ORIGINAL ARTICLE

Efficacy of Estradiol for the Treatment of Depressive Disorders in Perimenopausal Women

A Double-blind, Randomized, Placebo-Controlled Trial

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Background: Results of previous studies suggest that estrogen improves somatic and mild depressive symptoms experienced by perimenopausal women. This study investigated the efficacy of 17β-estradiol for the treatment of clinically significant depressive disorders in endocrinologically confirmed perimenopausal women.

Methods: Perimenopausal women (aged 40-55 years, with irregular menstrual periods and serum concentrations of follicle-stimulating hormone >25 IU/L), meeting criteria for major depressive disorder, dysthymic disorder, or minor depressive disorder, according to *DSM-IV*, were randomized to receive transdermal patches of 17β-estradiol (100 µg) or placebo in a 12-week, double-blind, placebo-controlled study. A 4-week washout period followed the 12-week treatment phase. Outcome measures were the Montgomery-Åsberg Depression Rating Scale and Blatt-Kupperman Menopausal Index scores.

Results: Fifty women were enrolled in the study; 26 met *DSM-IV* criteria for major depressive disorder, 11 for dysthymic disorder, and 13 for minor depressive disorder. Remission of depression was observed in 17 (68%) women treated with 17β-estradiol compared with 5 (20%) in the placebo group (P = .001). Subjects responded similarly to estradiol treatment, regardless of *DSM-IV* diagnosis. Patients treated with estradiol sustained antidepressant benefit of treatment after the 4-week washout period, although somatic complaints increased in frequency and intensity. Treatment was well tolerated and adverse events were rare in both groups.

Conclusion: Transdermal estradiol replacement is an effective treatment of depression for perimenopausal women.

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DEPRESSIVE symptoms are common during the transition to menopause.[1-3] Cross-sectional surveys describe high rates of depressive symptoms among women treated in menopause clinics.[4,5] We recently reported depressive disorders (major depressive disorder [MDD], dysthymic disorder, and minor depressive disorder) in 30 of 101 endocrinologically confirmed perimenopausal women attending a gynecological clinic.[6,7] Unlike clinic-based surveys, community-based studies found that perimenopause may be a period of risk for mood disturbance for some women but does not necessarily represent a time of risk for major depression.[8-10]

The use of estrogen replacement for the treatment of menopausal symptoms has been shown to enhance "psychological well-being."[11] However, clinical studies using diverse forms of estrogen replacement for the treatment of depression produced mixed results. Three estrogen treatment studies in perimenopausal and newly postmenopausal women failed to demonstrate superiority over placebo for the treatment of mood symptoms.[12-14] In contrast, 2 double-blind, placebo-controlled studies using transdermal patches of 17β-estradiol[15,16] and case series in which patients were treated with sublingual estradiol[17] suggested that estrogen improves mood in women with postpartum depression and severe premenstrual syndrome.

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More recently, Schmidt and colleagues[18] described that perimenopausal women with major (n=8) or minor depression (n=26) with or without hot flushes experience greater relief of depressive symptoms with estrogen than with placebo. However, data confirming these preliminary findings are lacking, particularly in a larger group of perimenopausal women with major depression.

The present study was designed to determine the efficacy of 17β-estradiol for the treatment of depressive disorders in endocrinologically confirmed perimenopausal women. Based on the results of previous reports,[15,16] we hypothesized that the use of transdermal 17β-estradiol would have a greater antidepressant benefit than placebo.

PATIENTS AND METHODS

PATIENTS

Subjects were recruited from a sample of 176 consecutive patients seeking care at the gynecological clinic ("menopause clinic") at the Pérola Byington Hospital–Brazil (n=101) and the psychiatric outpatient service for women at the Institute of Psychiatry of the University of São Paulo (n=75) between October 1996 and June 1998. Patients seen at both medical centers were self-referred or referred by other physicians. Prior to study entry, all women participated in a 2- to 4-week screening phase (2-4 visits), during which their mood and perimenopausal somatic symptoms were assessed and serum levels of follicle-stimulating hormone (FSH) and estradiol were obtained. Subjects with menses during the screening period had hormone levels measured in the early follicular phase (days 2-5) of the menstrual cycle. Those who presented with more prolonged periods of amenorrhea had blood drawn at the last screening visit.

