, and average BMI was 24.4 ± 2.8 kg/m^2. Treatment groups were also comparable with respect to adherence to therapy, with no evidence of a relationship between dose and adherence rate.

Key findings and clinical application

This section summarizes the key findings from the Women's HOPE Study in the context of current knowledge on HRT and discusses the clinical application of these data to menopausal health management and decisions about ERT/HRT initiation and continuation.

Vasomotor symptoms [1]

Vasomotor symptoms were analyzed in an efficacy-evaluable population (n = 241) that included women who recorded taking study medication and who had at least 7 moderate-to-severe baseline hot flushes on each of the last 7 days of screening, or at least 50 total hot flushes during the last 7 days combined. Women used the following weighting scale to indicate the severity of each hot flush: mild = fleeting warm sensation without sweating that does not disrupt activity; moderate = warm sensation with sweating that does not disrupt activity; severe = hot sensation with sweating that disrupts activity.

Data recorded on diary cards were used to determine the mean daily number and severity of hot flushes, which are shown in Figures 1 and 2.

This study showed that in generally healthy postmenopausal women with an intact uterus, lower-dose CEE/MPA regimens were effective in decreasing the number and severity of hot flushes, and in general were as effective for relief of vasomotor symptoms as the most commonly prescribed HRT regimen of CEE 0.625/MPA 2.5. The fact that the lower-dose regimens were effective in highly symptomatic women (at least 7 moderate-to-severe hot flushes per day

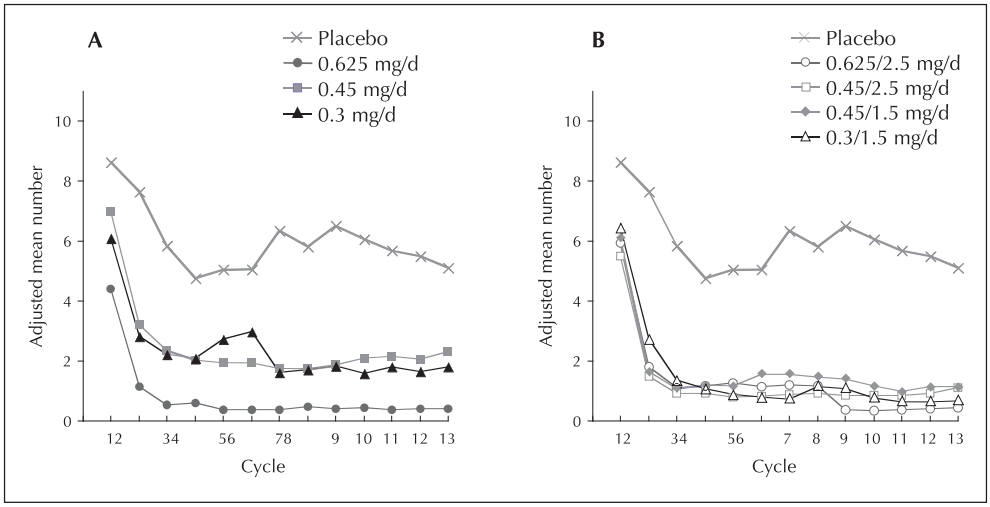

Figure 1. Mean daily number of hot flushes by cycle. 1A: Data for the placebo and the CEE alone groups. 1B: Data for the placebo and CEE/MPA groups. Data are adjusted for baseline.

