Symptom Relief and Side Effects of Postmenopausal Hormones: Results From the Postmenopausal Estrogen/Progestin Interventions Trial

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***Objective*: To assess pair-wise differences between placebo, estrogen, and each of three estrogen-progestin regimens on selected symptoms.**

***Methods*: This was a 3-year, multicenter, double-blind, placebo-controlled trial in 875 postmenopausal women aged 45–64 years at baseline. Participants were assigned randomly to one of five groups: 1) placebo, 2) daily conjugated equine estrogens, 3) conjugated equine estrogens plus cyclical medroxyprogesterone acetate, 4) conjugated equine estrogens plus daily medroxyprogesterone acetate, and 5) conjugated equine estrogens plus cyclical micronized progesterone. Symptoms were self-reported using a checklist at 1 and 3 years. Factor analysis reduced 52 symptoms to a set of six symptom groups.**

***Results*: In intention-to-treat analyses at 1 year, each active treatment demonstrated a marked, statistically significant, protective effect against vasomotor symptoms compared with placebo (odds ratios [ORs] 0.17–0.28); there was no additional benefit of estrogen-progestin over estrogen alone. Only progestin-containing regimens were significantly associated with higher levels of breast discomfort (OR 1.92–2.27). Compared with placebo, women randomized to conjugated equine estrogens reported no increase in perceived weight. Those randomized to medroxyprogesterone acetate reported less perceived weight gain (OR 0.61–0.69) than placebo. Anxiety, cognitive, and affective symptoms did not differ by treatment assignment. Analyses restricted to adherent women were not materially different than those using intention-to-treat, except that women adherent to medroxyprogesterone acetate and micronized progesterone regimens reported fewer musculoskeletal symptoms (OR 0.62–0.68).**

***Conclusion*: These results confirm the usefulness of postmenopausal hormone therapy for hot flashes, show convincingly that estrogen plus progestin causes breast discomfort, and demonstrate little influence of postmenopausal hormones on anxiety, cognition, or affect. (Obstet Gynecol 1998;92:982–8. © 1998 by The American College of Obstetricians and Gynecologists.)**

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The decision to use hormone replacement therapy (HRT) is complicated. To help the decision-making process, physicians are advised to counsel their patients about individual patient goals and concerns, the presence or absence of menopausal symptoms, comorbidities, family history, potential effects of estrogen on numerous chronic diseases, possible symptom amelioration, and unwanted side effects.[1] Knowledge about the effects of HRT on symptoms and potential side effects is surprisingly limited, except for the well-established relief of hot flashes and night sweats.[2] The putative benefit of hormone treatment on other possibly

menopausal symptoms, such as memory and mood, remains uncertain.[3–5] Many of the "known" side effects of HRT have not been evaluated in placebo-controlled clinical trials.

Only a randomized, controlled, masked trial can obviate concerns regarding confounding by indication, treatment bias, and placebo effects.[6,7] In one of the earliest placebo-controlled, randomized clinical trials of estrogen, Campbell and Whitehead[8] noted a remarkable placebo benefit for many symptoms.

The Postmenopausal Estrogen/Progestin Interventions Trial was a randomized, double-masked, placebo-controlled trial conducted in 875 postmenopausal women, to examine the effects of estrogen alone or in combination with three progestin regimens on selected outcomes. The study also was planned to collect information systematically on a wide range of self-reported symptoms at baseline and during the 3 years of treatment. We present here side effects and symptom relief resulting from treatment with estrogen and each of three estrogen-progestin treatment regimens versus placebo.

Materials and Methods

Between December 1989 and February 1991, the Postmenopausal Estrogen/Progestin Interventions Trial enrolled 875 postmenopausal women at seven clinical centers in the United States in a randomized, double-blind, placebo-controlled trial of the effects of oral conjugated equine estrogen, 0.625 mg daily, or conjugated equine estrogen plus one of three oral progestin regimens, on selected cardiac risk factors, other health outcomes, and symptoms. Sample size calculations were based on the primary cardiac endpoints.[9] The progestin regimens were medroxyprogesterone acetate, 10 mg for 12 of 28 days (conjugated equine estrogen + medroxyprogesterone acetate [cyc]); medroxyprogesterone acetate, 2.5 mg daily (conjugated equine estrogen + medroxyprogesterone acetate [con]); and micronized progesterone, 200 mg for 12 of 28 days (conjugated equine estrogen + micronized progesterone). All medication was identical in appearance, and tamper-proof randomization was accomplished by computer. Subject recruitment, eligibility criteria, study design, and baseline characteristics of the sample have been reported in detail.[9] Women were required to be between 45 and 64 years of age; at least 1 year, but not greater than 10 years, postmenopausal; not taking estrogen or progestin for at least 2 months before screening; if treated with thyroid replacement, to have been on a stable dose for at least 3 months before screening; and to be free of major medical contraindications to hormone use. Four women with self-defined severe menopausal symptoms (characterized by a positive response to "Do you have severe menopausal symptoms that cannot be tolerated without treatment?") also were excluded because they would have been unable to take placebo.

