

# NEWS & Commentary

## Past estrogen use decreases Alzheimer's disease in older women

Zandi PP, Carlson MC, Plassman BL, et al, for the Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women: The Cache County study. *JAMA* 2002;288:2123-9.

Use of hormone therapy is associated with a reduced risk of Alzheimer's disease (AD), especially use for longer than 10 years, according to results from this prospective observational study conducted in Cache County (Logan, Utah). A total of 1,889 women (mean age, 74.5 years) were enrolled. A similarly aged group of men ( $n = 1,357$ ) served as controls. History of hormone therapy use (either estrogen alone or estrogen plus a progestogen), as well as intakes of calcium and multivitamin supplements, were assessed at baseline. After 3 years of follow-up, 88 women (4.7%) and 35 men (2.6%) had developed AD. Women aged 80 and older had more than twice the rate of AD as men of that age (hazard ratio [HR], 2.11; 95% CI, 1.22-3.86). Overall, hormone therapy significantly reduced the risk of AD by 41% compared with nonusers (95% CI, 0.36-0.96). Hormone use for at least 10 years resulted in a 69% reduction in risk (95% CI, 0.17-0.86), which was statistically the same as the risk for matched males. When the results were assessed by current and former hormone use, current use (72% unopposed estrogen) was not associated with decreased AD risk unless the duration of treatment exceeded 10 years. For former users, 3 or more years of use significantly reduced the AD risk, with more than 10 years' use reducing the risk by 83% (95% CI, 0.01-

0.80). No similar effects were seen with either calcium or multivitamin use.

**Comment.** This article helps clarify the role of hormone therapy in the expression of neurodegenerative diseases. These findings are consistent with a previous observational study (Matthews, *J Am Geriatr Soc* 1999) demonstrating that past, but not current, use of hormone therapy delayed age-related decline in cognitive function in healthy volunteers. In that study, past users had initiated hormone therapy earlier (predominantly at the time of menopause) compared with current users. As noted in the editorial accompanying the Zandi article (Resnick, *JAMA* 2002), the opportunity to have the maximum impact on cognitive decline and the expression of AD may be limited to the menopausal transition period. In ongoing clinical trials examining the effects of estrogen on cognitive decline and the expression of AD (including the Women's Health Initiative), participants were older than age 65 at baseline. An appropriate clinical trial to demonstrate the effect of hormone therapy on AD is not feasible because of the long duration of follow-up required. These results remind us that some questions in medicine cannot be answered by randomized clinical trials. Therefore, we need to rely on carefully designed observational studies, such as this study, in counseling menopause-aged women.

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**Comment.** This article by Zandi et al recounts a well-executed study of AD incidence in a stable population of women. The authors report that early and protracted use of estrogen (with or without a progestogen) resulted in a graded decrease of AD incidence. These results are not surprising given the burgeoning evi-

dence of the brain-protective effect of estrogen in studies thus far. Zandi's report is noteworthy for revealing that the use of other health aids did not influence the incidence of AD, thus making it less likely that a healthy-user bias affected the study.

This article is published at an important time in the field of menopause/geriatrics. The recent appearance of results from the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) has been interpreted by some to indicate that long-term HRT is contraindicated. The Zandi trial results should be further cause for reconsideration of such opinions and for increased support of preclinical and clinical investigations regarding the preventive effects of maintaining an estrogen-rich milieu in women. Such studies should start early enough to be primary prevention trials and should take pains to separate the effects of estrogens from progestins. In my opinion, this would be a much better use of research funds than for long-term studies of the outcomes of trials such as HERS and WHI, in which primary prevention against cardiovascular and brain disease is not biologically plausible.

Healthcare practitioners should read the Zandi study, as well as the accompanying editorials, and take these findings into account when counseling women regarding hormone therapy.

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## Teriparatide associated with greater bone increases, fracture reduction than alendronate

Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002;87:4528-35.