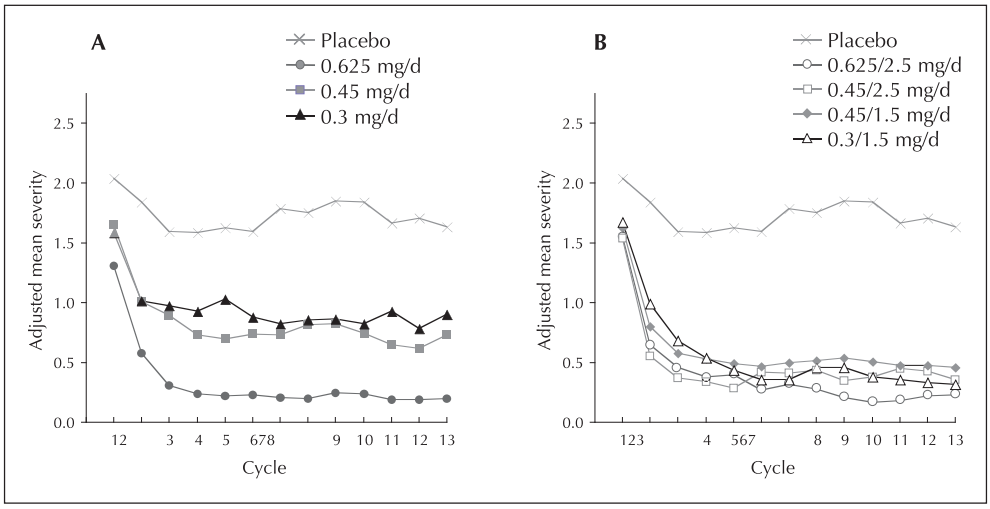

Figure 2. Mean daily severity of hot flushes by cycle. 2A: Data for the placebo and the CEE alone groups. 2B: Data for the placebo and CEE/MPA groups. Data are adjusted for baseline. All values for mean severity of hot flushes (unadjusted) were significantly less than baseline ($P < .05$) for all cycles.

prior to beginning treatment) suggests that women with less frequent or less severe symptoms also should receive adequate relief.

Lower doses of CEE/MPA also appeared to be more effective for vasomotor symptom relief than comparable doses of CEE alone, suggesting that the benefits of MPA may extend beyond protection of the endometrium. Previous studies have indicated that progestins alone can relieve vasomotor symptoms [32–34] and that there may be a possible synergistic effect on vasomotor symptoms when progestins are combined with lower doses of estrogen [35]. Although further research on the additive effects of MPA is warranted, for hysterectomized women who are not getting adequate relief from vasomotor symptoms with ERT, it may be worth considering the addition of MPA as an alternative to increasing the estrogen dose.

Vaginal atrophy [1]

The effect of lower-dose CEE and CEE/MPA regimens on vaginal atrophy was assessed using the vaginal maturation index (VMI). VMI was reported as the proportion of vaginal superficial cells relative to the number of parabasal and intermediate cells in a lateral vaginal wall smear. The VMI analysis was done in an intent-to-treat population that included all women who recorded taking study medication. The results of the VMI analysis are shown in Figure 3.

All doses of CEE and CEE/MPA significantly increased VMI compared to baseline and placebo, although the increases were smaller with lower CEE doses and with the CEE/MPA combinations compared with CEE alone. However, these data alone cannot be used to predict the effectiveness of lower-dose ERT/HRT regimens for symptom improvement or to compare lower and standard doses, since the clinical significance of differences in VMI and the relationship between VMI and symptom severity are unknown [36]. If symptoms of vaginal atrophy are not adequately relieved with an oral lower-dose regimen that adequately controls vasomotor symptoms, the addition of a vaginally-administered estrogen may be more appropriate than an increase in systemic estrogen dose. Vaginal preparations appear to be as effective for urogenital atrophy as oral products and have a lower level of systemic absorption [37].

Bleeding profile [2]

The bleeding profile of each treatment regimen was determined by women's entries on daily diary cards throughout the duration of the study. The following definitions were used to describe and analyze endometrial bleeding.

- *Bleeding* – bleeding requiring sanitary protection
- *Spotting* – bleeding not requiring sanitary protection
- *No bleeding* – occurrence of no bleeding that required sanitary protection
- *Amenorrhea* – occurrence of no bleeding or spotting
- *Cumulative rate of amenorrhea* – proportion of women who experienced no bleeding or spotting in a given cycle and all subsequent cycles
- *Cumulative rate of no bleeding* – proportion of women who experienced no bleeding that required sanitary protection in a given cycle and all subsequent cycles

Cumulative rates of amenorrhea and no bleeding were determined for cycles 1–

13 in an efficacy-evaluable population (n = 1.555) that included all women enrolled in the study who recorded taking study medication and completed 13 cycles of treatment; filled out all thirteen 28-day diary cards without any missing bleeding data; and did not miss, during any treatment cycle, = 3 consecutive days or = 5 discontinuous days of taking or recording study medication. For women who discontinued treatment, only the cycles up to the last completed cycle were included in the analyses. Cumulative rates of amenorrhea and no bleeding are shown in Figures 4 and 5, respectively (for more information, please refer to Archer et al [2]).

