Initial 17β-Estradiol Dose for Treating Vasomotor Symptoms

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***Objective*: To compare the efficacy of different doses of 17β-estradiol (E2) for relief of vasomotor symptoms in menopausal women.**

***Methods*: This was a randomized, double-masked, placebo-controlled, 12-week study in which 333 menopausal women with moderate or severe hot flushes were assigned to treatment with 0.25 mg, 0.5 mg, 1 mg, or 2 mg oral micronized 17β-E2, or placebo. The number and severity of hot flushes were recorded daily.**

***Results*: There was a significant linear correlation between increased dosage of 17β-E2 and decreased moderate to severe hot flushes per week ($P < .001$). Rapid reduction in moderate to severe hot flushes was only achieved with 1 and 2 mg, showing a significant difference from placebo at week 4 ($P < .05$). At week 4, half the women on placebo had reduced moderate to severe hot flushes of at least 52%; the corresponding figures were 56%, 69%, 86%, and 91% for 0.25, 0.5, 1, and 2 mg, respectively. At week 12, all doses except 0.25 mg were significantly better than placebo for reducing moderate to severe hot flushes ($P < .001$). Although there were no significant differences, twice as many women in the 2-mg group discontinued treatment due to adverse events, compared with the placebo group.**

***Conclusion*: Oral micronized 17β-E2 showed a dose-response effect for reducing moderate and severe hot flushes in menopausal women. 17β-E2 1 mg appeared to be the most useful initial dose. (Obstet Gynecol 2000;95:726–31. © 2000 by The American College of Obstetricians and Gynecologists.)**

Estrogen has been used for several decades for treating estrogen deficiency symptoms.[1,2] However, only a few dose-ranging studies have been done to determine the dose-response effect of 17β-estradiol (E2) on vasomotor symptom relief.[3,4] Several studies evaluated vasomotor symptom relief associated with moderate and high dosages of 17β-E2 ranging from 1 to 4 mg,[3,4] but the efficacy of lower dosages has not been investigated.

Although estrogen dosages are adjusted during therapy according to individual responses, it is of interest to establish the dose that confidently can be used to initiate therapy. Factors relevant to identifying the ideal initial dose of 17β-E2 include rapid and adequate relief of vasomotor symptoms, and appropriateness for most women. Besides being effective, the ideal initial dose should be well tolerated. The present study evaluated a range of 17β-E2 doses for symptom relief in menopausal women who needed treatment for moderate and severe vasomotor symptoms, and used the collected data to identify the ideal initial dose.

Materials and Methods

A double-masked, randomized, placebo-controlled study was conducted in 15 centers in the United States. To properly establish the baseline level of vasomotor symptoms, subjects had a 2-week, no-therapy screening period, followed by a 12-week treatment period. Ap-

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Statistical support was provided by Won-Chin Huang, PhD, from Novo Nordisk Pharmaceuticals Inc., Princeton, New Jersey.

The following investigators also participated in the trial: W. Abelove, A. L. Abt, A. B. Aven, G. Davila, S. F. Gordon, M. W. Heine, H. McQuarrie, L. S. Mihalov, M. Parr, C. Schwenker, and L. Speroff.

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proval was obtained from the institutional review boards of the participating centers.

The study comprised 333 healthy menopausal women who signed informed consent forms. Each subject had an intact uterus, was 40–60 years old, and had at least 56 moderate or severe hot flushes per week, as defined, during the screening period. Menopausal status was defined as at least 6 months of amenorrhea, E2 levels at most 20 pg/mL, and FSH levels at least 50 IU/L. Exclusion criteria included history of endometrial hyperplasia; abnormal bleeding of unknown origin; endometrial thickness at least 5 mm (assessed by transvaginal ultrasound); known, suspected, or history of estrogen-dependent tumors; gallbladder, liver, kidney, or endocrine diseases except controlled thyroid disease; active or history of venous thromboembolism or cerebrovascular accidents; myocardial infarction or ischemic heart disease; history of severe headaches or migraines associated with estrogen use; systolic blood pressure (BP) more than 160 mmHg or diastolic BP more than 100 mmHg treated or untreated; alcohol or drug abuse or smoking more than 15 cigarettes per day; weight above 20% of ideal body weight according to Metropolitan Life Insurance Height-Weight tables[5]; and concomitant use of any steroid hormones or drugs known to influence estrogen metabolism.

