Effects of Estrogen on Cognition, Mood, and Degenerative Brain Diseases

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Objective: To review research findings on the effects of estrogen on cognition, mood, memory, and degenerative brain disease in women.

Data Sources: English-language journal articles published primarily since 1995, retrieved from a MEDLINE search and from bibliographies of selected reviews.

Study Selection: Investigational studies, clinical trials, and review articles examining the effects of estrogen on the central nervous system.

Data Synthesis: Although scientific study of the brain is in its infancy, numerous studies indicate that estrogen is essential to optimal brain function. Estrogen has been shown to increase cerebral blood flow, act as an anti-inflammatory agent, enhance activity at neuronal synapses, and exert direct neuroprotective and neurotrophic effects on brain tissue. Through these varied mechanisms, estrogen strongly influences mood and cognition, and the decline of this hormone at menopause can produce significant emotional and cognitive problems in women.

Conclusion: Pharmacists can educate women about the various mood and memory changes that can occur during perimenopause and how estrogen replacement therapy may lead to improvements in brain function. The potential use of estrogen replacement therapy to reduce the risk of Alzheimer's disease and ease the symptoms of Parkinson's disease could have a profound effect on women, their families, and society as a whole.

The brain remains the least understood of all major organs. The precise mechanisms of the very characteristics we use to define our humanity, cognition and affect, remain an enigma. Afflictions such as Alzheimer's disease and Parkinson's disease continue to compromise the lives of millions, even as scientists strive to find effective treatments.

Recent research in neurophysiology has provided valuable clues to some of these mysteries. Computed tomography scans and magnetic resonance imaging (MRI) have recently allowed researchers to localize certain functions and diseases to specific areas of the brain. Studies of neurotransmitters have deepened understanding of depression and made possible the development of new antidepressants. Much additional research has focused on the function of sex hormones in the brain, and neuroscientists now appreciate that gonadal steroids are perhaps the most powerful peripherally generated biologic signals to the central nervous system (CNS).

This last finding has significant implications for women, who normally experience a profound decrease in estrogen and progesterone production at menopause. Symptoms that arise during that time, including memory problems, mood changes, and hot flushes, have been related to lack of estrogen activity in the brain. Alzheimer's disease, which is more prevalent in women than in men, has also been associated with estrogen deficiency.

With a knowledge of these relationships, pharmacists can advise patients about the possible source of symptoms they may experience at mid-life. Pharmacists can also play an important role in educating women about the benefits of estrogen replacement therapy (ERT), including improved cognition, enhanced sense of well-being, and reduced risk of Alzheimer's disease.

Estrogen directly influences brain function throughestrogen receptors located on neurons in multiple areas of the brain.[1,2] The hormone also appears to have direct membrane-mediated effects on neurons. Its effects are both neuroprotective and neurotrophic.[2] Estrogen has been shown to protect isolated neurons in vitro from oxidative stress, ischemic injury, hypoglycemic injury, and damage by amyloid protein, which is implicated in the pathogenesis of Alzheimer's disease.[2] It also stimulates production of nerve growth factors, thereby promoting neuronal growth

and viability, repair of damaged neurons, and dendritic branching. Brain aging and Alzheimer's disease are thought to represent an imbalance between neuronal injury and repair.[1-3]

At neuronal synapses, estrogen increases the concentration of neurotransmitters such as serotonin, dopamine, and norepinephrine.[4] It affects their release, reuptake, and enzymatic inactivation. It also increases the number of receptors for these neurotransmitters.[2]

Another significant effect of estrogen on the brain is its influence on blood supply. Unlike many other organs, which can use reserve fuel sources or alternative metabolic pathways, the brain depends solely on blood flow to function. In fact, roughly one-third of the brain is composed of blood vessels.[5] Estrogen increases cerebral perfusion, presumably by mechanisms similar to those known to occur in the coronary arteries.[3,6,7] By binding to receptors in the endothelium, estrogen stimulates the release of nitric oxide, which causes vasodilation.

