A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women

Presentation by Kevin Duff, PhD:

**Introduction:** Depleted endogenous estradiol has been linked with AD in postmenopausal women. However, estrogen treatment trials have failed to reduce the risk of AD. This has led researchers to hypothesize that there is a critical period during which estrogen can assert beneficial effects on the brain, and after which no benefit can occur. In fact, treatment with estrogen after this critical period may result in additional damage to the brain and it’s functioning. The current study sought to further examine if hormone therapy (HT) could produce beneficial effects in older women with normal to mildly impaired memory.

**Methods:** Participants: Subjects were participating in the Estrogen Memory Study, a 2-year randomized, double-blind, placebo-controlled study run solely at the University of Toronto. All subjects needed to be women over age 60 and at least 1 year postmenopausal. Subjects also had to fall in the normal to below normal range on a memory screening task (which was to increase the chance of finding cognitive decline across 2 years of the study). Exclusion criteria included: dementia, conditions likely to affect cognition, or taking cognitive enhancers or HT. APOE genotype was assessed at baseline.

**Outcome measures:** CVLT is a 16-word list learning task with 5 learning trials, an interference trial, and short- and long-delayed free and cued recall trials, as well as a recognition trial. The primary outcome was short-delayed free recall of the CVLT, and the secondary outcomes were: 1. Total recall, 2. List B, 3. Cued Recall, 4. Recognition memory.

**Intervention:** All study personnel were blinded to treatment assignment. The active treatment was one estrogen capsule per day for 4 days followed by one combined estrogen and progestin capsule per day for 3 days. Placebo capsules were identical in appearance. Medication was given in weekly doses at start of the trial, 1 month, and 3-months. Subjects were considered to have discontinued the study if they took <80% of pills. Serum estradiol levels were measured at baseline and year 2 visits.
A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women

(continued from page 1)

Statistical analyses: Three sets of analyses:

1. Intention-to-treat for the entire sample where repeated measures ANCOVA would examine if the two treatment groups (HT vs. placebo) differed on the CVLT at 1 and 2 years. Covariates included age, education, APOE 4, and prior HT.

2. Compared average or better on baseline CVLT vs. below average.

3. Compared “normal” CVLT vs. “MCI” CVLT

Results: Figure 1 (p. 3) shows flow of potential and actual participants. 142 were randomized and completed baseline assessments. Table 1 (p. 5, left two columns) shows demographic and clinical variables for entire sample. Table 2 (p. 6) shows serum estradiol levels at baseline and year 2 visit. Tables 3 and 4 (p. 6) show uncorrected and corrected primary outcome measures on the CVLT at baseline, year 1, and year 2. Overall, the results of the first repeated measures ANCOVA on the entire sample was nonsignificant, indicating no treatment benefits at year 1 or 2.

Tables 1 – 4 (right four columns) shows demographic, clinical, estradiol, and CVLT scores for those subjects split into average or better vs. below average groups (based on baseline CVLT scores). A significant interaction was observed between treatment group (HT vs. placebo) and CVLT group (average vs. below average). In the average or better group, the placebo group significantly declined at year 1 and year 2, whereas the HT group appeared to remain stable. No significant treatment effects were observed in the below average subgroup.

In the third set of analyses, there was no interaction between treatment group and MCI group. None of the secondary outcome measures of the CVLT were significant, for either the entire sample or any of the subgroup comparisons. Adverse events are reported in Table 5 (p. 7). The HT group reported significantly more symptoms of breast tenderness, vaginal bleeding, vaginal discharge, and GI disturbance.

Discussion: In the entire sample, there was no significant treatment effect on verbal memory over the 2 years of the study. However, subgroup analyses did find that women with average or better verbal memory performance at baseline who were in the HT group had significantly better CVLT scores at 1 and 2 year follow-ups compared to their peers taking placebo. Do these findings support the hypothesis about a critical period during which estrogen treatment is most effective?

Some researchers think this critical period is only for the first few years after menopause, but the current participants were 20+ post-menopausal. It remains unclear why some women experience cognitive decline after menopause and others do not.

Why no effects on any of the secondary outcome measures? As the authors note, decline on some of these measures are not expected until more significant cognitive decline is observed (e.g., recognition memory). However, the failure to observe findings on Total Recall is surprising, as this is one of the most commonly used measures of the CVLT.

Limitations noted were single center design (so possible site effects), well-educated and exclusively white sample (so questionable generalizability), and possible “unblinded” by participants and personnel due to the heightened symptoms in the active treatment group.

Overall, can cognitive tests be used to determine who will benefit from treatment???
The Winchester falls project: a randomized controlled trial of secondary prevention of falls in older people


Objective: The objective of this cluster randomized controlled trial was to determine the effectiveness of two interventions, one primary care and the secondary care to prevent further falls or recurrent falls.

Methods: There were 450 participants over 65 between the two arms. Eighteen general practices were randomized to three groups. 1. The primary care group was assessed by a nurse in the community using a risk factor review and referred to other professionals. 2. The secondary group received assessment by a multi-disciplinary in a day hospital followed with appropriate interventions. 3. The control group received usual care. Participants were followed monthly for 12 months.

Results: The conclusion is that a multidisciplinary structured specialist team is effective in reducing falls, but the nurse led group was not: however there was no statistical difference between the two intervention groups and control group for fractures and hospital admission or moves to institutional care. The results concur with previous studies and current guidelines and indicate that individuals that sustain recurrent falls require assessment and management by individuals with appropriate skills and expertise.

A prospective observational study of falling before and after knee replacement surgery


Arthritis is the nation's most common cause of disability and costs the U.S. economy more than $128 billion annually. Knee osteoarthritis, the most frequent form of lower extremity arthritis, contributes to 418,000 knee replacement procedures annually and in 2006 accounted for 496,000 hospital discharges and $19 billion in hospital costs. In 2005 in England and Wales, 62,155 total knee arthroplasty (TKA) were done. However, the history of falling before and after TKA is unknown.

Purpose: The purpose of this study was to prospectively monitor falls in pre- and post-operative TKA patients and to identify independent risk factors for post-operative falling.

Methods: A prospective observational study was conducted with a 1-year follow-up. The participants were community-dwelling older people recruited from a regional orthopaedic centre while they were on the waiting list for surgery. Patients completed monthly falls diaries, pre-operatively and 1 year post-operatively. Data on knee status (WOMAC: pain, stiffness and function), balance confidence (the Activities Balance Confidence Scale-UK) and mood (Geriatric Depression Scale) were collected at quarterly intervals.
A prospective observational study of falling before and after knee replacement surgery

(continued from page 3)

Results: One hundred and eighteen subjects were recruited for the study and 99 received a primary TKA. 24.2% fell in the last pre-operative quarter (24 patients reported 44 falls) and this decreased to 11.7-11.8% in the first four post-operative quarters. 45.8% of people who fell pre-operatively fell again in the first post-operative year. Higher pre-operative geriatric depression scale scores and a history of falling were significant independent predictors of post-operative falling.

Conclusion: A recent history of falling is common in people undergoing TKA and approximately 45% of patients fall again in the year following surgery. Patients being considered for TKA should be asked about falls history and undergo falls risk assessment and intervention.