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Cognitive Changes After Menopause: Influence of Estrogen

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Abstract

The natural menopause is not associated with substantial cognitive change. Limited clinical trial evidence suggests that estrogen-containing hormone therapy has little effect on cognition during midlife, but prompt initiation after surgical menopause may improve aspects of memory. Among older postmenopausal women, strong clinical trial evidence demonstrates that hormone initiation does not improve cognition. More limited clinical trial evidence indicates no improvement in Alzheimer symptoms, and the Women's Health Initiative Memory Study found an increase in dementia risk among older women. Observational findings of reduced Alzheimer risk may reflect early hormone use in younger women, or findings may be biased. Cognitive effects of selective estrogen receptor modulators are not yet well studied.

Keywords

Alzheimer disease; cognition; estrogen; memory; menopause; selective estrogen receptor modulators

Estrogen and the Brain

About 40 million American women have reached the menopause. Ovarian estrogen production begins to decline 1 or 2 years before menopause and reaches a stable nadir about 2 years after the final menstrual period. Compared with levels during a woman's reproductive years, serum concentrations of estradiol and estrone—the primary circulating estrogens—are very low thereafter.

The brain is an important target organ for estrogen. In addition to direct effects, estrogen influences brain function through effects on the vasculature and the immune system. Two classes of intracellular estrogen receptors, α and β , are expressed within specific regions of the human brain. Other receptors located in the plasma membrane help regulate intracellular signaling cascades and mediate rapid effects that do not involve genomic activation.

Many estrogen actions are potentially relevant to cognitive changes occurring after menopause, but for most the clinical implications are yet unclear. Estrogen enhances synaptic plasticity, neurite growth, hippocampal neurogenesis, and long-term potentiation. The latter is a physiologic process involved in formation of episodic memories. Estrogen protects against apoptosis and against neural injury in a variety of experimental settings, including toxicity induced by excitatory neurotransmitters, β -amyloid, oxidative stress, and ischemia.

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Conflicts of Interest: None.

Off-label use: There is no approved indication for estrogen for the treatment or prevention of cognitive aging or Alzheimer disease.

Estrogen influences several neurotransmitter systems, including acetylcholine, serotonin, noradrenalin, and glutamate. Acetylcholine is important in memory processes. Cholinergic neurons in the basal forebrain express estrogen receptors, and estrogen enhances cholinergic function after ovariectomy. These neurons are specifically affected by the pathology of Alzheimer disease. Other estrogen actions are both proinflammatory and anti-inflammatory. Prothrombotic properties of some estrogens may contribute to cerebrovascular disease, and vascular pathology increases dementia severity in the presence of Alzheimer pathology.

Estrogen and Cognition in Midlife

Functional brain imaging studies demonstrate that estrogen modulates neural activity during performance of cognitive tasks.¹ Around the time of the menopausal transition, many women report problems with memory, perhaps suggesting that hormonal changes associated with menopause are linked to memory complaints. This is a potentially worrisome symptom, because the inability to learn and consciously recall new information (impaired episodic memory) can be a very early sign of Alzheimer disease or other forms of dementia. However, forgetfulness is a common symptom at almost any age, and a complaint of poor memory can emerge in the setting of anxiety or depression. The complaint might also refer to other, more specific symptoms. These include poor concentration, difficulty recalling an acquaintance's name, forgetting why one has entered a room, and failing to recall appointments and events. Only the latter symptom is closely linked to episodic memory impairment. Clinicians must therefore consider a number of alternatives when memory is reported to be poor.

Serum estrogen levels at midlife are unrelated to episodic memory.^{2,3} Moreover, despite the frequent complaint of forgetfulness, evidence from cohorts in Melbourne, the United Kingdom, and rural Taiwan suggests that the natural menopausal transition probably does not have important effects on episodic memory or most other cognitive skills.^{2,4,5} Such factors as perceived stress, mood, and physical health may contribute to memory symptoms,⁶ and these may be more relevant to memory symptoms than demonstrable impairment in episodic memory.

In contrast to the natural menopausal transition, estrogen could impact memory when ovarian estrogen production is abruptly curtailed. For younger women undergoing oophorectomy or receiving a gonadotropin-releasing hormone agonist, small clinical trials imply that prompt estrogen administration improves episodic memory for verbal information, at least in the short run.^{7,8} These findings also contrast to negative results in clinical trials of younger women after natural menopause,⁹ although trials in this population lack statistical power to detect small cognitive effects. The largest such trial involved 180 healthy postmenopausal women aged 45 to 55 years with cognitive symptoms, who were randomized to placebo or a combined formulation of conjugated equine estrogens and medroxyprogesterone acetate.¹⁰ After 4 months, there were no significant between-group differences on memory or other cognitive measures.

