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Menopause and cognitive impairment: A narrative review of current knowledge

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Abstract

A severe impairment of cognitive function characterizes dementia. Mild cognitive impairment represents a transition between normal cognition and dementia. The frequency of cognitive changes is higher in women than in men. Based on this fact, hormonal factors likely contribute to cognitive decline. In this sense, cognitive complaints are more common near menopause, a phase marked by a decrease in hormone levels, especially estrogen. Additionally, a tendency toward worsened cognitive performance has been reported in women during menopause. Vasomotor symptoms (hot flashes, sweating, and dizziness), vaginal dryness, irritability and forgetfulness are common and associated with a progressive decrease in ovarian function and a subsequent reduction in the serum estrogen concentration. Hormone therapy (HT), based on estrogen with or without progestogen, is the treatment of choice to relieve menopausal symptoms. The studies conducted to date have reported conflicting results regarding the effects of HT on cognition. This article reviews the main aspects of menopause and cognition, including the neuroprotective role of estrogen and the relationship between menopausal symptoms and cognitive function. We present and discuss the findings of the central observational and interventional studies on HT and cognition.

Key Words: Menopause; Cognition; Dementia; Estrogens; Hot flashes; Cognitive decline

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Core Tip: Cognitive complaints are more common in postmenopausal women than in premenopausal women. Due to the reduction in ovarian function, a progressive decrease in serum estrogen levels occurs, leading to menopausal symptoms with an emphasis on vasomotor symptoms. In addition to these symptoms, cognitive impairment can affect postmenopausal women to varying degrees. Several aspects of the relationship between menopause and cognitive function were reviewed. We report the latest evidence on the topic. In this sense, considering current knowledge, we do not recommend the prescription of hormone therapy to prevent cognitive decline or dementia in postmenopausal women.

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INTRODUCTION

Approximately 50 million people worldwide live with dementia, with Alzheimer's disease (AD) being the most frequent cause[1]. Dementia is characterized by severe cognitive decline and subsequent functional disability[2]. It is the fifth leading cause of death and is responsible for 28.8 disability-adjusted life-years[3]. A few decades before the onset of Alzheimer's dementia, AD-related neuropathological changes are observed in the brain, which may be accompanied by subtle cognitive decline[4]. Accordingly, patients with early cognitive symptoms are at increased risk of dementia [5,6].

Mild cognitive impairment (MCI) is defined as individuals with objective cognitive deficits in neuropsychological tests (usually defined as a performance of 1.5 standard deviations below the mean established for age and education) and preserved functional independence for activities of daily life[2]. MCI is related to a nine-fold increase in the risk of dementia compared to the general population[5]. Subjective cognitive complaints with normal performance on neuropsychological tests are related to a two-fold increase in the risk of dementia compared to the general population[6]. Identifying and understanding the predisposing and triggering factors of the neurobiological mechanisms underlying early cognitive decline may contribute to the development of preventive interventions to mitigate the risk of dementia.

Female sex is a consistent risk factor for dementia, and the greater longevity of women does not fully explain this relation. In addition, estrogen plays an essential role in the neurobiology of cognitive processing and neuronal function, and the menopausal transition is associated with subtle cognitive decline. However, the relationships among decreased estrogen levels in menopause, the effects of hormone therapy (HT) on cognition, and the risk of dementia are still conflicting and puzzling.

Considering the relevance of the issue and seeking to contribute to the existing literature, several aspects of the relationship between menopause and cognitive function were reviewed in this paper. We describe the most recent evidence, presenting what we know and the gaps in knowledge on the subject.

SEARCH METHODS

A search was conducted in Medline and Embase for the period from 1980 to 2020. The search terms cognition, climacteric, cognitive decline, estrogen effects, menopause, menopausal symptoms, hot flashes, middle-aged women, perimenopause, neuropsychology, HT, progestogen, MCI, subjective cognitive decline, risk of dementia, neuroimaging, and vasomotor symptoms were used.

Original articles, systematic reviews, meta-analyses, narrative reviews, and consensus reports were evaluated. Both human and animal studies published in

English were considered. The bibliographies of the articles were searched to identify related studies. All articles were critically evaluated by the authors, including those more specifically related to the theme of this narrative review and those that resulted in agreement between the authors for their inclusion.

EVIDENCE OF THE RELATIONSHIP BETWEEN MENOPAUSE AND COGNITIVE DECLINE

Subjective cognitive decline is one of the most frequent complaints of women undergoing the menopausal transition, with a 44%-62% prevalence estimated in population-based studies[7,8]. Reports of memory problems are associated with the perimenopausal period compared to pre- or postmenopausal periods[9]. The incidence of MCI was 4.5% in 6376 postmenopausal women evaluated for 5.4 years in the Women's Health Initiative Memory Study (WHIMS)[10], but the relationship between MCI and menopausal factors has still been poorly studied. In contrast, changes in women's cognitive test performance, regardless of cognitive complaints or cognitive impairment, are consistently related to the reproductive period and menopausal transition.