Demographic characteristics, medical history, physical activity, and consumption of cigarettes and alcohol were collected by standardized questionnaires. Symptoms were assessed at baseline and 12 and 36 months using a self-administered checklist. When the protocol was developed, no validated checklist of menopausal symptoms or estrogen side effects had been reported. Therefore, Postmenopausal Estrogen/Progestin Interventions Trial investigators compiled a list of 52 possible symptoms from the published literature, augmented by the experience of the clinical investigators and a validated instrument designed to assess the premenstrual syndrome.[10] The order of the symptoms was randomized and formatted into a dichotomous (yes-no) checklist.

Women who took at least 80% of their pills during the 6 months before each annual visit were defined as adherent, with 612 meeting this definition. Medications were blister-packed, and pill counts were performed at each visit by clinic staff. The protocol required permanent drug interruption for the following conditions: possible estrogen-dependent tumors, stroke, transient ischemic attack, pulmonary embolus, deep vein thrombosis, or complex (adenomatous or atypical) hyperplasia. Other participants elected to discontinue study drug permanently or temporarily for symptoms or for personal reasons. Narrative summaries of the reason(s) for treatment discontinuation were completed by clinic staff, and the primary reason for each interruption was coded. Women could not transfer between treatment arms within the Postmenopausal Estrogen/Progestin Interventions Trial. Those who chose to institute hormone therapy did so under the care of their personal health care provider.

For analysis, the original set of 52 symptoms was first reduced to a more manageable set of symptom groups. Each group consisted of symptoms that were correlated highly with each other, as determined by a factor analysis at baseline.[11] For each symptom group, a score was created for each subject by counting the number of symptoms she endorsed in each symptom group. Scores for each symptom group were calculated at baseline and at 12 and 36 months. The effect of treatment at each visit on each symptom group score was examined using logistic regression models for ordinal data.[12] Specifically, we modeled the odds of having a higher versus lower symptom score as a function of treatment assignment, baseline symptom score, clinical site, and uterus status. (Clinical site and uterus status were randomization blocking variables.) The correla-

tion between symptom group scores at 12 and 36 months was accounted for using the statistical approach of Heagerty and Zeger.[13] Each symptom group was considered in a separate logistic regression analysis. Significant interactions between treatment assignment and follow-up year and treatment assignment and baseline symptom scores were included in final models. Pairwise comparisons between treatment effects were tested using two-sided generalized Wald tests. Because the changes in the effect sizes (odds ratios [ORs]) were small in the two cases in which baseline score interactions were significant, and because presenting ORs for each baseline level would increase the number of tables many times over, all tables show the ORs calculated without baseline symptom score interaction terms. All analyses were repeated restricted to adherent women only. The entire analysis also was done in the subset of women (n = 612) who were adherent to study medication.

Results

The average age of the participants was 56.1 years at baseline: 41% were between 45 and 54 years old, and the remainder were between 55 and 64 years old; 89% were white, and 32% had undergone hysterectomies. Among women with a uterus (n = 596), 52% were within 5 years of their last menstrual period, and the remainder were between 5 and 10 years postmenopausal. Participation at the 1- and 3-year visits was 97% and did not vary by treatment assignment.

During the 3 years of follow-up, 210 women (24%) stopped treatment permanently; 51 (24%) of these were protocol-mandated, the majority (n = 32) due to endometrial abnormalities. Among the remaining 159 women, primary reasons for stopping treatment were symptoms (n = 127), concerns about health risks (n = 11), and personal circumstances (n = 21). The most often cited symptoms were vaginal bleeding (n = 25); premenstrual-like symptoms (n = 17); vasomotor symptoms (n = 11); headaches (n = 10); anxiety-depression (n = 10); and breast tenderness (n = 7). By the year 3 visit, 19 women in the placebo group (11%) had begun taking privately prescribed hormones.

