Published in final edited form as:

Semin Reprod Med. 2009 May ; 27(3): 283–293. doi:10.1055/s-0029-1216281.

Estrogens, Episodic Memory, and Alzheimer's Disease: A Critical Update

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Abstract

Estrogen-containing hormone therapy initiated during the late postmenopause does not improve episodic memory (an important early symptom of Alzheimer's disease), and it increases dementia risk. Cognitive consequences of exogenous estrogen exposures during midlife are less certain. Observational evidence implies that use of hormone therapy at a younger age close to the time of menopause may reduce risk of Alzheimer's disease later in life. However, there are concerns that observational findings may be systematically biased. Partial insight on this critical issue may be gleaned from results of ongoing clinical trials involving midlife postmenopausal women (Early versus Late Intervention Trial with Estrogen; Kronos Early Estrogen Prevention Study). The effects of exogenous midlife estrogen exposures and Alzheimer risk can also be approached through better animal models, through carefully designed cohort studies, and through use of surrogate outcomes in randomized controlled trials in midlife women. Selective estrogen receptor modulators have the potential to affect cognitive outcomes and also merit additional study.

Keywords

Alzheimer's disease; estrogen; memory; SERM

Introduction

Natural menopause is defined by a woman's final menstrual period and occurs at an mean age of 51 years. This midlife transition reflects the failure of ovarian follicle formation and the consequent loss of ovarian estrogen production. About two years before the final menstrual period, blood concentrations of the two primary ovarian estrogens, 17 β -estradiol and estrone, begin to decline; and they reach permanent low values about two years after the last menstrual period.^{1,2} Estrone continues to be formed in adipose tissue from androstenedione, and estradiol is formed in low concentrations from the peripheral conversion of estrone. Within the ovaries, the corpus luteum produces progesterone, a progestogen, levels of which also decline at menopause. Androgen precursors continue to be produced by ovarian stromal cells and by the adrenal gland. Circulating concentrations of testosterone, the principal androgen, are largely unchanged after natural menopause but are decreased after surgical menopause.³

The brain is a target tissue of ovarian hormones, and effects of menopause and midlife hormonal changes on brain function are beginning to be understood more clearly. One of the

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Disclosures: The author has no financial conflicts of interest. There is no approved indication for estrogens or selective estrogen receptor modulators for the prevention or treatment of memory impairment or dementia.

most dreaded accompaniments of aging is cognitive impairment, especially when impairment is severe enough to warrant the designation of dementia. It is clear from functional imaging studies of the brain that estrogens can influence neural activity during performance of certain kinds of cognitive tasks.⁴ Whether the loss of ovarian estrogens after menopause influences cognitive abilities and the risk of developing dementia is a matter of obvious concern and ongoing controversy. In recent years, some relevant questions have been answered by basic scientists, epidemiologists, and clinical investigators. Other important issues remain unresolved. The following sections consider these questions and available answers, with an emphasis on clinical research pertinent to estrogen-containing hormone therapy and Alzheimer's disease.

Overview of Alzheimer's Disease and Episodic Memory

Alzheimer's disease is the most common cause of severe cognitive impairment in old age. In many countries, it represents one-half to two-thirds of all cases of dementia cases.^{5,6} In this disorder, cognitive symptoms begin insidiously and worsen gradually over a course of about a decade. Life expectancy is longer for women than for men, and women are therefore more likely than men to develop Alzheimer's disease, simply on the basis of greater longevity. In fact, about twice as many women are affected by Alzheimer's disease as men. Even when differences in life expectancy are taken into consideration, however, some studies (but not all) suggest that Alzheimer risk remains increased for women compared to men.⁷

Gross cerebral atrophy is common in Alzheimer's disease and affects hippocampus and other regions of the cerebrum. Microscopic characteristics are the accumulations of neurofibrillary tangles within vulnerable neuron populations and neuritic plaques in specific brain regions. However, there is only a modest relation between dementia severity and quantified measures of tangles and plaques. Recent studies suggest that dementia is much more likely to emerge when Alzheimer pathology is accompanied by other age-associated brain changes, such as Lewy bodies or vascular disease.⁸ Vascular disease assumes several forms. These include small and large vessel occlusion recognized clinically as ischemic stroke, and small vessel ischemia, which may be clinically inobvious but is associated with cognitive impairment in its own right.

