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The Effects of Age and Estrogen on Stress Responsivity in Older Women

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Abstract

Prior studies have shown that estradiol improves mood in women around the menopause transition [1, 2] but does not improve mood for older postmenopausal women (Morrison et al. 2004). Newhouse et al. [3] have previously shown that estradiol treatment in non-depressed women resulted in increased negative mood after psychosocial stress. The current study examined whether age after menopause impacted the effect of estradiol on mood after a psychosocial stress manipulation. Participants were 22 postmenopausal women placed on either oral placebo or 17 β -estradiol (1 mg/day for 1 month, then 2 mg/day for 2 months). At the end of the 3 month treatment phase they performed the Trier Social Stress Test (TSST) followed by mood ratings. To examine the effects of age on the estrogen-stress interaction, we performed a median split on age and created four groups of participants: younger-placebo (mean age 55.5), younger-estradiol (mean age 55.5), older-placebo (mean age 73.0), and older-estradiol (mean age 76.8). The results showed that both older and younger estradiol-treated participants exhibited a significant and similar increase in negative mood after psychosocial stress compared to placebo-treated women. These results suggest that estradiol may play a significant role in modulating emotional reactivity to stressful events and that this effect persists in older women. Furthermore, responsivity to estradiol effects on emotional processing appears to be intact even years after menopause in contrast to other cognitive and behavioral effects of estradiol which may be limited to the early postmenopausal years.

Keywords

Stress; Aging; Menopause; Estrogen

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Introduction

The relationship between estrogen and mood before and after menopause is complex and appears to be influenced by psychiatric history, study design, and age among other factors. Perimenopause is associated with increased mood vulnerability for depressive symptoms and an increase in diagnosis of first onset depression [4, 5]. However, incidence of depression has been shown to be decreased in postmenopausal women relative to men of similar age [6, 7]. A metaanalysis of experimental studies in postmenopausal women showed that hormone therapy reduced depressed mood in postmenopausal women (Zweifel & O'Brien 1997). Reviews by Zec and Trivedi (2002) and Miller (2003) summarized that the benefits of estrogen treatment on mood and depression in postmenopausal women depended on whether the study was experimental or observational in design. Estrogen treatment was beneficial in observational studies that assessed mood and had no effect in experimental studies in non-depressed women. In studies with depressed women, estrogen treatment improved depression in experimental studies and had no effect in observational studies. Thus, the study design and psychiatric diagnosis influenced estrogen's effects on mood in postmenopausal women. Additionally, estrogen monotreatment for major depression has been examined in a number of studies and its effectiveness appears to depend on age (e.g. [1, 2, 8]).

The Women's Health Initiative (WHI) study found no effects of conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) on mood [9]. However, similar to the cognitive findings, it is possible that the subject group was older (average age 67) and thus past the time to experience the beneficial effects of hormone therapy on mood measures. Evidence for this proposal has been seen in other studies. Klaiber and colleagues [10] found that psychiatric history and years since menopause altered the mood response to hormone therapy. Specifically, estrogen alone (estropipate) improved mood ratings compared to placebo for non-depressed recently menopausal women and women who were five years past menopause. However, estrogen plus a progestin (estropipate + noethindrone) improved mood ratings for the recently menopausal group only [10]. Thus, time since menopause and hormone combination influenced whether benefits of hormone treatment were observed on mood measures in non-depressed women.

A number of studies have examined the effects of estradiol as an antidepressant, and similar to the data on mood effects in non-depressed women, the results suggested different effects by age. In perimenopausal women, transdermal estradiol was an effective antidepressant after three weeks [1] and after 12 weeks of treatment [2]. The average age of women in both of these studies was approximately 49 years and all women were classified as perimenopausal. However, estradiol's effectiveness as an antidepressant appears to be age dependent. In an older group of menopausal women, average age of 62, Morrison et al. [8] showed that 8 weeks of transdermal estradiol treatment was not effective as an antidepressant. Thus, time since menopause may influence the effects of estradiol on mood for non-depressed as well as depressed older women around menopause.