At the conclusion of the study, women were asked to guess what treatment they had received. Among placebo-assigned women, 17.7% thought they were taking conjugated equine estrogens, and 23.8% believed they were treated with conjugated equine estrogens plus progestin. Of conjugated equine estrogen–assigned women, 13.6% guessed that they had taken placebo and 40.1% guessed conjugated equine estrogen plus progestin. Among combination treated women, 10.6% guessed placebo and 17.6% guessed conjugated equine estrogen.

Table 1. Symptom Groups and the Prevalence of Each Symptom at Baseline (n = 875)

Symptom group	Percent reporting
Cognitive-affective	
Forgetfulness	34
Easily distracted	25
Difficulty concentrating	24
Decreased efficiency	18
Short temper	18
Loss of interest in work	13
Lowered work performance	13
Avoidance of social affairs	8
Confusion	7
Weight-appetite	
Weight gain	32
Increased appetite	22
Decreased appetite	5
Weight loss	4
Musculoskeletal	
Aches-pains	48
Joint pain	44
Muscle stiffness	42
Skull-neck aches	34
Breast discomfort	
Breast sensitivity	9
Painful breasts	4
Anxiety	
Suffocation	5
Difficulty breathing	4
Fuzzy vision	4
Vasomotor	
Hot flashes	46
Night sweats	36
Cold sweats	7

Results of the factor analysis used to derive symptom groups are displayed in Table 1. The six factors shown explained 45.1% of the total variation in the baseline symptoms. Symptom groups were similar in women with and without hysterectomy (data not shown). Vasomotor, musculoskeletal, increased appetite-perceived weight gain, and cognitive-affective symptoms were cited most frequently; anxiety and breast discomfort symptoms were less common (Table 1).

At 1 and 3 years, women in each active treatment group had significantly lower vasomotor symptom levels compared with women in the placebo group, adjusted for baseline vasomotor symptom level, clinic, and uterus status (Table 2). At year 1, the ORs comparing treatments to placebo (column 1 of Table 2) ranged between 0.17 and 0.28 ($P < .001$ for each comparison), indicating substantial protection against vasomotor symptoms, but the ORs were between 0.26 and 0.53 ($P \leq .03$ for each comparison) at follow-up year 3, indicating a less pronounced difference between treated and untreated women.

The remaining columns of Table 2 show pairwise comparisons between the active treatments. None of

Table 2. Adjusted Odds* of Having Higher Vasomotor Symptom Scores for Each Treatment Group (Row) Compared With an Alternative Treatment Group (Column) at 1 and 3 Years

Treatment assignment† and year	Comparison group‡,§			
	Placebo	CEE + MPA (cyc)	CEE + MPA (con)	CEE + MP
Year 1				
CEE	0.28 (0.16, 0.48)	1.20 (0.63, 2.29)	1.62 (0.81, 3.25)	1.32 (0.69, 2.49)
CEE + MPA (cyc)	0.23 (0.13, 0.40)		1.35 (0.67, 2.68)	1.09 (0.58, 2.06)
CEE + MPA (con)	0.17 (0.09, 0.32)			0.81 (0.41, 1.60)
CEE + MP	0.21 (0.12, 0.37)			
Year 3				
CEE	0.53 (0.31, 0.93)	1.25 (0.68, 2.30)	1.36 (0.73, 2.51)	2.05 (1.08, 3.90)
CEE + MPA (cyc)	0.43 (0.24, 0.75)		1.09 (0.58, 2.03)	1.64 (0.86, 3.15)
CEE + MPA (con)	0.39 (0.22, 0.69)			1.51 (0.78, 2.91)
CEE + MP	0.26 (0.14, 0.47)			

* Odds ratios are adjusted for baseline symptom level, clinical site, and uterus status.

† CEE = 0.625 mg conjugated equine estrogens (daily); CEE + MPA (cyc) = 0.625 mg conjugated equine estrogens (daily) and 10 mg medroxyprogesterone acetate (days 1–12); CEE + MPA (con) = 0.625 mg conjugated equine estrogens (daily) and 2.5 mg medroxyprogesterone acetate (daily); CEE + MP = 0.625 mg conjugated equine estrogens (daily) and 200 mg micronized progesterone (days 1–12).

‡ Entries in table are odds ratios with 95% confidence intervals from generalized Wald tests in parentheses.