Since irregular endometrial bleeding is the most common reason why women discontinue HRT [12], the improved bleeding profile seen with lower-dose HRT regimens may offer many women who would have otherwise stopped therapy an acceptable way to continue. In particular, the significantly higher incidence of amenorrhea with lower-dose regimens during the early cycles of treatment (for example, 72% in the CEE 0.45/MPA 1.5 group compared to 51% in the CEE 0.625/MPA 2.5 group in cycle 1) should help prevent early discontinuation of HRT since the discontinuation rate is highest during the first 6 months [38]. It is also possible that women not currently on HRT will be more willing to start on a regimen that is known to have a lower bleeding rate. Nevertheless, it will be important to educate women about the bleeding rates associated with lower-dose HRT to

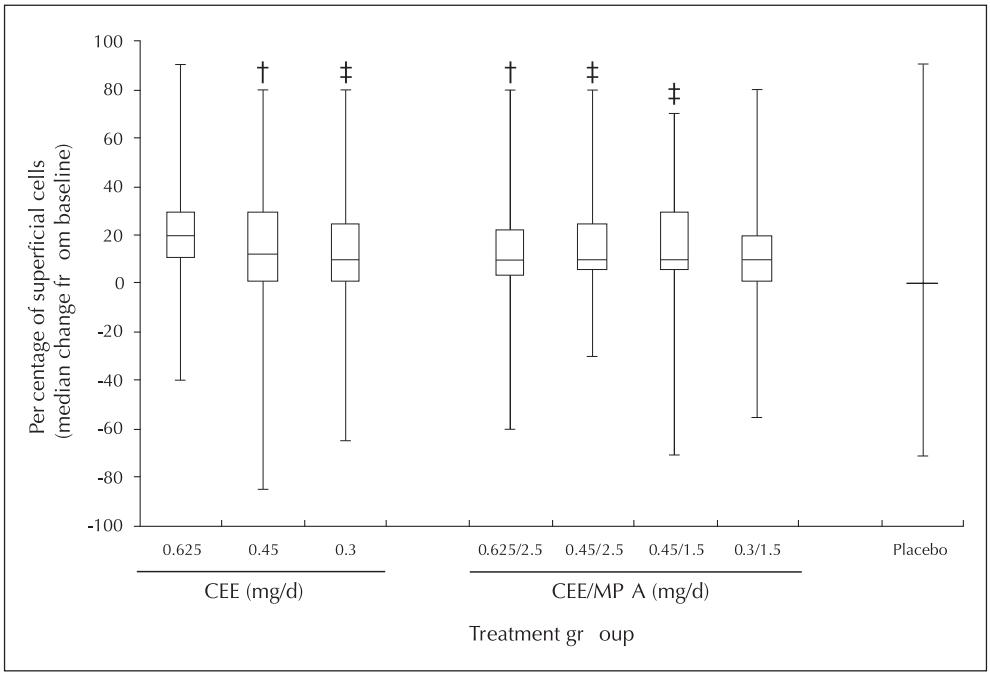

Figure 3. Box and whiskers plots of median change from baseline in VMI for superficial cells (%) at cycle 13. For each treatment group, the box shows the distance between the 75th and 25th percentiles, with the median marked as a line, and the "whiskers" show the maximum (top) and minimum (bottom) values. *Significantly different from CEE 0.625 mg, P < .001. † Significantly different from CEE 0.625 mg, P < .05. ‡ Significantly different from CEE 0.3 mg/MPA 1.5 mg, P < .05.

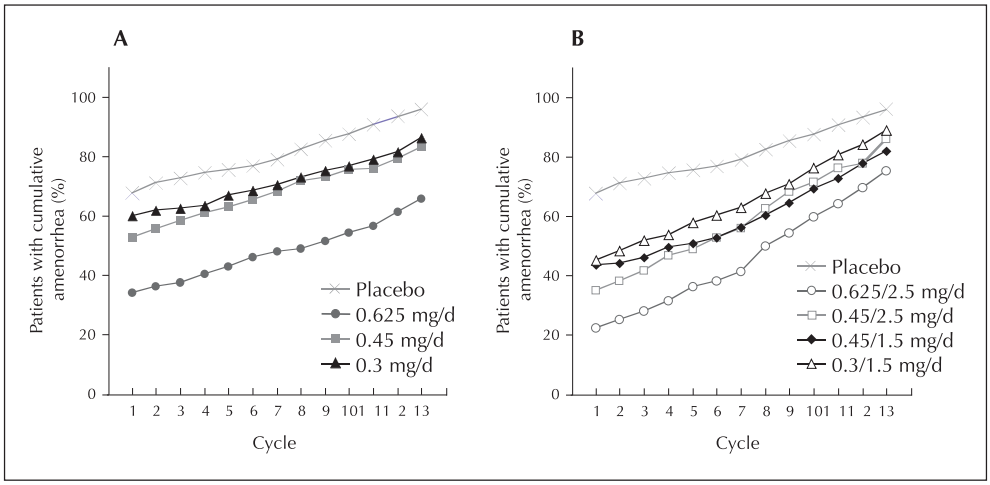

Figure 4. Cumulative rates of amenorrhea in the efficacy-evaluable population. 4A: Data for the placebo and CEE alone groups; 4B: Data for the placebo and CEE plus MPA groups.

avoid unreasonably high expectations. Women starting lower-dose HRT should be advised that although the lower-dose regimens have a better bleeding profile, it is still possible to experience irregular bleeding, particularly during the first few months of therapy, which should resolve with time.