The mechanisms underlying the effect of estradiol on mood remain to be fully explored. Walf and Frye [11] proposed that estradiol's antianxiety and antidepressant effects are related to its interaction with the hypothalamic-pituitary-adrenal (HPA) axis. Specifically, they propose that individual differences in responses to estradiol effects on mood measures are related to individual differences in how the HPA responds during stress[11]. Laboratory models in animals as well as humans have examined the relationship between HPA axis function, mood, and cognition. Mild and moderate laboratory stressors, such as the forced swim test [12] and tail suspension [13] have been used to induce depressive symptoms in animal models of depression. Similarly, psychosocial stressors have been used as negative

mood inducing procedures in human studies of mood and cognition [14–16]. HPA function during the stress response may also be affected by circulating estradiol levels and hormonal status. There is increased HPA axis response to psychosocial stress during low estrogen phases of the menstrual cycle compared to high estrogen phases [17, 18] and after menopause [19, 20]. However, explicit studies examining the interaction of gonadal steroids and HPA axis function on mood and cognition have not been done.

The current study examined whether age modulated the effects of estradiol treatment on mood after a psychosocial stressor in two groups of younger and older postmenopausal women. We have shown previously that estradiol treatment increased negative mood scores and impaired cognition after a psychosocial stress manipulation in postmenopausal women [21, 22]. Newhouse et al. (2008) examined the relationship between postmenopausal estradiol treatment and brain monoamine levels after a psychosocial stress manipulation. While some of the prior literature showed estrogen alone was beneficial to mood measures, Newhouse et al. [21] showed that the estradiol treated group had significantly worse mood ratings after the psychosocial stress manipulation and monoamine depletion. Interestingly, there was no interaction of estradiol treatment and the monoamine manipulation procedure. Estradiol thus appears to have effects on mood that are independent of monoamine systems. A second study showed that estradiol impaired performance on some of the cognitive measures after the psychosocial stress manipulation [22]. However, neither study addressed the question about the influence of age or time since menopause. As these prior studies have shown, the addition of a psychosocial stress manipulation affected the direction of the estradiol effect on mood and cognition and appears to be an additional factor that should be considered in addition to hormone preparation, years since menopause, and psychiatric history when assessing estrogen's effects on mood and cognition.

Based on prior studies examining the effects of estrogen treatment on mood, we hypothesized that estradiol treatment would interact with the effects of the psychosocial stress manipulation to increase negative mood ratings for the younger postmenopausal women compared to the older postmenopausal women. While estradiol has been shown to be beneficial to younger postmenopausal women on mood measures, the addition of a psychosocial stress manipulation produced negative effects. We proposed that these negative effects will be smaller for the older postmenopausal women because of predicted reduced responsiveness to estradiol treatment.

Method

Participants

Participants were 22 cognitively normal postmenopausal women with no current or past history of any mood disorders. They were recruited through newspaper advertisements and health newsletters published by our Medical Center, public information sessions, and random mailings. Study participants were first screened by phone for eligibility. At the end of the study each participant received \$100 as compensation for their time and a small gift pack after each study session. The study was approved by the University of Vermont Committee for Human Research in the Medical Sciences.

Participants were randomly assigned to receive either three months of 2.0 mg oral 17- β estradiol (E2) per day (first month at 1 mg per day, months two and three at 2 mg per day) or placebo. The participants who received estradiol were ages 52–83 ($M(SD) = 65.2(11.8)$, $N = 11$). The participants who received placebo were ages 52–80 ($M(SD) = 63.5(9.8)$, $N = 11$). There was no significant difference between the ages of these two groups ($t(20) = .37$, $p = .71$).

To test the age difference hypothesis regarding estradiol effects on mood after psychosocial stress, we performed a median split on age for each treatment group. We also examined the split of the subjects into groups using years since menopause as the grouping factor and these groups were exactly the same as using age. There were six participants in each of the younger groups and there were five participants in each of the older groups. See Table 1 for demographic characteristics.