Estrogen and Cognition Later in Life

Results of observational research involving older women are not fully consistent in delineating putative cognitive effects of hormone therapy in the late postmenopause. In the Nurses' Health Study, comparisons between current hormone users and never users suggested very few differences, but long-term users were at increased risk of cognitive decline, particularly when hormone therapy was initiated at older ages.¹¹ In the Cache County, Utah cohort, women who reported hormone use at any age showed slower rates of cognitive decline, particularly women who were aged 85 and older.¹²

Results from large randomized clinical trials of older postmenopausal women provide a more consistent picture of hormone therapy and cognition.⁹ In this setting, hormone initiation does not substantially influence episodic memory or other cognitive skills (Table 1).

Findings from the Women's Health Initiative Memory Study (WHIMS) have been widely discussed. In this study of postmenopausal women who were 65 years of age or older at the time of randomization, active treatment consisted of conjugated equine estrogens (0.625mg/d) with or without a progestogen (medroxyprogesterone acetate 2.5mg/d), depending on the presence or absence of a uterus.^{18,19} The parent trials were halted prematurely because adverse health outcomes among women with a uterus (the estrogen-progestogen trial) or because of no overall health benefit among women who had undergone hysterectomy (the estrogen-alone trial). Consistent with other trials, hormone therapy initiation in WHIMS did not substantially affect global cognition during follow-up that averaged about 5 years; small differences favored women in the placebo group.^{18,19} More detailed neuropsychologic assessment was conducted in a subset of women (the Women's Health Initiative Study of Cognitive Aging).¹⁶ Here, analyses among women with a uterus showed no differences or only small differences on a variety of cognitive tasks (Table 1).

The possibility that midlife initiation of hormone therapy might have a long-lasting beneficial effect on cognitive skills later in life has been examined in several analyses,^{20,21} but current evidence is inadequate for any conclusion. Well-designed clinical trials to evaluate this possibility would require large numbers of women followed for extended periods of time.

Alzheimer Disease

Dementia is a symptom with multiple causes. Of these, Alzheimer disease is the most common in most countries. In Alzheimer disease, cognitive loss begins insidiously and progresses gradually over a period of about a decade. An early and consistent feature of Alzheimer disease is impairment in episodic memory. Most Alzheimer patients also have problems with language, attention, visuospatial skills, abstract reasoning, and judgment. Behavioral symptoms such as apathy, depression, agitation, or delusions are sometimes seen as well.

Key histopathologic features of Alzheimer disease are neurofibrillary tangles, found within nerve cell bodies, and neuritic plaques, found in the neuropil between cell bodies. Key biochemical abnormalities are hyperphosphorylated tau, a microtubule-associated protein, and β -amyloid, a polypeptide derived from a longer precursor protein. The relation between tau and β -amyloid is unclear. Tangles are composed largely of tau protein. Plaques often include a central core of β -amyloid. β -amyloid is also found as soluble fibrils and as nonfibrillar oligomers; the later are been implicated in synaptic dysfunction.

The pathogenesis of Alzheimer disease is unknown, although it is apparent that different genetic and nongenetic factors contribute to the characteristic clinical and pathologic picture. Early-onset Alzheimer disease, in which dementia symptoms emerge before about age 60, is often transmitted as an autosomal dominant disorder. The risk of early-onset and late-onset Alzheimer disease is influenced by polymorphic variations in the gene that encodes apolipoprotein E, a lipid transport protein. Elevated risk is associated with the $\epsilon 4$ allele, and interestingly, this polymorphism increases Alzheimer disease risk more for women than for men.²² In the laboratory, estrogen reduces β -amyloid formation, diminishes hyperphosphorylation of tau protein, and increases apolipoprotein expression. The clinical relevance of these biologic effects is not fully known.

Hormone Therapy and Dementia Risk

The relation between hormone usage and Alzheimer risk has been addressed in a large number of observational studies and in 1 primary prevention trial. This body of clinical research has led to important conclusions regarding hormone therapy and dementia, although some important clinical issues remain unsettled.

Protective associations of hormone therapy are reported from a number of studies. These include the Leisure World retirement community [relative risk estimate (RR), 0.65; 95% confidence interval (CI), 0.49–0.88],²³ a community-based cohort in northern Manhattan (RR, 0.5; 95% CI, 0.25–0.9),²⁴ the Baltimore Longitudinal Study of Aging (RR, 0.46; 95% CI, 0.21–1.00),²⁵ the Italian Longitudinal Study on Aging (RR, 0.28; 95% CI, 0.08–0.98),²⁶ the Cache County cohort (RR, 0.59; 95% CI, 0.36–0.96),²⁷ and the Multi-Institutional Research in Alzheimer Genetic Epidemiology study (RR, 0.70; 95% CI, 0.51–0.95).²⁸ No protective association of hormone use was reported from a Seattle area health maintenance organization (RR, 1.1; 95% CI, 0.6–1.8).²⁹ Meta-analyses suggest risk reductions of about a third.^{30,31} Long-term hormone use in these studies is associated with greater risk reductions than short-term use.^{23,24,27}