Recent studies have documented the vasodilatory effect of estrogen. Using Doppler flow ultrasound, Penotti et al.[6] examined the carotid and cerebral arteries of 120 women aged 20 to 59 years who were not taking any hormones. Compared with the premenopausal women participating in the study, the postmenopausal women exhibited a significant decrease in blood flow, and flow decreased further with time past menopause. No significant decrease was attributable to aging alone. Another Doppler flow study of 63 postmenopausal women before and after starting ERT demonstrated that this hormonal therapy reduced impedance to blood flow in carotid circulation.[7] Improvement in perfusion was significant by the second month of ERT, and a gradual increase in perfusion continued over the entire 52 weeks of the study.

Estrogen also influences cerebral blood supply by acting as an anti-inflammatory agent at the blood vessel wall, protecting it from damage by cytokines and free radicals and impeding plaque formation.[1,2,8] Pretreatment with estrogen has been demonstrated to prevent damage to blood vessel walls when a toxic protein is injected into rats' cerebral arteries.[9] MRI was used to document ischemic brain injury in 210 postmenopausal women followed for 10 years.[10] The 70 women taking ERT in this study had fewer and smaller damaged areas than the 140 controls. In addition, the longer the duration of ERT use, the smaller the total area of ischemia.

Hot flushes, the classic symptom of menopause, are experienced by up to 85% of perimenopausal women.[11] (Perimenopause begins several years before menopause, when ovarian function starts to decline, and continues for several years after menopause, until ovarian function has reached its nadir.) A hot flush consists of a sudden sensation of heat in the upper body, often followed by perspiration and a chill. Peripheral vasodilation, tachycardia, decreased skin resistance, and sweating have all been documented to occur during a hot flush. Although poorly understood, the episodes certainly originate in the brain, most likely as a direct response to hypoestrogenism in the thermoregulatory center of the hypothalamus.[12]

It now appears that hot flushes are not merely symptoms of low estrogen levels; they may themselves lead to other neurologic problems. In oophorectomized women, hot flushes have been directly correlated with memory impairment.[13] In addition, single proton emission computed tomography (SPECT) of healthy menopausal women revealed decreased cerebral blood flow during hot flushes.[14] The greatest change occurred in the hippocampus, a center for memory and cognition. Regional patterns of cerebral blood flow during hot flushes resembled those characteristic of Alzheimer's disease. ERT resolved the hot flushes and restored normal patterns of cerebral blood flow.

Based on this evidence, reproductive biologists have hypothesized that hot flushes contribute to degenerative or aging changes in the brain.[15] Frequent vasoconstrictive episodes might lead to cerebral ischemia and free radical formation. The resulting damage may be analogous to that seen in the coronary arteries with plaque formation. The population of healthy neurons might be reduced, particularly in the hippocampus, leaving the brain with impaired ability to tolerate the neurodegenerative processes of aging and Alzheimer's disease.

Even in healthy older women, brain volume begins to decline as estrogen levels fall in the perimenopausal period.[16] This atrophy occurs particularly in the hippocampus and parietal lobe, areas primarily associated with memory and cognition. A similar loss in brain volume does not begin in men until a decade later (around age 60), most likely because male sex hormone production declines much more gradually with age. In fact, because of aromatization of testosterone to estrogen, men over the age of 60 have approximately three times more circulating estradiol than women of a similar age.[17]

In women, these cerebral changes may contribute to the frequent perimenopausal complaints of decreased mental clarity and short-term, verbal memory problems (see Table 1).[18] Studies of the effects of ERT on cognitive symptoms have generated inconsistent results, perhaps because dropouts and nonparticipants are more likely to be cognitively impaired.[19] A recent meta-analysis yielded only weak evidence that ERT improves cognition and prevents dementia.[20] However, many research groups have found a significant association between ERT and cognition, particularly in the area of verbal memory. For example, in one study of 727 postmenopausal women, history of estrogen use was associated with significantly higher scores on verbal memory and abstract reasoning tests.[21]

Shaywitz et al.[22] used positron emission tomography to observe brain activity in 46 postmenopausal women performing cognitive tasks. In a crossover design, participants were given conjugated equine estrogens (CEE; 1.25 mg) or an identical placebo for 21 days, then, after a washout period, given the opposite treatment. During the cognitive tasks, women taking CEE demonstrated increased activation of areas involved in verbal and nonverbal memory.

