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Memory or Mammaries? The Controversy about HRT Continues . . .

ABSTRACT & COMMENTARY

Synopsis: *Long-term and prior hormone replacement therapy (HRT) is associated with a reduced risk of Alzheimer's disease.*

Source: Zandi PP, et al, for the Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women. *JAMA*. 2002;288:2123-2129.

THIS PAPER IS THE PRODUCT OF A LARGER, PROSPECTIVE STUDY of the genetic and environmental risk factors for Alzheimer dementia (AD). Participants are 1357 men and 1889 women recruited from a single county in Utah. Enrollment occurred in 1995-1997, and this report is based on 3 years of follow-up. Determination of AD included the Mini-Mental State examination, the Dementia Questionnaire, and then clinical assessment, if warranted. Neuropsychological tests, a structured interview, examination by a geriatric psychiatrist, laboratory tests, and a panel of experts were involved in making each determination of dementia. Most participants were also screened for the "Alzheimer's gene," the polymorphic genetic locus for Apolipoprotein E (APOE). Information of Hormone Replacement Therapy (HRT) was collected by interview; use was classified by duration into categories of less than 3 years, 3-10 years, and longer than 10 years. Of note, 72% of those using HRT were taking an unopposed oral estrogen.

Over the 3-year follow-up, 35 men (2.6%) and 88 women (4.7%) developed AD. The development of AD was more common in women than in men, but less common among women with any history of HRT. Further analysis indicated that the risk of AD for men and women is equivalent until about 80 years of age, but the risk is roughly twice as high for women after the age of 80 (the mean ages of the men and women in this study at enrollment were 73.2 and 74.5 years, respectively). Logistic regression, which controlled for education, age, the number of APOE alleles, coexistent medical illness, depression, and medications including multivitamin and calcium use, showed a persistent benefit of HRT, in a dose-dependent

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manner. Former users (mean age, 74.5 years) of HRT had relative hazards of AD of 0.58 for < 3 years' use, 0.32 for 3-10 years' use, and 0.17 for more than 10 years' use compared with nonusers (though the reduction for those with less than 3 years' use was not statistically significant). For those currently using HRT (mean age, 71.9), the relative hazards were 2.41 for < 3 years' use, 2.12 for 3-10 years' use, and 0.55 for more than 10 years' use (only those current users with 10 or more years' use had significant changes). Zandi and colleagues note that there appears to be a "time window" for the protective effect of HRT against AD, and speculate that use of hormones within 10 years of AD onset does not confer benefit.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

One only has to pick up a woman's magazine or a lay news publication to grasp the public confusion and interest in the issue of hormone replacement for women. *US News and World Report*'s cover blares, "Making sense of menopause. New drug options. Tailor-made treatments. Choosing the right therapy.[1]" Women are increasingly sophisticated and informed as they seek our guidance about what to do when faced with this universal issue for women who survive into their 50s. The landmark study from the Women's Health Initiative last summer[2] resulted in the termination of the estrogen-progestin arm (but *not* the estrogen-only arm) after only 5.2 years because women who got combined HRT had small but significant increases in coronary heart disease, a nonsignificant trend toward invasive breast cancer, and a significant increase in the global index of a variety of adverse outcomes, including strokes and pulmonary emboli. Why was this not discovered earlier? Women using HRT in the earlier, observational studies were healthier than those not using it. Thus, it is important to note that the current study about AD is prospective, not observational, and its findings are likely to be "real." It is also important to note that these and other authors[3] suggest that there is a critical period for HRT use if it is to protect against AD; once the disease has begun (within 10 years of onset), HRT appears to offer little benefit. Timing is everything.