Medical Screening

Participants were without menses for at least one year, had an FSH level greater than 30 mIU/ml, were nonsmokers, had a normal mammogram within the last year, and were without surgically-induced menopause (bilateral oophorectomy). They were not taking hormone therapy or oral contraceptives and were at least one year without such treatment. Participants were physically healthy, had a body mass index ≤ 30 kg/m², and had no cardiovascular disease other than mild hypertension. Participants with major concomitant illnesses were excluded on the basis of history, physical exam, and laboratory tests assessing hematopoietic, renal, hepatic and hormonal function. Participants were physically examined by a gynecologic specialist to establish general physical health and for specific physical contraindications for E2 therapy (e.g. adnexal mass, large uterine fibroids, etc.)

Participants were excluded if they had specific contraindications for E2 treatment or current or past Axis I psychiatric disorders. No participants were taking centrally active drugs or drugs with cholinergic properties. No participants were taking selective estrogen receptor modulators (SERMs) or herbal menopause preparations. A minimum of 14 days elapsed between discontinuing centrally active or psychoactive agents and this study.

Cognitive and Behavioral Screening

Participants were cognitively evaluated using the Mini Mental State Exam (MMSE; [23], Brief Cognitive Rating Scale [24], and the Mattis Dementia Rating Scale (DRS, [25] to establish a Global Deterioration Scale score (GDS) which rated the degree of cognitive impairment [26]. Participants were required to have an MMSE score greater than or equal to 27, a DRS score of 123 or greater, and a GDS score of 1 or 2.

Behavioral screening consisted of a partial Structured Clinical Interview for DSM-IV-TR (SCID; [27] to establish the presence/absence of Axis I psychiatric disorders. Subjects were excluded if they had any current or past Axis I disorder. In addition, participants completed the Beck Depression Inventory (BDI). A cut off score of 10 was used for the BDI, and participants scoring over this criterion were discontinued from further participation. All participants met these criteria for the cognitive and behavioral screening.

Estrogen/Placebo Treatment

After passing the screening, each participant was placed randomly and blindly on either oral placebo or 17- β estradiol (E2) for three months. Women in the estradiol group were initially placed on 1 mg E2 per day for 30 days, and then were increased to 2 mg per day. This was done because early pilot trials revealed that typical estrogen-related side effects (e.g. breast tenderness or spotting) tended to be troublesome if a subject took 2 mg of estradiol per day from the beginning. Using 1 mg of estradiol for the first 30 days minimized these problems. At the end of the three month treatment period, subjects participated in a series of challenge studies designed to examine differences in sensitivity to acute transmitter depletion and psychosocial stress. Estradiol or placebo treatment continued throughout the challenge/stress studies. Twelve days of medroxyprogesterone acetate (MPA) were given at the end of the study to produce shedding of the endometrial lining.

Acute Depletion Challenges

After the three month treatment phase, all participants took part in three amino acid depletion challenges. All studies took place on the University of Vermont General Clinical Research Center (GCRC). Each participant underwent three test days, at least seven days apart, in which they received the each of two amino acid depletion mixtures and a control mixture. These methods are described in detail elsewhere (Newhouse et al. 2008; Newhouse et al. 2010). In these prior studies, the amino acid depletion effects did not interact with estradiol treatment after psychosocial stress. Because the median split on the age factor reduces the sample size by half in each treatment group and the amino acid depletion has not interacted with estradiol treatment in our prior studies [3, 22], we have not included the depletion factor in the analyses described below.

Trier Social Stress Test

Five hours after amino acid ingestion, participants performed a mildly stressful psychological task, the Trier Social Stress Test (TSST; [28]). The TSST consisted of three parts, a brief Instruction Period, a 10-min Anticipation Period, and a 10-min Test Period. For the brief Instruction Period, subjects were taken to the TSST room where three experiment confederates were already sitting at a table and a visible video camera was set up. The participant was asked to stand on an “X” on the floor in front of the panel of people. The Instructor presented the participant with one of three scenarios and asked the participant to prepare a 5-min speech about the topic. Participants were told that the panel was specially trained to monitor nonverbal behavior and that a voice-frequency analysis of the speech would be performed. Following the instructions, the participant returned to her room.

