Estrogen Augmentation of Antidepressants in Perimenopausal Depression: A Pilot Study

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Objective: To investigate the effects of estrogen augmentation on mood and memory in women with perimenopausal depression who had experienced a partial response to antidepressant medications.

Method: In a double-blind, placebo-controlled trial, 17 subjects taking antidepressant medication were randomly assigned to either 0.625 mg/day of conjugated estrogen (N = 11) or matching placebo (N = 6) for 6 weeks. Women between the ages of 40 and 60 years with DSM-IV major depressive disorder (MDD) in partial remission who had been taking antidepressant medication for a minimum of 8 weeks and were experiencing 1 or more perimenopausal symptoms (hot flashes, night sweats, irregular periods, sleep disturbance, memory impairment) were recruited from the community. The primary outcome measures were the final scores for the Hamilton Rating Scale for Depression (HAM-D) and the Buschke Selective Reminding Test. Data were gathered from April 2002 to August 2003.

Results: Women receiving estrogen had a significantly larger decrease in HAM-D scores than women receiving placebo ($t = 2.86$, $df = 15$, $p = .012$). Group differences in tests of verbal memory were not significant, although improved scores in verbal memory were significantly correlated with a decrease in follicle-stimulating hormone ($p = .021$).

Conclusion: Short-term, low-dose estrogen augmentation of antidepressant medication was significantly associated with improved mood, but not memory, in perimenopausal women with MDD in partial remission.

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Depressive symptoms are reported to occur in 10% to 40% of perimenopausal women.[1–3] Even with antidepressant medication, many patients may not return to euthymic mood. Estrogen may be a useful antidepressant augmentation agent, although there are no guidelines on how to enhance antidepressant effectiveness with estrogen.[4] Previous research studies have shown beneficial effects of hormone replacement therapy on both mood[5–7] and cognitive function.[8,9] Studies that have shown a positive effect have generally focused on single hormonal treatment with estrogen, and researchers have suggested that the addition of a progestin may counteract the effect of estrogen.[10,11]

The long-term prevention study conducted by the Women's Health Initiative (WHI) reported greater health risks associated with combined hormone treatment than placebo.[12–14] In older postmenopausal women, the Women's Health Initiative Memory Study, an ancillary study within the larger WHI study, concluded that estrogen (as a single agent) did not reduce dementia or mild cognitive impairment[15] and that the scores on the Modified Mini-Mental State Examination were 0.25 units lower in women assigned to take estrogen compared with those taking placebo.[16] Therefore, physicians, researchers, and

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consumers are reexamining chronic hormone treatment in nonclinical *post*menopausal populations as a prevention strategy. Many questions remain unanswered regarding hormone treatment in different populations, including the effects of different preparations, dose, route of entry, sequencing, duration of hormone deficiency, lifetime estrogen exposure, and menopausal status.

Given that an estimated 1.3 million women will enter menopause each year,[17] and that depression is the number one cause of disease burden in women according to the World Health Organization's Global Burden of Disease Study,[18] depressive symptoms during the menopausal transition will continue to be an area of great public/mental health importance. Our current study focused on the specific situation of perimenopausal depression in partial remission and investigated the effectiveness of short-term estrogen augmentation of antidepressant medication.

METHOD

The study was initially designed as a 14-week crossover study, with 6 weeks on each treatment (estrogen and placebo) and an intervening 2-week washout period. There was a differential dropout rate between groups, with more subjects treated with placebo dropping out prior to crossover than those treated with active medication. Because of difficulties in recruitment within the restrictive entry criteria of the study, as well as the higher dropout rate in the placebo group, the study was suspended, and we are reporting only on the first 6 weeks of the trial.

Subjects

Women between the ages of 40 and 60 years were recruited from the community who (1) met diagnostic criteria for major depressive disorder (MDD) in partial remission as ascertained by the Structured Clinical Interview for DSM-IV,[19] (2) had residual symptoms of depression defined by a Hamilton Rating Scale for Depression (HAM-D)[20] score > 7 and ≤ 14, (3) were taking antidepressant medication for a minimum of 8 weeks, and (4) were experiencing 1 or more perimenopausal symptoms (hot flashes, irregular periods, memory impairment, night sweats, or sleep disturbance). Subjects with cessation of menses for 12 months (i.e., postmenopausal women) were excluded from the study. Subjects with psychiatric disorders in addition to MDD or with medical conditions that contraindicated estrogen therapy were excluded. The Medical Institutional Review Board at the University of California Los Angeles approved the research protocol. Written informed consent was obtained from the participants after the study procedures were fully explained. Data were gathered from April 2002 to August 2003.