A deficit in episodic memory is an early symptom of Alzheimer's disease. Episodic memory refers to the ability to learn new information and then to recall this information in a conscious manner after some interval of time. In clinical settings, memory is often assessed by the ability to learn and recall a list of words or details from a paragraph-length story. Episodic memory formation requires integrity of the hippocampus and other structures in the medial temporal lobes of the cerebrum. Episodic memory deficits in the absence of dementia, sometimes referred to as *mild cognitive impairment* (or as the amnesic variety of mild cognitive impairment) convey a high risk of developing clinically-evident Alzheimer's disease during the ensuing few years.⁹

The CA1 region of the hippocampus, a region of the brain crucial to episodic memory formation, is profoundly affected in Alzheimer's disease. In this region, estradiol acts in concert with progesterone to increase numbers of dendritic spines on pyramidal neurons.¹⁰ These small protuberances represent excitatory synapses. In animal studies, estradiol also enhances long-term potentiation in the hippocampus;¹¹ this physiological process is held to be important in the encoding of episodic memories. In other regions of the hippocampus, estradiol promotes survival of new neurons.¹² In addition to these hippocampal effects, estrogens are neuroprotective and can reduce formation of β -amyloid,^{13,14} a toxic peptide that accumulates in Alzheimer's disease. In the basal forebrain area of the brain, neurons

using acetylcholine as a neurotransmitter develop neurofibrillary tangles during the course of Alzheimer's disease. These cholinergic neurons express receptors for estrogen,¹⁵ and estradiol elevates choline acetyltransferase activity in cortical projection areas of these neurons.¹⁶

Estrogens and the Menopausal Transition

How important are estrogens to human cognition in adult life? During a woman's reproductive years, some investigators report mild fluctuations in cognitive performance across the menstrual cycle attributed to cyclical changes in concentrations of estradiol and progesterone. Although not all findings are consistent, higher estrogen levels have been linked to better verbal fluency, perceptual speed, and manual dexterity.¹⁷ Moreover, if ovarian function is pharmacologically suppressed, or if a woman undergoes surgical menopause (i.e., bilateral oophorectomy), there is short-term evidence that therapy with estradiol or conjugated estrogens can help maintain episodic memory on verbal tasks (e.g., recalling information from a paragraph story).^{18,19}

Memory symptoms are common during midlife around the time of the menopausal transition²⁰ when circulating levels of estradiol and estrone are expected to decline. This observation is concerning because of the close association between episodic memory deficits and Alzheimer's disease.

Given the near ubiquity of midlife memory complaints, it is perhaps surprising then that circulating concentrations of estradiol during middle age do not bear a strong relation to episodic memory scores.^{21,22} This finding, however, is consistent with research showing that the natural menopausal transition *per se* does not appear to affect episodic memory. This conclusion is based on studies in midlife cohorts where memory was objectively measured. These analyses come from Melbourne, Australia; the United Kingdom; rural Taiwan; Sweden; and the United States.^{21–25} Forgetfulness is a common symptom,²⁶ however, and not just during midlife. Psychological problems like depression or anxiety can lead to memory complaints. Poor concentration and other problems not directly related to episodic memory *per se* are sometimes described by patients as poor memory. For reasons such as these, self-reports of poor memory do not necessarily mean that the clinician will uncover objective evidence for memory impairment on tasks that assess new learning and delayed recall.

Estrogens and Episodic Memory

A number of clinical trials among middle-age postmenopausal women have assessed short-term effects of various estrogens, or an estrogen plus a progestogen, on cognitive performance. Most are limited by small sample size, and most have shown no effect on episodic memory performance (reviewed by Henderson and Sherwin²⁷). The largest randomized trial in this age group involved 180 healthy naturally-menopausal women age 45–55 years, where active treatment was with conjugated estrogens combined with medroxyprogesterone acetate. After four months, there were no significant between-group differences on measures of episodic memory or other cognitive outcomes.²⁸ These clinical trial findings are consistent with other research that indicates no large cognitive consequence during midlife of natural menopause. Outcomes may be different, however if ovarian function is abruptly curtailed by oophorectomy. As already noted, parenteral estradiol has shown short-term memory benefit for relatively young women undergoing surgical menopause.^{18,29}

Within the past few years, cognitive function has also been systemically examined in large randomized clinical trials involving postmenopausal women in their 60s or older. In the

Women's Health Initiative Memory Study (WHIMS), which is discussed further below in the context of dementia, scores on a test of global cognition were slightly lower among women randomized to conjugated estrogens with or without a progestogen, although mean differences between treatment groups were too small to be clinically apparent.³⁰ A WHIMS ancillary study (the Women's Health Initiative Study of Cognitive Aging³¹) found that combined estrogen-progestogen might enhance nonverbal memory (memory for a design) but have a deleterious effect on verbal memory (memory for a list of related words). However, mean differences in this ancillary study were again quite small and unlikely to be clinically important.