§ N = 858–862 (due to missing data); N randomized to each arm: placebo (174); CEE (175); CEE + MPA (cyc) (174); CEE + MPA (con) (174); CEE + MPA (178).

these comparisons were significant at year 1, indicating that conjugated equine estrogens plus progestin was not more effective than conjugated equine estrogens alone against vasomotor symptoms. Comparisons at year 3 showed similar equivalence of treatments with one exception: conjugated equine estrogens appeared to be less effective than conjugated equine estrogens plus micronized progesterone (indicated by the OR of 2.05 in the last column of Table 2), although conjugated equine estrogens and conjugated equine estrogens plus micronized progesterone were each more effective than placebo. Women with more severe vasomotor symptoms at baseline experienced a greater treatment effect (data not shown); this interaction was statistically significant only for conjugated equine estrogens plus medroxyprogesterone acetate [con] (P = .001) and conjugated equine estrogens (P = .056).

For vasomotor symptoms, results confined to adherent women paralleled those seen in the intent-to-treat analysis (data not shown). All treated women had lower symptom levels compared with those taking placebo; there were no differences between treatments, and the effects of treatment in year 3 were weaker than those in year 1. The effect of all active treatments on vasomotor symptoms, however, was greater in the adherent compared with the intent-to-treat analysis. Compared with placebo, the odds of having more severe vasomotor symptoms ranged from 0.11 to 0.13 for women adherent to the active treatments in year 1 ($P < .001$ for each comparison) and 0.16 to 0.29 for the adherent women in year 3 ($P \leq .001$ for each comparison).

Vasomotor symptoms were the sole symptom group that demonstrated differences in the effects of treatments at year 1 versus year 3. Notably, the crude prevalence of any hot flash symptom in women assigned to placebo declined over time; it was 55.7%, 38.7%, and 29.5% at baseline, year 1, and year 3, respectively. Among placebo-adherent women, corresponding prevalence figures were 52.9%, 43.7%, and 30.3%.

Women assigned to active treatment did not differ at years 1 or 3 in the domains of cognitive-affective, anxiety, or musculoskeletal symptoms compared with placebo-assigned women (ORs between 0.7 and 0.9, comparisons not statistically significant, data not shown). Among adherent participants, the effect of estrogen on cognitive-affective symptoms was not substantively different than was found for all women (data not shown). With respect to anxiety symptoms, the results of the adherent analysis also were similar to the intent-to-treat results, with the exception that anxiety symptom levels were lower in conjugated equine estrogens–adherent women compared with those who received placebo (OR = 0.52, P = .05). A protective effect of active treatment on musculoskeletal symptoms was evident in the adherent analysis (ORs 0.62–0.68 compared with placebo). These results were statistically significant for women adherent to cyclic (P = .02) and continuous (P = .04) medroxyprogesterone acetate regimens and of borderline significance for the women taking conjugated equine estrogens (P = .08) and conjugated equine estrogens + micronized progesterone (P = .06).

Breast discomfort was significantly more common with each combination estrogen-progestin treatment compared with both placebo and unopposed conjugated equine estrogens treatments (Table 3); the odds of having more severe breast discomfort compared with

Table 3. Adjusted Odds* of Having Higher Symptom Scores for Each Treatment Group (Row) Compared With an Alternative Treatment Group (Column)

Treatment assignment† and symptom group	Comparison group*,§			
	Placebo	CEE + MPA (cyc)	CEE + MPA (con)	CEE + MP
Breast discomfort				
CEE	1.16 (0.70, 1.93)	0.52 (0.33, 0.82)	0.61 (0.38, 0.98)	0.50 (0.32, 0.79)
CEE + MPA (cyc)	2.27 (1.39, 3.56)		1.17 (0.76, 1.81)	0.97 (0.63, 1.46)
CEE + MPA (con)	1.92 (1.16, 3.09)			0.83 (0.53, 1.26)
CEE + MP	2.33 (1.46, 3.74)			
Perceived weight gain				
CEE	0.80 (0.54, 1.19)	1.15 (0.78, 1.71)	1.31 (0.87, 1.95)	0.92 (0.63, 1.35)
CEE + MPA (cyc)	0.69 (0.47, 1.03)		1.13 (0.87, 1.70)	0.80 (0.54, 1.18)
CEE + MPA (con)	0.61 (0.41, 0.91)			0.70 (0.47, 1.05)
CEE + MP	0.87 (0.60, 1.26)			
Perceived weight loss				
CEE	1.22 (0.61, 2.46)	0.80 (0.41, 1.55)	0.66 (0.35, 1.26)	0.55 (0.29, 1.02)
CEE + MPA (cyc)	1.52 (0.78, 2.97)		0.82 (0.45, 1.49)	0.68 (0.38, 1.20)
CEE + MPA (con)	1.85 (0.97, 3.56)			0.83 (0.47, 1.45)
CEE + MP	2.22 (1.17, 4.30)			

* Odds ratios are adjusted for baseline symptom level, clinical site, and uterus status.