Participants meeting inclusion criteria were randomly assigned to either conjugated estrogen (0.625 mg/day) or matching placebo. Participants returned at 2-week intervals for a new supply of study medication and evaluation of mood symptoms. Serum levels of estrogen and follicle-stimulating hormone (FSH) were assessed on day 3 of the menstrual cycle and at 6 weeks. Participants continued on treatment with the antidepressant medication prescribed by their primary treating physician throughout the study.

Instruments

Primary outcome measures were the final scores on the HAM-D and the Buschke Selective Reminding Test (BSRT).[21] The BSRT was used to assess verbal learning, memory, and delayed recall. Verbal memory was assessed using the delayed recall score of the BSRT. The Digit Span[22] was used as a measure of short-term memory. Vasomotor symptoms were recorded daily using the Menopause-Specific Quality of Life Questionnaire.[23] Anxiety symptoms were also assessed using a subscale of the HAM-D focused on anxiety.

Data Analysis

Differences in HAM-D scores between subjects receiving estrogen versus subjects receiving placebo were assessed with t tests. Group differences in demographic characteristics, serum hormone levels, and measures of short-term memory were also evaluated with t tests. Correlation analyses were used to investigate the relationship between change in depressive symptoms and serum hormone levels, as well as change in depressive symptoms and change in measures of short-term memory. Missing data on the HAM-D were imputed using the last observation carried forward (LOCF).[24,25] Results are reported both with and without LOCF imputation.

RESULTS

Seventeen women with partial response to antidepressant medication entered the trial. Table 1 presents the HAM-D scores for each subject over the course of the study, specifying the antidepressant medication used and the treatment assignment (estrogen or placebo). The length of time on treatment with antidepressant medication ranged from 6 months to 7 years. Several different strategies had been used in the past to optimize treatment for the subjects, including dose adjustment, medication changes, and concomitant use of 2 or more antidepressant medications. At the time of entry into the study, all subjects had been on their current regimen for at least 8 weeks.

Thirteen subjects completed the trial, and 4 dropped out of the study before completing 6 weeks. Three dropped out of the placebo group, and 1 dropped out from the medication group. All 4 subjects who withdrew from the study reported unsatisfactory therapeutic effects in conjunction with uncomfortable physical complaints, which they at-

Table 1. Hamilton Rating Scale for Depression (HAM-D) Score for Each of 17 Perimenopausal Subjects at Baseline and 2, 4, and 6 Weeks

		HAM-D Score			
Antidepressant/ Subject No.	Treatment	Baseline	2 Weeks	4 Weeks	6 Weeks
Fluoxetine					
1	Estrogen	10	2	8	5
2	Estrogen	14	2	5	4
3	Estrogen	8	12	5	5
4	Estrogen	9	5	5	7
Paroxetine					
1	Placebo	9	11	11	11
2	Estrogen	8	6	6	6
Sertraline					
1	Placebo	13	7	3	11
Citalopram					
1	Placebo	12	11	11	11
2	Placebo	8	8	7	5
3	Estrogen	14	17	10	9
4	Estrogen	12	5	1	2
Venlafaxine					
1	Estrogen	10	4	13	5
Bupropion					
1	Placebo	14	11	13	12
2	Placebo	13	11	15	15
3	Estrogen	13	5	6	8
4	Estrogen	12	7	9	10
5	Estrogen	9	7	6	7

tributed to the study medication. Baseline demographic data are presented in Table 2. There were no significant group differences in demographic characteristics, baseline HAM-D scores, or baseline hormone levels.

Depressive Symptoms

A significant group difference existed between subjects receiving estrogen versus placebo in the mean decrease in HAM-D scores at the end of 6 weeks ($t = 2.86$, $df = 15$, $p = .012$) using LOCF. A significant difference also existed if observed cases only were analyzed ($t = 2.56$, $df = 11$, $p = .027$). Changes in HAM-D scores over time are shown in Figure 1. Within the estrogen-treated group, there were significant decreases in baseline depressive symptoms at all time points, which were not seen in the placebo group. Of the 10 subjects who received estrogen and completed the study, 8 achieved remission (defined as a HAM-D score ≤ 7) with a mean decrease of 5 points.

Hormone Levels

In women receiving estrogen, serum estradiol levels increased significantly ($t = 2.58$, $df = 9$, $p = .029$), and FSH levels decreased significantly ($t = 2.35$, $df = 9$, $p = .045$). In women receiving placebo, there were no significant changes in serum levels of either estradiol or FSH.

