Effects of Estrogen on Mood and Cognition in Aging Women

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The population of the world is aging rapidly and the majority of the elderly are women. The average life expectancy for women in the United States is 80 years. Thus, a woman may spend one-third or more of her life in the hypoestrogenic postmenopausal state. There has been increasing interest in understanding the scientific basis of the aging process and, in particular, the central nervous system and peripheral effects of low estrogen levels and the potential benefits of estrogen replacement therapy (ERT) for mood and cognition in aging women. In this article, clinical evaluation for ERT and the risks and benefits of ERT are discussed. Current data on estrogen and mood and cognition in older women are presented.

CLINICAL ASPECTS OF ERT

Estrogen is prescribed for postmenopausal women to treat the physical symptoms of menopause or to prevent medical problems associated with prolonged low estrogen levels. The physical symptoms of menopause (e.g., hot flushes or flashes, vaginal dryness, and urinary incontinence) are a direct result of declining levels of estrogen. The hot flush, which is a rapid feeling of warmth often accompanied by marked perspiration, is a hypothalamic response resulting from a change in estrogen status. For some women, hot flushes can be uncomfortable and result in sleep disturbance and the need to change clothes. Mental symptoms associated with menopause (e.g., sleep disturbances, mood swings, depression, anxiety, and memory problems) are also attributed to estrogen deficiency. ERT has also become a standard treatment for women undergoing oophorectomy to ease the abrupt hormonal transition of surgical menopause.

Benefits of Estrogen

Estrogen's role in the prevention of heart disease and osteoporosis has established the importance of estrogen replacement for maintenance of the health of postmenopausal women. Estrogen protects women against coronary heart disease by favorable alteration of lipids and vasodilatation of the coronary arteries. However, there is controversy as to whether estrogen prevents myocardial infarction in women with established coronary artery disease. Estrogen prevents bone loss associated with osteoporosis by decreasing bone resorption. ERT appears to reduce the risk of colon cancer. Finally, estrogen also increases collagen (the elasticizing agent of skin), thereby improving the atrophic vaginal wall and some urinary incontinence.

ERT Regimens

There are a wide variety of ERT regimens with equivalent effectiveness. These include oral tablets, transdermal patches, subcutaneous injections and implants, and percutaneous gels or creams, all of which deliver varying concentrations of estradiol or estrone. Oral preparations are the most commonly prescribed and
consist of conjugated or esterified estrogens. Therapeutic doses range from 0.3 to 1.25 mg/d. Because oral estrogens are first metabolized in the liver, transdermal and subcutaneous preparations more closely resemble endogenous hormone activity. However, transdermal patches are more expensive than oral forms. Alternatively, local estrogen preparations such as creams, pessaries, and vaginal inserts can help relieve local dryness and atrophy, but they have negligible systemic effects. Finally, subcutaneous injections and implants are effective, elevating hormone levels well beyond premenopausal ranges.

Risks of ERT

The major concerns of women receiving ERT are the long-term risk of breast cancer and the inconvenience of vaginal bleeding in those who have not had a hysterectomy. A review of the literature proposes that large doses of estrogen and prolonged administration (20+ years) are required to induce breast cancer. However, some experts find the risk greater. Supraphysiologic levels of estrogen (such as those achieved through ERT) can precipitate endometrial hyperplasia, uterine cancer, or both. Therefore, women who have not had a hysterectomy must supplement ERT with progesterin to stimulate endometrial shedding and reverse the propagative effects of estrogen.

Progesterin may be added to the ERT regimen either cyclically or continuously. Cyclic hormone replacement regimens consist of 2 to 10 weeks of estrogen alone followed by 10 to 14 days of progesterin and estrogen combined. The progesterin produces withdrawal bleeding monthly or quarterly, depending on the length of the cycle. Withdrawal bleeding can complicate compliance with hormone replacement therapy. Therefore, continuous combined estrogen–progesterin therapies have been developed to prevent cyclic bleeding. Although the addition of progesterone to ERT regimens actually reduces a woman’s chances of having uterine cancer, patients should have annual pelvic examinations. Similarly, women receiving hormone replacement therapy need annual mammograms to monitor the potential development of breast cancer.

