

Estrogen Replacement Therapy in the Treatment of Major Depressive Disorder in Perimenopausal Women

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Background: Increased vulnerability to mood disorders has been reported during perimenopause. Fluctuating estrogen levels accompany the perimenopausal transition. Thus, estrogen replacement therapy (ERT) has been proposed as a potentially effective treatment for mood disorders occurring during perimenopause. **Method:** We examined the efficacy of ERT in the treatment of depression in 16 perimenopausal women with DSM-IV–defined major depressive disorder who were participating in the Mood Disorders Research Program at the Department of Psychiatry of the University of California, Los Angeles. Ten antidepressant- and ERT-naïve women received ERT alone. Six women who were nonresponders or partial responders to an antidepressant received ERT in addition to existing treatment with fluoxetine. The Hamilton Rating Scale for Depression (HAM-D) was administered to all patients at baseline and weekly thereafter during the 8-week open-protocol trial. Partial response was operationalized as a final HAM-D score $\leq 50\%$ of the baseline score. Remission was defined as a final HAM-D score ≤ 7 . **Results:** All patients exhibited clinical improvement as measured by HAM-D scores after the first week of treatment. Of the 10 perimenopausal depressed women receiving ERT alone, 6 remitted, 3 partially responded to treatment, and 1 did not respond by the end of the trial. Of the 6 women receiving antidepressant treatment with ERT, 1 patient remitted and 5 had a partial response by the end of the trial. **Conclusion:** This small study suggests that for some antidepressant-naïve perimenopausal women with clinical depression, ERT may have antidepressant efficacy. In depressed women who have minimal response to a selective serotonin reuptake inhibitor, ERT may augment response. Further controlled trials are needed. (J Clin Psychiatry 2002;63[suppl 7]:45–48)

An increased vulnerability to mood disorders has been reported in women during perimenopause.^{1,2} Perimenopause is the time of transition from regular ovarian cyclicity to complete cessation of menstruation. It has been defined as irregular menses or absence of menses (amenorrhea) for fewer than 12 months. An absence of menses for 12 or more months denotes postmenopause. Several epidemiologic studies have demonstrated an increased frequency of depressive symptoms during the perimenopausal and postmenopausal periods, although neither period has been associated consistently with depression.^{3,4}

The role of estrogen replacement therapy (ERT) in the treatment of depression has been suggested by animal

studies. Considerable evidence from basic research has shown that estrogen modulates neurotransmission at multiple points in the serotonin (5-HT) pathway.^{5,6} The 5-HT system is known to contribute to the regulation of behavior and mood, especially in mood disorders.^{7–9} Estrogen is thought to down-regulate 5-HT₂ receptors, increase the release of endogenous catecholamines from the hypothalamus, and inhibit monoamine oxidase.¹⁰ In animal studies, 5-HT levels rise through the estrogen displacement of the 5-HT precursor tryptophan from albumin,¹¹ and estrogen has been shown to increase the number of sites available for active transport of 5-HT into brain cells.¹²

Few investigations have assessed the use of ERT in the perimenopausal-specific population. One recent double-blind study¹ evaluated the efficacy of estradiol in the treatment of major depression (Structured Clinical Interview for DSM-III, Revised) and minor depression (Schedule for Affective Disorders and Schizophrenia-Lifetime Version) in perimenopausal women. Significantly decreased mood rating scores were reported after 3 weeks of ERT compared with baseline scores and compared with a placebo-controlled group.

The potential efficacy of estrogen as an augmenting agent for perimenopausal women with a partial response to standard antidepressant therapy has not been studied. A review of the literature on the use of adjunctive ERT for

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postmenopausal women reveals mixed results. One study⁸ found that antidepressant response is facilitated by estrogen, while another¹³ found no improvement in treatment response.

In this article, we present results from an ongoing prospective study evaluating the effects of ERT in the treatment of clinical depression in perimenopausal women with major depressive disorder. The purpose of this study was to assess the effects of ERT in the treatment of clinical depression in perimenopausal women (1) as a single treatment agent and (2) as an adjunct in the treatment of women who are nonresponders or partial responders to selective serotonin reuptake inhibitors (SSRIs).

