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# FOR YOUR INFORMATION



## PHARMACY NEWSLETTER



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### **The Psyche of Estrogen Part II: Estrogen and Cognitive Function**

#### **Introduction**

Aside from the well-established hormonal replacement value, estrogen therapy has been found useful in other areas, including mood, cognition, and dementia. This is the second in a series of two newsletters evaluating the psychotherapeutic effects of estrogen. The effects of estrogen on cognitive function are basis of this review.

#### **CNS Effects of Estrogen**

Current data demonstrate a potential for estrogens in neuroprotection, exerted in particular through the preservation of neural plasticity and neurotransmitter pathways. Estrogen increases blood flow and glucose utilization in the brain, displays anti-inflammatory and antioxidant properties, lowers lipoprotein levels in the blood, and induces choline acetyltransferase and acetylcholinesterase activity. Estrogen also regulates synaptogenesis in the hippocampus; a region in the brain intimately involved in memory and severely affected by the pathology of Alzheimer's disease (AD). These effects of estrogen in the central nervous system are thought to modulate various aspects of cognitive functioning. To this end, estrogen levels may impact the course of dementia in several ways.

#### **Hot Flushes and Cerebral Blood Flow**

Hot flushes, the classic symptom of menopause, are experienced by up to 85% of perimenopausal women. It now appears that hot flushes are not only symptoms of low estrogen levels, but may lead to other neurological problems. Studies have revealed hot flushes to be associated with decreased regional patterns of cerebral blood flow, a phenomenon also characteristic of that in AD. An abnormal pattern of cerebral blood flow predisposes the individual to developing cerebral ischemia and free radical

formation. The resultant damage could reduce the population of healthy neurons leaving the brain with impaired ability to tolerate the neurodegenerative processes of aging. In this regard, hot flushes have been hypothesized to contribute to degenerative or aging changes in the brain. Estrogen therapy can resolve the hot flushes and restore normal patterns of cerebral blood flow.

#### **Bone Density**

In the Study of Osteoporotic Fractures, women in the lowest quintile for bone density also exhibited the highest incidence of dementia. Loss of estrogen in menopause can slow the speed of brain processing. 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. The risk of fracture in women with osteoporosis appears to be related not only to bone density, but also to postural stability. The fact that estrogen improves both postural stability and bone density likely explains why it has proven superior to raloxifene and alendronate in preventing nonvertebral fall-related fractures. More importantly, increased bone density can intuitively decrease the injuries and/or death related to fall-related fractures, particularly among elderly individuals with AD.

#### **Response to Stress**

Chronic stress is believed to accelerate the aging of the brain by activating the hypothalamic-pituitary axis and increasing production of the stress hormone cortisol. Brief exposure of the brain to stress has been shown to enhance memory whereas sustained exposure results in long-lasting and even irreversible

impairment of the hippocampus, the region of the brain involved in declarative memory. Estrogen dampens the response of the hypothalamic-pituitary axis to stress, which may protect the brain from the damaging effects of glucocorticoids.

### **Estrogen and Cognition**

Besides neuroprotection, endogenous estrogens can influence cognitive functioning in women. It is thought that the facilitating action of estradiol on cognitive functions such as learning, short-term memory and attention may be directly related to genomic estrogenic effects as a growth factor on estrogen-responsive dendritic neurons with new synapse formation.

### **Studies**

There have been numerous published reports investigating the effects of estrogen therapy on cognitive function. A small study conducted by Philips and Sherwin on bilaterally oophorectomized women who were given estradiol valerate intramuscular 10 mg monthly found that only immediate memory recall and associated learning improved, whereas delayed recall, visual reproduction and digit span did not. In a large study by Barret-Connor and Kritz-silverstein of 800 women age 65 to 95 years, no improvement was seen in the estrogen-treated groups in terms of mental status, visual and verbal memory. Baker et al randomized 45 women to receive estrogen alone, estrogen plus progesterone, estrogen plus testosterone, or placebo. In this 3-month study, results showed that the women who received estrogen alone or with another hormone performed significantly better on verbal memory tests than those receiving the placebo. In addition, the estrogen-treated group as a whole outperformed the placebo group on a test of visual-spatial memory.

From a 2001 meta-analysis that evaluated hormone replacement therapy (HRT) and cognition, results showed HRT to be beneficial in cognitive functions in women with menopausal symptoms, but not in asymptomatic women. However, it may not affect all cognitive processes equally. In symptomatic postmenopausal women, estrogen improved cognitive performance, especially on tests of verbal

memory, vigilance, reasoning and motor speed. However, there were inconsistent effects on visual recall, working memory, complex attention, mental tracking, mental status or verbal function. No conclusions can be drawn about progestins or whether specific dosages or formulations of estrogen are more protective.