Loss of cognitive function also can be related to endogenous estrogen deficiency. In the Study of Osteoporotic Fractures,[23] women in the lowest quintile for bone density also exhibited the highest incidence of dementia.[23] In another study, premenopausal women who underwent oophorectomy, which results in abrupt and severe decline in estrogen levels, were more likely than naturally postmenopausal women to exhibit memory impairment 5 years later.[24] Decline in cognitive function has been observed as early as 2 months postoperatively,[25] and has been shown to be reversible with ERT.[26]

Another effect of menopause and loss of estrogen on the brain is a slowdown in the speed of brain processing.[27] This change is particularly significant for postural stability, which depends on recognition of sensory input and initiation of an appropriate physical response. After menopause, the incidence of falls among women is three times that of men.[1] The risk of fracture in women with osteoporosis appears to be related not only to bone density, but also to postural stability.[28,29]

Brain processing speed and postural stability are significantly improved with ERT. One study documented a 60% decreased risk of falling in a group of postmenopausal women on ERT compared with a group not taking it.[28] Another study compared sway velocity (an indicator of tendency to fall) in 16 postmenopausal long-term users of 17 b-estradiol and 16 postmenopausal women who had never taken estrogen.[29] The postmenopausal women taking estrogen evidenced postural stability similar to premenopausal women, whereas balance deteriorated significantly in the postmenopausal women not on ERT. The fact that ERT improves both postural stability and bone density likely explains why it has proven superior to raloxifene[30] and alendronate[31] in preventing nonvertebral, fall-related fractures.

In general, perimenopausal women do not appear to be more susceptible to clinical depression than women at other life stages.[32] However, in certain groups of women, including those with a history of postpartum or premenstrual depression, those who undergo the abrupt hormonal changes of surgical menopause, and those in whom perimenopause is prolonged, risk for depression may be increased during this time.[33] In addition, up to 80% of perimenopausal women develop mild depressive symptoms beyond the malaise that might be attributed to hot flushes, night sweats, and insomnia.[34] These symptoms may occur because areas of the brain involved in emotion are rich in estrogen receptors and estrogen directly influences synaptic concentrations of neurotransmitters.

The neurotransmitter serotonin plays a key role at brain synapses involved in mood regulation. In oophorectomized rats, administration of estradiol induced a significant increase in serotonin uptake in the frontal cortex and hypothalamus.[35] Also in rats, the antidepressant imipramine did not exert its therapeutic effect on synaptic concentrations of serotonin unless estrogen was present.[36]

In women of reproductive age, serum estradiol levels have been shown to correlate positively with blood levels of serotonin.[37] Researchers have also demonstrated that blood serotonin is decreased in postmenopausal women and that ERT raises it to premenopausal levels.[37] Estrogen also competes with tryptophan, the precursor of serotonin, for binding sites on plasma albumin, thus making tryptophan more available to the CNS.[38]

Estrogen affects concentrations of other neurotransmitters and neuromodulators as well. It competitively inhibits the enzyme that inactivates norepinephrine, thus providing a stimulatory effect similar to that of many antidepressant medications.[39] Like pharmaceutical monoamine oxidase (MAO) inhibitors, estrogen reduces MAO activity, resulting in higher levels of both catecholamines and serotonin in the brain.[40] Estrogen also increases opioid and endorphin production by the hypothalamus.[41]

Clinically, women taking the selective estrogen receptor modulator tamoxifen[42] and women on gonadotropin-releasing hormone therapy,[43] which induces hypoestrogenism, have been shown to exhibit increased depressive symptomatology. In randomized controlled trials oophorectomized and perimenopausal women undergoing ERT have experienced a heightened sense of well-being and improved mood.[44] A recent meta-analysis of 26 studies in postmenopausal women found that ERT had a moderate-to-large beneficial effect on depressed mood.[45] This positive effect often was not apparent until after 3 months of treatment, was dampened by the addition of a progestin, and was enhanced by supplementation with an androgen.