After adjusting for age, cognitive performance during postmenopause tended to be lower than that during pre- and perimenopausal periods, particularly verbal delayed memory and executive function[11], which involve cognitive domains that are assumed to be more sensitive to changing estrogen levels[12]. The Study of Women's Health Across the Nation evaluated 2362 American women by repeated administration of neuropsychological tests for four years. Women's scores on delayed and immediate memory tests in the early and late perimenopausal periods did not improve over time with test repetition. However, the incremental changes in scores normalized in the postmenopausal period, returning to the pattern observed during premenopause[13]. Similarly, Kilpi *et al*[14] studied 2411 middle-aged United Kingdom women, verifying that processing speed and immediate and delayed verbal episodic memory decreased in the perimenopausal period; additionally, changes in verbal episodic memory tests correlated with follicle-stimulating hormone and luteinizing hormone levels.

Several studies have also reported that prolonged lifetime estrogen exposure results in better cognitive outcomes[15]. A younger age at first menses, older age at menopause, age at birth of a first child more than 20 years, and an extended reproductive period were related to a more remarkable performance on neuropsychological tests at postmenopause[16,17]. However, the data are conflicting regarding reproductive period factors and the risk of progressive cognitive decline or dementia. Although the meta-analysis by Georgakis *et al*[15] found that age at menopause and the reproductive period were not associated with the risk of dementia, two more recent population-based studies documented an increased risk of dementia by up to 23% with late menarche, early menopause and a short reproductive period[18,19]. Interestingly, patients who underwent bilateral oophorectomy before menopause had a higher risk of cognitive impairment over time than age-matched natural menopausal women; additionally, oophorectomy at ≤ 45 years of age was associated with an increased risk of dementia[20,21]. In women with Down syndrome, a condition with a higher incidence of AD than the general population, age at menopause was directly correlated with the age of dementia onset[22].

Evidence on AD biomarkers in middle-aged women strengthened the hypothesis that decreased estrogen levels in the menopausal transition explain cognitive decline during perimenopause and the greater risk of dementia related to the female sex. Rahman *et al*[23] compared 40- to 65-year-old women with age-matched men in terms of cerebral volumetry using structural magnetic resonance imaging, cerebral metabolism using 18F-fluorodeoxyglucose positron emission tomography, and the β -amyloid load using 11C-Pittsburgh compound B positron emission tomography. Women presented lower gray and white matter volumes, lower glucose metabolism, and higher deposition of β -amyloid; this neuroimaging pattern was consistent with an AD endophenotype. Menopause was the strongest predictor of these findings. Other studies reported a gradient of AD biomarkers, with the most remarkable abnormalities in menopausal women, an intermediate number of abnormalities in perimenopausal women, and the lowest number of abnormalities in premenopausal women[24,25]. In addition, cerebral glucose hypometabolism in AD-vulnerable regions of peri- and postmenopausal women correlated with reduced platelet mitochondrial cytochrome oxidase activity; mitochondrial cytochrome oxidase is an enzyme involved in

adenosine triphosphate (ATP) synthesis that is regulated by estrogen[24]. Based on these findings, the decrease in estrogen levels during the menopausal transition disrupts brain bioenergetics due to mitochondrial cytochrome oxidase dysfunction that is accompanied by reduced cerebral metabolism, β -amyloid deposition, synaptic loss, and cognitive decline.

PATHOPHYSIOLOGY

Estrogen and the brain

Accumulating evidence shows a significant neurotrophic and neuroprotective effect of estrogen on the central nervous system. Cognitive deficits have been described in women during the menopausal transition, particularly in cognitive domains such as working memory, attention, reduced processing speed, and reduced verbal memory. This review briefly describes the plausible biological functions of estrogens in aspects of cognitive function and the mechanisms involved[26].

The effects of estrogen on the brain include complex cellular mechanisms ranging from classical nuclear to nonclassical membrane-mediated actions. In classical mechanisms, estrogen modulates gene transcription by interacting with nuclear receptors. The estrogen receptors (ER) α and ER β have distinct differences in their binding affinities for different ligands and selective ER modulators[27].

Through genomic mechanisms, steroids exert long-term effects on neurons, modulating the synthesis, release, and metabolism of many neuropeptides and neuroactive transmitters and the expression of their receptors. The nongenomic (nonclassical) estrogen action is probably mediated by receptors integrated or associated with the cell membrane and by the activation of distinct intracellular signaling cascades through the high-affinity membrane-associated G protein-coupled estrogen receptor GPR30/GPER1[28,29].

These effects of estrogens include rapid actions on the excitability of neuronal and pituitary cells, activation of cyclic adenosine monophosphate and mitogen-activated protein kinase pathways that affect the activity of targets such as kainite and insulin-like growth factor-1 receptors, modulation of G-protein coupling, modulation of calcium currents, modulation of calcium channels and calcium ion entry and protection of neurons from damage by excitotoxins and free radicals[30-33].

Decreases in estradiol levels may impact three systems. Researchers must determine how therapeutic modulation of estradiol levels may augment normal or disease-related cognitive decline. The three predominant systems postulated to be involved in cognitive aging concerning hypoestrogenism include the basal forebrain cholinergic system, the dopaminergic system, and the mitochondrial bioenergetic system[34].

