Effects of hormone therapy on cognition and mood

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Objective: Results of the Women's Health Initiative (WHI) and Women's Health Initiative Memory Study (WHIMS) suggested that hormone therapy (HT) may be detrimental to cognitive health. This article reviews clinical studies that address issues relevant to those results.
Design: Literature review.
Intervention(s): A search of Pubmed and Web of Science was conducted using the search terms HT and cognition, HT and mood. Clinical and observational studies were selected if they were published after the year 2000. Theories of HT mechanisms of action, pharmacology, biology, and observational and clinical trials are discussed.
Result(s): Although observational and clinical trials show conflicting findings, methodologic considerations must be acknowledged. HT formulation and dose, route of administration, timing of initiation, length of treatment, and health of participants all contribute to inconsistencies in results. Transdermal estradiol and micronized progesterone administered at time of menopause are generally associated with cognitive and affective benefit.
Conclusion(s): At the present time, results from existing studies are equivocal regarding the benefits of HT on cognition and affect. Future studies, such as the Kronos Early Estrogen Prevention Study (KEEPS), should address methodologic inconsistencies to provide clearer answers to this important question. (Fertil Steril® 2014;101:898–904. ©2014 by American Society for Reproductive Medicine.)
Key Words: Hormone therapy, cognition, mood

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A woman born in the United States in the second half of the twentieth century is expected to live 71–83 years (1), such that 20 to 30 years may be lived after menopause. Precipitated by a substantial decline in circulating endogenous estrogen, postmenopause is by no means a disease state. However, relative to pre-menopause, it represents a distinctly different physiologic stage, for which there may be systemic consequences (e.g., osteoporosis). Indeed, estrogen, a complex gonadal hormone with receptor sites throughout the brain and periphery (2), appears to facilitate numerous functions, including autonomic regulation, mood, and cognition. As a result, hormone therapy (HT) has been widely prescribed to partially replace naturally occurring declines in hormones (both estrogen and progesterone) at menopause.

The general term estrogen refers to three different hormones, estradiol (E_2), estrone (E_1), and estriol (E_3). E_2, the most potent form of the hormone, is predominant before menopause, whereas E_1 is the primary form postmenopausally. During pregnancy, E_3 is produced by the placenta and becomes predominant (3). Before menopause, E_2 and E_1 are produced by the ovaries and circulate freely throughout the body, dynamically interacting with each other, such that E_1 may metabolize into E_2 and vice versa (4). After menopause, however, E_2 is produced from aromatization of E_1 and androstenedione in adipose tissue, and the volume of circulating E_2 drops to ~10% of earlier levels (5). In contrast, E_1 declines to a much less degree, and continues to be synthesized by fatty tissue (6). Thus the ratio of E_2 to estrone changes markedly at menopause.

NEUROBIOLOGY OF ESTROGEN'S EFFECTS ON COGNITION AND MOOD

Estrogen works synergistically with many biologic systems to promote physical, cognitive, and affective function. Basic science reveals that administration of estrogen (E_2 alone and E_2 plus P) results in increased levels of antioxidants, reduces free radicals, and substantially lowers oxidative

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damage to mitochondrial DNA (7). Critical to neuronal health, estrogen also regulates glucose and oxidative metabolism, mitochondrial function, and promotes adenosine triphosphate (ATP) (8). Indeed, declines in these processes are characteristic of neurodegenerative diseases such as Alzheimer disease (AD) (9).

Estrogen promotes neural plasticity both directly and indirectly. Normal aging is associated with a decline in dendritic spines and synapses in dorsolateral prefrontal cortex and hippocampus (10 [review], 11). In animal studies, impaired memory function is correlated with reductions in hippocampal dendritic spines (12). Estrogen treatment (estrogen α and β receptors) promotes the growth of long thin spines in the hippocampus and prefrontal cortex (13–15). Higher levels of presynaptic estrogen α receptors are associated with stronger memory performance in ovariectomized animals treated with exogenous estrogen (15). Neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), represent another mechanism of neural plasticity in the brain. These substances facilitate the growth of dendritic spines in the hippocampus (13 [review]). In vitro investigations support a favorable effect of estrogens on the activity of neurotropins (16, 17). By increasing hippocampal BDNF levels, estrogen transiently increases dendritic spines, thereby potentiating opportunity for increased connectivity and plasticity (14).