Most other side effects associated with ERT such as breast tenderness or enlargement, bloating, nausea, and headache resolve within approximately 2 months. The irritation or rash experienced by 10% of transdermal patch users is easily managed. However, the more serious side effects such as exacerbation of gallbladder disease and development of blood clots require careful monitoring. ERT to prevent coronary artery disease and osteoporosis is likely to be a lifelong commitment. The patient must be educated regarding the risks and benefits of hormone replacement therapy as it applies specifically to her and assisted in choosing the therapy that best suits her needs.

Evaluating a Patient for ERT

Several critical features of a patient’s medical history determine her eligibility for ERT. Although estrogen has few interactions with other drugs and medical conditions, a complete physical examination, including a pelvic examination with Pap test, breast examination, and mammogram, should be performed prior to beginning ERT. Annual pelvic examinations and mammograms are an important part of ERT maintenance. Laboratory analyses of blood, including liver function tests and routine chemistries, should be performed to rule out active liver disease or gallbladder disease because both of these conditions are exacerbated by estrogen use. Serum hormone levels (eg, estradiol and follicle-stimulating hormone) can be documented prior to beginning ERT and periodically thereafter to evaluate absorption and assess adherence.

Contraindications to estrogen use are a history of hypercoagulable states, endocrine-related cancer (eg, breast, uterine, or ovarian), and undiagnosed postmenopausal vaginal bleeding. Although the risk is small—approximately 1 in 10,000 women are affected—estrogen use has been associated with deep venous thromboembolism. Because of the potential seriousness of deep venous thromboembolism or other hypercoagulable states, patients with such a history should be carefully assessed and counseled before beginning ERT. Similarly, estrogen use is cautioned in women with a personal history of breast, uterine, or ovarian cancer and in women who have a strong family history (classified as three or more blood relatives) of such cancers.
This is because estrogen may potentiate dormant cancer in these women. Vaginal bleeding in postmenopausal women may be indicative of endometrial hyperplasia, a precancerous condition, or a previously asymptomatic uterine carcinoma. Therefore, women with undiagnosed vaginal bleeding must be evaluated by a gynecologist before beginning ERT.

**ERT for Mood Disorders**

One of the most striking and consistent findings in psychiatric epidemiology is that women have higher rates of depression (2 to 3 times greater) than do men. Some psychiatric epidemiologists believe that the gender difference in major depression ends at age 50 to 54 years, consistent with the theories that implicate the menstrual cycle in the increased risk of depression in women.\(^4\) Because affective symptoms have been noted in women undergoing changes in reproductive endocrinology, differences in sex steroids have been investigated as factors that may contribute to the differential susceptibility to depression between women and men. Indeed, much of the data on natural and surgical menopause and clinical observations in women receiving antiestrogen therapy for breast cancer suggest that estrogen deficiency may actually contribute to the depressive symptoms and lack of response to antidepressant medication observed in aging women. However, this does not explain why postmenopausal women have a higher prevalence of depression than do men their age.

**Clinical Trials of ERT to Improve Mood**

Current data suggest that in both premenopausal women and surgically menopausal women, ERT is associated with improved mood. However, in unselected groups of depressed postmenopausal women, studies have shown a high response to placebo and no clear difference between estrogen and placebo.

Surgical menopause has been studied as a clinical model for the effects of estrogen on mood in women who have menopause through normal, age-related ovarian failure. In one study, premenopausal women who had had an oophorectomy received supraphysiologic doses of either estrogen, androgen, or a combination of the two and attained lower depression scores coincident with their higher plasma estrogen and testosterone levels.\(^5\) When hormones were withdrawn, the depression scores of all women who had had an oophorectomy were higher than those of the control subjects who had not had an oophorectomy. Thus, estrogens and androgens both appeared to improve depressive symptoms in these women.