Reduced nicotinic cholinergic binding sites in the cortex and reduced cholinergic acetyltransferase activity (a marker of cholinergic neurons) have been shown to correlate with reduced cognitive performance[35]. Choline acetyltransferase-expressing neurons are a marker for cholinergic neurons, and thus the expression of GPR30/GPER1 on cholinergic neurons provides increasing evidence for an interaction between estrogens and the cholinergic system. Clinical magnetic resonance imaging studies have shown that estradiol treatment also modulates anti-muscarinic and anti-nicotinic induced brain activity. Estradiol treatment alters anticholinergic-related brain activation during working memory in postmenopausal women[36].

The effects of estradiol on dopaminergic signaling have been less well characterized than its effects on the cholinergic system. *In vitro*, estradiol protects against 6-hydroxy-dopamine toxicity in dopamine neurons[37]. Magnetic resonance imaging evidence has shown that dopaminergic agonists increase working memory activity, suggesting that the dopaminergic system is responsive to pharmacological manipulation after the menopausal transition[38]. The potential mechanism by which estradiol exerts its neuroprotective effects on dopaminergic neurons is to modulate the neurotoxic effects of the renin-angiotensin system[39].

The mitochondrial aging hypothesis is related to increased mitochondrial DNA damage, leading to increased reactive oxygen species-mediated damage and a reduction in mitochondrial activity[40]. Clinical studies support the postulated role for estradiol in maintaining appropriate mitochondrial bioenergetics; clinical studies also support the hypothesis that decreasing estradiol levels are correlated with reduced synaptic plasticity, an indicator of cognitive performance, suggesting that a failure of glucose metabolism might influence cognitive deficits. As glucose uptake decreases, ATP production also decreases, consistent with aerobic cellular respiration[41].

Finally, low-grade inflammation has also been identified as a potential cause of cognitive decline. Postmenopausal women present an increase in the levels of inflammatory markers such as interleukin (IL)-1, IL-6, and tumor necrosis factor- α . These increases in inflammatory markers appear to be normalized following treatment with sex HT, exerting a relevant anti-inflammatory effect[42,43].

Neuroprotective effect of estrogen

A reasonable hypothesis is that estrogen might exert an important protective effect on the deterioration of cognitive functions that occurs with normal aging. The potential mechanisms involved in the neuroprotective effects of estrogens include modulation of neuropeptides, neurotransmitters, and neurosteroid synthesis and activity[44,45]; reduced cell apoptosis[46]; modulation of neuronal growth and synaptic plasticity[47] and mitochondrial activity[48]; antioxidant properties[49]; modulation of the brain immune system[50]; and reduced formation of β -amyloid[51].

Importantly, the effects of treatment with sex hormones on cognitive symptoms appear to be more evident during the menopausal transition or in the first years of menopause when the levels of estradiol and estrogen receptors are initially decreasing [52].

Moreover, some selective estrogen receptor modulators, such as tamoxifen and raloxifene, have shown promising effects by interacting with ER α , ER β , and GPR30[53] and exert neuroprotective effects[54]. Selective estrogen receptor modulators have shown efficacy in reducing anticholinergic effects on cognitive performance in some cognitive domains by reducing proinflammatory cytokine levels[55].

Findings from primary studies have shown that testosterone also exerts neuroprotective and anti-inflammatory effects on the brain. Testosterone protects against oxidative stress, serum deprivation-induced apoptosis, and soluble amyloid β (A β) toxicity; this effect is mediated by estrogen. A β toxicity induced by testosterone appears to involve an androgen receptor-dependent mechanism that leads to the upregulation of the A β -catabolizing enzyme neprilysin[56,57].

Notably, testosterone studies in women have yielded differing findings according to the women's ages, the testosterone dose administered, and the study duration. Observational and interventional studies have shown an association between verbal learning and memory and physiological concentrations of testosterone administered to postmenopausal women exogenously. The effects of testosterone on verbal learning and memory in postmenopausal women do not seem to rely on the aromatization of estradiol. The statistically significant improvements in verbal memory following testosterone therapy in postmenopausal women suggest that further investigations of the ability of testosterone to enhance cognitive performance or delay cognitive decline are warranted, but the results currently do not justify using testosterone for this purpose[58].

In conclusion, increasing evidence linking menopausal hormone changes and cognition has revealed a complex biological mechanism. A better understanding of this mechanism is fundamental to enable earlier and personalized pharmacological treatment with the potential to delay the onset of cognitive decline during the menopausal transition.

CLIMACTERIC FACTORS AND COGNITIVE DECLINE

The climacteric period often involves problematic symptoms, including vasomotor symptoms, vaginal dryness, decreased libido, insomnia, and fatigue[59]. In clinical practice, cognitive changes are also frequently observed during this period, with subjective reports of "cerebral fog" affecting daily cognitive performance. Some of the most common symptoms are deficits in attention, processing speed, and memory, which subsequently manifest as lack of focus, slow thinking, and forgetfulness[60].

