Minireview: Effects of Different HT Formulations on Cognition

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Evidence from preclinical studies, randomized clinical trials (RCT), and observational studies underscores the importance of distinguishing among the different forms of estrogen and progestogens when evaluating the cognitive effects of hormone therapy (HT) in women. Despite this evidence, there is a lack of direct comparisons of different HT regimens. To provide insights into the effects of different HT formulations on cognition, this minireview focuses on RCT of verbal memory because evidence indicates that HT affects this cognitive domain more than others and because declines in verbal memory predict later development of Alzheimer's disease. Some observational studies indicate that estradiol confers benefits to verbal memory, whereas conjugated equine estrogens (CEE) confer risks. RCT to date show no negative impact of CEE on verbal memory, including the Women's Health Initiative Study of Cognitive Aging. Similarly, the Women's Health Initiative Memory Study showed no negative impact of CEE on dementia. Transdermal estradiol in younger postmenopausal women improved verbal memory in one small RCT but had no effect in another RCT. RCT of oral estradiol in younger and older postmenopausal women had neutral effects on cognitive function. In contrast, RCT show a negative impact of CEE plus medroxyprogesterone acetate on verbal memory in younger and older postmenopausal women. Small RCT show neutral or beneficial effects of other progestins on memory. Overall, RCT indicate that type of progestogen is a more important determinant of the effects of HT on memory than type of estrogen. **(*Endocrinology* 153: 3564–3570, 2012)**

Understanding the effects of different formulations of hormone therapy (HT) on cognition is important because of compelling findings from the Women's Health Initiative (WHI) showing significant cognitive and other health risks associated with conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) (1, 2). CEE/MPA (0.625 mg CEE plus 2.5 mg MPA per day) increased the risk of coronary heart disease, stroke, pulmonary embolism, and breast cancer (1, 2). A later WHI report examined whether the risks of CEE/MPA differed depending on age at randomization or years since menopause (3). The risks of CEE/MPA were similar regardless of age at randomization, but there was a trend ($P = 0.05$) for the effects of CEE/MPA on coronary heart disease to be worse as years since menopause increased (3). The results of the CEE-alone arm of the WHI differed from those of the CEE/MPA arm. In contrast to CEE/MPA, among the primary outcomes in the WHI, CEE increased only the risk of stroke (4). Also in contrast to CEE/MPA, age at randomization was later shown to be a critical determinant of the effects of CEE on a variety of outcomes, including coronary heart disease, myocardial infarction, colorectal cancer, total mortality, and a global index of chronic diseases (3, 5). CEE had more favorable effects on each of these health outcomes among women aged 50–59 yr at randomization compared with women in older age groups (3, 5). These findings suggest that HT effects on a variety of systems depended on progestin use and the timing of initiation of treatment, with potential benefits of estrogen if initiated early during a critical window.

ISSN Print 0013-7227 ISSN Online 1945-7170
Printed in U.S.A.

doi: 10.1210/en.2012-1175 Received February 13, 2012. Accepted May 10, 2012.
First Published Online June 6, 2012

Abbreviations: AD, Alzheimer's disease; APOE-E4, apolipoprotein E ϵ4; CEE, conjugated equine estrogen; ELITE, Early *Versus* Late Intervention Trial with Estradiol; ET, estrogen-alone therapy; HT, hormone therapy; KEEPS, Kronos Early Estrogen Prevention Study; MPA, medroxyprogesterone acetate; RCT, randomized clinical trial; WHI, Women's Health Initiative; WHIMS, WHI Memory Study; WHISCA, WHI Study of Cognitive Aging.

This minireview presents an overview of the impact of different estrogen and progestin formulations on cognitive function. The focus is on placebo-controlled randomized clinical trials (RCT) of HT on dementia and verbal memory. The focus on verbal memory is justified by a meta-analysis of clinical trials showing that verbal memory is particularly sensitive to the effects of estrogen (6), by women's subjective complaints of verbal memory deficits during the menopausal transition (7), and by a wealth of prospective studies demonstrating that verbal memory is a valid predictor of risk of dementia (8–10). Using standard definitions in the neuropsychological and clinical trials literature (6, 11), this review defines verbal memory tests as tests that require recall of word lists, paragraphs, and stories. The majority of RCT to date, including the largest trials to date (12, 13), used word-list learning tests.