The entry criteria for the study included (1) age between 40 and 55 years; (2) history of menstrual cycle irregularity or amenorrhea for less than 12 months; (3) serum level of FSH greater than 25 IU/L (to document the gonadotropins' attempt to stimulate the declining ovarian function and, therefore, to confirm the perimenopausal status as the cause of menstrual irregularities); and (4) diagnoses of MDD, dysthymic disorder, or minor depressive disorder, according to *DSM-IV*.[19] Diagnostic assessments were performed by the study psychiatrist (C.d.N.S.) using a clinician-administered diagnostic instrument (Primary Care Evaluation of Mental Disorders [PRIME-MD] questionnaire,[20] supplemented by the specific module of PRIME-MD for Mood Disorders). Exclusion criteria included medical illness (assessed by general practitioners or gynecologists at the study entry), use of hormone replacement therapy and/or psychoactive drugs in the 3 months prior to assessment, contraindication to estrogen therapy, and presence of psychotic features, suicidality, or severe aggressive behavior. The Hospital das Clinicas ethics review board approved the research protocol and written informed consent was obtained from all participants.

MEASURES

The following 2 outcome measures were used: (1) Montgomery-Åsberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale designed to assess the severity of depressive symptoms[21]; and (2) the 12-item version (0-3 scale) of the Blatt-Kupperman Menopausal Index (BKMI),[22] which was used to quantify the severity of perimenopausal somatic symptoms, particularly hot flushes and night sweats, as well as joint pains, headache, vertigo, and sleep disturbance. We also examined the severity of vasomotor symptoms (hot flushes and night sweats—items 1 and 2 from the BKMI, respectively) separately. Hot flushes and night sweats were considered significant if scores were greater than 4 on a 0 to 12 subscale and greater than 2 on a 0 to 6 subscale, respectively.

Improvement of depression was determined by end-of-treatment MADRS scores. Full remission was achieved if the end-of-treatment MADRS score was less than 10.[23] Decline of 50% or more on baseline BKMI scores was considered indicative of significant improvement of somatic symptoms.

PROCEDURES

The clinical trial comprised 2 phases. Phase 1 was a double-blind, randomized study comparing the efficacy of 100 µg of transdermal 17β-estradiol with placebo. The randomization scheme was externally controlled and based on a list of random numbers generated by computer. Of 176 subjects initially screened for the study, 71 (40.3%) met criteria for *DSM-IV* depressive disorders and for perimenopause. Eight patients were excluded due to the presence of psychotic symptoms (n=3), aggressive behavior (n=2), significant suicidal thoughts (n=1), and history of bipolar disorder with sporadic use of mood stabilizers (n=2). In addition, 13 subjects declined enrollment in the clinical trial and/or did not attend all screening visits. Thus, 50 patients (25 per arm) were randomly assigned to treatment with either patches of 100 µg of 17β-estradiol (Systen/Evorel; Janssen-Cilag Laboratories, São Paulo, Brazil) or identical placebo patches for 12 weeks (phase 1). During phase 1, subjects were evaluated every 4 weeks when depressive symptoms (MADRS scores) and somatic symptoms (BKMI scores) were reassessed. After phase 1, subjects underwent a 4-week washout period and were then reassessed. The evaluation after the washout period was aimed to examine differences between the course of depressive and somatic symptoms after treatment discontinuation. Measurements of serum levels of FSH and estradiol were repeated at week 12.

To avoid compromising the double-blind design, the occurrence of menstrual bleeding (spontaneous cycling and/or bleeding secondary to estrogen use/withdrawal) was recorded by an independent gynecologist. The study psychiatrist remained unaware of these events. In addition, at the study entry, subjects were informed that menstrual bleeding could occur regardless of the type of treatment received.

Forty-five (90%) of the 50 randomized subjects completed 12 weeks of treatment (phase 1). Four subjects randomized to placebo patches dropped out of the study due to patch-related skin irritation (n=1), "poor response" (n=2), and nausea (n=1). One subject treated with estradiol dropped out because of adverse effects (headaches and nausea). Two additional subjects (1 from each arm) dropped out during the washout period due to increased depressive symptoms.

STATISTICAL ANALYSIS

Data were analyzed with the SPSS statistical software.[24] Frequencies of categorical data were analyzed using the Pearson χ^2 test or Fisher exact test, when appropriate. The independent *t* test (2-tailed) was used for between-group comparisons. A paired *t* test (2-tailed) was used for within-group comparisons. A preliminary exploratory study showed that the data were fit for parametric procedures. Of note, nonparametric analyses (Mann-Whitney and Wilcoxon paired rank tests) produced similar results (data not shown). All efficacy results reported are on an intent-to-treat basis in which the last observation was carried forward into all subsequent time points for patients who dropped out before the end of the study. Statistical significance was set at the $\alpha = .05$ level. Data are presented as mean±SD.