In the Study of Women's Health Across the Nation with 16065 women between the ages of 40 and 55, 31% of premenopausal women reported complaints of forgetfulness, compared to 44% of women in early perimenopause, 41% of women in late perimenopause, and 41% of postmenopausal women[61]. This study later reported a compromise in cognitive performance, mainly in learning skills during the menopausal transition, with a subsequent improvement in the postmenopausal period. Cognitive changes that occur late after menopause are associated with aging and not with the last menstrual period[8].

In the Kinman women's health investigation, a longitudinal study, the cognitive performance of 694 premenopausal Chinese women was evaluated. Verbal memory,

mental flexibility, verbal fluency, and processing speed were measured at baseline and after 18 mo. An improvement in cognitive test scores was observed, which was expected due to the learning effect of repetition of neuropsychological tests. However, perimenopausal women recorded worse results than those who remained in the premenopause group[62].

Studies indicate that this decreased cognitive performance during perimenopause appears to normalize in postmenopause[8,62]. If this pattern of change in memory during the menopausal transition is valid, the decreases in estradiol levels alone are not likely solely responsible for cognitive changes, as memory appears to recover while decreases in estradiol levels persist[13,63].

Although self-reported vasomotor symptoms (VMSs) are generally not related to memory performance[64], when this relationship was observed using 24-h monitoring to measure physiological VMSs, verbal memory differences were found. Among middle-aged women, moderate to severe VMSs related to worse verbal memory were recorded with ambulatory skin conductance monitors and not self-reported VMSs[65,66].

Another cross-sectional study was performed with women with moderate to severe VMSs. Researchers recorded physiological VMSs using ambulatory monitors associated with or without a diary to record subjective VMSs and performed a battery of neuropsychological tests. A higher frequency of physiological VMSs, but not subjective VMSs, particularly during sleep, was associated with poor verbal memory testing performance[67]. Recently, a study evaluating the association between VMSs and worse memory was replicated in breast cancer survivors, confirming evident associations only with physiological VMSs[68].

Thus, in addition to being passive predictors of depressed mood, sleep problems, and worse quality of life during menopausal transition, VMSs also appear to be linked to the leading indices of physical and neurocognitive health[65,68].

HT AND COGNITION

Although many questions remain about the effects of HT on cognitive function, two factors seem to be consistently involved: Age and time of exposure concerning menopause. Researchers have postulated that a critical window exists that explains the more evident effects of HT when administered early when symptoms manifest and when administered to young women. However, published studies have reported conflicting results in this regard and are presented and discussed below.

Contradictory evidence presented to date

Although a considerable number of studies have examined the effects of HT on cognitive function in postmenopausal women, the results are still conflicting. Some studies showed benefits[69-71], others showed a lack of effect[72-74], and worsening of cognitive function was observed in some, including a more significant risk of MCI and various types of dementia[75,76]. Importantly, observational studies are prone to biases, such as selection bias, type, time of HT use, and age at HT initiation, which are often not controlled. These biases may at least partially explain the divergence between the findings of observational and interventional studies.

Many investigators presented their results for different aspects of HT and cognition at the same time. Because the same study published data on global cognitive function, MCI, and dementia, we chose to discuss the best evidence available, presenting the data jointly, as in the original articles of the critical observational and interventional studies on this topic.

Observational studies

Evidence from older women: The Cache County Study (CCS), a longitudinal, population-based study, investigated the association between HT and global cognitive function. The modified Mini-Mental State Examination (MMSE) was administered to 2073 women over 65 years old with no prior diagnosis of dementia. After three years of follow-up, HT was associated with an apparent benefit in global cognitive function and reduced cognitive decline, especially in older women (75 years or older) and even more so in women older than 85 years[77]. In another CCS publication, the relation between HT and AD was evaluated in 1889 women with an average age of 74.5 years. Compared to nonusers, women who received HT for more than ten years presented a 2.5-fold lower risk of AD incidence[78]. With seven more years of follow-up, the CCS cohort verified that starting HT (any type) within five years of menopause was

associated with a 30% reduction in the risk of developing AD. However, if HT was initiated after five years of menopause, no associations were observed.

Furthermore, if HT was initiated within five years of menopause and used for ten years or more, the reduction observed in AD risk was 37%. Additionally, the use of estrogen alone within five years of menopause reduced the risk of AD by 35%[79], which supports the critical window hypothesis. The main information obtained from the observational studies is shown in Table 1.

In a recent 12-year update of the follow-up of the CCS cohort, which included 2,114 women, a longer HT duration was associated with better cognitive function. Additionally, women who initiated HT within five years of menopause presented better cognitive performance than those who initiated it six or more years after menopause, once again supporting the critical window hypothesis. However, another interesting finding in the CCS was that even women who initiated HT after six years of menopause still presented cognitive benefits compared to women who never used HT [71].

In a French longitudinal study, the Three-City Study, 3310 postmenopausal women aged 65 years and over were followed every two years and were subjected to a series of cognitive tests to examine the association of HT with dementia and some specific cognitive domains. After a 4-year follow-up period, no associations were observed between HT and dementia or AD. Additionally, active HT users had significantly better performance on verbal fluency, working memory, and psychomotor speed tasks than those who never used HT. These associations varied according to the type and duration of HT. The findings of this study suggest that transdermal estrogen combined with progestogen and a lengthier HT duration are better at improving cognitive function. Notably, current HT users exhibited a reduction in the detrimental effect of apolipoprotein E (ApoE) E4, a known risk factor for dementia, on the incidence of dementia and AD. Moreover, starting HT near menopause had no relation to improved cognition[69], potentially refuting the critical window hypothesis.