When evaluating amenorrhea rates with lower-dose HRT, it is important to consider how the study's criteria for data collection and analyses compare to a real world situation. In the Women's HOPE study, women were instructed to record all episodes of bleeding or spotting on daily diary cards regardless of their significance. The occurrence of any spotting during a cycle resulted in exclusion from the amenorrhea group during that cycle. It is also important to keep in mind that the amenorrhea data were presented as cumulative rates and not incidence at each cycle. For example, a cumulative rate of amenorrhea of 50 % at cycle 4 meant that 50 % of women experienced amenorrhea (absolutely no instances of bleeding or spotting) from cycle 4 through cycle 13. A woman who experienced amenorrhea throughout the study with the exception of an episode of spotting in cycle 5 would be counted in the cumulative amenorrhea rate for cycle 6 onward. For these reasons, it is not unexpected that amenorrhea rates in the study were lower than those that would be expected under non-study conditions where occasional light spotting may be acceptable to many women. Study findings that may more closely reflect women's expectations of HRT are the cumulative rates of bleeding. At cycle 13, 6–8% of patients taking lower-dose CEE/MPA experienced bleeding that required sanitary protection.

Consistent with the results of a previous study that examined the relationship between the bleeding profile of CEE 0.625/MPA 2.5 and time since menopause [39] the Women's HOPE study found higher cumulative rates of amenorrhea in the CEE 0.625/MPA 2.5 group among women who were ≥3 years past menopause. In contrast, among the lower-dose CEE/MPA groups, there was no consistent rela-

tionship between cumulative amenorrhea rate and years past menopause, suggesting that time since menopause may not be as important a factor when using lower-dose HRT, and that higher amenorrhea rates may be achieved in early post-menopausal women with lower-dose regimens. The effects of lower-dose regimens on bleeding profiles in older women (> 65 years) starting on HRT and those who switch from a standard- to a lower-dose regimen remain to be determined.

Contrary to previous findings that higher MPA doses cause less bleeding [40, 41] the Women's HOPE study found no difference in bleeding profile between the CEE 0.45/MPA 2.5 and CEE 0.45/MPA 1.5 groups. In light of these data, it is possible that the ratio of estrogen to progestin dose is an important determinant of vaginal bleeding, and that lower estrogen doses can be combined with lower progestin doses to achieve a more favorable bleeding profile. Although further study is warranted, in women who are experiencing unacceptable bleeding with CEE 0.625/MPA 2.5, a downward adjustment in estrogen and progestin dose rather than an increase in progestin dose may be appropriate.

Safety and side effects [1]

The most common reason for discontinuation from the Women's HOPE study were adverse events. The highest rate of discontinuation due to adverse events was in the CEE 0.625 group (18%, n = 61) and the most common reasons for discontinuation were vaginal bleeding and endometrial hyperplasia [5]. Discontinuation rates ranged from 4–9% in the other treatment groups. Discontinuations due to lack of efficacy were greatest in the placebo group (8%, n = 27), but no greater than 2% in the active treatment groups ($P < .001$).

In addition to irregular bleeding, another common reason for HRT discontinuation is breast tenderness/discomfort [12, 42]. Breast pain was the most commonly reported (15% of women) treatment-emergent adverse event in the Women's HOPE study for which there were statistically significant differences among treatment

