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Under the editorship of Wulf H. Utian, MD, PhD, DSc(Med), NAMS Medical Director, Honorary Trustee, and Executive Director Emeritus, First to Know presents commentary on the latest, breaking scientific articles as suggested by members of The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women’s health and quality of life through an understanding of menopause and healthy aging. Opinions expressed in the commentary are not necessarily endorsed by NAMS or by Dr. Utian.

You Are the First to Know About the New First to Know

With this issue, First to Know returns to its original purpose—providing NAMS members with notifications and commentary about imminent or breaking new scientific publications.

Under the Editorship of Dr. Wulf Utian, NAMS Medical Director, the new First to Know will only appear on an as-needed basis, not a regular publication schedule.

In place of the old First to Know, a new NAMS publication called Menopause Management Updates will launch bimonthly through 2015 and monthly in 2016 under the Editorship of the Chair-Elect of the NAMS Professional Education Committee, currently Dr. Nancy Jasper. Menopause Management Updates will review key papers from the past 2 to 3 months that may direct changes in clinical practice or thinking and will include expert commentary. Dr. Isaac Schiff will continue to provide his Editor Picks from Menopause.

All educational products of NAMS are under review. Practice Pearls under the Editorship of Dr. Andrew Kaunitz and reviewed and approved by the NAMS Board will be published more frequently, as will Menopause e-Consult.

We at NAMS are working in your interest to keep you at the cusp of knowledge.

Wulf H. Utian, MD, PhD DSc(Med)
Editor, First to Know

KEEPS-Cog study: hormone therapy does not alter cognition in recently postmenopausal women

For mood, women treated with oral conjugated estrogens over 4 years showed improvements in depression and anxiety symptoms


Summary. The primary outcome of KEEPS (the Kronos Early Estrogen Prevention Study), a randomized, double-blind, placebo-controlled trial conducted at nine US academic centers, was to determine whether hormone therapy (HT) delayed or prevented heart disease in recently postmenopausal women. The ancillary KEEPS Cognitive and Affective Study (KEEPS-Cog) examined the effects of HT on cognition and mood for up to 4 years of treatment in this demographic.
Of 727 women enrolled in KEEPS, 693 were part of KEEPS-Cog. Two hundred twenty women were randomized to 4 years of 0.45 mg oral conjugated equine estrogens (CEE) plus 200 mg micronized progesterone (m-P) per day for the first 12 days each month, 211 women to 50 µg transdermal estradiol (E2) plus 200 mg m-P for the first 12 days each month, and 262 women to placebo.

On average, participants were 52.6 years old and 1.4 years past their last menstrual period, with low cardiovascular risk profiles. Primary outcomes were an examination that assessed four cognitive factors—verbal learning and memory, auditory attention and working memory, visual attention and executive function, and speeded language and mental flexibility—and a mood measure. Hormone therapy effects were measured using linear mixed-effects models. Mean length of follow-up was 2.85 years (standard deviation [SD], 0.49) for cognitive outcomes and 2.76 (SD, 0.57) for mood outcomes.

No treatment-related benefits were found on cognitive outcomes; however, improvements in mood, specifically for depression and anxiety symptoms, were seen in women treated with CEE over 48 months compared with placebo. Mood outcomes for women treated with E2 were similar to placebo.

**Comment.** With a sample size of 693 women, KEEPS-Cog is the largest randomized, controlled trial of the effects of hormone therapy (HT) on cognition and mood in the early postmenopausal period. One strength of the study was the focus on cyclic HT regimens in which 200 mg m-P with either 0.45 mg oral CEE or 50 µg E2 was used on the first 12 days of each month.

Previous large-scale, randomized trials of CEE plus medroxyprogesterone acetate (CEE/MPA) have shown cognitive risks with MPA in older women. Specifically, continuous combined CEE/MPA doubled the risk of all-cause dementia\(^1\) and decreased verbal memory\(^2\) in older women (aged ≥65 y) and led to either near-significant or significant\(^3\) decreases in verbal memory in younger postmenopausal women.

Findings from the Women’s Health Initiative Memory Study of Younger Women (women aged 50-55 y at time of randomization), however, showed neutral effects of CEE/MPA and CEE-alone on cognitive function assessed several years after stopping HT, suggesting that any negative effects of MPA on cognitive function in younger postmenopausal women are not enduring.\(^4\)

KEEPS-Cog showed neutral cognitive effects with either cyclic regimen while women were receiving treatment. Thus, these data suggest that these cyclic HT regimens are safe for cognitive function when used in the early postmenopausal period. Moreover, beneficial mood effects were found with oral CEE on some subscales in KEEPS-Cog, and E2 was associated with neutral mood and affective outcomes.

Many questions remain after publication of KEEPS-Cog data. Perhaps the most critically important unanswered question is whether HT improves cognition in women with moderate to severe vasomotor symptoms (VMS).

Hormone therapy is not indicated for the treatment or prevention of cognitive complaints or problems but is the gold-standard treatment for VMS. About 40% of women in KEEPS experienced moderate to severe VMS at baseline. Both HT treatment groups showed similarly large reductions in symptoms, and the magnitude of reduction was greater than in the placebo group at 12 months. Results indicated that group differences in VMS lessened over time because VMS decreased spontaneously for women in the placebo group. In addition to exerting direct effects on neural systems subserving cognition, HT could improve cognition in women with VMS indirectly by improving VMS and sleep.
Another remaining unanswered question is whether there are immediate or long-term benefits of HT for cognition and brain function that are not evident on cognitive tests. Three observational studies provide support for the view that timing of HT initiation is a significant determinant of risk for Alzheimer disease (AD) and that early initiation confers protection against AD. It is not feasible to do a randomized clinical trial of early use of HT and AD risk, but neuroimaging methods can be applied to evaluate AD biomarkers such as tau and beta-amyloid.

To date, there are no large-scale randomized trials of the effects of estrogen alone on cognitive function in younger postmenopausal women. Large-scale clinical trials in older women show neutral cognitive effects with estrogen regimens. Nonhuman primate studies suggest that neuroprotection occurs with cyclic E2 but not with E2 plus cyclic progesterone, continuous estrogen plus progesterone (either cyclic or continuous), or unopposed continuous estrogen. The effects of estrogen therapy when combined with a selective estrogen receptor modulator (SERM) such as bazedoxifene are also unknown but are of interest, given evidence from randomized clinical trials that the SERM raloxifene enhances verbal memory.

Last, the cyclic HT regimen using CEE improved scores on a depression subscale but not on a widely used depression inventory. That regimen also improved scores on an anxiety subscale, which is important given the link between VMS and anxiety. The basis and clinical significance of the more favorable mood effects with oral CEE than with E2 warrants further study.

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References

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