In another longitudinal study with 5504 postmenopausal women conducted at the Kaiser Permanente Medical Care Program of Northern California, women who used HT only during their midlife period presented a 26% reduced risk of dementia than women who never used HT. Those who used HT in late life experienced detrimental effects, with a 48% higher risk of dementia in the 8-year follow-up[80]. These findings support the critical window hypothesis.

The largest longitudinal study was the Nurses' Health Study, a prospective cohort study that included a subgroup of 13087 participants aged 70 or older to evaluate global cognitive function, attention, verbal memory, and category fluency. Generally, few differences were observed between average cognitive decline when comparing current users or former users of HT and those who had never used it. On the other hand, the data suggest an increased risk of cognitive decline in long-term users (*i.e.*, 5 to 10 years) of estrogen alone or estrogen combined with progestogen, with a greater risk identified in women who initiated HT at an older age than in those who never received HT [relative risk: 1.74; 95% confidence interval (CI): 1.08-2.81]. The authors also did not identify a relation between HT and the ApoE E4 allele. The authors concluded that postmenopausal HT provides no relevant cognitive benefit in older women[76].

In a population-based nested case-control study that included 59 women with AD and 221 controls, no relationship was observed between the use of HT (estrogen with or without progestogen) and AD risk[72], corroborating the findings from a previous case-control study[81]. The Multi-Institutional Research in Alzheimer's Genetic Epidemiology case-control study included 971 postmenopausal women from different countries (426 patients with AD and 545 nondemented patients). HT was associated with a 30% reduction in the AD risk. The ApoE genotype did not influence the relationship between HT and AD. The protective effect of HT was modified by age, as it was observed only in younger women aged between 50 and 63 years, who presented a 65% reduction in the AD risk[82].

These findings suggest that HT use during the first years after the last menstrual period, named the critical window, may protect cognitive function. In another case-control study conducted in Finland, 84739 women diagnosed with AD and 84739 women without an AD diagnosis were included. Systemic HT was associated with a 9% to 17% increased risk of AD, with no significant difference between those who used estrogen alone and those who used estrogen and progestogen in combination. The exclusive use of vaginal estradiol did not increase the risk of AD. Moreover, the age at which HT was initiated (younger than 60 years or older than 60 years) had no effect on the AD risk. Notably, in women who initiated HT before 60 years of age, the increase in the AD risk was associated with the use of HT for ten years or more. The

Table 1 Observational studies on hormone therapy and cognition in women

Ref.	Study	Country	Design	n (%)	Age (yr)	Hormone therapy	Main findings
Carlson <i>et al</i> [77], 2001	Cache County Study	United States	Longitudinal	2073	≥ 65	ET or EPT	HT reduced cognitive decline
Seshadri <i>et al</i> [72], 2001		United Kingdom	Case-control	AD: 59. Controls: 221	Mean: 66.7	ET or EPT	HT was not associated with AD
Kang <i>et al</i> [76], 2004	Nurses' Health Study	United States	Longitudinal	13807	≥ 70	ET or EPT	HT was not associated with relevant cognitive benefits
Henderson <i>et al</i> [82], 2005	Mirage Study	United States, Canada, Germany	Case-control	AD: 426. Controls: 545	Mean: 71.1	ET or EPT	HT reduced the AD risk by 30%
Ryan <i>et al</i> [69], 2009	Three City Study	France	Longitudinal	3130	≥ 65	ET or EPT	HT was not associated with dementia or AD, but current users had better cognitive performance in specific domains
Shao <i>et al</i> [79], 2012	Cache County Study extended	United States	Longitudinal	1768	≥ 65	ET or EPT	HT initiated within five years of menopause decreased the AD risk by 30%
Whitmer <i>et al</i> [80], 2011	Kaiser Permanente Medical Care Program of Northern California	United States	Longitudinal	5504	Mean in midlife: 48.7	ET or EPT	The use of HT only in midlife reduced the dementia risk. On the other hand, the use of HT in late-life increased this risk
Imtiaz <i>et al</i> [70], 2017	Kuopio Osteoporosis Risk Factor and Prevention study	Finland	Longitudinal	8195	46 a 56	ET or EPT	Long-term HT users (> 10 yr) exhibited a 47% reduction in the AD risk
Savolainen-Peltonen <i>et al</i> [83], 2019		Finland	Case-control	AD: 84739. Controls: 84739	Mean age at onset of systemic HT: 52	ET or EPT	HT increased the AD risk by 9%-17%, regardless of the age of onset of use and the type of HT

ET: Estrogen-only therapy; EPT: Estrogen-progestogen therapy; HT: Hormone therapy; AD: Alzheimer's disease.

authors concluded that prolonged use of systemic HT might be accompanied by an increased risk of AD, which is not related to the type of progestogen or the age of HT initiation[83].

