Cognitive Effects of Hormone Therapy Continuation or Discontinuation in a Sample of Women at Risk for Alzheimer Disease

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Objective: *Use of estrogen-based hormone therapy (HT) as a protection from cognitive decline and Alzheimer disease (AD) is controversial, although cumulative data support HT use when initiated close to menopause onset with estrogen formulations containing 17β-estradiol preferable to conjugated equine estrogen formulations. Little is known regarding specific populations of women who may derive benefit from HT.* **Methods:** *Women with heightened risk for AD (aged 49–69), all of whom were taking HT for at least 1 year and most of whom initiated HT close to menopause onset, underwent cognitive assessment followed by randomization to continue or discontinue HT. Assessments were repeated at 2 years after randomization.* **Results:** *Women who continued HT performed better on cognitive domains composed of measures of verbal memory and combined attention, working memory, and processing speed measures. Women who used 17β-estradiol versus conjugated equine estrogen, whether randomized to continue or discontinue HT, showed better verbal memory performance at the 2-year follow-up assessment. An interaction was also found with HT randomization and family history of AD in a first-degree relative. All female offspring of patients with AD declined in verbal memory; however, women who continued HT declined less than women who discontinued HT. Women without a first-degree relative with AD showed verbal memory improvement (likely because of practice effects) with continuance and declined with discontinuance of HT.* **Conclusion:** *Continuation of HT use appears to protect cognition in women with heightened risk for AD when initiated close to menopause onset.* (Am J Geriatr Psychiatry 2015; ■:■–■)

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INTRODUCTION

Estrogen-based hormone therapy (HT) remains a controversial intervention for use in menopausal and postmenopausal women. Cumulative studies of HT use in middle-aged and older postmenopausal women suggest possible protection against normal age-related cognitive decline and Alzheimer disease (AD).[1,2] Negative cognitive findings appear to be related to type of HT formulation, with better verbal memory associated with use of 17β-estradiol (17β-E) compared with conjugated equine estrogen (CEE).[3] In addition, timing of initiation is associated with increased probable dementia when HT is started in late menopause (i.e., after age 65 years).[4] Little is known, however, regarding use of HT in a population of younger postmenopausal women with heightened risk for late-onset AD. Presence of apolipoprotein E ε4 (*APOE-ε4*) and family history of AD are known risk factors for late-onset AD and cognitive aging. History of depression is also considered a putative risk for cognitive decline and AD.[5,6] Herein, we present secondary analyses of cognitive findings from a 2-year prospective brain imaging study and randomized trial of HT continuation (HT+) or discontinuation (HT−) in a sample of middle-aged postmenopausal women (aged 49−69 years) using HT with one or more of these risk factors.

Study design included brain imaging and extensive neuropsychological testing at baseline[3,7] and 2-year follow-up after randomization (see Rasgon et al.[8] for imaging follow-up). We hypothesized that HT use would provide protection from age-related cognitive changes in a sample of women with an elevated risk for dementia. We also explored relationships between HT continuation or discontinuation with *APOE-ε4* carriership, family history of AD, personal history of depression, surgical versus natural menopause, and use of progestogens.

METHODS

Subjects were participants who completed a National Institute on Aging−funded longitudinal study that recruited cognitively normal (verified by neuropsychological assessment results within normal range for age and education in addition to clinically normal positron emission tomography [PET] and magnetic resonance imaging [MRI] scans and normal physical and neurologic examinations) euthymic, postmenopausal women aged 49−69 years with heightened risk for AD, all of whom were receiving estrogen-containing HT for at least 1 year. Heightened risk for AD was characterized as having a first-degree relative with AD, documented carriership of *APOE-ε4*, and/or a history of major depression. Only women who were not in a current mood episode were recruited into the study. For the full list of inclusion and exclusion criteria, please see Wroolie et al.[3]

After a baseline evaluation (Time 1), subjects were randomized to HT continuation (HT+) or discontinuation (HT−) and re-evaluated at a 2-year follow-up (Time 2). No changes in HT regimens were implemented by the investigators before randomization or thereafter (in the HT+ group). Additionally, as part of the study agreement, no HT regimen changes were implemented by the participants' treating physician after randomization. Given the nature of the study design, participants were aware of their randomization condition (HT+ versus HT−), whereas members of the research team who performed evaluations and neuroimaging analyses were blinded to the randomization groups. Postrandomization HT exposure was monitored and verified each year by estradiol blood levels.

An extensive neuropsychological evaluation that included measures of attention and processing speed, verbal and visual memory, executive functioning, and subjective memory complaints was conducted at Time 1 and Time 2 by the study neuropsychologist. Measures included the Auditory Consonant Trigrams[9]; Benton Visual Retention Test[10]; Buschke Selective Reminding Test (BSRT)[11]; Color Trail Making Test (Color Trails 1 and 2)[12]; Rey-Osterrieth Complex Figure Test[13,14]; Delis Kaplan Executive Function System (DKEFS)[15]; Color-Word and Verbal Fluency Tests; Wechsler Adult Intelligence Scale-Third Edition[16] Digit Span, Letter Number-Sequencing, and Digit Symbol Coding; the Wechsler Memory Scale-Third Edition (WMS-III)[17] Logical Memory I and II; and the Memory Function Questionnaire.[18] The two-subtest version of the Wechsler Abbreviated Scale of Intelligence[19] was used to estimate intellectual functioning. (See Wroolie et al.[3] for complete description of neuropsychological measures.) Additionally,