Episodic memory was assessed in other large clinical trials of older women. Treatment durations in these trials ranged from 20 weeks to more than four years. These included two primary prevention trials, where active treatment was with oral estradiol³² or very low-dose transdermal estradiol.³³ Secondary prevention trials of women with coronary heart disease³⁴ and cerebrovascular disease³⁵ used conjugated estrogens plus medroxyprogesterone acetate³⁴ or oral estradiol.³⁵ In none of these were there significant differences on episodic memory scores between women randomized to hormone therapy or to placebo. Thus, within this older age group, there is strong, consistent evidence that estrogen initiation does not enhance this form of memory.

Estrogens and Alzheimer's Disease

Alzheimer's disease treatment

Primarily on the basis of a strong biological rationale, estrogens have been considered as possible therapy for women with Alzheimer's disease. Evidence from relatively small clinical trials, in aggregate, suggest no significant deleterious or beneficial effects of estrogen therapy initiation when compared to placebo. The largest of several positive trials involved only 20 women and reported improvements in some measures of attention and memory.³⁶ Active treatment was with transdermal estradiol, and treatment duration was eight weeks. Other randomized clinical trials found no overall effect from estrogen therapy. These trials involved 42 women with Alzheimer's disease followed for four months,³⁷ 50 women followed for 12 weeks,³⁸ 120 women without a uterus followed for one year,³⁹ and 117 women followed for 28 weeks.⁴⁰ In these latter trials, investigators found no cognitive benefit or global improvement with estrogen. Active treatment was unopposed conjugated estrogens^{37–39} or transdermal estradiol plus oral progesterone.⁴⁰ Earlier observational reports of better cognitive abilities among Alzheimer patients using hormone therapy compared to non-users^{41,42} may reflect a healthy-user bias (see below) or, more speculatively, late effects of early initiation not examined in these randomized clinical trials.

Alzheimer's disease prevention

A different and even more important issue is the potential effect of exogenous estrogens on dementia risk in healthy women, particularly exposures in the form of estrogen-containing hormone therapy. The association between hormone therapy use and Alzheimer's disease has been considered in over a dozen case-control and cohort studies. Most have reported significant risk reductions linked to hormone use. In meta-analyses, estimated risk reductions range from about 29% to 44%.^{43,44} Recall bias can affect validity of observational evidence, if estrogen exposures are differentially recalled by Alzheimer cases than by controls (or by their proxy informants).⁴⁵ Observational studies in which information on hormone therapy use was collected before the onset of dementia are less prone to recall bias, and results of these studies are summarized in (Table 1).

In two case-control studies — one from a Seattle area health maintenance organization⁴⁶ and the other from a United Kingdom general practice database⁴⁷ — measures of hormone

exposure were derived from computerized pharmacy databases. Such databases provide more precise estimates of who actually used estrogens and would be expected to provide more valid estimates of Alzheimer risks. In both case-control studies, estrogen use was unassociated with Alzheimer's diagnoses (Table 1). However, each database captured prescription data only during the preceding decade, so both would have systematically missed early hormone use by older women. Linked medical records were used in two case-control studies from the Mayo Clinic in Rochester, Minnesota, to identify hormone therapy use and dementia diagnoses. One study was based on incident Alzheimer's disease during the 1980–1984 quinquennium,⁴⁸ and the other during the ensuing five year period.⁴⁹ The first reported a protective association with hormone therapy use,⁴⁸ whereas the second found no significant overall association⁴⁹ (Table 1). It is unclear why there is a lack of consistency across time in this population.