During the Anticipation Period, participants were asked to prepare the five minute speech. They were given 10 minutes to prepare and take notes, but were not allowed to use the notes during the speech. After the 10-min Anticipation Period, participants were led back into the TSST room. During the Test Period, participants presented their five minute speech followed by five minutes of arithmetic problems. If a participant stopped her speech before five minutes, she was told, “You still have some more time left. Please continue!” If the subject stopped a second time before her five minutes were up, 20 seconds of silence were followed by the arithmetic problem solving. The arithmetic problems consisted of serial subtractions and upon every mistake, the subject was asked to begin again at the first number.

Outcome Measures

The main measure of interest was self-ratings on the Profile of Mood States (POMS, [29]). Participants rated 65 adjectives based on their current mood state from “Not at all” to “Extremely”. A total mood disturbance score as well as six factor scores were generated from this measure including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The POMS was administered three times during each study day, once at the beginning of the day before any experimental procedures began (Baseline), after the depletion but before the TSST (Time 2), and after the TSST (Time 3).

Blood samples were obtained for cortisol measures at two time points during the study day. The first was at baseline at approximately 0730. The second assessment was before discharge at approximately 1400 and after the TSST. These time points were not designed to optimally examine the cortisol response to the TSST but they did allow for an examination of the effects of age and estrogen treatment on cortisol secretion across the study day.

In addition to the mood and cortisol assessments, participants completed a cognitive battery once at Time 3 after the TSST. This battery consisted of tests of psychomotor speed, attention, and episodic memory and is described in detail in Newhouse et al. [22]. Participants and the experimenter also completed visual analog scales as described in Newhouse et al. [3]. The analyses for the POMS and cortisol measures were completed for the cognitive measures and VAS scales and the results were supportive of the effects of age on mood after psychosocial stress described below. The results in the current study focus on the age effects on mood after the estrogen and psychosocial stress manipulations and thus the cognitive data are not presented in the current paper.

Results

The outcome measure of interest in this study was the age effect on participant self-rated responses on the POMS after estradiol treatment and psychosocial stress. To examine this effect we used a 2 (age: younger and older) $\times$ 2 (treatment: E2 and placebo) $\times$ 3 (Time: Baseline, Time 2, Time 3) mixed model ANOVA for the POMS total mood disturbance and each of the factor scores (see Table 2). For the total mood disturbance there were main effects of treatment ($F(1,18) = 13.15, p = .002$) and time ($F(2,18) = 19.17, p < .0001$). There was also an interaction of treatment and time ($F(2,18) = 13.55, p = .0003$) as was demonstrated in Newhouse et al. (2008). Women in the estrogen treatment group reported greater mood disturbance overall and in particular at Time 3 after the TSST (E2 vs. placebo at Time 3: $t(18) = 4.21, p = .0005$). No main effects or interactions involved age for the total mood disturbance score (see Figure 1).

Next, we examined the effects of age, estrogen treatment, and psychosocial stress on the six mood factor scores: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. As the basic effects of psychosocial stress on mood after estrogen treatment have been described in Newhouse et al. [21] this study will focus on and main effects and interactions involving the age factor. For the tension-anxiety factor there was an interaction for age, treatment, and time ($F(2,18) = 5.15, p = .02$). The expected main effects of treatment ($F(1,18) = 7.20, p = .02$) and time ($F(2,18) = 34.7, p < .0001$) showed that subjects in the estradiol treatment group reported more tension-anxiety and all subjects reported greater tension-anxiety at Time 3 after the TSST. At Time 3, younger postmenopausal women reported greater tension-anxiety after estradiol treatment compared to placebo treatment ($t(18) = -2.51, p = .02$). For older women, there was no difference in tension-anxiety for the estradiol compared to placebo treatment groups ($t(18) = -.29, p = .78$).

The depression-dejection factor scores overall were close to 0 indicating low levels of depression and dejection. There was a main effect of age ($F(1,18) = 10.20, p < .005$) that showed the older group reported more depression-dejection than the younger group overall. There were no interactions involving age for this measure.

For the confusion-bewilderment factor there was an interaction of age, treatment, and time ($F(2,18) = 8.22, p = .003$). All women on estradiol treatment had greater confusion-bewilderment than placebo treated women ($F(1,18) = 12.47, p = .002$). This increase in confusion-bewilderment was greater at Time 3 for the estradiol treated group. At Time 3 there was no difference in confusion-bewilderment for younger postmenopausal women in the estradiol and placebo treatment groups ($t(18) = -1.52, p = .13$). For older postmenopausal women, estradiol treated women reported more confusion-bewilderment than the placebo group ($t(18) = -2.18, p = .04$).