Estradiol has been shown to favorably influence several factors potentially altering the health of the neurovascular unit, including antioxidative protection from by-products of mitochondrial energy metabolism (reactive oxygen species [ROS] and peroxides) (18), and reduced thrombolic (19) and endothelial inflammatory activity (20, 21). Additionally, estrogens exert a number of more general neuroprotective actions to maintain the health of the cerebrovasculature. For example, E_2 reportedly prevents glutamate-induced excitotoxicity (22, 23), protects neurons from ischemic insults (24), and offers antioxidant protection against several sources of cell damage and death (25, 26 [review]). By facilitating antiapoptotic actions of Bcl proteins, estrogens may also protect neurons from toxin-induced and ischemic brain injury (27, 28). Like other actions of the estrogens, characteristic of the substrate to which the hormones are applied, age appears to influence their efficacy. Preliminary evidence suggests that antiinflammatory and neuroprotective effects of the estrogens may be suppressed or abolished in aged animals (29, 30).

Estrogen also interacts with a number of neurotransmitters affecting cognition and mood. Animal research reveals that long-term use of estrogen prevented declines in cholinergic nerve cell fiber length and density at menopause (31). In humans, the negative effect of cholinergic challenge on cognitive performance and neural activation patterns was counteracted by prior exposure to E_2 (32, 33). Of note, naturally occurring higher levels of E_1 were associated with poorer cognition, specifically working memory performance (33).

Estrogen modulates mood via the serotonergic system at the cellular and synaptic levels (34, 35). Moreover, although tryptophan deletion reduced neural activation during functional magnetic resonance imaging (fMRI) during a verbal working memory task, women who received pretreatment with transdermal E_2 displayed less signal change/activation disruption (36). Estrogen contributes to up-regulation of serotonin 5HT-1 receptors and to down-regulation of 5HT-2 receptors and monoamine oxidase activity (37, 38). A serotonin agonist, estrogen responds via multiple mechanisms in brain regions supporting mood regulation (35, 37).

IMPLICATIONS OF THE WOMEN'S HEALTH INITIATIVE MEMORY STUDY

Before publication of the Women's Health Initiative (WHI) and Women's Health Initiative Memory Study (WHIMS) (39–42), HT was thought to be neuroprotective, and a large body of basic science and generally supportive epidemiologic evidence suggested that HT reduced the risk of AD by ~50% (43, 44 [reviews]). Approach to HT changed radically, however, following the results of the WHI and WHIMS. The largest clinical trials of HT ever conducted, these studies revealed an increased risk of cancer, dementia, and cognitive decline with prolonged administration of conjugated equine estrogen (CEE), and the studies were discontinued. Additionally, the Heart and Estrogen/Progestin Replacement Study (HERS), an investigation of long-term effects of HT on cognition and physical health, produced consistent results, indicating that long-term use of CEE was associated with poorer cognitive performance (45). In the wake of the WHI and HERS publications, there was an abrupt reversal of opinion, leading many to dismiss the previous epidemiologic evidence as spurious.

Although WHIMS and HERS were pivotal studies, closer evaluation suggested methodologic concerns that might explain at least partially explain their results. Both studies used orally administered opposed CEE (Prempro), which exerts different effects on the CNS than unopposed transdermal estrogen. Additionally, participants in both studies were older women over the age of 65 years. Various theories were offered to help assimilate the conflicting findings. We review several of these below.

Critical Window Theory

Differences in cognitive response to HT have been identified depending on women's age or timing of HT initiation. These discrepancies support the notion of a critical window during which HT may be beneficially initiated. The theory posits that HT administered at or around the time of menopause may elicit improved cognition, while HT initiated ≥ 5 years after menopause may engender no cognitive benefit or even cognitive detriment. Indeed a number of studies have revealed a positive association between early initiation of HT and cognition (2, 46 [reviews]). For example, exposure to HT at perimenopause resulted in improved memory and hippocampal function later in life (47). The REMEMBER pilot observational study revealed that early HT initiators demonstrated stronger global cognition and executive function than later initiators (48).