With the aging of the "baby boom" generation and increasing life expectancy, dementia has become a significant social and economic problem in the United States. Alzheimer's disease, a progressive disorder that impairs memory, thinking, and behavior, accounts for two-thirds of these dementia cases.[46] The disease is two to three times more common in women, a fact not fully explained by the reality that women live longer on average than men.[47]

The cognitive difficulties of Alzheimer's disease patients appear to be related to the presence of abnormal protein deposits in the brain. Accumulations of an abnormal, neurotoxic form of b-amyloid is characteristic of the disease.[48] Increasing evidence implicates inflammation in the pathogenesis of Alzheimer's disease.[49] b-amyloid fragments and other proteins may be either the cause or an effect of an exaggerated inflammatory response to brain or cerebral blood vessel injury. This theory is supported by the fact that anti-inflammatory drugs appear to provide some protection against Alzheimer's disease.[50]

Alzheimer's disease is at least partly genetic in origin.[51] The early-onset variety, which accounts for only 5% of cases, can be traced to autosomal dominant mutations in genes encoding for presenilin protein or amyloid protein.[51] Late-onset Alzheimer's, which represents the vast majority of cases, occurs after age 60.[51] This type can be related to multiple factors, including defects in several "susceptibility genes." The most common of these, a recessive gene located on chromosome 19, codes for apolipoprotein E, which aids in repairing damaged neurons. Approximately 15% to 20% of persons of European descent carry at least one abnormal copy of this gene. Whether it is expressed or not depends on multiple factors including female gender, low educational attainment, prior head injury, lack of exposure to anti-inflammatory agents, and, for women, lack of estrogen after menopause.[51]

Estrogen levels might affect the course of Alzheimer's disease in several ways.[1] Because the disease is thought to be inflammatory in nature, loss of estrogen and its anti-inflammatory effects might contribute to the development of Alzheimer's disease. Conversely, increased cerebral blood flow, along with neurotrophic and neuroprotective effects,might render the brain more resistant to the disease process. In addition, estrogen appears to have the ability to increase expression of the apolipoprotein E gene[52] and reduce formation of b-amyloid.[53]

Almost all epidemiologic studies performed thus far indicate that ERT can prevent or delay onset of Alzheimer's disease (see Table 2).[54-60] In the most recent, the Italian Longitudinal Study on Aging,[54] 2,816 randomly selected postmenopausal women were tested for Alzheimer's disease and senile dementia. Those who had ever used ERT had a 70% reduction in Alzheimer's disease risk, even when the data were adjusted for age, age at menopause, education, smoking, alcohol use, and parity.

The largest study on ERT involved women from the Leisure World retirement community in southern California.[55,60] A review of death certificates revealed that women who had ever taken ERT were one-third less likely to develop Alzheimer's disease. Moreover, the risk of Alzheimer's disease decreased significantly with increasing estrogen dose and with increasing duration of estrogen use.[60]

The Baltimore Longitudinal Study of Aging[56] is the only prospective study done thus far, and, although relatively small, it demonstrated the most dramatic effect to date. In 472 perimenopausal and postmenopausal women followed for 16 years, the risk of Alzheimer's disease was reduced by 54% in women who reported having ever used ERT.