Table 1. Subject Characteristics*

Characteristics	Estradiol Group (n = 25)	Placebo Group (n = 25)	Test Statistic†	P
Age, y	49.3 ± 3.8	50.3 ± 3.4	$t = 0.97$	.34†
Age at menarche, y	13.0 ± 1.7	12.5 ± 1.3	$t = -1.21$	.23†
Duration of amenorrhea, d	165.0 ± 123.0	137.0 ± 133.0	$t = -7.77$	.44†
Marital status				
Never married	2 (8)	2 (8)		
Married	10 (40)	17 (68)	$\chi^2 = 4.39$	.11
Divorced or widowed	13 (52)	6 (24)		
Education				
≤High school	21 (84)	16 (64)	$\chi^2 = 2.60$	.10
>High school	4 (16)	9 (36)		
Employed outside home	12 (48)	10 (40)	$\chi^2 = 0.32$	.87
History of successful pregnancies (≥1)	24 (96)	23 (92)	. . .	>.99‡
History of previous psychiatric symptoms	13 (52)	14 (56)	$\chi^2 = 0.81$	.78
History of puerperal mood changes	8 (32)	9 (36)	$\chi^2 = 0.09$	.76
Previous use of antidepressants, ever	4 (16)	3 (12)	. . .	>.99‡
Current depressive disorder				
Major depressive disorder	15 (60)	11 (44)		
Dysthymic disorder	4 (16)	7 (28)	$\chi^2 = 1.51$	.47
Minor depressive disorder	6 (24)	7 (28)		

*Data are given as mean ± SD or number (percentage) of subjects.
†Independent t test (2-sided) (df = 48); Pearson χ^2 test (df = 1, except for marital status [df = 2] and current depressive diagnoses [df = 2]).
‡Fisher exact test.

RESULTS

SAMPLE CHARACTERISTICS

Of 50 perimenopausal women with depression enrolled in the study, 36 (72%) reported that they originally had sought medical care due to menopause-related somatic symptoms. Twenty-six women (52%) met *DSM-IV* criteria for MDD, 11 (22%) for dysthymic disorder, and 13 (26%) for minor depressive disorder. More than half (14 [54%] of 26) of the women with MDD reported that the index episode was their first experience of depression. Characteristics of the 2 treatment groups are summarized in **Table 1**. There were no significant differences between the 2 groups with respect to demographic characteristics (age, marital status, education, employment), reproductive history (age at menarche, history of pregnancy, duration of amenorrhea), current *DSM-IV* diagnosis, or previous psychiatric history (as assessed by the study psychiatrist in a nonstandardized investigation of previous mood, anxiety, psychotic, or substance abuse episodes).

MOOD AND SOMATIC SYMPTOMS

Both groups (estradiol and placebo) had 21 (84%) of 25 subjects with moderate-to-severe depression (MADRS >17) at baseline. Subjects randomly assigned to estradiol had higher mean MADRS scores (24.60±6.69; range, 14-38) than those assigned to the placebo group (21.84±4.43; range, 14-30; $t = -2.47$, $P = .02$).

No significant differences between the 2 groups were observed with respect to the prevalence of menopausal somatic symptoms (BKMI scores, **Table 2**), particularly the prevalence of moderate-to-severe hot flushes (estradiol group, 64%, vs placebo group, 56%; $\chi^2 = 0.33$, $P = .56$) and night sweats (36% vs 32%, respectively; $\chi^2 = 0.09$, $P = .76$).

HORMONE LEVELS

No difference was observed between mean estradiol levels at baseline (estradiol group = 44.03±2.88 pmol/L [12±0.8 pg/mL]; placebo group = 52.01±8.59 pmol/L [14±2.3 pg/mL]; $t = 0.69$, $P = .48$). Mean serum FSH levels obtained at study entry were significantly higher in patients randomly assigned to receive 17β-estradiol (58.08±21.03 IU/L) compared with those having placebo (43.00±20.01 IU/L) ($t = -2.59$; $P = .01$). When the analysis was limited to subjects whose hormonal assessment was obtained during the early follicular phase of the menstrual cycle (estradiol group, n=12; placebo group, n=17), there were no significant differences between estradiol and placebo groups, with respect to mean levels of FSH (48.33±15.88 IU/L vs 37.49±18.14 IU/L, respectively; $t = -1.66$, $P = .11$) or estradiol (59.58±15.06 pmol/L [16±4.1 pg/mL] vs 45.21±6.9 pmol/L [12±1.9 pg/mL], respectively; $t = -0.97$, $P = .34$) at baseline.