Now our discussions with patients about HRT must take on a "good news, bad news" flavor. Cardiovascular disease, thromboembolic disease, and probably breast cancer are increased among users of combined therapy, but colorectal cancer, osteoporotic fractures, and the risk of dementia are reduced. Patients can choose between risks. To a woman in the throes of hot flashes, however, these abstract risks may not matter much; HRT remains the best treatment for menopausal symptoms.[4]

Meanwhile, the estrogen-only arm of the WHI continues, and we will continue to learn about the risk/benefit ratio of HRT with estrogen alone. ■

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Hyperbaric Oxygen in Acute Carbon Monoxide Poisoning

ABSTRACT & COMMENTARY

Synopsis: *Hyperbaric oxygen therapy used within 24 hours of acute symptomatic CO poisoning decreases the risk of cognitive sequelae at 6 weeks and 12 months.*

Source: Weaver LK, et al. *N Engl J Med*. 2002;347: 1057-1067.

Carbon monoxide (CO) poisoning is a serious and common public health problem leading to unfavorable neurological sequelae and death. CO has greater affinity for hemoglobin than oxygen and displaces oxygen from hemoglobin causing severe tissue hypoxia. The organs most commonly affected are those that have the highest oxygen demands (eg, brain and heart). Between 23-47% of patients exposed to CO develop delayed neurological sequelae within 2-28 days.[2,3] Overall, despite the serious sequelae associated with CO, the mechanisms of injury and methods of treatment remain poorly understood.

Weaver and colleagues conducted a prospective double-blind, randomized, controlled trial to evaluate the effect of hyperbaric oxygen treatment in symptomatic acute CO poisoning. One hundred fifty-two patients over 7 years met the enrollment criteria of documented exposure to CO or an obvious exposure to CO with presence of signs and symptoms suggestive of CO poisoning, elevated carboxyhemoglobin (COHB), or metabolic acidosis. Exclusion criteria included > 24 hours elapsed since CO exposure had ended, age < 16 years, pregnancy, and morbidly ill patients. Patients were randomized to either hyperbaric or normobaric protocols. In the hyperbaric group, 3 chamber sessions of hyperbaric oxygen were administered at 6-12 hour intervals within a 24-hour period. In the first session, 3 atmospheres (ATA) of 100% oxygen were administered for 1 hour and decreased to 2 ATA of 100% oxygen for the next hour. The second and third chamber sessions consisted of hyperbaric oxygen at 2 ATA for 2 hours. In the normobaric group, the first session consisted of 100% oxygen at 1 ATA. The second and third sessions consisted of normobaric room air. Neurological and neuropsychological tests were administered at enrollment, after the first and third treatment sessions, and at 2 weeks, 6 weeks, 6 months, and 12 months after enrollment. Primary end points were the incidence of cognitive sequelae at 6 weeks after CO poisoning. Patients were followed for 12 months although it was not included in the study design.

Seventy six patients were randomly assigned to each treatment group. Of the 76 in each group, 75 in the hyperbaric group, and 72 in the normobaric oxygen group completed the study. Baseline characteristics were similar in both groups except for cerebellar dysfunction before treatment, which was worse in the normobaric group (15% vs 4%; $P = 0.03$). The presence of cerebellar dysfunction before treatment was associated with a higher incidence of cognitive sequelae (odds ratio, 5.71 [95% CI, 1.69-19.31]; $P = 0.005$). Cognitive sequelae at 6 weeks were less frequent in the hyperbaric oxygen group than the normobaric oxygen group (25% vs 46.1%; $P = 0.007$). Cognitive sequelae were less frequent in the hyperbaric oxygen group at 12 months according to intention-to-treat analysis (18% vs 33%; $P = 0.04$). Even when baseline characteristics such as incidence of cerebellar dysfunction were accounted for, this remained statistically significant. Weaver et al concluded that treatment of patients with acute symptomatic CO poisoning with 3 hyperbaric oxygen treatments within 24 hours appears to reduce the rate of cognitive sequelae at 6 weeks and 12 months later.

COMMENT BY DAVID OST, MD, AND GNANARAJ JOSEPH, MD

Previous studies done on the use of hyperbaric oxygen treatment were inconclusive due to methodological difficulties.[1] Practice guidelines were developed based on clinical experience and uncontrolled studies. This study supports the use of hyperbaric oxygen treatment. No adverse effects due to hyperbaric oxygen treatment were reported.