In one study of perimenopausal women with depression, estrogen produced significant improvement in symptoms of tearfulness, emotional numbness, mood instability, and depression scores.\(^6\) In another study, perimenopausal women were randomly given one of three treatments for depressive symptoms: 50 mg of estradiol, 50 mg of estradiol plus 100 mg of testosterone, or placebo.\(^7\) Both hormonal treatments were significantly more effective than placebo at 2 months. However, at 4 months, depression scores increased somewhat in both hormonal groups. The response of these perimenopausal women can be contrasted with that of the postmenopausal women in the same study. The postmenopausal women responded to both active and placebo treatment interventions. Mean scores on psychological symptoms at 4 months demonstrated a decrease of approximately 49% in the placebo group, 25% in the estradiol group, and 51% in the estradiol plus testosterone group. Estrogen had either a specific effect of blocking the unusually high placebo effect in postmenopausal women or an independent dysphoric effect that is equal in magnitude to the placebo effect in this population.

In a more recent study, no difference in efficacy was found between transdermal estradiol therapy and placebo in treating menopausal depression.\(^8\) However, in a randomized, placebo-controlled trial, transdermal estradiol improved the quality of life for young, nondepressed postmenopausal women.\(^9\) The frequency of complaints related to health and involving life, family life, employment, housework, and hobbies was significantly reduced after 3 months of unopposed ERT (without progesterone). In young, Hispanic postmenopausal women without depression, two different doses of unopposed oral conjugated estrogens (0.625 and 1.25 mg) demonstrated a significant improvement in
depression scores. Apparently, beneficial effects could be achieved in nondepressed women by replacement doses of estrogen.

Thus, it is not clear from the literature whether estrogen is an antidepressant, a depressant, or a blocker of the unusually high placebo effect in most postmenopausal women with nonmajor depressive disorders. Either the studies themselves were flawed or there are as yet undetermined causes for heterogeneity in the antidepressant response to estrogen, particularly in the postmenopausal population.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are drugs developed to produce beneficial estrogen-like effects on bone and lipid metabolism. SERMs are estrogen antagonists in the breast and uterus, sites where estrogen can be carcinogenic. Because estrogen appears to have beneficial effects on the central nervous system of aging women, the identification of SERMs with beneficial effects on the central nervous system will be an important next step. Anecdotal clinical experiences of oncologists suggest that tamoxifen (a partial antiestrogen) increases depressive symptoms in some women with breast cancer. However, preliminary data from the National Surgical Adjuvant Breast and Bowel Project (>13,000 women) study suggest that tamoxifen use does not cause a significant increase in depressive symptoms in either premenopausal or postmenopausal women (P. Ganz, PhD, personal communication, December 1998).

There are few data regarding central nervous system functioning and raloxifene, the first antiestrogen to be labeled as a SERM. In a randomized, double-blind, placebo-controlled study, raloxifene was not associated with any changes in mood or cognition in postmenopausal women after 1 year. Raloxifene does not cause any significant adverse effects on the central nervous system of women after 1 year of use. Whether its beneficial effects on the central nervous system are comparable to those of estrogen will require further study.

Progestin and Mood

The effects of progestins on mood have clinical importance to a discussion of the effects of estrogens on mood. Progestins are prescribed to postmenopausal women receiving ERT to prevent endometrial cancer that has been associated with unopposed estrogen. Certain metabolites of progesterone are known to bind to the GABA_A receptor and produce sedative effects. Progestins have been noted to produce dysphoric effects in some women. However, there has been little study of the effects of progestins on mood. A meta-analysis of the effect of hormone replacement therapy on depressed mood suggested that although estrogen alone demonstrated a moderate effect in reducing depressed mood, progesterone alone and in combination with estrogen was associated with smaller reductions in depressed mood. However, these findings may not be generalizable to older women.