OUTCOME ASSESSMENTS

Phase 1

Effect of 17β-Estradiol on Mood. The end-of-treatment mean MADRS scores among women treated with estradiol were significantly lower than the mean MADRS scores in the placebo group (8.60±5.02 vs 16.84±5.12, respectively; $t = 5.28$, $P<.001$). The MADRS scores decreased significantly more from baseline in the estradiol group (–16.36±8.04) than in the placebo group (–4.16±5.09; $t = -6.41$, $P<.001$).

Remission of depression (week 12, MADRS score <10) was observed in 17 (68%) of 25 subjects treated with estradiol during 12 weeks compared with 5 (20%) of 25 women who received placebo ($\chi^2 = 11.69$, $P = .001$). The efficacy of estradiol treatment was similar across

Table 2. Depressive Symptoms (MADRS Scores) and Perimenopausal Symptoms (BKMI Scores) in Women Who Received Estradiol or Placebo for 12 Weeks, and After 4 Weeks of Washout (Week 16): Intent-to-Treat Analysis*

Group	Baseline	Week 4	Week 8	Week 12	Week 16 (After Washout)
			MADRS Scores		
Estradiol	24.60 ± 6.69	16.04 ± 4.83	12.32 ± 4.71	8.60 ± 5.02†	12.24 ± 5.31‡§
Placebo	21.84 ± 4.43	18.12 ± 5.49	17.44 ± 5.55	16.34 ± 6.29†	19.36 ± 5.12‡‖
Estradiol vs placebo (independent *t* test)	*P* = .02	. . .	. . .	*P*<.01	*P*<.01
			BKMI Scores		
Estradiol	29.56 ± 7.94	17.20 ± 9.07	13.34 ± 7.78	10.60 ± 6.76†	24.25 ± 8.50‡§
Placebo	25.84 ± 9.42	20.48 ± 10.81	19.96 ± 11.40	19.08 ± 9.88†	22.21 ± 10.51‖
Estradiol vs placebo (independent *t* test)	*P* = .14	. . .	. . .	*P*<.01	*P* = .44

**Data are given as mean ± SD. N = 25 for both groups. MADRS indicates Montgomery-Åsberg Depression Rating Scale; BKMI, Blatt-Kupperman Menopausal Index.*

†Within-group results (paired t test): baseline vs week 12, P<*.05.*

‡Within-group results (paired t test): week 12 vs week 16 (postwashout); P<*.05.*

§Within-group results (paired t test): baseline vs week 16 (postwashout); P<*.05.*

‖Within-group results (paired t test): nonsignificant differences.

DSM-IV diagnostic subgroups; remission of depression was observed in 12 of 26 subjects with MDD, 6 of 11 subjects with dysthymic disorder, and 5 of 13 subjects with minor depressive disorder (χ^2=0.62, *P*=.73).

There was no statistical association between response to treatment (remission of depression) and recruitment site, sociodemographic variables, reproductive history, psychiatric history, severity of depression, or hormonal conditions at baseline (*P*>.05 for all comparisons; χ^2 tests).

Effect of 17β-Estradiol on Somatic Symptoms. As shown in Table 2, at the end of 12 weeks of treatment, women who received estradiol had a significant decrease in their BKMI scores compared with their baseline scores (*P*< .001) and lower BKMI scores compared with women treated with placebo (*P*<.01). A greater than 50% decrease in mean BKMI scores occurred in 17 (68%) of 25 subjects treated with estradiol compared with 7 (28%) of 25 who received placebo (χ^2=8.11, *P*=.005). When we analyzed vasomotor symptoms separately, only 1 (4%) of 25 subjects who received estradiol was still reporting significant hot flushes at week 12 compared with 9 (36%) of 25 treated with placebo (χ^2=8.0, *P*=.005). No patients treated with estradiol reported moderate-to-severe night sweats, whereas 5 (20%) of 25 of those who received placebo still had these symptoms (Fisher exact test, *P*=.05).

Hormone Levels. As expected, mean serum levels of estradiol obtained during the last week of phase 1 (week 12) were significantly higher (256.57±57.52 pmol/L [70±15.6 pg/mL]) than those obtained at baseline in subjects treated with 17β-estradiol (*t*=–4.05, *P*<.001). In contrast, there were no significant changes (*t*=–1.48, *P*=.15) in the placebo group (end-of-treatment mean estradiol level, 85.52±20.12 pmol/L [23±5.5 pg/mL]). There was a significant difference in end-of-treatment mean estradiol levels between the 2 treatment groups (*P*<.001).