After the screening period, women were randomly assigned to treatment with placebo ($n = 66$) or one of the dosages of oral unopposed micronized 17β-E2: 0.25 mg ($n = 68$), 0.5 mg ($n = 64$), 1 mg ($n = 67$), or 2 mg ($n = 68$). The randomization code was generated centrally using a block size of five to ensure equal distribution of treatment groups. On entry, subjects were assigned to the lowest available randomization number for each site. Treatment consisted of one tablet taken orally once a day for 12 weeks. All study drugs were identical in appearance and packaging, and were manufactured and supplied by Novo Nordisk A/S, Bagsvaerd, Denmark.

Women kept daily diaries in which they recorded the number and severity (ie, mild, moderate, or severe) of hot flushes. A mild hot flush was defined as a flush without perspiration that did not interfere with daily activity or performance. A moderate hot flush was defined as a hot sensation or flush with perspiration that interfered with daily activities at onset of symptoms. A severe hot flush was defined as a hot sensation with perspiration that stopped any activity at onset of symptoms.

Moderate and severe hot flushes were totaled together for each week. A composite score taking into account number and severity of hot flushes, termed the hot flush weekly weighted score, was also calculated. The score weighs each hot flush according to its severity by multiplying the number of mild hot flushes by a factor of one, the number of moderate hot flushes by a factor of two, and the number of severe hot flushes by a factor of three, and summing those three numbers weekly. A responder analysis was done to help understand individual benefit over the dosage range. A decrease in the hot flush weekly weighted score of at least 90% was arbitrarily defined as adequate treatment response to differentiate the therapeutically active dosages and placebo, at earlier and later times. We recorded any adverse events observed by investigators or reported spontaneously by women during the 12 weeks of treatment.

Serum levels of E2, estrone (E1), E1 sulfate, and FSH were measured 2 weeks before the start of therapy and again three times during treatment (at weeks 4, 8, and 12). Samples were collected approximately 12 hours after dosing. Serum samples were forwarded to the central laboratory (Nichols Institute, San Juan Capistrano, CA) for storage and analysis. Except for the screening hormone assessments, serum samples collected during therapy were analyzed at the end of the study to preserve masking of treatment allocation of all centers and personnel related to conduct of this study. The assay methods for E2, E1, E1 sulfate, and FSH involved double antibody radioimmunoassay preceded by organic extraction and celite chromatography.

A sample of 60 subjects per group was required to detect a difference of 15 moderate to severe hot flushes between an active treatment group and placebo with an estimated standard deviation of 25 and a power of .90 at a significance level of .05.

Statistical analyses were made for the intent-to-treat population. We used the last-observation-carried-forward strategy, in which the last observation is used repeatedly at subsequent visits to compensate for missing observations. We analyzed differences in changes from baseline between active treatment groups and placebo (average of the 2-week no therapy screening period) in number of moderate to severe hot flushes per week, and in the hot flush weekly weighted score, at weeks 4, 8, and 12 of treatment. We used an analysis of variance model with treatment and center included as fixed effects, and baseline values included as the covariates. If overall treatment effect was significant in either of the variables at any time, linear contrasts were tested to investigate the linear dose-response relationship and the difference between each of the active treatments and placebo. Mantel-Haenszel was used to determine if there was a linear association between dose and adequate response to treatment. Subsequently, pairwise comparison of each active treatment group and placebo was made by Fisher exact test.