There were no main effects or interactions involving age for the anger-hostility, vigor-activity, or fatigue-inertia factors.

For the cortisol measure, there were main effects of age ($F(1,11) = 6.61, p = .03$), treatment ($F(1,11) = 18.75, p = .001$) and time ($F(1,11) = 45.91, p < .0001$; see Table 3). The age by time interaction was not significant ($F(1,11) = 4.58, p = .056$). The pattern of means showed that older women had higher cortisol responses over all and they had a greater decrease from the first to second assessment compared to younger postmenopausal women.

Discussion

The current study examined the effect of age on the estrogen-stress interaction and mood in postmenopausal women by evaluating the effects of estradiol and psychosocial stress in older and younger postmenopausal women. The current data showed that both age groups had substantial increases in the total mood disturbance measure after psychosocial stress. There were age by treatment interactions for two of the POMS factor scores, the tension-anxiety and confusion-bewilderment. Older women reported greater confusion-bewilderment after estradiol compared to placebo treatment, but there was no difference between treatment groups for tension-anxiety. The original findings from this study reported in Newhouse et al. [3] showed that estradiol compared to placebo treatment resulted in greater negative mood responses after the psychosocial stress manipulation. These data further specify this finding to show that the negative effects of estradiol on mood after a stressor are not limited to a short period of time after menopause. Older postmenopausal women are still partially to mostly responsive and show significant negative mood following psychosocial stressor after three months of estradiol treatment. We first discuss the implications of these findings as well as limitations below.

The current data showed that women who were approximately 25 years past the menopause transition were responsive to the effects of estradiol on mood. This data pattern was not what was predicted based on the prior literature on the effects of estrogen treatment on mood in depressed postmenopausal women (e.g. [8]). However, there are many differences between the current study in healthy women with the psychosocial stress manipulation compared to prior studies with depressed women that used estradiol as an antidepressant. In other laboratory studies examining stress responding in pre- versus postmenopausal women, data showed that blood pressure, ACTH and cortisol release in response to laboratory stressors were enhanced in postmenopausal women [19, 20]. This increase remained when postmenopausal women were compared to premenopausal women during low estrogen phase of the menstrual cycle suggesting that the difference was not entirely due to circulating estrogen levels [30]. However, there is evidence that the increased physiological response to psychosocial stressors following menopause may be attenuated by estradiol therapy. A number of studies have shown reduced blood pressure, cortisol, and ACTH response to stressors for women on estrogen therapy that is approaching the response seen in premenopausal women [19, 20, 31]. However, none of these studies measured mood responses or other subjective responses to the stressors.

Few of the prior studies included subjective measures of the psychosocial stress response, such as mood. Kudielka et al. [19] investigated the response to the TSST in postmenopausal women receiving transdermal estradiol or placebo and premenopausal women. Following the stressor, all three groups of women showed decreased mood on a multidimensional mood questionnaire. However, the decrease in mood after the TSST was similar in postmenopausal women receiving estradiol or placebo and premenopausal women. In a similar study Ceresini et al.[31] examined the effects of transdermal estradiol in postmenopausal women on the response to psychosocial stress, using the State-Trait Anxiety

Inventory as the subjective measure. Although transdermal estradiol was associated with decreased autonomic and HPA axis measures of stress responding, there was no difference in state anxiety after stress in the estradiol group compared to the women receiving placebo.

Previous studies investigating stress responding suggest that subjective stress responses may not correspond with physiological responses in women [32]. Although women may show decreased cardiovascular and HPA axis responses following estrogen therapy or during high estrogen phases of the menstrual cycle, there may not be similar reductions in the subjective mood response to stressors. Our prior study has shown that estradiol treated postmenopausal women reported greater mood disturbance after a psychosocial stressor compared to placebo treated women [3]. In the current study, the data showed that older postmenopausal women were still responsive to the effect of estradiol on mood after a psychosocial stressor. Additionally we observed the normal reduction in cortisol levels throughout the day for older and younger women which may indicate intact HPA axis function in the older women group. Future studies should explicitly examine the relationship between objective measures of the stress response such as blood pressure, cortisol, and ACTH and subjective measures of mood.