Additionally, shorter time between menopause and initiation of HT was associated with larger hippocampal volume, bilaterally (49). Support for the critical window theory has not been uniformly positive, however. A recent study found no evidence of influence of time since menopause on cognitive outcomes (50). Moreover, a report on prerandomization data from the Early Versus Late Intervention Trial (ELITE), specifically investigating the effect of length of time in menopause on cognition, found no influence of time since menopause on the relationship between verbal memory and endogenous concentrations of free E_2 (51). In light of these equivocal findings, additional research is needed to investigate the influence of time since menopause on HT efficacy.

Healthy Cell Bias Theory

A related framework with which to understand conflicting data of earlier clinical studies is the "healthy cell bias theory," proposed by Brinton and colleagues. This theory purports that women who use HT during the menopausal transition may be systematically healthier than nonusers, and it is these fundamental differences that result in HT's salutary effects (9, 52). Specifically, evidence is emerging that the health of the neuronal substrate may influence the effect of estrogen exposure such that the same group of compounds, the estrogens, could be both beneficial and harmful, depending upon when during the neuronal life time the estrogens are initiated. In healthy neurons, estrogen appears to provide multiple neuroprotective benefits, as described above, including increased mitochondrial respiration and ATP generation, while also protecting cells by improving the cell's tolerance for calcium influx and triggering antioxidant actions (8). These actions may sustain cardiovascular and cognitive health (8, 9). However, in diseased cells, calcium homeostasis is disrupted, and estrogen-induced calcium influx now becomes deleterious to the neuron incapable of maintaining calcium homeostasis (9). Thus, although women may benefit from HT before cells are exposed to neuropathologic changes associated with disease (53), once disease processes affect cells, HT may not confer cognitive benefit. Indeed, as neurologic health deteriorates, estrogenic effects may facilitate disease pathogenesis (9).

Differences in HT Formulation

As noted above, differences in hormone formulation may result in divergent cognitive and affective outcomes. Estrogen preparations are available in a variety of forms. Transdermal estrogen is composed of E_2, whereas oral CEE, a formulation of at least ten different hormones, is composed mainly of E_1 (54). Although both forms alleviate menopausal symptoms, HT utilizing E_2 more effectively recalibrates the E_2:E_1 ratio to approximate premenopausal levels. Moreover, oral CEE is metabolized by the liver which alters the E_1:E_2 ratio, and introduces risk of venous thromboembolic complications (55). Oral HT also increases binding glycoproteins that lower levels of biologically active free E_2 (56). In contrast, transdermal E_2 bypasses hepatic metabolism, avoiding these potential complications.

Differences in Progesterone Preparations

Progesterone, synthesized by the ovaries and adrenal glands, also has widely distributed receptors. Among its multiple roles is to function in an antagonistic manner to estrogen, modulating estrogen's trophic effects (57). In women who still have a uterus, HT is prescribed in combination form (estrogen together with progesterone) to counteract the potential for endometrial cancer which estrogen would otherwise facilitate. As with estrogen, progesterone may be taken in different forms. Medroxyprogesterone acetate (MPA), commonly prescribed with CEE in the HT Prempro, is a synthetic progestin that has been found to ameliorate the potential for cognitive benefit engendered in other hormones such as E_2 (58 [review]). Prempro has been associated with numerous side effects, including heart disease, adverse changes in lipid metabolism, and thromboembolic processes (59). In contrast, micronized progestin (MP), bioidentical to the progesterone produced in the ovaries, has not been associated with such side effects. Taken together, evidence suggests that the type of hormone preparation utilized may significantly influence outcomes.

HORMONE THERAPY AND COGNITION

Observational Trials

Despite findings from earlier epidemiologic studies failing to document cognitive-enhancing effects of estrogen and reduced risk of AD (60), a number of studies have reported salutary effects of HT on cognition. Early results of the Cache County Study found that use of HT for ≥ 10 years was associated with a 2.5 times lower incidence of AD compared with men (61). More recent results from the same study revealed that any HT initiated within 5 years of menopause resulted in a 30% reduced risk of AD, particularly if it was used for ≥ 10 years. Additionally, opposed HT initiated after the age of 70 years increased the risk of AD. HT use has also been shown to affect neural activation patterns (62). HT initiated at perimenopause and utilized continuously was associated with increased activation in left hippocampus and decreased bilateral activation in parahippocampal gyrus, compared with HT never used. These patterns were associated with improved memory performance on a task performed in the fMRI scanner (47).