METHOD

Patients

Female subjects with depressive symptoms were recruited through flyers, Los Angeles-area newspaper advertisements, or the Mood Disorders Clinic at the University of California, Los Angeles (UCLA). Thirty-one women presented for evaluation. The mean \pm SD age of the patients was 46.7 ± 3.3 years (range, 40–55 years). The mean number of years of education was 15.0 ± 3.1 (range, 12–20). The average socioeconomic level of the patients was middle class. The patient sample was 87.50% white (N = 14), 6.25% African American (N = 1), and 6.25% Asian American (N = 1). Twenty-five percent of the patients (N = 4) were married, 25% (N = 4) were single, 37.5% (N = 6) were divorced, and 6.25% (N = 1) had been widowed (demographic data were incomplete for 1 patient).

Inclusion/Exclusion Criteria

Patients were required to (1) have irregular menstrual periods or an absence of menstrual periods for less than 1 year, with plasma levels of follicle-stimulating hormone greater than 20 IU/L; (2) have discontinued ERT at least 12 weeks prior to enrollment (if applicable); and (3) have had mammogram, physical examination, and pelvic examination results within normal range within 6 months of their entrance into the study. Patients were excluded from the study if they (1) were suffering from a medical illness, e.g., cardiac disease, diabetes, renal or liver disease, clotting disorders, breast cancer, obesity, or current abnormal uterine bleeding; (2) had a history of drug or alcohol abuse or a psychiatric disorder other than a depressive disorder; or (3) were taking any hormonal medications (prednisone, insulin, or ovarian sex steroids).

Entry Diagnosis and Assessment of Depression

The diagnosis of unipolar major depressive disorder was made on the basis of the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P),¹⁴ which was administered at the initial visit. SCID-I/P interviewers were trained by a senior SCID trainer from

the Diagnosis and Psychopathology Unit of the UCLA Research Center for Treatment and Rehabilitation of Psychosis using a combination of videotapes and individualized instruction.¹⁵ SCID-I/P interviewers were required to achieve a minimum overall kappa of 0.75 (minimum kappa sensitivity = 0.75 and specificity = 0.75) on symptom agreement and 90% accuracy of agreement on major Axis I diagnosis. Patients were excluded if diagnosed with any other major Axis I psychiatric diagnoses, current or in remission. The 28-item Hamilton Rating Scale for Depression (HAM-D)¹⁶ was administered at the initial visit and weekly thereafter to all patients. An initial score of 18 or above on the 21-item HAM-D at the first visit was required for entry into the study. In patients who had received fluoxetine treatment for at least 8 weeks prior to screening, a score of 14 or above was required, as this was considered a nonremission response to an antidepressant.

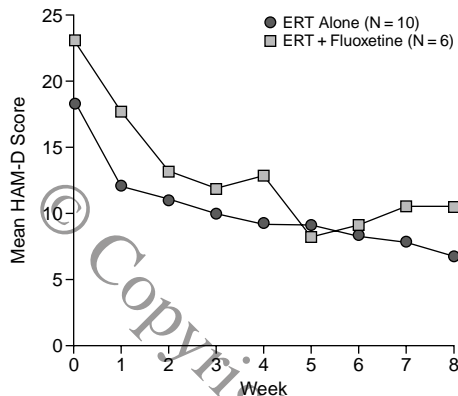
Of the 31 patients who met DSM-IV criteria for major depressive disorder, current episode, and had an appropriate HAM-D score, 16 met entry criteria. Of the 16, 6 patients were taking fluoxetine and 10 patients were taking no antidepressants. Fifteen women did not meet inclusion criteria (9 had medical contraindications and 6 declined participation). No substantial differences were found between women who agreed to or declined participation in the study.

All patients who met the criteria and agreed to participate signed the Human Subjects Protection Committee Consent Form after a complete description of the study and prior to their enrollment in the study.