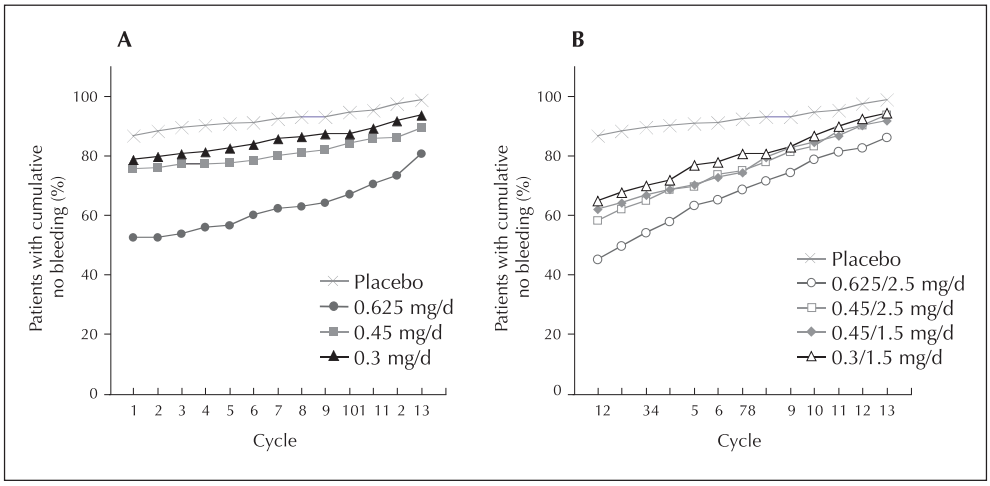

Figure 5. Cumulative rates of no bleeding in the efficacy-evaluable population. 5A: Data for the placebo and CEE alone groups; 5B: Data for the placebo and CEE plus MPA groups.

groups. More women in the CEE/MPA groups reported breast pain than in the CEE groups, and there was a trend toward a lower incidence of breast pain with lower doses of CEE/MPA. These data suggest a possible additional benefit of lower-dose regimens that may further reduce the rates of discontinuation due to unacceptable side effects.

Candidates for lower-dose HRT

In the context of the additional positive findings from the Women's HOPE study on endometrial safety [3], metabolic profile [4] and preservation of bone mass [5] with lower-dose regimens, many women are candidates for lower-dose HRT. Based on the generally accepted pharmacologic principle of using the lowest effective dose, a lower-dose regimen should be considered for any woman starting HRT for vasomotor symptoms. If symptoms do not improve substantially after a reasonable period of time, the dose can be increased as necessary. Lower-dose HRT should also be considered for older postmenopausal women who are starting HRT and for those on a standard-dose regimen who are no longer experiencing symptoms and whose treatment goals have changed, for example, from symptom relief to osteoporosis prevention. Women on standard doses who are experiencing unacceptable endometrial bleeding and are likely to discontinue therapy should also be offered the option of lower-dose HRT to enable them to stay on therapy and achieve the desired long-term benefits. However, there is no apparent benefit to switching a woman from standard- to lower-dose HRT if she has responded well to therapy and is satisfied with her current regimen.

Women who want to discontinue HRT due to concerns about safety may also be candidates for lower-dose HRT. In the Women's HOPE study, the rates of endometrial hyperplasia with the lower-dose HRT regimens were comparable to that of CEE 0.625/MPA 2.5. Data comparing breast cancer rates with lower-dose and standard-dose regimens are not available, although there appears to be an association between serum estrogen levels and breast cancer risk [43]. Nevertheless, lower-dose HRT may be an appropriate choice for women with a history of breast cancer or at high risk for breast cancer (atypical ductal hyperplasia, family history) who still seek relief from significant vasomotor symptoms. Since fear of breast cancer is a common reason why women do not want to start or decide to discontinue HRT [12, 44], it will be important to educate women that a lower-dose regimen may not reduce breast cancer risk.

Conclusions

The Women's HOPE study is the first large-scale, controlled clinical trial to examine the efficacy, safety, and tolerability of lower doses of ERT/HRT over a 1- to 2- year period. The published findings that are the focus of this review showed that lower doses of HRT provided vasomotor symptom relief and improvement in vaginal atrophy comparable to the most frequently prescribed regimen of CEE 0.625/MPA 2.5, with the added benefit of an improved bleeding profile, particularly during the first few months of treatment. Other recent publications from this study indicated that lower doses of

HRT provide adequate endometrial protection [3] and induce favorable changes in lipoproteins and modest changes in carbohydrate metabolism and hemostatic factors [4]. A future publication will present data on the effectiveness of lower-dose regimens for preservation of bone mass [5].

Lower-dose regimens represent an important addition to the clinician's armamentarium for menopausal health management by providing clinicians an option to better tailor ERT/HRT to individual patient needs. Based on the findings of the Women's HOPE study, a lower-dose regimen should be considered for all women who are starting or may start HRT, since a favorable clinical response is likely and there would still be the opportunity to increase the dose if necessary. Current HRT users may also benefit from a change to a lower-dose regimen, particularly if they have already or are planning to discontinue treatment due to side effects. By offering lower-dose HRT as a treatment option, the number of women who derive the short- and long-term benefits of HRT should increase as a result of higher rates of initiation and lower rates of discontinuation.

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