Few observational studies have evaluated the effects of HT exclusively in younger women. A recent prospective study conducted in Finland with 8195 women between 47 and 56 years of age with a 20-year follow-up showed little evidence of the protective effect of HT on dementia or AD, as only women who reported long-term (*i.e.*, more than ten years) use of HT presented a significant reduction in the AD risk of 47% compared to nonusers[70].

Interventional studies and the critical window hypothesis

As previously stated, the critical window hypothesis postulates that the effects of HT vary according to the moment of exposure, as related to menopause. According to this theory, estrogen administered closer to menopause would exert neuroprotective effects, whereas no benefit or harm would be observed when HT was administered years later[80]. Similarly, an ideal moment would exist to start HT and obtain cognitive benefits. Table 2 shows the main findings from the pertinent randomized clinical trials.

Evidence from older women

Due to possible biases regarding HT in observational studies, clinical trials were conducted to clarify these doubts. The WHIMS is an ancillary study of the Women's Health Initiative (WHI). The WHIMS included women aged 65 years or older. The effect of HT on the incidence of MCI and all-cause dementia (Alzheimer's, vascular and other types) was evaluated in hysterectomized women treated with conjugated equine estrogen (CEE), nonhysterectomized women treated with CEE plus medroxyprogesterone acetate (MPA), and the placebo group.

Table 2 Randomized clinical trials on hormone therapy and cognition in women

Ref.	Study	Country	n (%)	Age (yr)	Hormone therapy	Main findings
Shumaker <i>et al</i> [75], 2003	Women's Health Initiative Memory Study-WHIMS	United States	HT users: 2229. Placebo: 2303	≥ 65	CEE + MPA	HT increased the dementia risk
Shumaker <i>et al</i> [84], 2004	Women's Health Initiative Memory Study-WHIMS	United States	HT users: 1464. Placebo: 1483	65 to 79	CEE alone	Estrogen alone did not decrease the incidence of mild cognitive impairment or dementia
Greenspan <i>et al</i> [85], 2005		United States	HT users: 187. Placebo: 186	≥ 65	CEE with or without MPA	HT did not affect cognitive function
Yaffe <i>et al</i> [86], 2006		United States	HT users: 208. Placebo: 209	60 to 80	Ultra-low dose unopposed transdermal estradiol	Transdermal estradiol did not affect cognitive function
Espeland <i>et al</i> [87], 2010	Women's Health Initiative Study of Cognitive Aging-WHISCA	United States	HT users: 1125. Placebo: 1179	65 to 80	CEE with or without MPA	HT was associated with worsening global cognitive function and some specific cognitive domains. This worsening persisted after the interruption of HT
Espeland <i>et al</i> [73], 2013	Women's Health Initiative Memory Study of Younger Women-WHIMSY	United States	HT users: 696. Placebo: 630	50 to 55	CEE with or without MPA	HT did not alter global cognitive function or specific cognitive domains
Gleason <i>et al</i> [74], 2015	Cognitive and Affective Study-KEEPS-Cog	United States	HT users: 431. Placebo: 262	Mean: 52.6	CEE + micronized progesterone or transdermal estradiol + micronized progesterone	HT did not affect cognition
Henderson <i>et al</i> [92], 2016	Early vs Late Intervention Trial with Estradiol Cognitive endpoints-ELITE-Cog	United States	HT users: 284. Placebo: 283	Early postmenopause: 55.6. Late postmenopause: 64.9	Estradiol with or without micronized progesterone	HT did not affect verbal memory, executive function and global cognition, regardless of whether it was started < 6 yr or ≥ 10 yr after menopause
Espeland <i>et al</i> [91], 2017	WHIMSY extended + Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO)	United States	WHIMSY-HT users: 701. Placebo: 635. WHIMS-ECHO-HT users: 1402. Placebo: 1478	Two groups: 50 to 54; 65 to 79	CEE with or without MPA	HT prescribed to younger women had no significant effect on cognitive function in the long term. HT administered to older women produced decreased global cognitive function, executive function, and working memory

CEE: Conjugated equine estrogen; MPA: Medroxyprogesterone acetate; HT: Hormone therapy.

In the CEE/MPA arm of the study, in which 4532 women participated (CEE/MPA group: 2.229; placebo group: 2.303), the hazard ratio (HR) for dementia was 2.05 (95% CI: 1.21-3.48; 45 vs 22 per 10000 person-years; $P = 0.01$), resulting in 23 additional cases of dementia per 10000 women per year. AD was the most common dementia type in both groups. The effects of treatment on the risk of MCI did not differ between groups (HR: 1.07; 95% CI: 0.74-1.55; 63 vs 59 cases per 10000 person-years; $P = 0.72$). The authors concluded that HT with the combination of estrogen and progestogen increased the risk of probable dementia in postmenopausal women aged 65 years older. These data indicate a lack of protection from MCI in these women receiving HT [75].