The serum COHB was mildly elevated at the time of hyperbaric oxygen, and treatment benefits may not have been from removal of carbon monoxide alone but also from prevention of cellular damage due to CO exposure. Animal studies have shown that hyperbaric oxygen preserves adenosine triphosphate, prevents lipid peroxidation of the cell wall and decreases neutrophil adherence in the brain.[4]

Limitations to the use of hyperbaric oxygen are the limited availability of facilities and the risk of adverse effects. Adverse effects of hyperbaric oxygen are uncommon. The most severe complication is convulsions.

This study strengthens the rationale for using hyperbaric oxygen in acute CO poisoning but some important clinical issues remain unanswered. First, better predictive factors are needed for determining the risk of

delayed and permanent effects of CO poisoning. Second, the optimum frequency, dose and duration of treatment, as well as the therapeutic window of opportunity need to be defined. Third, the role of hyperbaric oxygen in mild CO poisoning needs to be elucidated. Finally, prevention is a key part of the public health issue. ■

Dr. Joseph is Fellow of Pulmonary and Critical Care Medicine, North Shore University Hospital, Manhasset, NY.

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Homocysteine and Risk of Ischemic Heart Disease and Stroke

ABSTRACT & COMMENTARY

Synopsis: *This meta-analysis suggests that elevated homocysteine levels are only a modest independent predictor of ischemic heart disease and stroke risk in healthy populations.*

Source: The homocysteine studies collaboration. Homocysteine and risk of ischemic heart disease and stroke: A meta-analysis. *JAMA*. 2002;288:2015-2022.

THE THEORY THAT AN ELEVATED BLOOD CONCENTRATION of the amino acid homocysteine may be a risk factor for ischemic heart disease (IHD) was suggested by the observation that children with homocystinuria and markedly elevated homocysteine levels suffered from premature IHD. Epidemiological data using case-controlled studies supported this theory. However, results from more recent prospective observational studies varied in the significance of the association.

In order to examine the effect of homocysteine level and IHD and stroke risk, this collaborative meta-analysis sought to combine individual participant data from all relevant observational studies to produce a better estimate of the association of total plasma homocysteine levels with IHD and stroke, while controlling for other cardiovascular risk factors.

Medline was searched from January 1966 to January 1999 for observational studies of the association between IHD or stroke and homocysteine concentrations. Additional studies were identified by examining the references and by communicating with relevant researchers. Data from 30 prospective or retrospective studies involving a total of 5073 IHD events and 1113 stroke events were included in the meta-analysis. Statistical adjustments were made between studies to control for known cardiovascular risk factors. Combined odds ratios for the association of IHD and stroke with blood homocysteine concentrations were obtained by using conditional logistic regression.

Stronger associations were observed in retrospective studies of homocysteine measure in blood collected after the onset of disease than in prospective studies among individuals without a history of cardiovascular disease when the blood was collected. After adjusting for cardiovascular risk factors and regression dilution bias in the prospective studies, a 25% lower usual homocysteine level was associated with an 11% (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.83-0.96), lower IHD risk and 19% lower stroke risk (OR, 0.81; 95% CI, 0.69-0.95).

■ COMMENT BY MARTIN S. LIPSKY, MD

This meta-analysis suggests that elevated homocysteine has only a modest independent effect as a predictor of IHD and stroke risk in healthy populations. The effect they found was weaker than initially reported in earlier retrospective studies. In an accompanying editorial, Wilson[1] notes that as although it appears likely that homocysteine will not be as important in determining cardiovascular risk as cholesterol, smoking, diabetes mellitus, and hypertension but it is still significant. As this meta-analysis notes, even though the risk reduction is modest, if the association of homocysteine with IHD is causal then the benefits for the general population by lowering homocysteine levels could be substantial.