Interestingly, reduced risk of Alzheimer's disease has been demonstrated even in women who take ERT only during the menopausal transition, presumably to prevent hot flushes. One group of researchers observed a 50% decrease in the disease in women on ERT for less than 1 year at the time of menopause.[57] This finding implies that neurons may be particularly susceptible to damage following an abrupt drop in estrogen levels and that, once damaged, neurons may be less able to respond to ERT. In a randomized, controlled trial in which 120 patients with established Alzheimer's disease received CEE 0.625 mg, CEE 1.25 mg, or placebo for 1 year, ERT failed to demonstrate a therapeutic effect.[61] However, ERT may potentiate the therapeutic effects of tacrine on the disease.[62]

Research on ERT and Alzheimer's disease is in its early stages, studies to date are retrospective and thus susceptible to bias. Notably, one population-based, case-control study involving 107 Alzheimer's disease patients and 120 age-matched controls failed to show a risk reduction in Alzheimer's disease among women who used ERT.[63] Nevertheless, prevention or delay of Alzheimer's disease appears to be a benefit of ERT that could offer substantial advantages to both women as individuals and society as a whole.

Parkinson's disease is a gradually progressive neurologic disorder characterized by tremor at rest, rigidity, bradykinesia (slowness of movement), and postural instability.[64] In patients with Parkinson's disease, dopamine-producing cells in the part of the brain known as the substantia nigra degenerate. Symptoms usually respond to treatment with levodopa for several years, after which the disease progresses despite this therapy. Recently, estrogen has been shown to potentiate the action of levodopa, and ERT to perhaps delay or prevent the onset of Parkinson's disease.

Animal models suggest numerous mechanisms by which estrogen may positively affect dopamine neurotransmission. Estrogen appears to be neuroprotective to dopamine-producing neurons.[65] It also increases sensitivity of neurons to dopamine[66] and decreases dopamine reuptake at synapses.[67]

Clinically, estrogen appears to exert a palliative effect on Parkinson's disease. One study correlated estrogen exposure (years of fertility plus years of ERT) with age at onset of Parkinson's disease. On average, women with low estrogen exposure developed the disease 6 years earlier than did women with high exposure.[68] In another study examining the medical histories of women recently diagnosed with Parkinson's disease, women who had taken ERT had significantly later onset of the disease and less severe symptoms.[69] ERT may also enhance cognition, especially memory, in women with Parkinson's disease,[70] and reduce the risk of developing Parkinson's disease-associated dementia.[67]

In addition, ERT appears to potentiate the effects of the anti-Parkinson's drug levodopa. Estrogen reduces the expression of catechol-O-methyltransferase (COMT),[72] the enzyme responsible for dopamine degradation. Because reduced COMT activity increases the bioavailability of dopamine, pharmacologic COMT inhibitors are often

used to enhance levodopa's effect. Estrogen has been shown to reduce levodopa response threshold,[73] levodopa clearance,[74] and the mean levodopa dose required in women.[75]

Research on ERT and Parkinson's disease is in its early stages, but results are promising regarding estrogen's effects on delayed onset, symptomatic improvement, and adjunctive treatment of the disease. Further study of these potential benefits is clearly warranted.

Patients often turn to pharmacists for information on risks and benefits of ERT (see Table 3).[76] Fear of breast cancer is foremost in many of their minds. Although this concern and other risks must be dealt with realistically, advantages of ERT should be carefully weighed against them. The emerging benefits of ERT on cerebral function merit serious consideration, especially in certain circumstances. Pharmacists can play an important role in educating patients about these potential benefits.

Many perimenopausal patients complain of decreased mental clarity and problems with short-term memory, and they may ask about gingko biloba and other preparations thought to enhance mental function. Pharmacists can educate these women that, when accompanied by other perimenopausal symptoms, cognitive problems may relate to estrogen deficiency and may respond most favorably to ERT.