In the WHIMS arm with CEE alone, 2947 participants were included (CEE group: 1464; placebo group: 1483), with ages ranging from 65 to 79 years. No significant differences in the dementia risk (HR: 1.49; 95% CI: 0.83-2.66) and MCI risk (HR: 1.34; 95% CI: 0.95-1.89) were observed between groups. However, the joint analysis of the MCI or dementia risk showed a greater risk for women who received CEE alone than the placebo group (HR: 1.38; 95% CI: 1.01-1.89; $P = 0.04$) [84]. Isolated estrogen therapy did not reduce the incidence of MCI or dementia. Based on the combination of WHIMS data, HT with estrogen alone and CEE/MPA resulted in an increased risk of dementia or MCI in women aged 65 or older, and HT was not recommended to prevent cognitive decline [84].

In two randomized clinical trials with a smaller population of older postmenopausal women, including a study with 373 women and a 3-year follow-up period[85] and another with 417 women and a 2-year follow-up period[86], HT had no significant effect on cognitive function. The WH Study of Cognitive Aging, another ancillary study of the WHI, had two arms, CEE alone and CEE/MPA with matching placebos, and included 2304 women. HT initiated after 65 years of age was associated with worsening global cognitive function and changes in a few cognitive domains; notably, this reduction persisted after the interruption of HT. The authors highlighted that this difference in cognitive function was small and might have no clinical meaning[87].

A meta-analysis that included 16 clinical trials with 10114 women reported no beneficial effect of HT (estrogen with or without progestogen) administered in the short or long term (up to five years) on the cognitive function of older postmenopausal women. Moreover, the authors were unable to establish definitive conclusions on the effects of different administration routes and HT dosages on women's cognitive function[88]. Another meta-analysis concluded that HT is not indicated to prevent cognitive decline or dementia in postmenopausal women[89].

Evidence from younger women

Since younger women more frequently receive HT, its effects on cognitive function when used precociously must be clarified. Clinical trials on this topic are rare.

A systematic review included data from nine randomized, double-blind, placebo-controlled clinical trials of HT with estrogen alone and two with estrogen combined with progestogen, in which cognitive tests were administered to women aged less than 65 years, although the sample size was small. Seven of nine studies reported a small advantage for estrogen treatment in at least one cognitive test, particularly in verbal memory and attention. Only two studies assessed the effect of combined HT (estradiol valerate and dienogest), showing some benefit only on verbal memory[90]. Thus, although scarce, evidence from HT in younger women suggests potentially beneficial effects on specific cognitive domains, particularly in symptomatic women and women who recently underwent menopause, as well as inadequate evidence of damage. Studies examining the cognitive effects of estrogen combined with progestogen on younger women are scarce[90].

In the WHIMS of Younger Women (WHIMSY), an ancillary study of the WHI study, the effect of HT (CEE/MPA, CEE-alone, and placebo) on cognition was evaluated in 1326 postmenopausal women aged 50 to 55 years. Cognitive testing was performed, on average, 7.2 years after the end of the WHI study, when participants had an average age of 67.2 years at their first evaluation. HT did not alter global cognitive function or the specific domains of cognition (verbal memory, working memory, verbal fluency, attention, and executive functions). WHIMSY data indicated that CEE-based HT administered to younger women in the initial postmenopausal period had no long-term beneficial or harmful effects[73]. Afterward, the authors published data from the extended follow-up accomplished through WHIMSY and WHIMS-Epidemiology of Cognitive Health Outcomes, in which HT was prescribed to women aged 65 to 79 years. The use of HT by younger women for up to 6 years had no significant effect on cognitive function in the long term. On the other hand, the use of HT for five years by older women was related to a decline in global cognitive function, executive functions, and working memory, which persisted for more than ten years after administration [91].

Another investigation that included younger women was the Cognitive Affective Study (KEEPS-Cog)[74], an ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS). The KEEPS-Cog studied the effects of HT administered for up to four years on cognition (global cognitive function, mental flexibility, verbal learning/memory, auditory attention, and executive functions) and humor in recently postmenopausal healthy women. In this randomized, double-blinded, placebo-controlled clinical trial, 0.45 mg of CEE was administered orally, plus 200 mg of micronized progesterone or 50 mcg of transdermal estradiol, plus 200 mg of micronized progesterone, as well as a placebo. Participants had a mean age of 52.5 years and were tested at an average of 1.4 years after menopause. HT did not affect cognition, and the use of oral CEE combined with micronized progesterone reduced anxiety and depressive symptoms, changes that were not observed in the group receiving transdermal therapy[74]. The KEEPS-Cog results regarding the lack of effect of HT on cognition are consistent with the WHIMSY findings.

The Early *vs* Late Intervention Trial with Estradiol (ELITE) was a randomized clinical trial in which participants received oral estradiol, micronized progesterone, or a matched placebo. The ELITE-Cog evaluated the effects of HT on cognition in postmenopausal women who were divided into two groups according to time since

menopause: early (less than six years, mean age of 55.6 years) or late (ten years or more, the mean age of 64.9 years). After an average of 57 mo of treatment, no significant differences in verbal memory, executive function, or global cognition were observed among women who initiated estradiol use within six years or ten years or more after menopause. These data suggest that estradiol has no beneficial or harmful effect on the evaluated cognitive domains, regardless of time elapsed since menopause; hence, the authors did not confirm the critical window hypothesis for cognitive function[92].