Other observational studies in which information on hormone therapy exposures were collected prospectively include a nested-case control study from the Leisure World retirement community in southern California⁵⁰ and cohort studies from New York,⁵¹ the Baltimore Longitudinal Study of Aging,⁵² and Cache County, Utah.⁵³ Each of these reported significant associations between hormone use and reductions in Alzheimer risk.

Dementia has been considered as an outcome in only one randomized clinical trial, the WHIMS trial referred to above (actually two trials, if women with a uterus and women without a uterus are considered separately). The primary WHIMS endpoint was incident dementia of any cause.^{54,55} Over 7000 women age 65 years of age or older were followed for an average of four to five years. One hundred eight women developed dementia during this time, and about half of these received diagnoses of Alzheimer's disease. For women without a uterus who were given conjugated estrogens alone, the risk was increased by half, and for women with a uterus, who received estrogens and progestogen, the risk was doubled (Table 2).⁵⁵ Use of hormone therapy prior to WHIMS enrollment showed associations similar to those reported in other cohort studies (see Table 1) but importantly did not modify harmful effects of on-trial use with respect to dementia outcomes.^{55,56}

Seminal findings from the WHIMS clinical trials have been controversial, given observational findings described above (e.g., Table 1), which suggest a protective association between hormone therapy and Alzheimer risk. Apparent discrepancies probably reflect several factors (Table 3).⁵⁷ A key consideration is that observational studies could be systematically flawed by the so-called healthy-user bias, since women who use hormone therapy in the first place are generally healthier and better educated than other women. Recall bias could have played an additional role, if women who later were diagnosed with Alzheimer's disease were unable to recall reliably their prior use of hormone therapy. Reductions of Alzheimer risk of about a third, as suggested by observational results,^{43,44} are certainly large enough to be of public health import, yet these observed reductions are too small to discount concerns about bias or confounding.

There were other distinctions between women included in most observational studies and participants in the WHIMS trials (Table 3). An important difference is that randomized allocation to hormone therapy in the WHIMS trials occurred at an older age than the usual age for hormone therapy use represented in observational studies. Most hormone therapy is initiated within a year of menopause or earlier, and the median duration of use is roughly five years.⁵⁸ Therefore, another possibility for differences between WHIMS trials and observational studies is that WHIMS results might not generalize to younger women close to the age of menopause, who tended to initiate hormone therapy for hot flashes during the menopausal transition and then discontinue usage prior to the age when they might have been eligible for WHIMS participation.

Is There a Critical Window for Estrogen Exposures and Alzheimer's Disease Risk?

The possibility that the effects of exogenous estrogens on Alzheimer risk might differ between younger and older women has been discussed in the context of a so-called critical window, or a window of opportunity.⁵⁹ One version of the critical window hypothesis suggests that estrogen-containing hormone therapy used close to the time of menopause or used at a relatively young age may protect against later Alzheimer's disease. Use at a later age remote from the time of menopause would not be protective and could actually increase risk. Mechanisms for such a difference are unknown. Speculatively, estrogen receptor down-regulation after a prolonged absence of exposure to its ligand could play a role. Various age-associated differences (e.g., changes in vascular health) might also be implicated.

Findings from the Cache County, Utah cohort are consistent with the critical window hypothesis. For older women who reported prior use of hormone therapy, the incidence of Alzheimer's disease was significantly lower than that for women reporting no hormone use (hazard ratio 0.33, 95% confidence interval 0.15–0.65).⁵³ For current use, there was no effect on Alzheimer risk (hazard ratio 1.1, 0.6–1.9). Prior use in Cache County may have represented limited exposures close to the time of menopause. In the Multi-Institutional Research in Alzheimer Genetic Epidemiology study involving 426 women with Alzheimer's disease and 545 controls without dementia, the effect of earlier hormone therapy use on Alzheimer risk were significantly modified by age.⁶⁰ The association was protective for younger women but not for older women. For women in the youngest age tertile (age 50–63 years), the estimated Alzheimer risk was reduced by nearly two-thirds. Risks were not significantly altered in the two older tertiles (Figure 1). Younger women in this study who used hormone therapy necessarily did so fairly close to the time of menopause. For older hormone therapy users, exposures would not necessarily have been confined to this earlier time period.