Treatment with recombinant human parathyroid hormone, teriparatide injection, is more effective than the bisphosphonate alendronate in increasing bone mineral density (BMD) and decreasing nonvertebral fractures, according to this randomized, double-blind, parallel-group study. A total of 146 postmenopausal women with osteoporosis were randomly assigned to either once-daily subcutaneous injections of teriparatide (40 µg) plus oral placebo or to oral alendronate (10 mg) plus placebo injection. Treatment lasted a median of 14 months. At 12 months, women receiving teriparatide had significantly greater increases of lumbar spine BMD than alendronate recipients (15.1% vs 6.6%, respectively). Teriparatide-treated women also had significantly greater increases at the femoral neck and total body BMD than alendronate recipients. However, measurements of the one-third distal radial BMD decreased significantly in the teriparatide group compared with baseline and the alendronate group. The nonvertebral fracture incidence was significantly lower in the teriparatide group compared with the alendronate group (4.1% vs 13.7%). Both treatments were well tolerated, despite some transient, mild, asymptomatic hypercalcemia with teriparatide therapy.

**Comment.** Prescribers will need to get acquainted with teriparatide, the first anabolic drug for osteoporosis. This article nicely points out the differences between the widely prescribed alendronate and the recently FDA-approved teriparatide. Alendronate is an antiresorptive drug that reduces bone turnover and increases BMD by enhancing bone mineralization (not making more bone). More mineral per unit volume of bone and reduced turnover both appear to contribute to reductions in fracture risk with alendronate. In contrast, teriparatide activates bone turnover and increases BMD through new bone formation. During the first months of treatment, teriparatide increases endocortical porosity in the long bones, hence the

early decrease in radial BMD. At the same time, periosteal appositional new bone is forming in long bones and more trabecular connectivity is noted in the spine; the end result is marked improvements in bone geometry and strength. Although the numbers of nonspine fractures in this trial are relatively small, the greater benefit from teriparatide over alendronate is consistent with greater percentage reductions in nonspine fracture observed in previously reported large clinical trials of these two drugs.

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### Transdermal estrogen-progestin therapy increases rates of CHD events in women with heart disease

Clarke SC, Kelleher J, Lloyd-Jones H, et al. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: The Papworth HRT atherosclerosis study. *Br J Obstet Gynaecol* 2002;109:1056-62.

Transdermal hormone therapy increases the rate of heart disease events in postmenopausal women with pre-existing heart disease, according to this randomized, placebo-controlled, double-blind study from the United Kingdom. A total of 255 postmenopausal women at least 55 years old (mean age, 66-67), hospitalized for coronary angiography related to ischemic heart disease, were randomized to either placebo or a transdermal hormone therapy patch. The estrogen-alone patch contained 2.5 mg 17β-estradiol (80 µg/day release rate). The combined therapy patch contained 3 mg 17β-estradiol and 4 mg norethisterone. Mean follow-up was 30.8 months. During follow-up, the hormone therapy group suffered 53 primary end point events (cardiac mortality, nonfatal myocardial infarction, and hospitalization for unstable

angina) compared with 37 in the placebo group. A per-protocol analysis yielded a nonsignificant 49% increased risk ratio (95% CI, 0.93-2.36) for hormone users. During the study, the average event rate for hormone users was 15.4 annually per 100 women compared with 11.9 for non-hormone users, a nonsignificant 29% increase (95% CI, 0.84-1.95).

**Comment.** Recent clinical trials of oral hormone therapy regimens have uniformly shown no cardiovascular benefit, and even some evidence of harm, in women with pre-existing coronary heart disease (CHD). The Papworth HRT Atherosclerosis (PHASE) study report extends these findings by showing that a transdermal hormone regimen also provides no benefit to women with established CHD. Despite the small sample size, short duration of follow-up, and 40% dropout rate in the active treatment arm, there was a troubling 30% increase in risk for acute coronary syndromes in the active treatment arm that ultimately led to early termination of the trial. Thus, the PHASE report strengthens the view that hormone therapy does not reduce, and may increase, risk for heart disease.

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*These news items with expert commentary come from the First-to-Know program offered to members of The North American Menopause Society (NAMS) by broadcast e-mail within days after publication of the studies. The items are then posted on the NAMS Web site ([www.menopause.org](http://www.menopause.org)). You can receive this valuable resource via e-mail by joining NAMS on the Web site or by calling 440/442-7550.*