At this time, the results support the recommendation that all of us should eat our fruits and veggies or at the very least to live like our mothers told us to. It also substantiates that there may be benefit to recommending those individuals at high risk for IHD and stroke supplement their diets with folic acid in order to lower their homocysteine level. Even though it is not clear whether lowering homocysteine will result in reducing the risk for IHD, the negligible risks for taking vitamin supplementation make it prudent to continue this practice until definitive data form a large randomized trial of the effects on vascular disease on lowering homocysteine with folic acid are available. ■

Reference

1. Wilson P. *JAMA*. 2002;288:2042-2043.

Very Mildly Demented Patients Can Draw Clocks

ABSTRACT & COMMENTARY

Synopsis: *The clock drawing test had unacceptably low sensitivity in detecting the very earliest stages of AD.*

Source: Powlishta KK, et al. The clock drawing test is a poor screen for very mild dementia. *Neurology*. 2002;59:898-903.

The clock drawing test is used by many physicians and other health professionals to rapidly detect signs of cognitive impairment. This test involves asking the patient to draw the face of an analog clock, fill in all the numbers, and set the hands to a fixed time. The Clock Drawing Test can be rapidly administered, scored in a quantifiable way, and is sensitive to deficits in a variety of cognitive domains. Although past studies have shown that the Clock Drawing Test is frequently abnormal in patients with mild dementia associated with Alzheimer's disease (AD), few studies have examined its usefulness in detecting the very earliest signs of dementia. In a longitudinal study of 75 patients that included 25 with the earliest detectable stage of dementia, Powlishta and colleagues found that clock drawing had unacceptably low sensitivity in detecting the very earliest stages of AD.

In this study, 6 different scoring systems for the Clock Drawing Test were compared. Good inter-rater reliability (91-97%) was found among all 6 scoring systems. Powlishta et al examined the performance on clock drawing as a function of dementia severity as measured by the Clinical Dementia Rating (CDR) scale. While 80-97% of patients with mild dementia (CDR = 1) scored abnormally on the Clock Drawing Test, only 20-60% of those with very mild impairment (CDR = 0.5) scored below the cutoffs for normal. The Mendez scoring system had the best sensitivity for very mild impairment but had the lowest (60%) specificity.

Powlishta et al emphasize that clock drawing should not be used in isolation when screen for the earliest signs of AD. Instead, diagnosis requires a thorough clinical assessment that incorporates medical assessment, multiple measures of cognition, and a careful history from a collateral source.

COMMENT BY NORMAN R. RELKIN, MD, PhD

Clock drawing is an appealing cognitive screening test in many respects. It is quick and easy to administer, easy to score, and results can generally be reproduced across examiners and multiple test sessions. Results correlate reasonably well with the Folstein Minimental State Examination in selected patient populations. The pattern of deficits found on clock drawing often provides valuable clues to the nature of the cognitive domains impaired by a variety of brain disorders. For example, the clocks drawn in the context of visuospatial impairments may be distinctly different from those produced by patients with executive dysfunction or memory loss as their primary deficits.

As with all brief cognitive tests, clock drawing has its limitations. This particular study examined a relatively small number of cases and used published cutoffs for distinguishing normal from demented cases. Unfortunately, it did not use a Receiver Operating Characteristic (ROC) analysis to evaluate which scoring system and cutoff values provide optimal sensitivity and specificity in detecting very mild dementia. Nevertheless, the results suggest that impaired performance on clock drawing is a useful correlate of frank dementia in conditions such as AD but may not be sensitive enough to detect the very mildest cases. A recent study suggests that Mild Cognitive Impairment (MCI) may be detectable by repeatedly performing a small set of computerized cognitive tests over a single day.[1] Until such approaches are validated, MCI is best identified through the use of sensitive tests of memory, particularly delayed recall, coupled with other cognitive measures and information culled from interviews with the patient and a knowledgeable informant. Clock drawing still has a place in screening for dementia but should not be used in isolation when screening for very mild cognitive deficits. ■

Dr. Relkin is Associate Professor of Clinical Neurology and Neuroscience, New York Presbyterian Hospital—Cornell Campus.

Reference

1. Darby D, et al. *Neurology*. 2002;59:1042-1046.

Pharmacology Update

Escitalopram Oxalate Tablets (Lexapro—Forest Laboratories)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

The FDA has approved the active (S-enantiomer) of citalopram for the treatment of depression.