While reports of therapeutic estrogen effects on cognition have not been unanimous, the consensus appears to be that some modalities, particularly memory, are improved. However, the extent of improvement in cognitive function from estrogen therapy has yet to be determined from the current literature. Large double-blind, placebo controlled trials with intervention arms containing estrogen with and without progestins are needed and two such primary prevention trials are under way.

### **Estrogen and Dementia**

Alzheimer's disease is two to three times more common in women; a fact not fully explained by the reality that women live longer than men. The cognitive difficulties of Alzheimer's patients appear to be related to the presence of the abnormal protein deposits in the brain. Cholinergic deficit is also contributory to worsening of symptoms of AD. The cholinergic system is crucially involved in several cognitive processes including attention, learning memory and arousal. The currently approved treatments for memory loss associated with AD are those designed to enhance cholinergic function. Research in rats suggests that estrogens facilitate the actions of the cholinergic system while estrogen deprivation results in compromised cholinergic function and learning impairment.

In addition, increasing evidence implicates inflammation in the pathogenesis of AD, which is supported by the fact that anti-inflammatory drugs appear to provide some protection against this condition. It has become apparent that estrogens may have major effects on the cerebral vasculature and glial cells. Although the majority of research in this area have come from animal studies, a combination of neuronal and vascular actions of estrogens may enhance memory and provide neuroprotection as seen in the following table.

**Table 1 Beneficial actions of estrogen in Alzheimer's disease**

<b>Neuronal actions</b>	<b>Vascular actions</b>
<i>Enhanced</i>	<i>Enhanced</i>
Neurotransmitter function (acetylcholine, serotonin, catecholamine)	Endothelial protection
Ion channel activity	Nitric oxide production
Axonal regeneration/synaptogenesis	Vasodilatation
Production of neurotropic factors	Blood flow
Anti-inflammatory mechanisms	Blood-brain barrier integrity
Antioxidant protection	Lipid profile
	Insulin sensitivity
	Anti-inflammatory mechanisms
	Antioxidant protection
	Angiogenesis
<i>Diminished</i>	<i>Diminished</i>
Oxidative damage	Oxidative damage
Apoptosis	Apoptosis
Amyloid- $\beta$ secretion	Platelet aggregation
Monoamine oxidase activity	Coagulation factors
Cerebral ischemia	Proliferation of smooth muscle cells
GABA activity	Atherosclerosis
	Cytokine production

GABA = gamma amino butyric acid

## Studies

In one study conducted on 59 postmenopausal women and 38 men, magnetic resonance imaging (MRI) was used to measure hippocampal volumes. The researchers found that the hippocampi in women taking estrogen were larger in volume than in the women who did not take estrogen and also larger than in the male subjects. The difference of size was roughly on the order of 10% after the volumes were corrected for head size. In men, a similar loss in brain volume does not begin until a decade later (around age 60), most likely because male sex hormone production declines much more gradually with age. Because of the aromatization of testosterone to estrogen, men over the age of 60 have approximately three times more circulating estradiol in comparison to women of similar age. The hippocampus, which is intimately involved in memory, is also severely affected by the pathology of AD. People with AD have smaller hippocampal volumes than those of the same age who don't have the disease. It appears that to some extent the volume of the hippocampus in older people seems to be a risk factor for progression to AD.

A 1998 Italian longitudinal study on aging selected randomly 2,816 postmenopausal women who were tested for AD and senile dementia. Those who had ever used ERT were one-third less likely to develop AD in comparison to women who had not been treated with estrogen. This study was also able to show that increasing estrogen dose and with increase duration of estrogen use correlated with a significant decrease in risk for developing AD.

Almost all epidemiological studies performed to date indicate that estrogen replacement can prevent or delay onset of AD. However, neutral effects have been reported. For example, a randomized,

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## References - November and December 2002

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controlled trial of 120 patients with established AD found no therapeutic effect in subjects treated with conjugated equine estrogens 0.625 mg, 1.25 mg or placebo for 1 year.

## Conclusion

Evidence has clearly shown that estrogen is essential to optimal brain function. Specifically, estrogen 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 can influence mood and cognition, and the loss of the hormone at menopause can produce significant emotional and cognitive problems. It is not surprising that estrogens used therapeutically can have a diverse range of benefits. There is evidence that exogenous estrogens can protect against and improve the symptoms of dementia.

However there are limitations with the studies, which include small sample sizes and variable assessment tools that are employed. In addition, exposure to hormonal replacement was often assessed retrospectively.

Due to heterogeneous nature of these studies, there is no definitive dose and/or regimen of estrogen best suited to treat or manage declining cognitive function. In using estrogen therapy, one needs to weigh the benefits with potential risks such as adverse cardiovascular effects. Thus far, there has been no head-to-head trial comparing the effects of estrogen to cholinergic agonists in the management of AD patients. Ongoing clinical studies will further improve the understanding of how estrogens may help the cognitive function of postmenopausal women.

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