Samples were collected for serum levels of E2, E1, E1

Table 1. Subject Disposition and Demographics

	Placebo	E2 0.25 mg	E2 0.5 mg	E2 1 mg	E2 2 mg
Randomized	66	68	64	67	68
Completed	55 (83%)	59 (87%)	57 (89%)	55 (82%)	54 (79%)
Discontinued	11 (17%)	9 (13%)	7 (11%)	12 (18%)	14 (21%)
Age (y)*	52.1 ± 4.6	50.9 ± 4.3	51.2 ± 3.7	50.8 ± 4.1	50.6 ± 4.0
Time since last menses (y)*	3.2 ± 3.4	2.5 ± 2.2	3.4 ± 3.1	2.6 ± 2.7	2.6 ± 2.5
Distribution					
<1 y	35%	29%	19%	39%	34%
≥1 and ≤5 y	38%	57%	58%	45%	54%
>5 y	27%	13%	23%	16%	12%
Weight (kg)*	66.9 ± 10	68.9 ± 10	67.2 ± 11	67.0 ± 11	68.3 ± 12
Total moderate to severe hot flushes per week*	72 ± 21	74 ± 25	73 ± 23	70 ± 18	70 ± 19
Hot flush weekly weighted score*	180 ± 59	189 ± 71	186 ± 68	182 ± 51	178 ± 49

* Data are presented as mean ± standard deviation.
E2 = 17β-estradiol.

sulfate, and FSH at weeks 4, 8, and 12. Steady-state levels of those hormones were calculated as a mean of the available data for each subject at weeks 4, 8, and 12. Differences in the steady-state levels between women with adequate and inadequate responses were tested using an analysis of variance with treatment, response, and their interactions included as the fixed effects. Pairwise comparisons were analyzed by Fisher exact test between groups by how many women withdrew from the study, withdrew because of bleeding, and reported bleeding and breast pain as adverse events.

A significance level of .05 was applied in all analyses. Statistical analyses were done using SAS version 6.08 (Statistical Analysis System, SAS Institute, Cary, NC).

Results

As shown in Table 1, demographic characteristics of women in this study appeared similar across treatment groups. The mean age of the women was 51 years, with a mean time of 3 years since their last menses. Approximately one third of the women (31%) had their last menses within 1 year before inclusion. The average number of moderate to severe hot flushes at baseline varied between 70 and 74 per week.

The changes in mean total of moderate to severe hot flushes per week reported in each group are shown in Figure 1. There was a similar pattern when the hot flush weekly weighted score was used to evaluate changes in vasomotor symptoms. A significant ($P < .001$) linear dose-response relationship was shown between dosage of 17β-E2 and reduction in vasomotor symptoms, assessed by the number of moderate to severe hot flushes and the hot flush weekly weighted score. At the end of the 12-week treatment period, decreases in the number of moderate to severe hot flushes and in the hot flush weekly weighted score were significantly greater ($P < .001$) in the 0.5-, 1-, and 2-mg groups compared with the placebo group. However, at week 4 only the 1- and 2-mg groups showed significance ($P < .05$) compared with the placebo group. The responses observed with 0.25 mg did not reach significance compared with placebo by the different variables at any point during the study. The distribution of individual relative change in number of moderate to severe hot flushes per week is shown for each group at weeks 4 and 12 in Figure 2. At week 4, half the women who took placebo had reductions moderate to severe hot flushes of at least 52% from baseline. For women who received 17β-E2, half the women in the 0.25-, 0.5-, 1-, and 2-mg groups had their moderate to severe hot flushes reduced by at least 56%, 69%, 86%, and 91%, respectively, from baseline to week 4. After 12 weeks of therapy, half the women had their moderate to severe hot flushes reduced by at least 71% with placebo, and by at least 77%, 97%, 100%, and 100% with 0.25, 0.5, 1, and 2 mg, respectively.

