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Estrogen and response to sertraline in postmenopausal women with major depressive disorder: A pilot study

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Abstract

Objective: Pilot study examining the effects of estrogen therapy (ET) on antidepressant response in postmenopausal women with major depressive disorder (MDD).
Methods: Twenty-two subjects received sertraline at 50 mg/day for one week, with an increase to 100 mg/day at week 2 for a 10-week trial. Transdermal estrogen or placebo patches 0.1 mg were randomly administered concurrent with the initiation of sertraline treatment. The 21 item Hamilton Depression Rating Scale (HDRS-21) was administered to all patients at baseline and weekly thereafter.
Results: Both groups showed a similar significant reduction in HDRS-21 scores by the end of the study. There was no significant difference between the two treatment groups at the end of the 10-week trial, but the women receiving sertraline with ET showed significantly greater early improvement (weeks 2–4) compared to the women receiving sertraline with placebo.
Conclusions: Sertraline is an effective antidepressant for postmenopausal women with MDD. ET does not alter the response rate to antidepressant therapy however ET may play a role in accelerating the antidepressant response.

Keywords: Postmenopausal; Estrogen therapy; Major depressive disorder; Antidepressant response

1. Introduction

The changing hormonal milieu during the perimenopausal transition is thought to contribute to the increased susceptibility of depression (Freeman et al., 2004; Rasgon et al., 2005) particularly when the perimenopausal period is long (Avis et al., 1994). However, postmenopause is associated with a decreased incidence of depression when other factors such as prior history of depression are excluded (Avis et al., 2001; Freeman et al., 2004; Weissman, 1979). In fact, the single most significant factor in the development of depression in menopause is a prior history of a depressive disorder (Amore et al., 2004; Dennerstein, 1996).

Available data show that postmenopausal women with low estrogen levels may be more susceptible to the development of depression (Almeida et al., 2005; Halbreich et al., 1995). Although depression in older postmenopausal women is shown to be associated with decreased serum estradiol, it is only when estradiol levels fall below a certain threshold (Almeida et al., 2005). A complex relationship between depression and estrogen status is likely due to a variety of confounding factors. For example, low serum estrogen levels are associated with decreased vigilance and abnormal frontal brain activation which, in turn is associated with increased depression (Saletu et al., 1996).

The failure to respond to antidepressant therapy may be in turn associated with low levels of estrogen (Schneider et al., 1997) but the use of estrogen/hormone therapy (E/HT) in the treatment of postmenopausal depression has

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yielded conflicting results (Amsterdam et al., 1999; Klaiber et al., 1979; Shapira et al., 1985). Whereas estrogen monotherapy has been shown to be beneficial for women with mild depressive symptoms (Ditkoff et al., 1991), it does not appear to be adequate as a primary treatment for postmenopausal women with major depressive disorder (Morrison et al., 2004; Schneider et al., 1997).

The influence of E/HT on antidepressant response is complex, and several factors may underlie the divergent findings between studies. These include differences in HT preparations (e.g., estrogen or estrogen plus progesterone, type of estrogen), study design (retrospective versus prospective), heterogeneity of clinical populations with respect to severity of depressive illness, phase of menopause, and type of antidepressants used (e.g., tricyclics versus SSRIs).

Few studies have examined the adjunctive use of ET alone to antidepressant response. Early studies with tricyclic antidepressants and a more recent retrospective analysis of selective serotonin reuptake inhibitors (SSRIs) did not demonstrate any benefit with the addition of ET in depressed women (Amsterdam et al., 1999; Prange et al., 1972; Shapira et al., 1985). In contrast, other studies have demonstrated better antidepressant response in women on ET compared to women taking placebo (Klaiber et al., 1979; Schneider et al., 1997).