Cognitive Effects of CEE and CEE/MPA: Insights from the WHI

Two ancillary studies from the WHI aimed to understand the effects of CEE and CEE/MPA on cognitive outcomes. The WHI Memory Study (WHIMS) is the only RCT of HT for the primary prevention of dementia. Alzheimer's disease (AD) was the *a priori* primary outcome, but the final primary outcome was all-cause dementia because there were too few cases of AD. WHIMS included 4592 participants with an intact uterus who were randomized to receive CEE/MPA or placebo for an average of 4 yr (14) and 2947 women without a uterus who were randomized to receive CEE or placebo for an average of 5.2 yr (15). The WHI Study of Cognitive Aging (WHISCA) was an ancillary study to WHIMS and examined the impact of HT on age-related changes in memory and other cognitive domains, with the first assessment on average 3 yr after randomization in WHI (12, 13). Both WHIMS and WHISCA suggest that the use of MPA is a critical determinant of cognitive effects of CEE treatment in postmenopausal women aged 65 and older. CEE/MPA doubled the risk of dementia (14), but CEE had no impact on dementia (15).

A similar pattern of results emerged in WHISCA (12, 13). The CEE and CEE/MPA arms of WHISCA, which are the largest RCT of HT and cognition, each used the California Verbal Learning Test (16) but showed different impact on the same measure of verbal memory. In a sample of 886 women participating in the CEE-alone arm of WHISCA, active treatment had no impact on longitudinal changes in verbal or figural memory (12). By contrast, in a sample of 1416 women participating in the CEE/MPA arm of WHISCA, active treatment decreased verbal memory performance and tended to improve figural memory (13). This pattern of results suggests that CEE alone has fewer negative effects on verbal memory than CEE/MPA, but CEE/MPA might offer some benefit to nonverbal abilities [see for additional evidence that CEE/MPA may confer benefits to nonverbal abilities (17)]. Such an interpretation, however, is not straightforward because of differences between the women in the CEE and CEE/MPA studies in variables shown to impact cognitive outcomes, including education levels, baseline cognitive status scores, ethnic diversity, history of stroke and coronary heart disease, and previous HT use. These factors, therefore, may have contributed to differences in patterns of results between the CEE alone and CEE/MPA arms of the WHI. Counter to the perspective that CEE alone may be safe or safer for cognitive function than CEE/MPA, WHI investigators do not distinguish between the effects of CEE and CEE/MPA on cognitive outcomes because in pooled analyses, there was no statistically significant difference in the cognitive effects of the two HT regimens (14, 18).

Meta-Analysis of Clinical Trials of HT

Our understanding of the effects of different HT regimens on cognitive function is greatly limited by the lack of RCT involving direct comparisons of different estrogenic and progestogenic agents. In the absence of direct clinical trials, it is helpful to consider results of a meta-analysis of 36 RCT of HT and cognitive function (6). That meta-analysis used a statistical approach (*i.e.* general linear models and χ^2 analyses) to test a variety of hypotheses, including the possibility that cognitive effects of HT may differ depending on the specific type of regimen. The authors coded each trial as yielding positive, neutral, or negative outcomes for each cognitive outcome. Then, they used a χ^2 analysis to test whether the direction of these outcomes was affected by such variables as CEE *vs.* estradiol. Most of the 36 trials intervened with estradiol (58%), and only a minority of those trials also used progesterone (21%). The next most common intervention was CEE (37%), and 21% of those had used CEE/MPA. The remaining 5% of studies involved use of estrone or estriol. Oral administration was most common (71%) followed by transdermal (21%). As expected, RCT of unopposed estrogen (*i.e.* estrogen alone without a progestogen) were more likely to be conducted in surgically menopausal women than in naturally menopausal women.