While we did not assess cortisol levels at time points that were optimal for using them as an objective measure of the stress response, the cortisol change across the study day showed an interesting age-related pattern. The normal pattern of decreased cortisol values across the day was observed for all participants. Additionally, older women had higher cortisol values. There was a trend for an age by treatment interaction that showed that older women had a greater decrease across the day compared to younger women. Future studies should examine cortisol levels at time points closer to the stressor to further examine the effects of estrogen treatment in postmenopausal women on the HPA axis acute stress response.

Prior studies of estrogen treatment for depression have shown mixed results that depend on the age of the women in the studies. The studies that found benefits of estrogen as an antidepressant examined younger perimenopausal women (e.g., [1, 2]), while the studies that showed no effect of estrogen as an antidepressant had older postmenopausal women as subjects (e.g., [8]). Time sensitive effects of estrogen treatment have been shown previously with regard to cognition [33] and cardiac function [34]. However, the current study does not support the finding for a time since menopause sensitivity effect of estrogen on mood after a psychosocial stressor in women. The mechanism responsible for the increased negative mood response to psychosocial stress in postmenopausal women after estradiol treatment is not clear from the current study.

Several potential explanations can be considered for the findings of exaggerated negative emotional response to psychosocial stress following estradiol treatment. It has been suggested that alterations in monoamine neurotransmitter systems important for mood regulation may be responsible in part for alterations in emotional processing in aging [35]. However this is an unlikely explanation for the findings in the current study because we have shown in a prior study (Newhouse et al. 2008) that there was no interaction between estradiol treatment and monoamine depletion and the effects of monoamine depletion by themselves were quite small. More fruitfully, the normal menstrual cycle altered the activity of both limbic and cortical areas involved in negative emotional appraisal in a cyclic fashion with phases of the menstrual cycle associated with higher estradiol levels showing lower activity of limbic structures during the exposure to negative emotional stimuli (e.g. [36]). Steady administration of estradiol, as was the case in this study, may have phase-shifted the activity and/or the relationship between limbic emotion-generating structures and cortical emotion-regulating structures in such a way as to amplify the negative emotional impact of psychosocial stress. However, confirmation of this will have to await imaging studies of

psychosocial stress in postmenopausal women with and without the administration of estradiol. Resolution of the neurobiological underpinnings of this exaggerated emotional response to estradiol administration following psychosocial stress will be assisted by future studies of estradiol treatment on cortical activity associated with the appraisal of psychosocial stress versus the induction of negative emotional states via other means.

There were a number of limitations that should be considered with regard to the interpretation of the data patterns in the current study. First, this is a small N study. This was an intensive repeated measures study that involved a large time commitment from subjects. Subjects were recruited such that there were subjects in the 50–60 age group and 70–80 age group with 2 exceptions in the 60s. Thus, there was a natural age split in the data to examine the four groups by age and treatment. The results showed no interaction of age and the estrogen and stress manipulations. One reason for this finding could be regression to the mean. These data should be replicated with a larger sample. Secondly, we did not measure cortisol at enough time points throughout the study to assess the effect of the stress manipulation on the objective stress response. Future studies should examine this effect.

These findings taken together with prior studies of age-related differences in stress reactivity and clinical studies of the impact of peri- and postmenopausal gonadal steroids on both normal and depressed individuals [1, 2] have important implications for the assessment and treatment of mood disturbances in aging. Unlike nonemotional cognition, these results imply that with gonadal steroid treatment, emotional circuitry remains intact and responsive through late life.

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Figure 1.

Total Mood Disturbance scores (*Least Squares Mean(SE)*) for younger and older women in the estradiol and placebo treatment groups.

Table 1

Demographic characteristics for younger and older postmenopausal women in the estradiol and placebo treatment groups. No age group or treatment differences existed for education, BMI, or years of prior estrogen use (largest $F(1,18) = 0.98$, smallest $p = .34$ for treatment group on education).

