Natural History of Cognitive Changes Across the Menopause Transition

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DISCLOSURES
• None

OBJECTIVES
1. Understand cognitive complaints and cognitive function across menopause stages
2. Understand the role of vasomotor symptoms (VMS) on cognitive changes across the menopause
3. Describe the “treated history” of cognitive changes across the menopausal transition.

In the SWAN, memory decline was the third most frequent symptom.

7899 healthy women from a multi-ethnic cohort

40-55 Years of Age

2nd most frequent symptom among early perimenopausal women


Complaints of forgetfulness increase during the menopausal transition even after controlling for age.


More severe memory complaints are associated with worse performance on memory tests.

Subjective memory complaints have also been shown to relate to scores on tests of attention in midlife women.

Memory performance worsens during the perimenopause even after controlling for age.

Memory, fine motor skills and attention/working memory/executive function is lower in the 12 months after the FMP.

Endocrine changes around the FMP.
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Memory performance is unrelated to reported vasomotor symptoms


Measuring Physiologic VMS Objectively with Ambulatory Monitors

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

Validation of monitor-measured VMS: Placebo effect is not evident when VMS are measured on monitors

Subjective

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<th>Treatment</th>
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<th>1-year</th>
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Women report less than 60% of monitor-measured VMS

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
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“Induced” menopause and verbal memory performance

- Verbal memory decreases following oophorectomy and following pharmacological suppression of estrogen
- Adding estrogen therapy reverses those effects

Prefrontal activation during a verbal memory task decreases after GNRHa treatment and rebounds afterward

Early use of HT has neutral effect on cognitive function in early postmenopause

WHIMSY (WHI Memory Study of Younger Women)
- CEE alone or with MPA in women (50 to 54 y) upon enrollment, n =1726
- Published: neutral cognitive effects when tested on average 7.3 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)
- 5-yr cyclic transdermal E2 (50 μg/wk) or CEE (0.45 mg) plus micro P (200 mg, 12 d/month) in 850 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)
- Cost 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

*P<0.05 for main effect of condition; Hit = Probability of a Hit; FAl = Probability of a False Alarm

Craig et al. Reversibility of the effects of acute ovarian hormone suppression on verbal memory and prefrontal function in premenopausal women
Psychoneuroendocrinology (2008) 33, 1426-31

In SWAN, hormone use, taken before the FMP, but not after, was associated with improved processing speed and memory

- Former hormone use, taken prior to the FMP, was associated with:
  - better processing speed (9% higher)
  - better verbal learning and memory (4-5% higher)

- Current hormone use among postmenopausal women predicted:
  - worse processing speed
  - worse verbal episodic memory performance over time compared to premenopausal performance


Women who initiate HT before the final menstrual period show better memory and hippocampal function

- No large clinical trials have been conducted in women with moderate-to-severe vasomotor symptoms, so it is unclear whether HT improves cognition in symptomatic women


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Take-home Messages

- Women report and show declines in memory during the menopausal transition; memory might rebound in postmenopause.
- Vasomotor symptoms, when measured objectively with ambulatory monitors, are linked to memory declines and structural and functional brain abnormalities; unknown if causal.
- HT has neutral effects on cognition in early postmenopausal women; cognitive effects on women with bothersome VMS and in Perimenopausal women are unknown.
- HT is not recommended for cognitive complaints.