Citalopram, a SSRI that is currently available as "Celexa," is the racemic mixture containing S and R enantiomers. Antidepressant activity for escitalopram (S-enantiomer) is about 100 times more potent than the R-enantiomer and twice as potent as racemic citalopram. Escitalopram is marketed by Forest Laboratories as Lexapro.

Indications

Escitalopram is indicated for the treatment of major depression.[1]

Dosage

The recommended starting dose is 10 mg once daily. It may be taken in the morning or evening without regard to meals. A 10 mg dose is also recommended for most elderly and those with hepatic dysfunction. No dose adjustment is required for those with mild or moderate renal dysfunction.[1]

Escitalopram is available as 10 mg and 20 mg tablets.

Potential Advantages

Escitalopram does not appear to provide any significant clinical advantage over the racemic citalopram. Greater potency or more rapid onset of action of the active enantiomer over the racemic mixture has not been clearly established. Like citalopram, escitalopram may have a lower incidence of drug/drug interactions compared to other SSRIs.

Potential Disadvantages

Escitalopram does not appear to have any significant disadvantage over the racemic citalopram.

Comments

Escitalopram was approved based on extrapolation of efficacy from racemic citalopram and an 8-week fixed-dose study.[2] In this study, 491 patients with DSM-IV major depression were randomized to placebo, escitalopram 10 mg, 20 mg, or citalopram 40 mg. The Montgomery-Asberg Depression Rating Scale (MADRS), the 24-item Hamilton Rating Scale for Depression (HAM-D), the Clinical Gobal Impressions (CGI) scales, the Hamilton Rating Scale for Anxiety (HAM-A), and patient-rated quality of life scales, assessed efficacy. Burke and colleagues concluded that escitalopram 10 mg was significantly better than placebo, and there was no significant difference among escitalopram 10 mg, 20 mg, or citalopram 40 mg. In addition, the incidence of discontinuation due to adverse events was not different among the treatment arms. Another study compared escitalopram 10 mg, citalopram 20 mg, and placebo in 469 patients. Montgomery and associates reported that at 4 weeks escitalopram 10 mg was more effective than placebo, while 20 mg citalopram was not.[3] A third study also found escitalopram 10 mg to be effective compared to placebo.[4] Unpublished studies presented at the XII World Congress of Psychiatry (Yokohama, Japan, August 2002) suggested that escitalopram may have greater efficacy and more rapid onset than citalopram.[5] The wholesale cost of escitalopram 10 mg is $1.78 compared to $1.93 for citalopram 20 mg.

Clinical Implications

Citalopram is well established as a safe and effective antidepressant. Its efficacy is similar to other SSRIs.[7] Its primary advantage over other SSRIs is a low potential for drug interactions involving the cytochrome P450 isoform.[6] For example, fluoxetine and paroxetine are considered as potent inhibitors of, and sertraline as a moderate inhibitor of, CYP2D6, while citalopram has little effect. Currently there are inadequate published data to clearly distinguish whether the single enantiomer is more potent or more rapid acting that racemic citalopram. Forest is expected to cease promoting citalopram in favor escitalopram as the former is scheduled to lose patent protection in January 2004.[7] ■

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CME Questions

32. What is the best treatment option in acute symptomatic carbon monoxide poisoning when patient presents within 24 hrs of exposure?

a. 100 % oxygen
b. Hyperbaric oxygen
c. Room air
d. No treatment

33. Combined HRT is associated with:

a. Reduced risk of hip fracture and cardiovascular disease, but increased risk of Alzheimer's Dementia.
b. Increased risk of hip fracture and cardiovascular disease, but decreased risk of Alzheimer's Dementia.
c. Reduced risk of hip fracture and Alzheimer's Dementia, but increased risk of cardiovascular disease. d. Increased risk of hip fracture and Alzheimer's Dementia, but decreased risk of cardiovascular disease.
e. Reduced risk of cardiovascular disease and Alzheimer's Dementia, but increased risk of hip fracture.