It is interesting that differences between experimental groups in the WHIMS trials began to emerge within a few years of randomization.^{54,55} WHIMS results were not reported by dementia subtype, but Alzheimer's disease represented about one-half of all cases in hormone therapy and placebo groups. Women with poor cognitive scores at baseline were at much greater risk for developing dementia, regardless of treatment arm.^{54,55} The preclinical phase of detectable cognitive deficits can precede the clinical diagnosis of Alzheimer's disease by many years.⁶¹ In the context of the WHIMS trials, this finding suggests that deleterious effects of conjugated estrogens, with or without medroxyprogesterone acetate, probably developed fairly rapidly among women presumed to have pre-existing Alzheimer pathology.

It appears unlikely that estrogens would directly exacerbate key biochemical changes of Alzheimer's disease. In laboratory models, estradiol reduces β -amyloid formation^{14,62} and hyperphosphorylation of the tau protein.⁶³ Other estrogen actions might contribute more importantly to attributable dementia in the WHIMS trials. Speculation in this regard has focused largely on vascular effects of estrogens. These effects are themselves complex and might include coagulation (thrombosis, thrombolysis, fibrinolysis), vascular endothelium or smooth muscle, atherosclerotic plaque formation and plaque stability, or some combination.

Thus far, findings with respect to estrogens and the vascular outcomes are inconclusive. In an animal model, estradiol improves vascular endothelium and smooth muscle function, but these beneficial effects are blocked by a cholesterol metabolite (27-hydroxycholesterol) found in atherosclerotic lesions.⁶⁴ There is clinical trial evidence that estradiol slows progression of carotid artery atherosclerosis among healthy postmenopausal women but not

older women with premorbid vascular disease.^{65,66} Monkeys given estrogens immediately after ovariectomy show significant reductions in coronary atherosclerosis progression, but no such benefit is apparent if hormonal treatment is delayed.⁶⁷ In the Women's Health Initiative trials, conjugated estrogens had deleterious effects on coronary heart disease among older women; for women in their 50s, allocation to hormone therapy tended to reduce coronary heart disease.⁶⁸ A similar age-related effect was not seen for stroke incidence, however.⁶⁸ Several years after termination of the WHIMS trials, magnetic resonance imaging brain scans were obtained on many trial participants.⁶⁹ Women who had been assigned to active hormone treatment did not differ from women assigned to placebo with regard to the volume of brain lesions thought to represent stroke or other forms of ischemic injury. However, overall cerebral volume was diminished in hippocampus and total brain among women in the estrogen groups. This difference was unrelated to scan findings of stroke or ischemia. Although clearly worrisome, it is difficult to interpret these cross-sectional finding in the absence of clear clinical distinctions. Relevant questions include, what is the significance of reduced volume for cognitive outcomes; what are the pathogenetic mechanisms; are findings specific to one class of estrogen exposures (e.g., oral conjugated estrogens but not oral phytoestrogens or not transdermal estradiol); are findings modified by age or timing of estrogenic exposures?

Selective Estrogen Receptor Modulators, Phytoestrogens, and Dementia

Selective estrogen receptor modulators (SERMs), also called selective estrogen agonists/antagonists, have estrogenic effects that vary with tissue type. Each SERM has a unique profile of effects. Both raloxifene, used for osteoporosis prevention, and tamoxifen, used in breast cancer prevention, are SERMs. The agonist and antagonist profiles of raloxifene and tamoxifen differ from each other within the brain, and the effects of each vary from one brain region to another.^{70,71} The Multiple Outcomes of Raloxifene Evaluation study was a multinational randomized placebo-controlled clinical trial whose participants were postmenopausal women with osteoporosis. In secondary analyses from this trial, raloxifene did not affect episodic memory,⁷² but high-dose raloxifene reduced the risk of cognitive impairment among study participants.⁷³ Less is known about how tamoxifen might affect cognition, although there is worry that the effect may be harmful.⁷⁴ Neurological effects of SERMs are an increasingly important concern as new compounds are developed and marketed for various health indications.