The interpretation and clinical relevance of these reported associations is challenged by seemingly discrepant findings from the WHIMS trials.^{32,33} At the time of enrollment, WHIMS participants were community-dwelling women between the ages of 65 and 79 years. Women were generally healthy, but there is suggestion that these volunteers were somewhat less healthy (eg, higher prevalence of obesity) than women in the general population. One hundred eight women developed dementia during the course of the 2 WHIMS trials during mean follow-up periods of about 5 years. Because the trials were halted prematurely, the number of incident cases of dementia was less than anticipated, and separate outcomes were not reported for Alzheimer disease or other specific dementia types. In the estrogen-progestogen trial, the risk of dementia among women in the active treatment group was twice that of women in the placebo group. In the estrogen-alone trial, the risk was elevated by about 50% in the hormone group (Table 2). The increased risk in these populations represents about 2 additional cases of dementia per 1000 women per year of hormone use.

Women with lower cognitive scores at the time of enrollment, and older women, were much more likely to develop dementia during the course of the trials. The increase in dementia risk became apparent within a few years after treatment allocation.^{32,33} Because the pathologic features of Alzheimer disease are presumed to begin a decade or more before overt appearance of dementia, WHIMS investigators speculated that hormonal effects on the cerebral vasculature may have contributed to the relatively quick appearance of dementia among women randomized to active treatment.

Women in the WHIMS trials who had used hormone therapy in the past were significantly less likely to develop Alzheimer disease or another form of dementia than women who had not used hormone therapy; prior use did not modify effects of randomized treatment allocation during the WHIMS trials.^{32–34} This association with prior use is consistent with findings described above from other observational studies of hormone therapy and Alzheimer disease. In general, women who use hormone therapy are better educated, enjoy better health, and engage in healthier lifestyles than nonusers. Such differences might account for protective associations seen in most observational studies.³⁵ Differential recall of prior hormone usage (recall bias) might also underestimate risks of hormone therapy.

There is a further consideration regarding these studies and the WHIMS clinical trials. WHIMS participants differed from many women in observational studies, particularly including the age at which hormone therapy was initiated and used.³⁵ Hormone therapy is most often prescribed

for vasomotor symptoms around the time of menopause, taken for several years, and then discontinued. Thus, most hormone use in observational studies occurred at a relatively young age, close to the time of menopause. In contrast, all hormone use during the WHIMS trials occurred only after age 64, remote from the time of menopause.

It is unknown whether estrogen effects on Alzheimer risk are modified by age of use or by use during a critical window close to the time of menopause.³⁶ A protective association was reported for past, but not current, hormone therapy in the Cache County cohort²⁷; and the protective association of hormone therapy was significantly modified by age in Multi-Institutional Research in Alzheimer Genetic Epidemiology study, being limited to younger postmenopausal women.²⁸

Estrogen and Alzheimer Disease Therapy

Estrogen has been considered as a potential treatment for women with dementia due to Alzheimer disease. Results of several randomized, double-blind, placebo-controlled trials—while not fully congruent—have been disappointing. Perhaps most encouraging was an 8-week trial of 20 women treated with transdermal estradiol or placebo.³⁷ Women receiving active treatment performed better on an executive function task and an episodic memory task, although between-group differences on most cognitive measures were not significant. In contrast, 4 somewhat larger clinical trials found no important effect on a variety of clinical and functional measures. These included a 16-week trial of 36 women, a 12-week trial of 47 women, a 12-month trial of 120 women, and a 28-week trial of 117 women.^{38–41} In the latter, active treatment was with transdermal estradiol, and in the others, with unopposed conjugated estrogens. In the longest of these trials, 74% of women randomized to placebo and 80% of women randomized to estrogen had declined after 12 months on a standard measure of global change.⁴⁰ Most investigators have concluded that initiation of estrogen in older women with Alzheimer disease does not improve dementia symptoms or slow disease progression.