Drug Treatments

The length of the open-label treatment phase for both groups of patients was 8 weeks. After the initial screening, all patients were assigned to receive ERT. Of the 16 patients, 10 women were taking no antidepressant at entry and thus received ERT monotherapy; 6 women received ERT as an adjunct to SSRI (fluoxetine) treatment. Fluoxetine was administered in a standard antidepressant dose. The mean dose of the fluoxetine at study entry was 30.0 ± 4.8 mg and was not altered throughout the study. ERT was administered as 17 β -estradiol (Estratab, Solvay, Marietta, Ga.) in both groups of patients. The dose of 17 β -estradiol (0.3 mg/day) was not changed throughout the trial period unless patients experienced side effects requiring alterations in treatment schedule. The study coordinator and the principal investigator (N.L.R.) met with patients weekly to evaluate changes in mood and to dispense medication. The patient's mood was monitored using the HAM-D at each visit. After 8 weeks of treatment, the patient's subsequent HAM-D scores were compared with her baseline scores. Operational criteria were established as previously described in the literature.¹³ Specifically, a partial response was operationalized as a final HAM-D score \leq 50% of the baseline score. Remission was defined as a final HAM-D score \leq 7.

Figure 1. Change in Mean Hamilton Rating Scale for Depression (HAM-D) Scores Over an 8-Week Trial of Estrogen Replacement Therapy (ERT) Alone or ERT With Fluoxetine in Perimenopausal Depressed Women



Statistical Analysis

To evaluate the usefulness of ERT in the treatment of depression in perimenopausal women, we assessed the change in the level of depression from baseline to the end of the 8-week trial for 10 women on ERT alone and 6 women on ERT plus fluoxetine. Repeated measures of analysis of variance were also used for comparison of HAM-D-21 scores, with time as a within-patient factor and treatment groups (ERT plus fluoxetine and ERT alone) as between-patient factors. HAM-D-21 scores were analyzed for each week from baseline to endpoint. Post hoc comparisons were performed using paired t tests.

RESULTS

Both groups improved significantly over time ($F = 10.71$, $df = 8, 112$; $p < .001$) by showing reduced levels of depression (Figure 1). Both the ERT and ERT-plus-fluoxetine groups showed a significant mean reduction in HAM-D scores following the first week of treatment (ERT: $t = 2.61$, $df = 9$, $p < .05$; ERT plus fluoxetine: $t = 3.41$, $df = 5$, $p < .05$), and this response was sustained throughout the trial. In the ERT-alone group, the mean initial HAM-D score was 18.30 ± 3.71 and the mean final score was 7.11 ± 7.70 . Depression remitted in 6 of the 10 women by the end of the study. Three patients had a partial response, and 1 patient had no response to treatment. In the ERT-plus-fluoxetine group, the mean HAM-D score at entry was 23.20 ± 5.72 and at the end was 10.60 ± 2.94 . Depression remitted in only 1 patient, and the remaining 5 patients showed a partial response.

DISCUSSION

Our results from this open-label study provide evidence that during perimenopause, ERT may have a role in the

treatment of clinical depression. In both groups of perimenopausal depressed women, a treatment response was statistically significant by the first week of the trial and was sustained throughout the trial.

Significant controversy still exists with regard to the efficacy of ERT in the treatment of depressive symptoms during perimenopause. Early studies¹⁷⁻¹⁹ found that ERT was more effective than placebo in improving psychological measures in a mixed group of perimenopausal and postmenopausal women, whereas other studies¹⁸⁻²¹ revealed no differences between ERT and placebo. In a double-blind, 12-week, placebo-controlled trial of conjugated estrogen alone in pharmacologic doses of 1.25 mg/day, treatment-refractory severely depressed women showed decline in HAM-D scores from 31 to 22 and remission in 6 of 23 patients, while none of the 18 placebo-treated patients improved significantly.²² These results are not surprising in view of the pharmacologic doses of estrogen, yet the clinical utility of such doses, even with the addition of progesterone, is questionable. Among the limitations of these studies were an inadequate methodology in defining menopause and a lack of separate analyses of the results for perimenopausal and postmenopausal women. In addition, the battery of rating tools varied between studies, and structured psychiatric interviews were lacking in most studies. Clinical trials have often been cross-sectional and/or retrospective, making a possible relationship between ERT and improvement of depressive symptoms difficult to determine. The present study provides evidence that ERT may improve mood ratings in a sample that had a more rigorous diagnosis of major depressive disorder and focused treatment on a perimenopausal population. The extent to which ERT can influence the course of depression in women during perimenopausal transition needs further investigation.