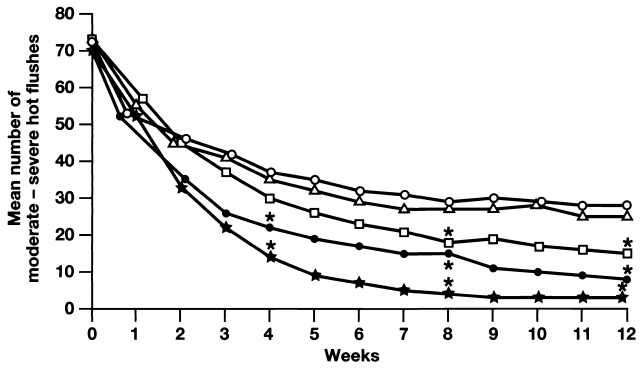

Figure 1. Mean number of moderate to severe hot flushes during 12 weeks of treatment with placebo (*open circles*) or 0.25 mg (*open triangles*), 0.5 mg (*open squares*), 1 mg (*solid circles*), or 2 mg (*asterisks*) 17β-estradiol. Stars indicate statistically significant difference versus placebo.

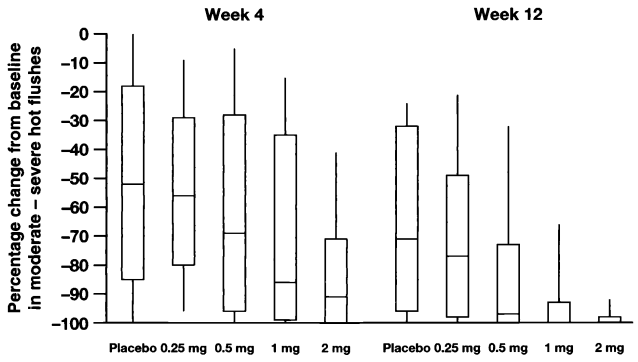

Figure 2. Distribution (10th, 25th, 50th (median), 75th, and 90th percentiles) of the individual percentage change from baseline in the total number of moderate to severe hot flushes per week for placebo and 0.25 mg, 0.5 mg, 1 mg, and 2 mg 17β-estradiol at weeks 4 and 12.

Figure 3 shows the percentage of women whose symptoms were adequately relieved (at least a 90% reduction in hot flush weekly weighted score) early in the study. After 4 weeks of therapy, the percentage of women [95% confidence interval (CI)] with adequate response to treatment was significantly higher ($P < .01$) with 1 mg (43%, 95% CI 31%, 55%) and 2 mg (46%, 34%, 95% CI 58%) compared with placebo (21%, 95% CI 11%, 31%), but not with 0.25 mg (14%, 95% CI 6%, 22%) or 0.5 mg (30%, 95% CI 19%, 41%). At the end of the study, a significant linear dose-response relationship ($P < .001$) was shown between the dosage of 17β-E2 and the percentage of women with adequate symptom relief. At week 12, the proportion of women who had adequate relief of symptoms in the 0.5-mg (61%, 95% CI 49%, 73%), 1-mg (71%, 95% CI 60%, 82%), and 2-mg (89%, 95% CI 82%, 96%) groups was significantly higher ($P < .001$) than the placebo group (25%, 15%, 35%), which was not the case for the 0.25-mg group (25%, 15%, 35%).

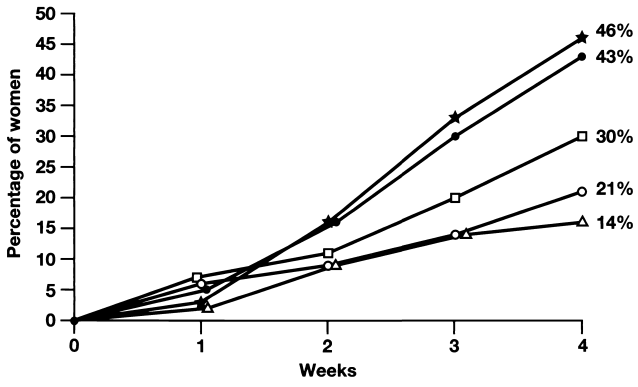

Figure 3. Percentage of women with at least 90% reduction in hot flush weekly weighted score during the first 4 weeks of treatment with placebo (*open circles*) or 0.25 mg (*open triangles*), 0.5 mg (*open squares*), 1 mg (*solid circles*), or 2 mg (*asterisks*) 17β-estradiol.