The Role of Progestogen

Some neurons express progesterone receptors. In the laboratory setting, different estrogens affect neuronal function differently; the same is true for different progestogens.⁴² However, the clinical relevance of these differential actions is uncertain. Although progesterone is neuroprotective in some experimental models, limited observational data raise the possibility that the progestogen component of combined hormone therapy could affect cognition deleteriously. In the Nurses' Health Study, for example, the risk of substantial cognitive decline appeared greater among long-term use of combined hormone therapy, although overall cognitive performances were similar for unopposed estrogen users and combined estrogen-progestogen users.¹¹ In the WHIMS trials, changes in global cognitive function and dementia risk were similar relative to placebo for women randomized to active treatment in the estrogen-progestogen trial and women randomized to active treatment in the estrogen-alone trial.^{18, 19, 33}

Estrogen Receptor Agonists/Antagonists

Selective estrogen receptor modulators (SERMs), also referred to as estrogen receptor agonists/antagonists, lack the basic steroid structure of sex hormones. They exert tissue-specific estrogenic effects by inducing unique conformational changes in the estrogen receptor. Two well-known SERMs are tamoxifen, used in breast cancer prevention, and raloxifene, used in osteoporosis prevention. Within the brain, agonist or antagonist profiles of tamoxifen and raloxifene differ from each other. For women with osteoporosis, cognitive outcomes were examined in ancillary studies of the Multiple Outcomes of Raloxifene Evaluation trial. Raloxifene had no effect on overall cognitive function in this large clinical trial,⁴³ but at higher

doses raloxifene reduced the likelihood that study participants would develop cognitive impairment.⁴⁴ For tamoxifen, there is some concern that tamoxifen might impair cognitive function,⁴⁵ but data are quite sparse. Neurologic effects of SERMs are an increasingly important area of consideration as newer compounds are developed and marketed.

Clinical Implications

Although much remains to be learned, considerable progress has been made in understanding cognitive effects of estrogen after menopause. Clinical implications of current evidence are summarized in Table 3.

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Hormone therapy in older postmenopausal women without dementia: randomized, double-blind, placebo-controlled trials*

Author, publication year	Study population	Number of women	Mean treatment duration	Significance, episodic memory tasks	Significance, other cognitive tasks
Grady, 2002 ⁴²	History of coronary heart disease	1063	50 months	NS	NS [†]
Viscoli, 2005 ⁴³	History of cerebrovascular disease	461	38 months	NS	NS [‡]
Almedia, 2006 ⁴⁴	Generally healthy	115	20 weeks	NS	NS
Resnick, 2006 ¹⁵	Generally healthy	1416	4 years	variable [§]	NS [§]
Yaffe, 2006 ⁴⁵	Generally healthy	417	2 years	NS	NS

* Limited to trials of at least 100 older women (mean age ≥ 60) treated for at least 1 month and including an objective measure of episodic memory

[†] Better performance in placebo group on 1 of 4 tasks (category fluency).

[‡] Less decline on the Mini-Mental State among women in the estrogen group in post hoc analyses restricted to women with a high baseline scores; no significant differences on other tasks.

[§] Women's Health Initiative Study of Cognitive Aging. No between-group differences on memory tasks 3 years after randomization; better digit span performance in placebo group, but no differences on other non-memory tasks. 1.4 years later, differences favored placebo on verbal memory tasks (total word-list recall score, short and long free delayed wordlist recall scores) and favored estrogen-progestogen on a nonverbal memory task (visual retention). Other comparisons were nonsignificant, and the magnitude of significant differences was small.

NS = non-significant probability $P > 0.05$

Table 2
Dementia outcomes in the Women’s Health Initiative Memory Study

Trial	Number treated	Mean duration, years	Dementia rate, active drug [*]	Dementia rate, placebo [*]	Hazard ratio (95% confidence interval)
Estrogen-progestogen trial ²⁸	4532	4.1	45	22	2.1 (1.2 – 3.5)
Estrogen-alone trial ²⁹	2947	5.2	37	25	1.5 (0.8 – 2.7)

^{*} Per 10,000 person-years

Table 3

Cognitive changes and menopause: clinical implications of initiating estrogen-containing hormone therapy*

Initiation during the menopausal transition or early postmenopause

- During the menopausal transition and after natural menopause: no substantial effect on cognition. (Observational evidence; limited clinical trial evidence)
- Immediately after surgical menopause: better episodic memory for verbal information, at least in the short term. (Limited clinical trial evidence)
- Effects on Alzheimer risk are unknown. Dementia risk may be elevated if WHIMS clinical trial findings in older women generalize to this younger group. Alzheimer risk may be reduced if observational findings of protective associations are valid. The absolute risk of Alzheimer's disease is very low in the decade after menopause, and the absolute risk of Alzheimer's disease associated with short-term hormone therapy for menopausal symptoms is likely to be very low. (Opinion)
- After early menopause or premature ovarian failure: almost no data.
- For women with early-onset Alzheimer's disease: almost no data.

Initiation by older women during the late postmenopause

- For healthy women: no substantial effect on cognition. (Strong clinical trial evidence)
- Increased dementia risk within several years of initiation, especially for women who already perform poorly on tests of cognitive function. (Clinical trial evidence from WHIMS)
- For women with late-onset Alzheimer's disease: no improvement of dementia symptoms or rate disease progression. (Limited clinical trial evidence)

* See text for details