The results of the meta-analysis indicated that overall HT did not impact cognitive function (6). Verbal memory was the cognitive domain most often affected by HT, although the direction of the effect differed across RCT. Notably, consistent with the critical window hypothesis,

there was a trend ($P = 0.07$) for verbal memory to be better in younger (than 62 yr of age) women after treatment and worse in older women. There was a trend for CEE alone (n = 5 studies) to be associated with a slightly worse outcome on tests than estradiol alone (n = 14 studies). Studies using either CEE alone or estradiol alone were more likely to be associated with positive results than studies using any estrogens combined with any progestogen. Addition of progestin, typically MPA, had significant negative effects on cognitive function. Perhaps most striking were the findings regarding duration of treatment regardless of MPA use; 79% of HT trials that had a positive outcome intervened for 12 wk or less, and all negative effects were found only with interventions longer than 12 wk. These findings suggest that it is important to consider the potential negative impact of progestin on cognitive function, but not necessarily the type of estrogen.

Ongoing RCT of HT will inform our understanding of HT and cognitive function with larger samples. The Kronos Early Estrogen Prevention Study (KEEPS) is a 5-yr randomized, placebo-controlled clinical trial of 720 women aged 42–58 yr within 36 months of their final menstrual period (19). KEEPS will provide insights into the impact of cyclic micronized progesterone (200 mg for 12 d monthly) in combination with transdermal estradiol (50 μg weekly) or CEE (0.45 mg) on cognitive function and cardiovascular outcomes. KEEPS results are expected in 2012. ELITE (Early *Versus* Late Intervention Trial with Estradiol) will provide insights into the effects of oral estradiol (1 mg/d) on cognitive function in younger and older postmenopausal women. ELITE will involve 643 postmenopausal women randomized based on years since menopause (*i.e.* less than 6 yr or 10 yr or more) to receive placebo or estradiol plus a vaginal progesterone gel for 10 d/month. ELITE results are expected in 2013.

RCT of Estrogen plus Progestogen

A particularly robust finding from the RCT literature is that continuous combined CEE/MPA decreases verbal memory, regardless of age and severity of vasomotor symptoms. As noted above, this finding was observed in WHISCA in 1416 women aged 65 and older (13). We published findings from two additional RCT in younger postmenopausal women that showed a trend toward a decrease in verbal memory ($P < 0.06$). The first trial included 180 healthy postmenopausal women aged 45–55 yr with subjective cognitive complaints and minimal vasomotor symptoms and who were randomized to CEE/MPA (0.625/2.5 mg/d) for 4 months (20). The second involved 66 postmenopausal women with 35 or more weekly hot flashes who were randomized to receive daily CEE/MPA (0.625/2.5 mg), red clover (120 mg), black cohosh (128 mg), or placebo for 1 yr (21). Small RCT suggest that other progestin formulations may have positive cognitive effects. In an RCT of 49 midlife women with insomnia (aged 46–67 yr), estradiol valerate (2 mg/d) and dinogest (3 mg/d) for 2 months improved verbal memory compared with estradiol valerate alone (2 mg/d) and placebo (22). Similarly, verbal memory improved significantly after 6 months of treatment with 2 mg estradiol valerate plus 0.7 mg norethisterone in a sample of 15 early postmenopausal women (23).

The largest RCT of a non-MPA progestin was a 2-yr trial of 142 women aged 61–87 who were randomly assigned to receive 1 mg estradiol daily plus 0.35 mg norethindrone 3 d/wk or daily placebo for 2 yr (24). Although there was no overall difference in verbal memory performance between the active treatment and placebo groups, *post hoc* analyses indicated benefit with HT among women whose baseline cognitive performance was at or above the level expected based on age. In contrast, women whose baseline scores fell below expected levels showed no benefit from HT. Overall, these RCT suggest that MPA has the most negative effect on cognition but that other progestins might have neutral or perhaps even beneficial effects even in older women.