† CEE = 0.625 mg conjugated equine estrogens (daily); CEE + MPA (cyc) = 0.625 mg conjugated equine estrogens (daily) and 10 mg medroxyprogesterone acetate (days 1–12); CEE + MPA (con) = 0.625 mg conjugated equine estrogens (daily) and 2.5 mg medroxyprogesterone acetate (daily); CEE + MP = 0.625 mg conjugated equine estrogens (daily) and 200 mg micronized progesterone (days 1–12).

‡ Entries in table are odds ratios with 95% confidence intervals from generalized Wald tests in parentheses.

§ N = 858–862 (due to missing data); N randomized to each arm: placebo (174); CEE (175); CEE + MPA (cyc) (174); CEE + MPA (con) (174); CEE + MPA (178).

placebo were roughly equal among all of the progestin formulations and did not differ by year of follow-up. Women assigned to conjugated equine estrogens (OR = 1.16, Table 3) and women adherent to conjugated equine estrogens (OR = 1.09, P = .82) had no higher levels of breast discomfort than the placebo group. Compared with the intention-to-treat analysis, women adherent to any progestin regimen had even greater levels of breast discomfort compared with those in the placebo group (ORs $\geq$ 2.26; $P \leq .006$).

The perceived weight-appetite symptom group included the self-reported symptoms of perceived weight gain, increased appetite, perceived weight loss, and decreased appetite (Table 1). Women assigned to continuous medroxyprogesterone acetate reported significantly less perceived weight gain and appetite increase compared with those in the placebo group (Table 3). Women reporting more perceived weight gain and increased appetite at baseline were less likely to report perceived weight gain 12 and 36 months, as a result of any active treatment (data not shown). Few women reported weight loss-decreased appetite; women assigned to conjugated equine estrogens + micronized progesterone were significantly more likely to perceive weight loss-decreased appetite compared to placebo assigned women (Table 3). A similar but marginally statistically significant effect was also apparent for continuous conjugated equine estrogens + medroxyprogesterone acetate [con]. None of the perceived weight-appetite symptoms differed between years 1 and 3 among all participants and adherent participants.

Two symptoms, headache and forgetfulness, were analyzed separately. There was an interaction between baseline headache score and treatment for conjugated equine estrogens only (P = .06). If headache was absent at baseline, the conjugated equine estrogens group was more likely to develop headache than placebo or progestin-treated groups. Conversely, if headache was present at baseline, the conjugated equine estrogens group reported less headache than placebo or progestin-treated women. Among women reporting no forgetfulness at baseline, there was no effect of treatment. In contrast, for those who reported forgetfulness at baseline, conjugated equine estrogens treatment was associated with more forgetfulness than combination treatments (data not shown).

Discussion

Previous clinical trials have shown near-complete amelioration of hot flashes after hormone therapy.[2] Because monotherapy with medroxyprogesterone acetate[14] decreases vasomotor symptoms, combination therapy with estrogen and progestin might be more effective than either treatment individually. We found convincing evidence that conjugated equine estrogens with the progestins tested is not more effective than conjugated equine estrogens alone in hot flash reduction. The single

pairwise comparison of conjugated equine estrogens versus conjugated equine estrogens + micronized progesterone at year 3 suggested that the latter combination was more effective, but this is likely artifact due to protocol-mandated estrogen discontinuations in the conjugated equine estrogens–only arm. Not surprisingly, vasomotor symptom reduction was more pronounced in women who had more severe hot flashes at baseline.

Most studies of hot flashes have been 1 year or less in length,[2] such that the natural history of hot flashes in an untreated group has not been examined well. In the Postmenopausal Estrogen/Progestin Interventions Trial, the difference in hot flash symptom–reporting between treated and untreated women diminished between years 1 and 3, compatible with the observed pattern of diminishing hot flashes over time in the placebo group.