Memory

Although the estrogen group on the average performed better in all categories of the BSRT than the placebo group, the differences did not reach statistical significance. Decreased levels of serum FSH were significantly correlated with improved scores on the BSRT and the Backward Digit Span regardless of group assignment (Figure 2).

Vasomotor Symptoms

There were no significant correlations between serum hormone levels and vasomotor symptoms. The change from baseline in vasomotor symptoms at week 6 did not correlate with change in HAM-D scores.

Correlation of Hormone Levels With Mood Symptoms

Exploratory analyses were undertaken to assess the relationship between serum hormone levels and mood symptoms. In the overall sample, the decrease of depressive symptoms at week 2 correlated significantly with the change in estradiol ($p = .026$) (Figure 3), but not with FSH ($p = .106$). In the group of women who received estrogen, the decrease of depressive symptoms correlated significantly with change in estradiol ($p = .001$) and FSH ($p = .0005$) levels at week 6.

A subscale of the HAM-D focused on anxiety (composed of symptoms of somatic anxiety, psychic anxiety, and agitation) showed a significant relationship between change in anxiety scores and change in serum estradiol ($r = 0.704$, $p = .007$) (Figure 3). When baseline scores were controlled for, the correlation remained significant ($p = .004$). In the group of women receiving estrogen, there was also a significant correlation ($r = 0.663$, $p = .037$) between the change in anxiety scores and change in serum estradiol.

DISCUSSION

We identified 4 important findings in analyzing the data. First, in partial responders to antidepressant medication, we found a significant decrease in severity of depressive symptoms in women who received estrogen augmentation versus those who received placebo. Second, FSH level was related to improved performance on tests of verbal memory. Third, perimenopausal vasomotor symptoms were not correlated with mood. Fourth, there was a relationship between serum estradiol levels and mood symptoms.

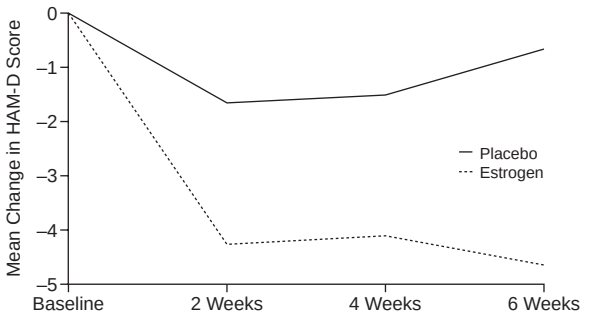
Both observationally and clinically, estrogen has been recognized as an agent that can affect mood. Animal studies have demonstrated that gonadal hormones modulate several of the neurotransmitters thought to be involved with affective disorders.[26,27] Although many observational, retrospective, and open-label studies exist, the findings are difficult to generalize across trials.[28–30] Many studies used progesterone and other hormones in conjunction with estrogen, did not clearly distinguish between clinical and nonclinical populations, or did not distinguish between *peri*menopausal and *post*menopausal status. The

Table 2. Demographic Characteristics of Perimenopausal Women With Major Depressive Disorder

Characteristic	Placebo (N = 6), Mean ± SD	Estrogen (N = 11), Mean ± SD	Total (N = 17), Mean ± SD	t	p Value
Age, y	47.17 ± 2.14	46.55 ± 3.17	46.76 ± 2.80	0.43	.68
Years of education	15.83 ± 2.04	15.82 ± 2.36	15.82 ± 2.19	0.03	.99
Body mass index	22.98 ± 3.99	24.54 ± 0.20	23.99 ± 4.74	–0.64	.53
Age at menarche, y	13.33 ± 2.07	13.64 ± 1.34	13.53 ± 1.58	–0.37	.72
Total pregnancies	1.67 ± 1.51	1.82 ± 1.99	1.76 ± 1.79	–0.16	.87
Total live births	0.50 ± 1.22	0.45 ± 0.69	0.47 ± 0.87	0.01	.92
Baseline estradiol level, pg/mL	45.83 ± 35.39	51.00 ± 33.56	49.18 ± 33.19	–0.30	.77
Baseline FSH level, mIU/mL	34.92 ± 31.98	17.58 ± 9.51	23.70 ± 21.19	1.23	.25
Baseline HAM-D score	11.50 ± 2.43	10.82 ± 2.27	11.06 ± 2.28	0.58	.57