Table 2 presents the median steady-state levels and distribution (25th and 75th percentiles) of E2, E1, E1 sulfate, and FSH for each treatment group, and for women with adequate responses, and women with inadequate responses within each treatment group. A significant linear relationship ($P < .001$) was found between dosage of 17β-E2 and the serum levels of E2, E1, E1 sulfate, and FSH. However, no significant linear correlation was found between individual levels of any of the hormones and reduction in vasomotor symptoms, assessed either by total moderate to severe hot flushes per week or hot flush weekly weighted score. As shown in Table 2, mean circulating levels of E2, E1, and E1 sulfate were significantly higher ($P < .01$) for women with adequate responses compared with women with inadequate responses within each active treatment group. Mean circulating FSH levels were similar in women with or without adequate responses to active therapy.

Among 333 women in the study, 280 (84%) completed it. Adverse events was the most frequent reason given for discontinuation. The number of women who discontinued because of adverse events tended to increase with increased dosage of 17β-E2: five women given placebo (8%), one woman given 0.25 mg (1%), three women given 0.5 mg (5%), six women given 1 mg (9%), and 11 women given 2 mg (16%). Although there were no significant differences between treatment groups, twice as many women in the 2-mg group discontinued treatment because of adverse events than in the placebo group. The difference was primarily attributed to rate of discontinuation because of bleeding, which was significantly higher ($P < .05$) with 2 mg than with placebo or any of lower 17β-E2 dosages: all 11 women who discontinued from the 2-mg group because of adverse events did so because of bleeding, whereas that was only the case for 3, 1, 0, and 3 women in the placebo, 0.25-, 0.5-, and 1-mg groups, respectively.

Bleeding and breast pain were the most frequently reported adverse events, with no significant differences between treatment groups. Bleeding was noted by 14% of women in the placebo group, 10% in the 0.25-mg group, 6% in the 0.5-mg group, 21% in the 1-mg group, and 37% in the 2-mg group. Breast pain was reported by 12% of women treated with 2 mg, but only by 3–6% of women who received placebo or 17β-E2 in the 0.25–1-mg groups.

Discussion

Studies have documented the efficacy of 1 and 2 mg 17β-E2 for alleviating vasomotor symptoms. However, the efficacy of lower 17β-E2 doses for reducing moderate and severe symptoms in menopausal women has

Table 2. Estradiol, Estrone, Estrone Sulfate, and FSH Levels (Median and Interquartile Range)

	Placebo	E2 0.25 mg	E2 0.5 mg	E2 1 mg	E2 2 mg
Estradiol (pg/mL)					
All subjects	6 (4; 13)	20 (11; 25)	33 (18; 45)	49 (32; 82)	97 (67; 144)
Inadequate response	6 (4; 10)	17 (11; 23)	33 (18; 40)	35 (27; 39)	67 (23; 112)
Adequate response	6 (4; 22)	23 (19; 61)	37 (28; 67)	60 (38; 89)	103 (70; 143)
Estrone (pg/mL)					
All subjects	27 (21; 35)	70 (51; 87)	119 (76; 178)	202 (153; 356)	546 (283; 793)
Inadequate response	27 (21; 32)	69 (50; 86)	123 (76; 142)	165 (126; 226)	431 (91; 793)
Adequate response	28 (21; 34)	85 (62; 121)	125 (76; 231)	243 (168; 412)	589 (329; 813)
Estrone sulfate (pg/mL)					
All subjects	343 (216; 522)	1601 (956; 2367)	3284 (1815; 5144)	5439 (3375; 10,372)	10,091 (7060; 15,426)
Inadequate response	356 (214; 531)	1582 (969; 2184)	3386 (2244; 5144)	4950 (2570; 7116)	7780 (1638; 8126)
Adequate response	316 (206; 350)	2512 (1222; 4180)	3402 (1938; 6219)	6323 (4451; 13,268)	10,372 (7370; 15,386)
FSH (IU/L)					
All subjects	73 (63; 96)	66 (49; 83)	61 (50; 77)	52 (40; 77)	38 (28; 52)
Inadequate response	79 (65; 100)	69 (57; 83)	63 (51; 76)	55 (45; 69)	44 (34; 68)
Adequate response	75 (64; 96)	49 (42; 65)	56 (50; 73)	52 (38; 77)	38 (28; 51)