CONSIDERATIONS FOR CLINICAL PRACTICE

Clinical management of cognitive symptoms in perimenopausal women should consider that cognitive impairment does not appear to be frequent in this population [10], and an increased risk of dementia due to menopause is not well established[15,16,18,19]. Nevertheless, patients with cognitive complaints and no objective impairment exhibited worse performance on cognitive tests than women without complaints[93]. Hence, some perimenopausal women might perceive the decline in verbal memory and learning performance compared to their ability during their premenopausal period, although they performed within normal parameters on neuropsychological tests[13]. Therefore, clinicians must validate the concerns about the cognitive decline of perimenopausal patients and evaluate their cognitive performance. Cognitive screening tests such as the MMSE[94] and the Montreal Cognitive Assessment (MoCA) [95], functional tests such as the Functional Assessment Questionnaire (FAQ)[96], and neurological examinations should comprise routine clinical evaluations. Due to the menopausal transition, cognitive symptoms are not expected to coincide with alterations on the MMSE, MoCA, FAQ, or neurological examination[97]. In these cases, patients should be advised that cognitive complaints are probably due to the menopausal transition associated with a subtle and transient cognitive decline[13]. Women with early menopause or those undergoing surgical or chemotherapy-induced menopause should be evaluated more carefully with repeated cognitive assessments during follow-up since these characteristics are more strongly associated with worse cognitive outcomes at older ages[15,20,21]. Scores less than 28 on the MMSE and less than 26 on the MoCA, indicating functional decline in daily activities (FAQ > 0), or altered neurological examinations are associated with cognitive impairment[98-100]. Notably, lower educational levels may bias cognitive tests, impairing their accuracy [101].

Suppose that screening tests indicate cognitive impairment in perimenopausal women. In that case, a comprehensive neuropsychiatric and neuropsychological assessment would be required to confirm the diagnosis of MCI or dementia in addition to a laboratory workup, neuroimaging examination, and, eventually, other tests to investigate underlying causes of cognitive decline. Thyroid hormones disturbances, vitamin B12 or folic acid deficiency, anemia, decompensated diabetes or hypoglycemia, electrolyte disturbances, renal or hepatic impairment, neurosyphilis or other infection of the central nervous system, and the use of benzodiazepines or medications with anticholinergic effects are potentially modifiable causes of cognitive impairment that should be excluded. Depression and other affective symptoms, such as anxiety, sleep disturbances, and attention deficit hyperactivity disorder, may exacerbate cognitive decline due to the menopausal transition, causing MCI in middle-aged women. In addition, presenile dementias such as familial AD, frontotemporal lobar degeneration, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy are uncommon neurocognitive disorders that may affect perimenopausal women.

Concerning the relationship between HT and cognition in postmenopausal women, the literature reports conflicting data. Notably, research differs in terms of the study design, age of the studied population, starting moment of HT, type, route of administration, and HT duration, among other aspects. An analysis of these studies allows us to verify dissonant findings, even among observational studies. Generally, observational studies have suggested some beneficial effects of HT on cognition, although some researchers, as previously described, have identified cognitive decline or an increased risk of dementia associated with HT. Regarding interventional studies, the findings are also not uniform concerning whether HT exerts detrimental or no effects on cognition. Overall, the results of interventional studies indicated detrimental effects of HT on older women, leading to cognitive decline and a greater risk of dementia, including AD.

Data on HT and cognition in younger postmenopausal women are scarce. Although observational studies suggest that HT may protect against future cognitive impairment in the early years of postmenopause, data from the WHIMSY trial[73,91], KEEPS-Cog trial[74], and ELITE-Cog trial[92] showed no benefits of HT in terms of the cognitive function of postmenopausal women compared to that of younger women. In younger symptomatic women, for whom benefits of using HT for symptom improvement have been reported, limited evidence suggests that these women do not appear to have a more significant risk of developing future cognitive problems.

Building big data and using data-driven approaches such as machine learning would help resolve conflicting data regarding the role of the menopausal transition in the risk of dementia and the effect of HT. In this context, big data may contribute to the prevention and early diagnosis of cognitive impairment in women undergoing the menopausal transition and facilitate evidence-based decision-making.

Based on the best available evidence, no robust data have been published that indicate that the use of HT with estrogen alone or combined with progestogen prevents cognitive decline or dementia in postmenopausal women. Thus, the prescription of HT is not recommended for this purpose.

CONCLUSION

The increasing number of people living with dementia will significantly impact life in years to come. Its effects will be felt individually, as it decreases the quality of life, both in patients and caregivers and at a population level, as it overburdens the health system and influences policies worldwide.

Being at greater risk of developing dementia, women are a target group of great interest for future studies. The link between sex and the risk of dementia still must be better understood. Along these lines, the menopausal transition is important, as it is a period of intense hormonal changes and symptomatic stress, which may be related to cognitive decline. Estrogen may play an essential role as a neuroprotective agent, although numerous other aspects are also relevant. A better understanding of the physiology involved in the cognitive impairment in this population, as well as the aspects of this decrease in cognition—which functions are affected and to what extent—may contribute to the elaboration of preventive measures and eventually may contribute to better treatment strategies, focusing on this possibly reversible cause of the cognitive decline.

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