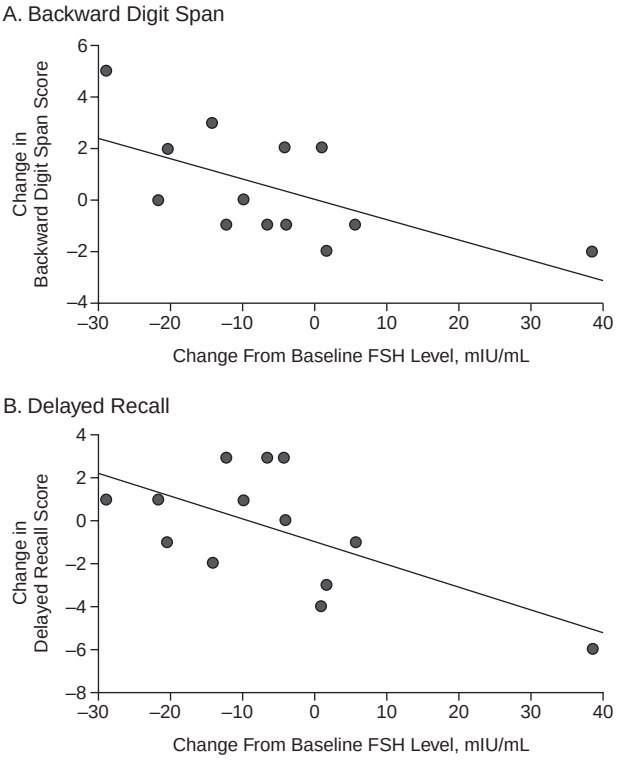
Abbreviations: FSH = follicle-stimulating hormone, HAM-D = Hamilton Rating Scale for Depression.

Figure 1. Change in Hamilton Rating Scale for Depression (HAM-D) Scores[a]



[a]Significant group differences were seen between estrogen and placebo after 6 weeks of treatment (t = 2.86, df = 15, p = .012). Within the estrogen-treated group, significant decrease was seen at 2 weeks (t = 2.95, df = 10, p = .014), 4 weeks (t = 3.59, df = 10, p = .005), and 6 weeks (t = 5.17, df = 10, p = .0004). In women receiving placebo, there were no significant changes in HAM-D scores.

Figure 2. Correlation Between Follicle-Stimulating Hormone (FSH) Levels and Memory as Measured With the (A) Backward Digit Span and (B) Delayed Recall Tests[a]



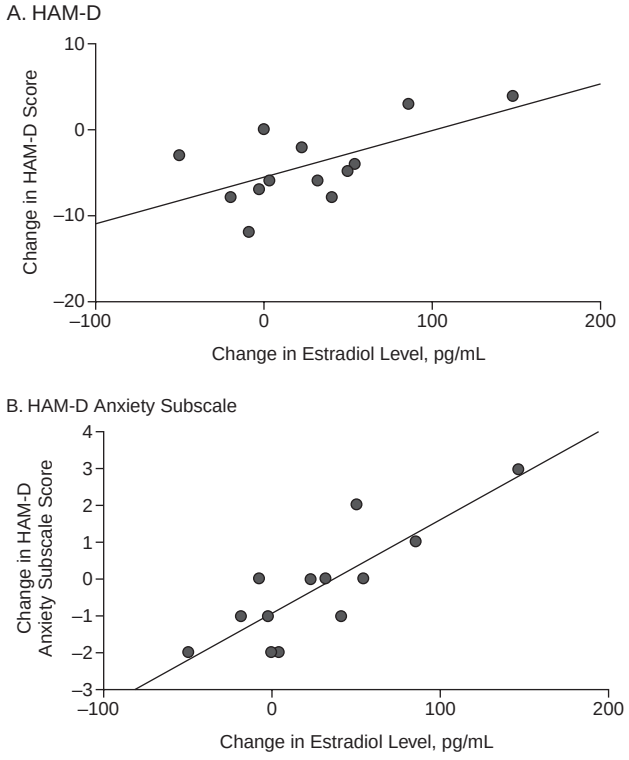
[a]Decrease in FSH correlated with improved performance on memory tests. Delayed Recall: r = –0.30, p = .021, N = 13. Backward Digit Span: r = –0.631, p = .026, N = 13.

distinction between perimenopause and postmenopause is particularly important because the psychotropic effects of estrogen may vary depending on menopausal status.

The majority of studies examine estrogen as a monotherapeutic treatment, rather than an augmentation or adjunct to treatment with antidepressant agents. Placebo-controlled, randomized studies of estrogen monotherapy for postmenopausal and perimenopausal depression have had mixed results.[31–36] We identified 6 studies in mixed populations, all open-label or retrospective, that combined estrogen and antidepressant medication.[1,37–41] Five[1,37–40] of the 6 studies found estrogen plus antidepressant medication more effective than antidepressant medication alone. Tam and Parry[42] report 5 case studies in which estrogen appeared to enhance the effect of serotonergic antidepressants. Our study built on the foundation of these studies by focusing only on augmentation of subjects with perimenopausal depression using a randomized, placebo-controlled study.