Although our inclusion/exclusion criteria did not discriminate against women experiencing vasomotor symptoms, our patients did not report significant vasomotor symptoms, such as hot flashes, night sweats, or vaginal dryness. The efficacy of ERT in depression in the absence of vasomotor symptoms suggests that the antidepressant effect is not solely a consequence of its ability to reduce the distress of these symptoms. In fact, Schmidt et al.¹ found no significant effect of the presence of hot flashes on the likelihood of response to depressive symptoms. However, for the symptoms of anhedonia and anxiety, a significantly more improved response to estradiol treatment occurred in the depressed women without hot flashes compared with the depressed women with hot flashes. Therefore, if confirmed by studies with larger samples, these findings suggest that ERT may have an antidepressant effect independent of its effects on the physical manifestations of perimenopause. Consequently, ERT may find its place among alternatives and/or adjuncts to antidepressant agents in the population of depressed perimenopausal women.

REFERENCES

A potential concern with long-term ERT is its association with increased risk of endometrial hyperplasia in non-surgically induced perimenopausal women. Progestins are added to menopausal hormone regimens in order to prevent endometrial hyperplasia; however, they have been associated with depressive symptoms.²³ Thus, the addition of progestins could theoretically reduce the antidepressant effects of ERT. Schmidt et al.¹ reported continuing improvement of depressive symptoms when medroxyprogesterone acetate was added to estradiol treatment. However, these results should be interpreted with caution, as the progesterone was used for a short duration. Future studies should investigate the long-term effects of combination hormone treatments on the clinically depressed population.

In addition, a potentially increased risk of breast cancer with estrogen use needs to be considered, even though there is no consensus as to whether estrogen use actually increases the risk. Many rigorous studies showed no association between estrogen use and breast cancer.²⁴ However, review of the literature concerning breast cancer and ERT revealed a slightly increased risk of breast cancer in women receiving ERT compared with women not receiving this therapy.²⁵ Dupont and Page²⁶ suggested that replacement with 0.625 mg/day or less of conjugated estrogens does not increase breast cancer risk. The low-dose replacement used in our study (0.3 mg/day) may not cause an increase in breast cancer risk, even in a longer trial.

Duration of ERT may affect risk. On the basis of studies in the United States, a relative risk of about 1.5 may be reached after 15 or more years of use.²⁷ Thus, it is important to evaluate the necessity of long-term ERT in the treatment of depression. It is possible that acute treatment or short-term recurrent trials with ERT may sustain an antidepressant response without increasing the risk for breast cancer, which should be a subject for future studies.

In conclusion, our data further support use of ERT to treat clinically depressed perimenopausal women. The study suggests that ERT could be used alone, as an alternative to antidepressant treatment in some cases, or as an adjunct to antidepressants. Even in this open-label trial of ERT, a rapid decrease in HAM-D scores was apparent following the first week of treatment in treatment-naïve women and women who were nonresponders or partial responders to an antidepressant. Therefore, an addition of ERT to antidepressant treatment may accelerate antidepressant response. Among the limitations of the present data are small sample sizes and lack of placebo control. Further controlled prospective studies are ongoing to evaluate the effects of ERT/hormone replacement therapy on the course of depression in perimenopausal and postmenopausal women.

Drug names: estradiol (Estratab and others), fluoxetine (Prozac and others).

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