Few preclinical translational studies directly compare the effects of different progestins on markers of neuroprotection and neurogenesis. The current evidence nevertheless supports the conclusion drawn from clinical trials that MPA has a negative impact on these markers. Progesterone, norgestimate, Nestorone, norethynodrel, norethindrone, and levonorgestrel have a positive impact on those markers (25). Consistent with findings that MPA decreases verbal memory, MPA antagonizes estrogen upregulation of brain mitochondrial function (26), inhibits adult rat neural progenitor cell proliferation and increases apoptosis (25), blocks estrogen-induced potentiation of glutamate-mediated rises in intracellular calcium (27), and attenuates estrogen-induced protection against glutamate toxicity (28). Preclinical studies have not yet addressed the neurobiological consequences of chronic progestin exposure.

RCT of Estrogen Alone

As noted above, a meta-analysis demonstrated a trend for estrogen alone to improve verbal memory in RCT involving younger women (6). Critically, none of the trials demonstrated a negative effect of estrogen alone on memory in younger women or in older women. RCT in women over

age 65 show neutral effects on verbal memory, including trials of 0.014 mg/d ultra-low-dose transdermal estradiol for 2 yr (n = 417) (29), 1 mg/d oral estradiol for 3 yr (n = 461) (30), 2 mg/d oral estradiol for 20 wk (n = 115) (31), 0.25 mg/d low-dose transdermal estradiol for 3 yr (n = 57) (32), and 0.625 mg/d CEE for 2.7 yr (n = 886) (12). Smaller RCT in younger women show beneficial effects on verbal memory with 10 mg estradiol valerate im monthly for 2 months (n = 19) (33), cyclic oral piperazine for 6 months (1.5 mg bid for 21 d; 7 d off) (34), and transdermal estradiol for 3 months (0.05 mg/d) (35). Neutral effects were observed with 2 mg oral estradiol for 8 wk (36) and 0.1 mg/d transdermal estradiol for 10 wk (37). An analysis of Modified Mini-Mental State Exam performance in 2808 WHIMS participants found that mean Modified Mini-Mental State Exam scores were significantly lower (*i.e.* 0.26 U out of 100) among women assigned to CEE compared with placebo ($P = 0.04$). Importantly, the magnitude of the effect was deemed by the study authors to be "too small to have relevance in clinical practice" (p. 2967) (18).

CEE *vs.* Estradiol: Observational Studies

In light of the lack of RCT directly comparing CEE and estradiol, it is helpful to review findings from two observational studies, each of which showed enhanced verbal memory with estradiol compared with CEE. Both studies focused on women who were at increased risk of AD because of a parental history of AD or other risk factor. Both studies also incorporated functional neuroimaging outcomes. The first study examined verbal memory performance and functional magnetic resonance imaging outcomes in 23 women (mean age 58.5 yr) (38). The HT regimens were standard therapies initiated around menopause. There was a significant main effect of group, with worst verbal memory performance with CEE, followed by no treatment and then by estradiol. The neuroimaging task involved encoding of geometric figures and produced a pattern of bilateral activation in the hippocampus and midtemporal lobe. Group comparisons showed increased activation in these regions in the CEE and estradiol groups compared with the HT-naive group, where increased activation was interpreted as indicative of better neuronal function.

A second observational study compared cognitive performance in 68 healthy, cognitively intact, postmenopausal women (aged 49–68 yr) who had been taking unopposed estradiol or CEE for at least 1 yr (39). Again, verbal memory was significantly better in the estradiol group than the CEE group (there was no HT-naive group). Fifty-three of the participants also completed positron emission tomography assessments of regional glucose metabolism during a resting condition (40). This subgroup of women showed the same pattern of better verbal memory performance with estradiol compared with CEE, and their verbal memory performance positively correlated with metabolism in Wernicke's area and auditory association areas. Another analysis revealed lower metabolism in temporal cortex and inferior temporal cortex among women on HT *vs.* those on unopposed estrogen.