NEUROTRANSMITTERS THAT MEDIATE ESTROGEN’S EFFECTS ON MOOD

Estrogen and Serotoninergic Function

In attempts to understand estrogen’s effect on mood, interactions with various mood-regulating neurotransmitters have been investigated. There is now evidence that estrogen’s effect on mood might be mediated through interactions with serotoninergic mechanisms. Estrogen acts on the serotonin (5-HT) neurotransmitter mechanisms in the brain, affecting 5-HT synthesis, uptake, and receptor modulation. Whether estrogen increases serotoninergic antidepressant efficacy in postmenopausal women is not yet clear, although a retrospective analysis of the sertraline response in depressed postmenopausal women suggested that estrogen may improve the selective serotonin reuptake inhibitor (SSRI) response in this population. Thus, the presence of estrogen may be important to the serotoninergic antidepressant response in postmenopausal women, but prospective studies of estrogen versus placebo combined with a serotoninergic antidepressant are needed.

Estrogen and Monoamine Oxidase

ERT is known to affect levels of monoamine oxidase. In a study of nondepressed postmenopausal women, platelet monoamine oxidase activity was inversely correlated with estradiol levels after ERT. Thus, estrogen’s salutary
effects on mood may result from inhibition of monoamine oxidase.

**Estrogen and Nitric Oxide**

Preliminary data suggest that increased release of nitric oxide may also be involved in the beneficial effects of estrogen on mood in some women. In a double-blind, placebo-controlled study, ERT demonstrated improvement of mood in selected depressed postmenopausal women and was associated with higher levels of nitric oxide metabolites.¹⁶

**ERT FOR COGNITIVE DISORDERS**

Memory loss and lack of concentration are frequent complaints among aging women, beginning most often during the transition to menopause. Although mild age-related cognitive changes occur naturally, at least 10% of persons older than 65 years have some form of cognitive impairment ranging from mild deficits to dementia. Alzheimer’s disease accounts for more than half of all dementias.¹⁷ It appears that women have a higher risk of Alzheimer’s disease,¹⁷ but this has been debated. In persons older than 90 years, the incidence rates of dementia are 86.7 per 1,000 person-years for women and 15.0 per 1,000 person-years for men.¹⁸ The gender difference observed with dementia is thought to be due to the age and gender differences of Alzheimer’s disease rather than vascular dementia.¹⁸ Several lines of evidence suggest that ERT may prevent the development of dementia or that it might decrease the severity of dementia in postmenopausal women. As the elderly population increases, the possibility that ERT may prevent or delay the onset of dementia is an exciting area of investigation.

**Estrogen and Cognition in Nondemented Women**

Studies that have evaluated whether ERT improves cognitive performance in nondemented women have had inconsistent results. Kampen and Sherwin found that scores on paragraph recall, a test of short-term verbal memory, were better (higher) for women who used estrogen compared with those who did not.¹⁹ Other studies in nondemented postmenopausal women have shown improved verbal recall with estrogen use,²⁰,²¹ but conclusions are limited by problems in study design and data analysis. In larger, longitudinal and nonrandomized studies of estrogen and neuropsychological function, no consistent long-term effects have been found.²²,²³ Thus, there is no compelling evidence for improved neuropsychological function as measured by specific neuropsychological tests. If there is improved cognitive function, particularly verbal memory, with estrogen use, the effects may be too mild to measure consistently with current testing paradigms. However, evidence that estrogen decreases the risk of dementia is mounting and is discussed in the next section.

**ERT and the Risk of Dementia**

Well-designed prospective studies suggest that ERT may prevent dementia, especially dementia related to Alzheimer’s disease. Thus, the hypoestrogenic state of menopause is thought to contribute to the development of dementia. Two prospective cohort studies found significantly lower risk of dementia developing in postmenopausal women taking estrogen compared with those who were not.²⁴,²⁵ A recently published meta-analysis of studies evaluating estrogen and the risk of dementia demonstrates an odds ratio of 0.71 for the risk of dementia developing and an odds ratio of 0.71 for the risk of Alzheimer’s dementia, in particular, developing among estrogen users.²⁶ Although many of the individual studies in this research area are plagued by confounding criteria (e.g., the estrogen users are likely to be more affluent, better educated, and more health conscious), the strength of the design of the two prospective studies and the results of the meta-analysis by Yaffe et al.,²⁶ strongly support the notion that ERT decreases the risk of dementia.