It is interesting that many dietary compounds found in plants have estrogenic properties or properties of a SERM. These phytoestrogens are found in a variety of grains, fruits, and vegetables, and many are consumed in large quantities. Hormonal effects of plant estrogens often do not mimic those of estradiol.⁷⁵ Genistein, for example, is found in high concentration in tofu and other soy products. It has a strong affinity for estrogen receptor beta but only a weak affinity for estrogen receptor alpha.⁷⁶ Potential effects of various phytoestrogens on dementia risk are largely unknown. In the Honolulu Heart Study, tofu consumption in midlife was associated with brain atrophy and poor cognitive test scores later in life.⁷⁷

Estrogens and Alzheimer's Disease: Clinical Implications and a Concluding Perspective

The prevalence of exogenous estrogen exposure in the form of hormone therapy has declined as health risks of hormone therapy have become more widely appreciated by women and their physicians. Millions of women, however, continue to use hormone therapy for treatment of moderate to severe vasomotor symptoms or for osteoporosis. Despite important new findings in recent years, the relation between estrogens (or SERMs) and

dementia remains controversial, and the issue is complicated by a number of largely unresolved issues related to class effects, exposure measurement, and other modifying factors (Table 4).

It is now evident that episodic memory is not improved by initiation of estrogen therapy in the late postmenopause. Clinical trial evidence is more limited for midlife exposures, but there is thus far no clear indication that estrogens substantially improve memory for younger women, at least after natural menopause and at least in the short-term.²⁷ Findings on episodic memory are directly relevant to considerations of Alzheimer's disease, but estrogens might also influence Alzheimer risk through mechanisms unrelated to memory effects in healthy women.

A remaining critical question is the following: Do estrogenic compounds promote Alzheimer's disease when used by relatively healthy midlife women around the time of menopause (generalized from WHIMS findings in older women), or do they reduce future risk (inferred from potentially biased observational research)? The fact that WHIMS does not address this question directly is not a shortcoming of the WHIMS trials; they were not designed with this goal in mind. The fact that observational studies are generally supportive of this hypothesis is also not decisive, since bias and residual confounding might in themselves account for these associations. The ideal approach would be a randomized clinical trial of a rationally-selected estrogenic formulation, with outcome determinations some two decades later. This is unlikely to occur. However, two ongoing placebo-controlled trials in the United States will test more carefully the possibility of cognitive benefit after midlife use of hormone therapy. These are the Early versus Late Intervention Trial with Estrogen (ELITE; ClinicalTrials.gov identifier NCT00114517) and the Kronos Early Estrogen Prevention Study (KEEPS; ClinicalTrials.gov identifier NCT00154180).

The former proposes to study 650 postmenopausal women divided into an early group within six years of menopause and a late group more than 10 years beyond menopause. The latter proposes to enroll 720 women within three years of natural menopause. Estrogen interventions differ in the two trials (oral estradiol in the Early versus Later Intervention Trial; oral conjugated estrogens or transdermal estradiol in the Kronos Study), but each incorporates robust outcomes measures of episodic memory and other cognitive domains. However, neither clinical trial will have the power to detect Alzheimer's disease outcomes in this age group, nor will women be followed for the many years necessary to detect these outcomes later in life.

In the absence of clear-cut clinical trial evidence, the issue of an early critical window as it pertains to Alzheimer's disease can still be addressed, albeit indirectly. Examples of these approaches include use of better animal models relevant to human menopause and menopausal hormone therapy, carefully designed cohort studies, as well as use of surrogate outcomes (e.g., brain imaging based on β -amyloid load) in shorter-term randomized controlled trials in midlife women. At present, it is reasonable to conclude and prudent to assume that estrogens should not be used after the usual age of natural menopause to improve episodic memory or to reduce Alzheimer's disease risk.⁷⁸ Dementia is rare during the midlife period when women are most apt to consider hormone therapy. If estrogens increase the relative risk of dementia as suggested by WHIMS findings in older women, then the risks attributable to hormone therapy in this age group are expected to be correspondingly rare.

Acknowledgments

Supported in part by NIH R01-AG023038 and 1R01-AG024154

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Figure 1.

Association between hormone therapy use and Alzheimer's disease risk in the Multi-Institutional Research in Alzheimer Genetic Epidemiology study⁶⁰: significant interaction with age*

* Error bars represent 95% confidence intervals. Reference is no hormone therapy use. Age groupings represent youngest, middle, and oldest age tertiles.