Randomized Controlled Trials

Although favorable results have been obtained from randomized controlled trials investigating the effects of HT on cognition, the evidence has been mixed. Combination HT (either norethisterone and E_2 or tibolone) was associated with improved semantic memory compared with placebo (63). Similarly, in a crossover study of early menopausal women taking CEE or placebo, participants on CEE exhibited better oral reading and semantic memory compared with control (64). Consistent with these results, compared with placebo, 12 weeks of E_2 was associated with improved verbal memory

in healthy postmenopausal women (65). Improvements in verbal memory (and very mild declines in auditory attention) were also observed among postmenopausal women randomized to 6 months of E_2 valerate plus norethisterone versus placebo (66). Sherwin and Grigorova (67) found that whereas CEE plus MPA was unassociated with any cognitive change after a 3-month trial, CEE plus MP resulted in a mild (not clinically significant) decline in verbal memory and a significant improvement in working memory. Conversely, 48 weeks of E_2 valerate plus placebo was associated with increased immediate verbal memory but decline in simple attention compared with E_2 plus testosterone (68). HT has also been shown to be beneficial among women with AD. Short-term high-dose E_2 was associated with significantly improved verbal memory, visual memory and attention in older postmenopausal women with AD (69). Furthermore, 3 months of HT (both opposed and unopposed) was associated with improvements in visual memory among postmenopausal women with moderate AD (70).

Findings from two randomized controlled trials of E_2 versus placebo produced equivocal results. In one crossover study, transdermal E_2 for 12 weeks resulted in cognitive benefit only in faster reaction time, whereas performance on measures of verbal and visual memory, attention, and working memory did not differ by group (71). Another study found that E_2 was associated with greater improvement on immediate face recall, whereas the placebo group demonstrated stronger verbal memory and fluency (72). Two other studies did not display any group differences (E_2 and E_2 plus MP compared with placebo; testosterone or oral E_2 compared with placebo) on cognitive measures (50, 73). Finally, the Cognitive Complaints in Early Menopause Trial (COGENT) study revealed no cognitive benefit of Prempro compared with placebo; indeed there was a close to significant mild decline in verbal memory in the HT group (74). The potential reasons for divergent findings reflecting methodological shortcomings are discussed in the previous sections.

HORMONE THERAPY AND MOOD/EMOTION

The higher prevalence of depressive disorders in women than men has been well established (35), and sex hormones contribute to this differential disease burden. Although not all women experience mood changes, for some women, substantial changes in estrogen during physiologic transitions such as pregnancy and menopause are particularly associated with worsening of depressive symptoms. Although the precipitous drop in estrogen levels during the menopausal transition is associated with higher depression rates, the evidence for treatment of depressive symptoms with exogenous estrogen remains unclear (37).

Observational Studies

Although results of observational studies have been mixed, recent investigations have not found positive associations between HT and improved mood. Early cross-sectional studies demonstrated correlations between estrogen use and reductions in depressive symptoms (75), but later research has not supported these findings. Use of HT in the previous month was associated with worse depression and anxiety among 6,000 peri- and postmenopausal women. No differences in mood were found based on type of estrogen preparation (76). Amore et al. (77) found that compared with perimenopause, postmenopausal women experienced higher levels of depression and sexual symptoms, and that HT (type not specified) was not associated with any change in mood. Neither HT (type not specified) nor menopausal status was associated with additional mood improvement in women taking antidepressant medication (78). Moreover, postmenopausal women taking HT for 3 months (either estrogen alone or estrogen plus progesterone) did not exhibit any change in mood when evaluated cross-sectionally. However, a separate group of 18 women taking HT (type not specified) who were followed prospectively for 3 months did demonstrate improvements in mood (79). Importantly, because hormone preparation was often not indicated, it is difficult to evaluate the degree to which type of estrogen or route of administration may have contributed to results.