Mood swings and mild depression are also common during perimenopause. Pharmacists and patients should be aware that these symptoms may be situational at this time of life, related to, among other issues, feelings about growing older, "empty nest syndrome," and the trials of caring for aging parents. However, these symptoms also may directly relate to estrogen deficiency. ERT can restore a sense of well-being by relieving hot flushes and insomnia, but patients should understand that it also exerts direct antidepressant effects. Mildly depressed perimenopausal women might be advised to discuss a trial of ERT with their physician before considering antidepressant medications. Of course, women with significant clinical depression should be referred to a mental health professional. Those with a history of serious postpartum or premenstrual depression also usually require referral. However, even women who take prescription antidepressants might consider asking their health care provider about adding ERT for its potentiating effect with these agents.[77]

The most effective forms and dosages of ERT for improving mood and cognition have not yet been determined. Much of the evidence for improvement has come from studies on CEE. Other forms of estrogen, including the new compounded preparations, are likely to yield similar results, but their effects are not yet substantiated by as much evidence. Some studies have indicated that transdermal estrogen may be preferable to oral therapy for psychological symptoms.[78] The continuous low blood levels of estrogen achieved with this form of therapy may more effectively increase serotonin at synapses.

Additional considerations in treating perimenopausal mood disturbances involve other hormones frequently used with ERT. To prevent endometrial proliferation, women with a uterus require hormone replacement therapy (HRT) – the addition of a progestin to estrogen therapy. Unfortunately, because they increase MAO activity and because they have an overall sedative effect, progestin tends to counteract estrogen's mood-elevating properties.[79] Pharmacists can suggest various strategies to address this problem, including minimizing the dose of progestin and recommending a trial of one of the newer progestin formulations, such as micronized progesterone, norethindrone acetate, and norgestimate. Cyclic mood and behavioral changes associated with sequential HRT can be avoided with continuous combined estrogen-plus-progestin therapy.

Because testosterone levels can also decline in postmenopausal women, androgens have been added to ERT to enhance both mood and libido.[80] Indeed, the largest study of mood and ERT substantiated the fact that depressed mood responded best to androgen or estrogen plus an androgen.[45] Pharmacists can counsel women about these positive effects of taking androgens, but should also warn them about possible androgenic side effects (acne, hirsutism), adverse changes in the lipid profile, and rare hepatic damage.[81]

When discussing the risks and benefits of ERT with patients, pharmacists should inquire about family history, probing such factors as coronary artery disease and osteoporosis in close relatives. Because Alzheimer's disease also has a significant genetic component, patients with a family history of the disorder should be encouraged to ask their physician about using estrogen to prevent or delay onset of this disease. These benefits may in fact apply to a substantial number of women, with or without a family history of the disease. By current estimates, a 65-year-old woman has a lifetime risk of one in three for developing Alzheimer's disease.[1] In addition, the possible relationship between hot flushes and Alzheimer's disease should be considered. Patients who experience frequent and/or severe hot flushes can be advised that ERT will not only ameliorate their symptoms but may also affect their cognitive abilities in the future.

The optimal dose and form of ERT for prophylaxis against Alzheimer's disease are also unknown. Most studies have involved the use of CEE, and the findings from some seem to indicate an increasing effect with increasing dose and duration of therapy. However, timing of ERT may be the most important factor. Estrogen given during the menopausal transition, especially in the presence of hot flushes, may have the most effect on future cognitive changes.

Although research on the brain is in its infancy, we now know that estrogen is essential to optimal brain function. The hormone has been shown to increase cerebral blood flow, decrease inflammatory changes, enhance activity at neuronal synapses, and exert direct neuroprotective and neurotrophic effects on brain tissue. Through all of these mechanisms, estrogen strongly influences mood and cognition, and the loss of the hormone at menopause can produce significant emotional and cognitive problems.

Pharmacists can play an important role in helping women understand these symptoms and how ERT can alleviate them. Pharmacists are also well positioned to educate women about the emerging long-term benefits of ERT on cerebral function and preventing or delaying onset of Alzheimer's disease and Parkinson's disease. Forestalling these disabling diseases could have a profound effect on women and their families, and would benefit society as a whole.

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