Adverse Events. Adverse events were spontaneously reported by 8 (32%) of 25 subjects receiving estradiol and 9 (36%) of 25 patients receiving placebo. With the exception of the 2 placebo dropouts (1 due to skin irritation and 1 due to nausea) and 1 estradiol-treated dropout (due to headaches and nausea) mentioned previously, most adverse events were considered mild and well tolerated and included local skin irritation (10%; 2 placebo and 3 estradiol), breast tenderness (12%; 2 placebo and 4 estradiol), headaches (6%; 3 placebo), and nausea (6%; 2 placebo and 1 estradiol). Spontaneous bleeding was reported by 4 (16%) of 25 subjects receiving estradiol and by 2 (8%) of 25 subjects receiving placebo, during the treatment phase (12 weeks).

Washout Period

The estradiol group showed a significant (*P*<.01) and the placebo group similar (*P*=.30) increases in MADRS scores 4 weeks after treatment was discontinued (estradiol group, +3.64±3.82; placebo group, +2.52±3.74). At week 16, subjects previously treated with estradiol still showed mean MADRS scores significantly lower (12.24±5.31) than those obtained at baseline (24.60±6.69) (*t*=8.15, *P*<.001). In contrast, patients who discontinued placebo reported mean MADRS scores (19.36±5.12) almost as severe as those observed at baseline (21.84±4.43) (*t*=1.92, *P*=.07) and significantly higher compared with subjects who discontinued estradiol treatment (*t*=5.03, *P*<.001).

When the analysis was limited to patients who had shown remission of depression at week 12, we observed that 10 (59%) of 17 subjects treated with estradiol remained well after treatment discontinuation, whereas none of the 5 subjects who previously responded to placebo sustained MADRS scores less than 10 (Fisher exact test, *P*=.04). Of note, sustained remission of depression was observed similarly across *DSM-IV* diagnoses (χ^2=1.72, *P*=.42).

With respect to somatic symptoms, subjects who discontinued estradiol treatment showed a significant increase in mean BKMI scores (+13.12±9.89; *t*=4.44, *P*<.001), whereas women who discontinued placebo patches had a nonsignificant increase in their mean BKMI scores (+2.36±6.99) (*t*=–1.69, *P*=.10). Seven of 10 subjects who discontinued estradiol treatment and remained well (MADRS <10) reported moderate-to-severe hot flushes.

COMMENT

The results of this study indicate that estradiol is an effective antidepressant treatment for women in perimenopause. Previous reports had already shown that estrogen replacement therapy improves menopausal somatic symptoms, subjective well-being, and quality of life during perimenopause.[11,12,25] Recently, in a 6-week study, Schmidt and colleagues[18] found that the use of 50 µg of 17β-estradiol improves mood in perimenopausal women who meet standardized criteria for major and minor depression. Our results support these findings, as estradiol improved mood in subjects with depressive disorders. Estradiol therapy was efficacious in treating depressive symptoms in a larger sample of women who met criteria for MDD (n=26)—67% of those receiving estradiol had full remission of depression. In addition, we were able to demonstrate the occurrence of continued mood improvement throughout the 12-week treatment phase (decreasing MADRS scores consecutively observed at weeks 4, 8, and 12). Our findings obtained with 100 µg of estradiol contrast with the aforementioned study,[18] which used a lower dose of estradiol, and in which increasing improvement in mood occurred only during the first 3 weeks of treatment.

The present investigation focused on treatment of endocrinologically confirmed perimenopausal women with depression. Reproductive endocrine criteria were used to obtain a relatively homogeneous group with respect to endocrine status[26] and to exclude women with other causes of irregular menstrual cycles and amenorrhea (eg, polycystic ovarian syndrome, hypothalamic amenorrhea). Previous investigations of the antidepressant effect of estrogen in perimenopausal women have been confounded by multiple factors, including the heterogeneity of methods to define and assess menopausal and hormonal status, lack of standardized diagnostic and outcome measures, differences in hormone preparations, and a wide range of doses and methods of administration.[1,26,27]

In the present study, we opted for using transdermal 17β-estradiol because of its demonstrated safety and efficacy.[16,17] Other estrogen trials that failed to detect an antidepressant efficacy in comparison with placebo used either oral preparations of conjugated equine estrogen[28,29] or estropipate.[30] Existing data suggest that the transdermal administration of estradiol (matrix-type system) to postmenopausal women provides a rapid rise in the serum concentration of estradiol and nearly constant serum levels (ie, constant estradiol-estrone ratios) over the entire application period.[31,32] Oral administration, on the other hand, results in highly variable serum levels of estradiol, and lower bioavailability compared with estrone.[33] It is unclear, however, whether a more constant estradiol level could be expected in our sample, which consists exclusively of perimenopausal women, given the endogenous hormone fluctuation this subpopulation may exhibit and the lack of serial hormone measures in our study.