**ERT for Alzheimer’s Disease**

ERT is being studied for its therapeutic effects on Alzheimer’s disease in women. Although the clinical course of age-related cognitive decline and Alzheimer’s disease is similar in men and women, some investigators believe that women with Alzheimer’s disease suffer greater deficits in naming ability, verbal memory, figural memory, and language. Two pilot studies support the
notion that estrogen use results in cognitive improvement in patients with Alzheimer's disease. However, these trials were neither blinded nor placebo controlled. Other, short-term studies of patients with Alzheimer's disease demonstrate improved performance on at least one cognitive task with ERT, but not on other tasks. Larger, longitudinal clinical trials evaluating estrogen's role in the treatment of Alzheimer's disease are under way.

Mechanisms of Estrogen's Effect on Cognition

There are several viable theories explaining how estrogens may affect neuropsychological function. These include (1) modulation of neurotransmitters, particularly acetylcholine; (2) enhancement of cerebral blood flow; and (3) interactions with the gene thought to be important to Alzheimer's disease, apolipoprotein E (apoE). Cholinergic neurons in the brain project into the hippocampus and cortex, areas that play a critical role in cognitive processes. Animal studies have shown that ERT in oophorectomized rats is associated with an increase in the release of acetylcholine and survival of cholinergic neurons. This increase in acetylcholine activity correlates with superior performance on behavioral memory tasks in rats treated with estrogen. It is well established that Alzheimer's disease is associated with a significant loss of cholinergic neurons in the brain, and that the clinical course of Alzheimer's disease is a progressive loss of learning, memory, and other cognitive functions. Thus, it appears that estrogen may play a role in the preservation and enhancement of cholinergic neurons, thereby preserving cognitive function in women with dementia.

Estrogen prevents vascular disease in women and has vasodilatory effects on diseased blood vessels. Estrogen also improves blood flow to the brain, particularly to regions affected by neurodegenerative processes such as Alzheimer's disease. Potentially, estrogen's improvement of cognitive function in patients with dementia may be attributed to its enhancement of regional cerebral blood flow. In fact, in one study, postmenopausal women with cerebral vascular disease treated with estrogen showed significant improvement on measures of cognitive function. This improvement was associated with increases in cerebral blood flow.

Theoretically, estrogen could also reduce the risk of Alzheimer's disease in women via alterations in apoE. The apoE gene has recently been identified as a major biological risk factor for Alzheimer's disease. Treatment with estradiol modulates expression of apoE in rodents and enhances synaptic sprouting in response to injury through an apoE-dependent mechanism. Thus, the interaction between estrogen and the apoE gene may be important in understanding Alzheimer's disease.

CONCLUSION

Estrogen is recommended for postmenopausal women for the prevention of osteoporosis and heart disease. There are no conclusive data on the effects of estrogen on mood in postmenopausal women. Current data suggest that estrogen improves mood in surgically menopausal, perimenopausal, and nondepressed postmenopausal women. There are no data to support the use of estrogen alone for postmenopausal major depression. Retrospective data suggest that estrogen may improve the antidepressant response to SSRIs in postmenopausal women. Although research data are minimal, this is a reasonable treatment option to explore for the depressed postmenopausal patient with a partial response to SSRIs who is interested in ERT.

Data from well-designed prospective studies suggest that estrogen may decrease the risk of dementia and Alzheimer's disease, in particular. No consistent specific area of neuropsychological benefit has been demonstrated for the short-term use of estrogen for demented and nondemented postmenopausal women. The role of estrogen and other hormones in the prevention and treatment of mood and cognitive symptoms in aging women is complex and requires further study.

REFERENCES