E2 = 17β-estradiol.

not been evaluated. The present study found that reduction in vasomotor symptoms with 17β-E2 dosage ranging from 0.25 to 2 mg followed a linear dose-response curve. Dosage of 1 and 2 mg rapidly alleviated the number and severity of hot flushes in highly symptomatic women, whereas lower doses of 17β-E2 (0.25 mg) were not effective or required more time (0.5 mg) to significantly reduce symptoms. It appears that 1 and 2 mg 17β-E2 rapidly and extensively relieved vasomotor symptoms and were adequate for most women. That conclusion was similar to one reported in a small placebo-controlled study, in which oral micronized 1 and 2 mg 17β-E2 similarly reduced vasomotor symptoms (91% and 92% reductions in daily frequency of vasomotor events after 12 weeks of therapy, respectively), suggesting that both doses were efficacious.[3] Lower doses of oral 17β-E2 and therapies associated with low levels of circulating E2 have been efficacious in preserving bone in elderly women and younger women.[6,7] However, our study suggests that lower dosages do not appear to adequately relieve symptoms or there is a lag before effects are noticed.

The high placebo response in this study was similar to those in other studies.[3,8] We observed an approximate reduction of half in number of moderate to severe hot flushes and the hot flush weekly weighted scores in the placebo group. By the end of the study, nearly a quarter of the women in the placebo group reported an almost complete reduction of vasomotor symptoms. The large reduction of symptoms in women who received placebo could be explained by sporadic episodes of release of endogenous E2. However, when evaluating the placebo group in this study, we did not find higher levels of E2 in women who had achieved adequate responses at the end of the study compared with those with inadequate responses. We also investigated whether there was a certain circulating level of hormones above which most women in the active treatment groups achieved adequate symptom relief. Although women with adequate responses had higher levels of E2 and its metabolites compared with women with inadequate responses, there was a great overlap of values. We were unable to show that individual circulating levels of E2, E1, E1 sulfate, or FSH were good predictors of who would respond satisfactorily to treatment, or for level of symptom relief. These data suggest that monitoring serum hormone levels is probably less useful than observing women's own perceptions of symptom improvement.

17β-E2 dosage that can provide the established clinical benefits of estrogen while minimizing incidence of adverse events would be expected to maximize treatment adherence. The incidence of frequently reported adverse events associated with estrogen therapy, such as breast tenderness and vaginal bleeding, are believed to be somewhat dose dependent.[3] Therefore, lowering the dose of 17β-E2 should have better tolerability. In this study, the 1- and 2-mg dosages were efficacious, but tolerability differed. We found that discontinuations because of adverse events increased with increasing dosage of 17β-E2, and that the 2-mg group had an adverse event discontinuation rate double that of the placebo group. All dosage of 17β-E2 below 2 mg appeared well tolerated, with discontinuations because of adverse events similar or lower than the placebo group. Similar findings were reported of higher incidence of adverse events during treatment with 2 mg 17β-E2 compared with 1 mg or placebo.[3]

Although individualization of therapy according to each woman's needs is encouraged during treatment,

our data suggest that oral micronized 1 mg 17β-E2 is the most useful starting dose for treating moderate and severe vasomotor symptoms in menopausal women. Lower doses require more time (0.5 mg) or are ineffective (0.25 mg) for symptom relief in women who present with moderate and severe hot flushes. A higher dose of 2 mg is effective for symptom relief, but is associated with increased estrogen-related adverse events and higher discontinuation rates, and should be indicated only for women who do not have adequate symptom relief with lower doses. Further studies are needed to establish the effect on vasomotor symptom relief and tolerability when a progestogen is added to these doses of micronized 17β-E2.

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