	Younger Placebo N=6	Younger Estradiol N=6	Older Placebo N=5	Older Estradiol N=5
Age	55.5 (2.2)	55.50 (3.3)	73.0 (5.0)	76.80 (5.1)
BMI	26.75 (4.5)	25.74 (2.2)	26.48 (6.7)	25.95 (5.3)
Education	15.50 (2.5)	14.67 (2.3)	15.60 (3.6)	14.00 (3.1)
Years since menopause	7.05 (4.6)	5.38 (4.1)	22.40 (8.6)	25.60 (4.4)
Prior estrogen use	4/6	5/6	2/6	4/5
Years of prior estrogen use	5.69 (6.2)	3.93 (4.7)	*	0.21 (0.8)

* data not available

Table 2

Profile of Mood States (*Least Squared Means(SE)*) Total Mood Disturbance and six factor scores for younger and older postmenopausal women on estradiol and placebo treatments at Baseline, Time 2 and Time 3.

	Younger		Older	
	PLC	E2	PLC	E2
POMS – Baseline				
Total Mood Disturbance	−4.12 (3.7)	3.03 (3.7)	−8.78 (4.0)	6.79 (4.0)
Tension-Anxiety	3.53 (0.7)	4.77 (0.7)	3.25 (0.8)	6.57 (0.8)
Depression-Dejection	1.10 (0.4)	2.24 (0.4)	−0.14 (0.5)	−0.31 (0.5)
Anger-Hostility	0.19 (0.1)	0.41 (0.1)	0.05 (0.1)	0.07 (0.1)
Vigor-Activity	18.05 (2.4)	15.83 (2.4)	18.07 (2.6)	16.00 (2.6)
Fatigue-Inertia	3.88 (1.0)	3.37 (1.0)	2.75 (1.1)	2.72 (1.1)
Confusion-Bewilderment	2.4 (0.5)	3.81 (0.5)	3.71 (0.5)	4.41 (0.5)
POMS – Time 2				
Total Mood Disturbance	−3.94 (5.1)	13.08 (5.0)	−7.89 (5.5)	24.0 (5.5)
Tension-Anxiety	3.19 (1.0)	5.41 (1.0)	3.67 (1.0)	7.78 (1.04)
Depression-Dejection	−0.20 (0.3)	1.59 (0.3)	−0.10 (0.3)	0.42 (0.3)
Anger-Hostility	0.15 (0.2)	0.46 (0.2)	0.02 (0.2)	0.15 (0.2)
Vigor-Activity	15.69 (2.4)	12.06 (2.4)	16.07 (2.6)	11.60 (2.6)
Fatigue-Inertia	5.42 (1.7)	7.05 (1.7)	5.85 (1.9)	6.02 (1.9)
Confusion-Bewilderment	3.09 (0.6)	4.72 (0.6)	2.61 (0.7)	6.52 (0.7)
POMS – Time 3				
Total Mood Disturbance	1.66 (9.0)	33.33 (8.9)	−1.74 (9.8)	21.60 (9.8)
Tension-Anxiety	6.63 (1.8)	13.05 (1.8)	10.0 (2.0)	10.80 (2.0)
Depression-Dejection	0.44 (1.4)	6.72 (1.3)	−1.45 (1.48)	0.50 (1.5)
Anger-Hostility	0.64 (0.7)	0.36 (0.7)	0.10 (0.8)	2.50 (0.8)
Vigor-Activity	16.81 (2.4)	9.72 (2.4)	15.47 (2.6)	8.53 (2.6)
Fatigue-Inertia	3.83 (1.9)	5.42 (1.8)	5.46 (2.0)	5.83 (2.0)
Confusion-Bewilderment	3.96 (1.0)	6.22 (1.0)	4.07 (1.1)	7.46 (1.1)

Table 3

Cortisol levels at baseline and before discharge at the end of the study day for younger and older postmenopausal women after estradiol or placebo treatment.

	Younger		Older	
	PLC	E2	PLC	E2
Baseline	11.60 (2.9)	17.43 (2.6)	15.36 (2.3)	26.98 (2.0)
Time 2	7.97 (1.6)	11.49 (1.5)	7.48 (1.3)	16.46 (1.2)