Each of these two observational studies indicated that CEE decreased memory in women at increased risk of developing AD. The observational studies, however, had limitations beyond the lack of random assignment. These limitations included 1) findings regarding CEE that contradicted findings from much larger RCT including WHISCA (12) and WHIMS (15), 2) lack of a pre-HT baseline to ensure that groups were initially equated on cognitive function, 3) questionable internal validity in the smaller study because CEE was associated with a better pattern of brain activation but worse verbal memory performance, 4) frequent use of progestogens among study participants, and 5) the confounding of CEE with MPA use. In the larger study, two thirds of the study sample used a progestin, and use of MPA was more common among those treated with CEE (nine of 11) than those treated with estradiol (five of 24). The authors statistically controlled for any progesterone use, but this statistical control does not fully address the concern because only two of the 11 women on CEE did not take MPA. MPA, as noted above, has negative effects on verbal memory so the finding of lower performance of CEE may be due to confounding with MPA.

In general, the literature of HT effects in women at increased risk of dementia is mixed. A recent observational study in 3130 French women found that women exposed to transdermal estradiol combined with a progestogen, especially synthetic progestin, were less likely than other women to show poor cognitive performance in each of three domains of cognitive function measured (*i.e.* verbal fluency, working memory, and psychomotor speed) (41). The study also examined estrogen effects in relation to the apolipoprotein E ϵ4 (APOE-E4) genotype. The APOE-E4 allele is the most prominent risk factor for late-onset AD (*i.e.* onset after age 65) and has a 50% greater impact on risk in women than men (42). In the French study, current HT use attenuated the risk of dementia in women with the APOE-E4 allele compared with APOE-E4-positive women not currently on HT (41). In contrast, an RCT of 1 mg estradiol and 0.5 mg norethisterone for 1 yr in women diagnosed with AD found benefit only among women without the APOE-E4 genotype (43).

Summary and Future Directions

Since the WHI publications, there have been substantial decreases in prescriptions for CEE/MPA and CEE and greater dominance of transdermal estradiol (44, 45). Overall, RCT indicate that type of progestogen is a more important determinant of the effects of HT on memory than type of estrogen. The clinical trial data indicate no negative impact of estrogen-alone therapies (ET) on cognitive outcomes. Current consensus guidelines for the use of HT cite the greater safety profile associated with ET compared with HT but recommend that all women with an intact uterus who use systemic ET should also be prescribed adequate progestogen to negate the increased risk of endometrial cancer from systemic HT use (46, 47). Evidence indicates that women who underwent either unilateral or bilateral oophorectomy before the onset of menopause had an increased risk of cognitive impairment or dementia compared with referent women, and the magnitude of that risk increased as the age at oophorectomy decreased (48). Critically, use of ET until the typical onset of the menopause protected women against that risk. Together, these studies suggest that use of ET among surgically menopausal women, particularly among those with early oophorectomy, confers cognitive benefits. Minimally, such women should be counseled about the general health benefits of using ET until the typical age of onset of the menopause and should be counseled about the greater safety profile associated with longer-term ET (49).

Given the negative impact of MPA on memory, a top priority is to identify combination HT regimens that treat vasomotor symptoms and confer either beneficial or neutral cognitive effects. As reviewed above, small RCT indicate that when combined with estrogen, norethisterone (23) and dinogest (22) conferred benefits to memory in younger postmenopausal women. Norethindrone had neutral cognitive benefits in older postmenopausal women overall and benefits in older women whose cognitive performance was at or above expected levels (24). It would be helpful to compare the cognitive effects of these progestins directly. Initial preclinical data suggest greater safety with those progestins compared with MPA. Similarly, it is important to understand the impact of low-dose HT on cognition because of all oral HT, use of low-dose HT use (*i.e.* CEE 0.3 or 0.45 mg or lower and micronized estradiol at 0.5 mg) increased from 5 to 29% from 2001–2009 (45). Although KEEPS should provide important new insights into this topic, there are insufficient data currently to advise women on the cognitive impact of different HT regimens.

Acknowledgments

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Disclosure Summary: The author has received consultant fees from Noven Pharmaceuticals.

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