The relationship between exogenous estrogen administration and cognitive function is not conclusive, although the specific cognitive domain of verbal memory continues to show a positive relationship with estrogen. Fundamental studies have provided theory and evidence that the action of reproductive hormones on the central nervous system can influence aspects of verbal memory[43,44] and is involved in nerve and synapse growth and formation.[45–47] Observational and prospective experimental studies have found that estrogen helps maintain memory in both clinical and nonclinical populations[48–53]; however, we did not find significant changes in verbal memory between participants treated with estrogen versus placebo.

Figure 3. Correlation Between Estradiol Levels and Mood Symptoms as Measured With the (A) HAM-D and the (B) HAM-D Anxiety Subscale[a]



[a]Change in estradiol level correlated with change in HAM-D score (r = 0.613, p = .026, N = 13) and change in anxiety symptoms (r = 0.704, p = .007, N = 13).
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

The low dose and short duration of estrogen exposure, in addition to the small sample, may contribute to the null findings. We did find that changes in FSH levels, but not estradiol levels, were significantly related to improvement in memory. Typically, the relationship between FSH and estradiol is characterized by a negative feedback mechanism; during the menopausal transition, however, the variability is unpredictable, and it is not unusual for the fluctuation between the 2 hormones to lack synchronization. In our sample, FSH and estradiol were not correlated at any time point.

Sleep dysregulation is a common complaint during perimenopause, and thus it has been theorized that mood lability should stabilize once there is relief of vasomotor symptoms and a return to normal sleep. Our findings, however, did not show a relationship between mood and vasomotor symptoms, suggesting that dysphoric mood may be independent of hot flashes and night sweats. This finding concurs with previously reported studies by Schmidt et al.[32] and Soares and Cohen.[54]

In women taking estrogen, we found a strong correlation between the change in mood symptoms, particularly anxious-depressive symptoms, and the change in estradiol levels. Women who had large increases in estradiol were more likely to have *smaller* improvements in symptoms (smaller HAM-D change scores). Research on the relationship between serum estradiol levels and severity of mood symptoms is inconsistent.[55–58] A standard dose of estrogen may be insufficient in some women, while in other women an average dose may result in intolerable side effects. Effects of different doses should be further examined in conjunction with monitoring serum hormone levels.

There are several limitations to this pilot study. The small sample and differential dropout rate limit the ability to make generalizations. The heterogeneous treatment history of the subjects, in addition to the variety of antidepressant medication used in the study, may confound the findings. In future research, it will be important to prospectively operationalize treatment history and antidepressant medication. Measurement of serum antidepressant levels before and during treatment would also provide important information about estrogen's effect on antidepressant pharmacokinetics. Improvement in mood symptoms could be due to the exogenous estrogen's effect on plasma levels of the psychotropic medication.[59] Although the levels of estrone and estradiol can be measured when administering a conjugated estrogen, there are other equine estrogens that are very difficult to measure. In future studies, it would be prudent to use estradiol rather than conjugated estrogen. In addition, the route of administration may modulate the effect of estrogen on cognition and memory.[8] Steingold et al.[60] concluded that transdermal or subcutaneous routes of administration, which avoid initial hepatic metabolism, will allow more estrogen to be available to the brain. This may account for improved memory in studies using transdermal rather than oral estrogen.[41,42]

Because the subjects entered the study with a diagnosis of MDD in partial remission, we do not have information on the HAM-D scores at the onset of the current depressive episode, which limits our ability to interpret the overall effect of the augmentation. We can conclude that the women who received estrogen improved significantly, but we cannot quantify the change from prior to the initial antidepressant administration.

In light of the current climate surrounding estrogen research, one must be careful not to prematurely apply the results of a pilot study such as this to clinical practice. Conversely, it also is important not to overgeneralize the results of a large-scale public health prevention study to individualized clinical treatment. Large-scale studies performed to date suggest that long-term combined hormone treatment may have health risks, but the risks of short-term single hormone treatment such as that performed here are unclear. The pilot data from our clinical treatment study suggest that there may be psychiatric benefits

to short-term treatment in women with MDD in partial remission and are encouraging for future work in the specific area of estrogen augmentation strategies in perimenopausal depression.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), estrogen (Premarin, Cenestin, and others), fluoxetine (Prozac and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

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We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene Freeman, M.D., at marlenef@email.arizona.edu.