Randomized Controlled Trials

In contrast, findings from clinical trials support a positive effect of estrogen on mood. Despite negative findings from one small single-blind study in which 14 women randomized to two forms of HT revealed no effect of either drug on mood after 6 months (63), five recent randomized placebo-controlled trials demonstrated significant beneficial associations between HT and mood. Eighty percent of women randomized to E_2 reported significantly decreased mood symptoms after 3 or 6 weeks, compared with only 22% of women on placebo (80). Similarly, E_2 resulted in improved mood in 68% of perimenopausal women with depressive disorders, whereas only 20% of women on placebo experienced similar benefit (81). Onalan et al. (82) prospectively examined the effects of three preparations of HT (CEE plus 2.5 mg MPA, CEE plus 5 mg MPA, or 2.5 mg tibolone) on mood over a 12-month period. Results showed that all three preparations improved depressive symptoms in menopausal women compared with placebo. In a randomized placebo-controlled cross-over trial, transdermal E_2 was associated with significantly improved psychological well-being compared with placebo (71). Moreover, administration of transdermal E_2 with or without norethisterone over 3 months was associated with significantly improved scores on anxiety and depression screening measures (83). Taken together, the data suggest that for the subset of women who experience depression associated with menopause, HT may be beneficial in addressing mood symptoms.

SHORTCOMINGS OF THE CLINICAL TRIALS TO DATE

Dose, timing of HT initiation, duration of HT, and type of HT preparation are all important factors to consider in interpreting study results. Much of the research demonstrating no benefit of HT on cognition and mood has been marred by

methodologic flaws or inconsistencies. Many studies were small, initiated hormone treatment >5 years after the menopausal transition, or used a less potent form of estrogen (e.g., CEE), a small dose, or a brief duration of treatment. As noted earlier, the effects of progesterone (especially MPA) are generally antagonistic to those of estrogen, and studies of cognition and affect using opposed HT display weaker results. Route of administration also affects outcomes. Moreover, there has been little attempt to mimic the premenopausal hormonal milieu, in which a complex array of hormones interact temporally and synergistically to promote cognitive, affective, and physical function. Steady-state HT may produce effects differently from a cyclic pattern (46). Although inconsistencies in findings remain, trials that address these methodologic considerations remain promising.

KRONOS EARLY ESTROGEN PREVENTION STUDY (KEEPS)

One of the studies that addresses several methodologic short-comings of earlier trials is the Kronos Early Estrogen Prevention Study (KEEPS) and its ancillary study, the KEEPS Cognitive and Affective Study (KEEPS-Cog). All women enrolled in the clinical trial are nonhysterectomized, $\leq$3 years since their last menstrual period, and are at low risk for cardiovascular disease. The KEEPS-Cog will evaluate the efficacy of 4 years of therapy with oral CEE and transdermal E_2 on mood and cognition. Micronized progesterone or matching placebo is administered cyclically, with dosing occurring during the first 12 days of the 30-day cycle. The parent KEEPS will examine surrogate markers of cardiovascular disease, osteoporosis, lipid profile, and coagulation cascade in this group of healthy, recently menopausal women. The findings of this study will test many of the theoretical explanations offered since the WHI study. For example, the long-term follow-up (anticipated for 20–25 years) of the KEEPS cohort will provide the opportunity to evaluate whether HT initiated at menopause may reduce the incidence of neurodegenerative diseases such as AD at later ages (4, 54).

CONCLUSION

The relationship between estrogen, cognition, and mood is complex. HT has not yet succeeded in achieving a postmenopausal hormonal milieu that approaches the intricate and dynamic premenopausal interactions between reproductive hormones and their multiple target systems. Despite negative findings, which, however, are marred by methodologic concerns, evidence continues to mount regarding the beneficial effect of HT, especially transdermal E_2 and MP, on cognitive and affective function. Like KEEPS, future trials should systematically address inconsistencies in methodology to accurately characterize HT's effects. The potential for benefit is large. In addition to the possibility of increasing postmenopausal cognitive and affective function, HT may eventually represent a means to delay or even prevent neurodegenerative diseases.

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