Hormone Therapy and Cognition in the Menopause Transition: Critical Questions Remain Unanswered

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First – Acknowledge Progress!!!

- WHIMS-Y
- KEEPS
- ELITE

Early use of HT has neutral effect on cognitive function

WHIMSY (WHI Memory Study of Younger Women)¹
- CEE alone or with MPA in women (50 to 54 y) upon enrollment; n =1326
- Published: neutral cognitive effects when tested on average 7.2 years after the trials ended
- “CEE-based therapies produced no overall sustained benefit or risk to cognitive function when administered to postmenopausal women aged 50–55 years”

KEEPS (Kronos Early Estrogen Prevention Study)²
- 5-yr cyclic transdermal 8.0 (20 µg/patch) or CEE (0.45 mg) plus micronized P (200 mg,12 d/month) in 693 women (42-58 yrs) < 36 m of FMP
- Neutral cognitive effects after 48 m; some mood benefit with CEE on depression and anxiety

ELITE (Early Versus Late Intervention Trial with Estradiol)³
- Oral E2 (1 mg/d) + vaginal P gel for 10 days per month in 567 younger (< 6 y since FMP) and older (> 10 y since FMP)
- Neutral effects


DISCLOSURES

- No conflicts of interests
KEY GAPS IN KNOWLEDGE

1. Does HT affect cognition in women for whom HT is indicated – i.e., women with moderate to severe VMS?
2. Does use of HT or oral contraceptives in the perimenopause – as distinct from the early postmenopause – enhance cognition?
3. Does early use of HT have effects on Alzheimer’s disease risk and the neuropathology underlying risk?
4. Is HT effective in preventing cognitive decline in women who undergo early surgical menopause?

Measuring Physiologic VMS Objectively with Ambulatory Monitors

- Biolog Skin Conductance Monitor
  - Objective hot flash defined as a 2 mmho increase in skin conductance across a 30 second period
  - Button press used for subjective recognition of hot flash

Objective VMS are associated with worse verbal memory

Decreases in physiologic VMS relate to improvements in verbal memory in a clinical trial of stellate ganglion blockade.


Physiologic VMS are associated with adverse brain outcomes


More white matter hyperintensities


Hyperconnectivity in brain at rest, especially in hippocampus

Maki, P et al. (in preparation); n=13; mean age 54.7; Memory performance is unrelated to reported vasomotor symptoms


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ENDOCRINE CHANGES AROUND THE FMP

PRELIMINARY DATA SUGGEST THAT ORAL CONTRACEPTIVES ENHANCE VERBAL MEMORY
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SUPPORT FOR THE CRITICAL WINDOW HYPOTHESIS FOR AD

- Three prospective studies have examined timing of initiation of HT in relation to risk of AD
- Each of the three provides support for the timing hypothesis
- Unfortunately, a randomized clinical trial to test that hypothesis is not feasible


NEUROIMAGING IN KEEPS


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**Removal of Ovaries Before Age 48 Increases Risk of AD by 70%**

- Mayo Clinic Cohort Study of Oophorectomy and Aging
- Use of estrogen therapy until age 50 removed that risk

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