Estrogen-containing hormone therapy and Alzheimer's disease risk: observational research in which information on hormone therapy exposure was recorded prior to dementia onset

Table 1

Study (year)	Design	Number of Alzheimer cases	Number of controls	Estrogen use, controls (%)	Source of information on exposure	Relative risk estimate (95% confidence interval)	Significant risk reduction?	Comment
Puget Sound, Seattle (1994) ⁴⁶	Case-control	107	120	48%	Pharmacy records	1.1 (0.6–1.8)	No	
Leisure World, California (1996) ⁵⁰	Nested case-control	248	1193	48%	Self	0.65 (0.5–0.9)	Yes	
Manhattan, New York (1996) ⁵¹	Cohort	167	957	15%	Self	0.5 (0.25–0.9)	Yes	
Baltimore Longitudinal Study of Aging (1997) ⁵²	Cohort	34	438	47%	Self	0.5 (0.2–0.997)	Yes	
Rochester, Minnesota (1999) ⁴⁸	Case-control	222	222	10%	Medical records	0.4 (0.2–0.96)	Yes	Incident Alzheimer's disease, 1980–1984
United Kingdom (2001) ⁴⁷	Case-control	59	221	24%	Pharmacy records	1.2 (0.6–2.4)	No	
Cache County, Utah 2002 ⁵³	Cohort	84	1866	58%	Self	0.6 (0.4–0.96)	Yes	Protective association limited to current use
Rochester, Minnesota (2006) ⁴⁹	Case-control	245	245	11%	Medical records	1.1 (0.6–1.9)	No	Incident Alzheimer's disease, 1985–1989
Women's Health Initiative Memory Study participants (2007) ⁵⁶	Cohort	53	7047	31%	Self	0.4* (0.2–0.85)	Yes*	Based on hormone use before clinical trial enrollment

* Randomized allocation to estrogens or estrogens and progestogen during the Women's Health Initiative Memory Study clinical trials significantly *increased* incidence of all-cause dementia. Self-reported prior use of hormone therapy did not modify harmful effects of on-trial treatment.

Estrogen-containing hormone therapy and dementia in the Women’s Health Initiative Memory Study clinical trials^{54,55}

Table 2

Active treatment	No. randomized	Mean duration	No. dementia cases (rate*), placebo group	No. dementia cases (rate*), active group	Hazard ratio (95% confidence interval)	Significant risk increase?
Conjugated estrogens and medroxyprogesterone acetate	4532	4.1 years	21 (22)	40 (45)	2.1 (1.2 – 3.5)	Yes
Conjugated estrogens alone	2947	5.2 years	19 (25)	28 (37)	1.5 (0.8 – 2.7)	No

* Incidence per 10,000 person-years.

Estrogen-containing hormone therapy and Alzheimer’s disease risk: experimental and observational findings compared⁵⁷

Table 3

Experimental (WHIMS)		Observational
1. Dementia outcome	Dementia (any cause)	Alzheimer’s disease
2. Consistency of findings	Increased risk in both WHIMS trials (Table 2)	Generally consistent; multiple studies, (e.g., Table 1)
3. Concerns with bias or unrecognized confounding	Small: differential dropout and unblinding	Large: healthy-user bias, recall bias, residual confounding
4. Estrogen exposure	Conjugated estrogens	Variable; usually conjugated estrogens
5. Progestogen exposure	Medroxyprogesterone acetate; Continuous combined	Usually medroxyprogesterone acetate; Sequential
6. Menopausal vasomotor symptoms	Uncommon	Common
7. Age at exposure	Age > 64 years	Variable; more often younger
8. Timing of exposure	Remote from menopause	Variable; more often near menopause

WHIMS = Women’s Health Initiative Memory Study

Table 4

Effects of exogenous estrogens on brain function: some barriers to an understanding of clinical implications from observational and experimental research

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- Blood levels may not accurately reflect brain levels
 - Some effects are modified by a progestogen
 - Different estrogens have different effects mediated, for example, but differential affinities for estrogen receptor alpha and beta
 - Different progestogens have different effects
 - Estrogen effects during an early critical window close to menopause may differ from later exposures in older women
 - Some effects of a sequential estrogen–progestogen formulation differ from those of a continuous combined formulation
 - Some effects of an oral estrogen (hepatic first-pass effect) differ from those of a transdermal estrogen
 - Effects vary by exposure levels (dose, duration)
 - Endogenous estrogen exposures vary based on body mass index, genetic polymorphisms, and other individual differences
 - Effects after surgical menopause may differ from effects after natural menopause
 - Effects after premature menopause may differ
 - Dietary estrogens and selective estrogen receptor modulators (pharmacological or dietary) may modify effects of hormone therapy
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