Some authors have suggested that relief of vasomotor symptoms associated with estradiol treatment risks unblinding clinical trials designed to evaluate the efficacy of estradiol for the treatment of perimenopausal depression.[27] Others have speculated that the capacity of estrogen to improve mood is secondary to the relief of menopausal symptoms (nocturnal hot flushes and sleep disturbance).[1,13] However, Schmidt and colleagues[18] demonstrated that estradiol reduces symptoms of depression in perimenopausal women who do not have hot flushes. This reinforces the concept that the effects of estrogen on mood and vasomotor symptoms may be independent. Recently, Bloch and colleagues[34] examined the effects of gonadal steroids in 16 euthymic women aged 22 to 45 years (half of whom had a history of postpartum depression) by simulating hormonal conditions related to pregnancy and parturition. Women with a history of postpartum depression (but not the comparison group) showed increased mood symptoms during the hypogonadal phase, produced by the administration of a gonadotropin-releasing hormone analog (leuprolide acetate). More important, the emergence of mood symptoms during the hormone withdrawal phase preceded the occurrence of hot flushes.

Our findings also suggest independent effects of estrogen on mood and vasomotor symptoms. Specifically, we observed a sustained antidepressant benefit after discontinuation of estradiol treatment despite recrudescence of somatic symptoms. Seven of 10 patients who remained well (MADRS <10) after estradiol discontinuation reported reemergence of moderate-to-severe hot flushes.

The good treatment tolerability, scarcity of significant adverse events, and placebo response rates observed in our study are consistent with previous reports using transdermal matrix patches of estradiol.[18,35,36]

Although mounting evidence indicates that estrogen influences neuronal function via serotonergic-, noradrenergic-, dopaminergic-, and γ-aminobutyric–mediated systems,[37-39] a mechanism by which estradiol may have an antidepressant effect remains unclear.

Our investigation has some methodological limitations. First, subjects were recruited from 2 specialized outpatient services and presented with different types of depressive disorder and menopause-related physical symptoms. It is unclear how well this relatively small sample represents the population of perimenopausal women with depression living in the community and/or seeking treatment for mood symptoms. The recruitment of subjects with depression who primarily sought treatment for physical symptoms in a gynecological outpatient clinic appears to be appropriate and consistent with previous reports showing that depressive disorders are frequently encountered in medical care settings.[40,41] In addition, their first appearance may be dominated by the physical symptoms of the syndrome, and minor depressive episodes are particularly common.[24,42]

The second limitation that might be considered is the maintenance of the double-blind design. We attempted to maintain the blind by keeping the psychiatric rater unaware of possible adverse events associated with drug assignment—6 women had bleeding episodes during the trial (2 of whom were treated with placebo) and another 6 during the washout period (all treated with estradiol). We also estimated the degree to which the blind was maintained by asking the subjects and the psychiatric rater to guess to which group the patient was assigned. Twelve (57%) of the 21 subjects treated with placebo and 12 (50%) of 24 women who received estradiol guessed their treatment correctly, while the psychia-

trist rater correctly identified the treatment assignment for 64.5% of placebo-treated women and 62.5% of estradiol-treated women. Although we acknowledge that the blinding of placebo-controlled trials of estradiol is problematic, the assessment of blindness in this case suggested that it was acceptable.[43]

To date, this is the largest study examining the impact of estradiol on MDD. The results of this investigation indicate that transdermal estradiol has a clinically significant antidepressant effect in perimenopausal women. This finding may support a potential role of estrogen replacement therapy for the treatment of perimenopausal mood disturbance, complementing other established benefits of this compound. Larger clinical trials, which use a longer treatment follow-up and evaluate the potential alteration of antidepressant benefit with concomitant progesterone, are needed. Further investigation also will be crucial to delineate the putative role for estrogen in other subgroups of patients who have a spectrum of depressive illnesses.

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