The etiology of mastalgia in both premenopausal and postmenopausal women is obscure.[15] Most attention has focused on estrogens rather than progestins as the potential cause,[16,17] and lower starting doses of estrogen are recommended to minimize this side effect.[18] However, norethisterone also is reported to cause breast pain with HRT.[19] In the Postmenopausal Estrogen/Progestin Interventions Trial, worsened symptoms of breast pain and discomfort were confined to the combination estrogen-progestin treatment groups, suggesting that the combination is responsible for the mastalgia associated with postmenopausal hormones. Neither a smaller daily progestin dose (as in the 2.5-mg medroxyprogesterone acetate daily arm) nor use of micronized progesterone was less likely to produce mastalgia than the traditional cyclic dose of medroxyprogesterone acetate (10 mg). Because there was no progestin-only treatment in the Postmenopausal Estrogen/Progestin Interventions Trial, we cannot determine whether estrogen must be present to observe progestin-related mastodynia.

In practice, many women are concerned that hormone use leads to weight gain.[18] Although weight gain occurs at menopause,[20] studies have not found that postmenopausal hormones cause or prevent weight gain.[21,22] In the Postmenopausal Estrogen/Progestin Interventions Trial, measured weight gain was not caused by conjugated equine estrogens only or conjugated equine estrogens–progestin regimens.[23] This study finds that women who used unopposed conjugated equine estrogens did not perceive weight gain compared with placebo. Those using conjugated equine estrogens–progestin sensed weight loss.

Prior studies of cognition and estrogen use have been inconsistent. Barrett-Connor and colleagues[24] found no effects of estrogen on numerous complex tests of memory and cognitive function, as did Ditkoff and colleagues[25] in a randomized controlled trial among women of similar age to the Postmenopausal Estrogen/Progestin Interventions Trial sample. In contrast, other intervention studies have found memory benefit from estrogen use among women of varied ages and using different measures.[26] Reports that estrogen may protect against dementia also are contradictory,[26] but dementia is quite distinct from the outcomes assessed in the Postmenopausal Estrogen/Progestin Interventions Trial. Symptoms such as forgetfulness and difficulty concentrating are common, but not sensitive for specific measures; our results do not support a relationship between HRT and these symptoms.

In the United States and Europe, musculoskeletal complaints are not prominent during menopause.[27,28] In Japan, however, muscle and neck pain may be concomitants of the menopause.[29] The Postmenopausal Estrogen/Progestin Interventions Trial was not designed to determine the symptoms that characterize the menopause transition, because women were postmenopausal at entry. It is notable that adherence to treatment was associated with less muscle and joint pain, provocative findings that warrant further investigation.

The higher frequency of migraine among women and its relation to menses and, in some reports, menopause suggests the hypothesis that these vascular events are mediated by changing estrogen levels.[30] The Postmenopausal Estrogen/Progestin Interventions Trial symptom checklist did not distinguish headache types. Curiously, women in the study with headache at baseline who took conjugated equine estrogens were less likely to have headache at follow-up, whereas those without headache at the beginning of the study were more likely to develop headache in conjugated equine estrogens treatment. This interaction might explain why previous studies produced inconsistent results with respect to HRT and headache symptoms.

Even in a randomized controlled trial, it is difficult to interpret side effect data because the symptoms being evaluated as outcomes also could cause discontinuation or institution of treatment. The effect of treatment crossovers, relatively uncommon in the Postmenopausal Estrogen/Progestin Interventions Trial, would be to diminish the difference between active treatment and placebo for both beneficial (eg, vasomotor) and deleterious (eg, breast tenderness) effects. Thus, neither intention-to-treat nor adherent analyses characterize symptom relief or side effects perfectly. To address the potential problems of symptom-related discontinuations and crossovers, we presented both adherent and assigned treatment results. In most instances, the results were not affected materially, suggesting that the flaws of each analysis are not large.

This study assessed only those items that were in-

cluded on the symptom checklist, which was not a validated scale of menopause symptoms. We also did not assess symptom severity or the effects of improvement or worsening of symptoms on functional status. Unfortunately, standard tests of cognitive function were not obtained. Symptoms were not measured uniformly during the estrogen-only or estrogen-progestin portion of the cyclical treatments, which could dilute between-group differences. We expect this error to be random and not to introduce bias into the results.

We confirmed a beneficial effect of estrogen on vasomotor symptoms with no additional advantage of added progestins. Breast discomfort was restricted to the three estrogen-progestin treatment groups. Neither estrogens nor estrogens and progestins caused perceived weight gain. Postmenopausal hormone therapy did not affect self-reported cognitive, affective, or anxiety symptoms but may have improved muscular aches and joint pains. This information will help clinicians counsel women more effectively about benefits of hormone use and will assist in managing treatment-related side effects, such as mastalgia.

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