The 5-HT (serotonin) system is known to contribute to the regulation of behavior and mood, especially in affective disorders (Meltzer, 1990; Schneider et al., 1997), and changes to this system in the course of normal aging may explain the delayed response to antidepressant treatment in later life. Studies suggest that estrogen is effective in reducing depressive symptoms in menopausal women (Zweifel and O'Brien, 1997) possibly by enhancing serotonin synthesis, decreasing serotonin reuptake (Shors and Leuner, 2003), augmenting serotonergic activity (Halbreich et al., 1995), and/or inhibiting of monoaminoxidase (MAO) (Luine et al., 1975). Additionally, ET has been shown to increase the number of sites available for active transport of 5-HT into brain cells (Sherwin and Suranyi-Cadotte, 1990). In contrast, HT that contains progesterone may mitigate some of the antidepressant effects of estrogen in women (Stahl, 1998) by increasing monoamine oxidase activity and GABA-inhibitory action resulting in mood-destabilization (Sherwin and Suranyi-Cadotte, 1990; Stoppe and Doren, 2002). Progesterone is commonly prescribed in addition to estrogen for prevention of uterine cancer and most, if not all, studies use hormone preparations that contain progesterone. Finally, menopause status, i.e., age and time since menopause may affect outcomes of studies of ET/HT in depression (Grigoriadis et al., 2003; Kornstein et al., 2000).

Results presented below are part of a larger study evaluating the neuroendocrine and neurocognitive effects of ET in postmenopausal women with and without major depressive disorder. The results below pertain to the effects of ET on antidepressant response. Neurocognitive findings have been published elsewhere (see Dunkin et al., 2005). Here, we report on the effects of ET vs. placebo on the overall response to sertraline in a group of postmenopausal women with a current diagnosis of unipolar major depression. We postulated that ET enhances the antidepressant response in a cohort of postmenopausal women with MDD.

2. Methods

2.1. Subjects

Postmenopausal women ages 41–65 with major depressive disorder (MDD) were recruited from the UCLA Mood Disorders Research Program and newspaper advertisements. Patients were required to be postmenopausal, i.e., one year or more post complete cessation of menstruation (plasma levels of follicle stimulating hormone (FSH) >40 mIU/ml, and estradiol (E2) levels <20 pg/ml), and to have had a normal mammogram, physical examination, and pelvic examination within 6 months of entrance into the study. Among exclusion criteria were: (1) significant menopausal symptoms (e.g. vasomotor symptoms such as hot flashes and night sweats; vaginal dryness), (2) history of substance abuse, smoking, or psychiatric disorders other than MDD, (3) current use of any hormonal medications including prednisone, insulin, thyroid replacement, as well as steroidal contraceptives or E/HT use within one year, (4) negative medical screen for history of a major organic disease (e.g., heart disease, diabetes, renal disease, clotting disorders, breast cancer, obesity, or current abnormal uterine bleeding). All but one subject had been treated for previous MDD episodes, but none had received treatment for their current episode prior to enrollment into the study.

All subjects signed the human subject protection consent form prior to enrollment into the study. Diagnosis of MDD was made on the basis of structured clinical interview for DSM-IV axis I disorders-patient edition (First et al., 1997). Patients were excluded if they did not meet diagnostic criteria for MDD or if they had any other Axis I psychiatric diagnoses. The Hamilton Rating Scale for Depression (HDRS) – 21 items (Hamilton, 1960) was administered to all patients at the screening and each weekly visit.

All subjects received sertraline in an open fashion. The dose for the first week of treatment was 50 mg/day with a subsequent increase to 100 mg/day after 7 days as this is the most effective dose for outpatients with unipolar major depressive disorder (Suri et al., 2000). It has also been shown that approximately 25% of patients need a higher dose that 50 mg/day (Bennie et al., 1995). ET or placebo was administered in a double-blinded fashion simultaneously with the initiation of antidepressant treatment using the transdermal estradiol system. ET (release rate 0.1 mg E2/day) or placebo patches were applied twice weekly at rotated application sites to ensure estrogen levels remained as steady as possible. Doses of sertraline and ET were similar for all subjects and were not altered throughout the trial period. Response to treatment was operationalized as a 50% decrease in HDRS-21 scores.