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By Louis Kuritzky, MD

Stroke Reduction in Older Hypertensives with Abnormal Nocturnal Blood Pressure Dipping

THE RELATIONSHIP BETWEEN adverse cardiovascular events and blood pressure (BP) is direct and linear. Numerous prospective randomized trials indicate that reduction of BP produces a substantial reduction in stroke, with less impressive benefits demonstrated for coronary heart disease (CHD) end points. Since most clinical trials have been based upon clinic or 'casual' BP measurements, rather than 24-hour monitoring (ABPM), we have much less information about whether specific attributes of BP during the circadian pattern variations are important indicators of cardiovascular risk. Some data have indicated that not only is ABPM a much more potent prognosticator for cardiovascular risk, but that specifically, persons whose blood pressure does not evidence the normal 10% or greater decline in the evening (so-called "non-dippers") are at substantially greater risk for target organ damage.

In this prospective study of elderly hypertensives (n = 811) who underwent ABPM, the cardiovascular end point effect of treatment upon nondipper hypertensives was much more dramatic than on dippers (ie, 'normal pattern'). Additionally, individuals who were determined to be 'white-coat' hypertensives by ABPM did not show the beneficial reduction of CV end points as seen in nondippers. Increasing application of ABPM may help discern high-risk HTN groups most likely to benefit from intervention. ■

Hishide Y, et al. Am J Hypertens. 2002;15:844-850.

Primary Prevention of Hypertension

ACCORDING TO JNC VI REPORTING, as many as 43 million adults in America have hypertension (HTN), defined as blood pressure > 140/90. Although treatment with a variety of agents has been shown to reduce cardiovascular morbidity and mortality, effective primary prevention would be a more desirable goal. The National High Blood Pressure Education Program Coordinating Committee has provided evidence-based recommendations for primary prevention of hypertension in this communication.

The interventions documented to be efficacious in prevention of HTN include weight loss, reduction in dietary sodium, moderation in alcohol, increased physical activity, increased dietary potassium, and adherence to a DASH type diet.

Specifically, the interventions recommended include maintaining BMI < 25, keeping dietary sodium to < 2.4 g daily, engaging in at least 30 minutes of vigorous activity (such as brisk walking) most days of the week, limiting daily alcohol to 30 mL of ethanol (or the equivalent) including at least 3500 mg/d of dietary potassium, and following a diet that is rich in fruits, vegetables, and low-fat diary products, but modest in saturated and total fat.

Blood pressure reductions from these interventions may be as large as those seen with pharmacotherapy for HTN, and have been demonstrated to be sustainable. ■

Whelton PK, et al. JAMA. 2002;288: 1882-1888.

Effect of Aggressive Screening and Treatment on Prostate Cancer Mortality

THERE REMAINS A GREAT DEAL OF heated debate about the appropriate use of PSA screening amongst asymptomatic men. Although mortality for prostate cancer has declined since the mid-1990s, it remains uncertain whether this favorable outcome is indeed attributable to enhanced screening. Insight about the relationship between prostate cancer mortality and screening may be gained by comparing two different populations of men who underwent different patterns of PSA screening. During the 1987-1990 time period, men in the Seattle-Puget Sound region (n = 94,000) were more than 5 times more likely to undergo PSA testing than men in Connecticut (n = 120,000). Correspondingly, biopsy rates in the West Coast population were more than twice that of the East Coast population.

Over an 11-year follow-up, there was no discernible difference in prostate cancer mortality between the 2 populations. In ensuing years, the prostate cancer screening rates became much more similar. The men in these analyses were all 65 years or older, hence applicability for younger men is uncertain. Nonetheless, the mortality of prostate cancer effects mostly men older than age 70, so the age of this group matches the demographic consequences of the disease. This study suggests that more avid PSA screening may not reduce prostate cancer mortality. ■

Lu-Yao G, et al. BMJ. 2002;325:740-743.

In Future Issues: Suspected Pulmonary Embolism in Pregnancy