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The Psyche of Estrogen Part I: Estrogen and Mood

Introduction

There has been much controversy with regard to the risks and benefits of hormone replacement therapy (HRT) for postmenopausal women. Results from the JAMA 2002 Women's Health Initiative concluded that despite the benefits of fewer colorectal cancers and hip fractures, estrogen plus progestin showed higher incidences of coronary heart disease events, strokes, pulmonary embolisms, and invasive breast cancers. The results indicate that this regimen should not be initiated or continued for primary prevention of coronary heart disease. The results also raise the safety concerns of continued HRT in women with risk factors for coronary heart disease. Despite these recent findings, the benefits of estrogen therapy for menopausal symptoms such as hot flashes, vaginal dryness and lower urinary tract problems are well established. In addition, estrogen has been shown to have psychotherapeutic effects on mood, cognition, and dementia. The effects of estrogen on mood are the basis of this review.

Pharmacological effects

Estrogen has broad effects on the central nervous system (CNS) owing to its ability to alter the concentration and availability of neurotransmitters such as serotonin and noradrenaline. For example, estrogen increases the rate of degradation of monoamine oxidase, thus resulting in higher levels of catecholamines as well as serotonin. Estrogen also increases the binding of GABA agonists and upregulation of GABA receptors that appear to be altered in the depressed state. In regards to its effects on the dopamine system, some studies suggest that estrogen enhances the sensitivity of the dopaminergic system. However, other studies have shown that estrogen can also have inhibitory

effect on dopamine activity, specifically D₂ receptors. Although estrogen has some influence on the dopamine system, it is unclear whether these effects are clinically significant or relevant. A table highlighting estrogen's effects on central neurotransmitter levels is listed below.

Table 1 Neurotransmitter involvement in depression and estrogen's effects on central neurotransmitter levels

Depression	Estrogen
↓ Norepinephrine	↑ Norepinephrine
↓ GABA	↑ GABA
↓ Opioid	↑ Opioid
↓↑ Dopamine	↑↓ Dopamine
↑ β-Adrenergic receptors	↓ β-Adrenergic receptors
↑ MAO	↓ MAO

GABA. Gamma Amino Butyric Acid; MAO. monoamine oxidase

Evidence exists suggesting that female hormones have an impact on the susceptibility of mood disturbances in women. The following points illustrate this fact:

- ∨ Although the occurrence of major depression is twice as common in women as in men, this is only from the onset of puberty to menopause.
- ∨ In perimenopausal women, as many as 80% of women have been shown to develop mood disturbances.
- ∨ In premenopausal menstruating women, suicide attempts are more frequent in the first week and after the fourth week of the menstrual cycle when there is a fall in estradiol (E₂) production.

- ∇ In pregnant women, depression is rare in the last trimester when hormonal levels are stable, but rates climb to 20% in the postpartum period that coincides with a significant drop in estrogen levels.

These trends suggest that hormonal rates of change, rather than absolute hormonal values, are more indicative of affective disorders.

Relevant Studies

The proposed domino effect of depression in postmenopausal women proposes that estrogen deficiency results in vasomotor symptoms (such as hot flashes and night sweats) causing sleep disturbances which then lead to the psychological symptoms of depression. When women categorized as having “worsening PMS” with below normal estrogen levels were treated with low-dose estrogen, improved mood and energy level, with decreased irritability, was noted. These pharmacological effects of estrogen have formed the basis for utilizing this hormone in women with mood disorders. Since the first manuscript in 1932 identifying estrogen’s antidepressant effect in perimenopausal women, several reports have been published documenting the effects of estrogen therapy on mood. Nonetheless, there is no definitive agreement on the role of estrogen in the treatment of depression and other mood disorders. The following is a sampling of the many published reports associating estrogen therapy and mood.

A 1995 meta-analysis of 111 articles published on the psychological symptoms of women who were either naturally or surgically menopausal and subsequently treated with HRT concluded a lack of clear positive correlation between HRT and psychological improvement. Methodologically, these reports employed different HRT strategies including various forms and routes of administration of both estrogens and progestins. Several researchers from these 111 studies noted that progestins have an adverse effect on mood as demonstrated by worsening scores on depression rating scales. The mechanism by which progestins adversely affect mood may not be directly related to its effect on CNS neurotransmitters, but rather due to receptor depletion. This same meta-analysis did however find evidence to support the use of estrogen

replacement therapy (ERT) in improvement of psychological symptoms in women who have undergone surgical menopause. In fact, mood disorders occurred twice as frequently in women who had undergone surgical menopause when compared to women going through natural menopause. This supports the theory that the rate of change of estradiol, rather than the absolute value, is a critical variable influencing affective disorders.

A 1994 outpatient study conducted on 72 elderly depressed women showed a significant interaction between ERT (variable preparations) and fluoxetine 20mg. Patients who received ERT and fluoxetine showed statistically significant improved HAM-D scores compared to patients receiving ERT and placebo. Among the group of women who did not receive ERT, no significant benefit was noted between the fluoxetine-treated group and those treated with placebo. The authors concluded that ERT may augment fluoxetine response in elderly depressed outpatients and the presence of ERT should be considered as a factor in clinical trials investigating depression in elderly women.

An international study (2001) evaluated the efficacy of transdermal estrogen therapy for the treatment of depression in perimenopausal women. Fifty women with mixed diagnoses of major depression, dysthymic disorder and minor depressive disorder were randomized to either 7β-estradiol 100 mcg transdermal patches or placebo. Subjects were treated for 12 weeks which was followed by a 4-week washout period. The results showed that subjects responded similarly to estradiol treatment regardless of diagnosis. Remission of depression was observed in 68% of women treated with estradiol compared to 20% of the women in the placebo group. Women in the active treatment group maintained improvement in their depressive symptoms following the 4-week washout period in contrast to the women in the placebo group. The authors concluded that transdermal estradiol replacement was an effective treatment for depression in perimenopausal women.

Similar positive results were identified in a small 2002 study conducted in California. This study evaluated ERT (17β estradiol 0.3mg tablets each day given as Estratab®) in the treatment of depression using 16 perimenopausal women diagnosed with

major depressive disorder. One treatment arm consisted of 10 antidepressant and ERT naïve women who received ERT alone. The other group consisted of 6 women who were non-responders or partial responders to antidepressant and who received ERT in addition to existing treatment with fluoxetine (average dose 30 ±4.8mg). After the first week of treatment, all patients exhibited statistically significant clinical improvement as indicated by the HAM-D scores. Of the 10 perimenopausal depressed women receiving ERT alone, 6 had remitted, 3 responded partially to treatment and 1 did not respond by the end of the 8-week 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. This study suggested that ERT could, in some cases, be used alone, as an alternative to antidepressant treatment, or as an adjunct to antidepressants.

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Conclusion

Although there are data to support the use of estrogen in mood related disorders, the defined role of estrogen therapy as an antidepressant (either alone or as an augmenting agent) in post-menopausal women has not been adequately assessed. Studies have been heterogeneous in nature, each with its own inherent confounding variables. In addition, dosing and formulation of estrogen therapy employed in previous studies have varied. Nonetheless, there exists the possibility of an association between affective disorder or mood change and relative estrogen deficiency. Although ERT is often under utilized for the treatment of mood, its potential benefits merit further investigation.

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