

Donepezil May Cut Death Risk in Severe AD by 50%

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

MADRID — Donepezil appears to decrease the risk of death among patients with severe Alzheimer's disease by about 50% but may be dangerous for patients with vascular dementia, Dr. Lon Schneider said at the 10th International Conference on Alzheimer's Disease and Related Disorders.

"The unexpected benefit of donepezil means we should be looking at this drug more carefully for those with severe Alzheimer's," said Dr. Schneider, professor of psychiatry, neurology, and gerontology at the University of Southern California, Los Angeles. "The magnitude of this effect implies that for every 41 such patients treated with donepezil, 1 death could be prevented."

Conversely, he said, statistical variability among the vascular dementia trials indicates a potential for an increased risk of death as high as three times among vascular dementia patients taking the drug, which should alert physicians to be more cautious when prescribing it in that population.

Both risk analyses emerged as part of an ongoing Cochrane database review of mortality associated with the use of drugs approved for Alzheimer's disease.

The study was sparked by reports of increased death among patients with mild cognitive impairment taking galantamine (an almost fivefold increased risk compared

with placebo), and by a recent phase III clinical trial of donepezil as a possible treatment for vascular dementia. In the phase III trial, there were 11 deaths in the active group, but none in the placebo group.

The review found no evidence of an overall increased risk of death for any of the cholinesterase inhibitors or memantine. The differences emerged only when the researchers stratified the results by disease type or severity. The four trials of donepezil in moderate to severe Alzheimer's showed a decreased risk of death in active patients compared with placebo. Two of the three trials of donepezil in vascular dementia showed an increased risk of death, while one showed a decreased risk.

"We can speculate that patients with vascular dementia have underlying cardiovascular disease which donepezil and other cholinesterase inhibitors may adversely affect," Dr. Schneider said in an interview. "In patients with severe Alzheimer's who have the most severe cholinergic deficits, the drug may have beneficial effects on parasympathetic function, or may so substantially improve their levels of attention that they can be better cared for."

Donepezil is not approved for vascular dementia or severe Alzheimer's, but Eisai Inc. has submitted a supplemental new drug application for use in severe Alzheimer's.

The conference was presented by the Alzheimer's Association. ■

Subclinical Cognitive, Memory Declines Seen in Apo E4 Carriers

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

MADRID — Even though they appear cognitively intact, carriers of the apo E4 gene show significant longitudinal decline on measures of frontally mediated cognitive skills and memory, Dr. Richard Caselli reported at the 10th International Conference for Alzheimer's Disease and Related Disorders.

"This shows that decline can occur in carriers even when it cannot be detected clinically," said Dr. Caselli, chairman of neurology at the Mayo Clinic, Scottsdale, Ariz. "If these changes reflect early stage Alzheimer's disease, they suggest that Alzheimer's may have a preclinical phase that lasts for years and occurs even before the onset of mild cognitive impairment."

His prospective study followed 35 apo E4 carriers and 33 noncarriers for at least 6 years, during which time all study participants received neuropsychological testing every other year. To ensure that only cognitively intact carriers were followed, Dr. Caselli excluded any patient who developed mild cognitive impairment, Alzheimer's disease, or any other form of symptomatic cognitive impairment during the study.

At baseline, the patients were a mean 56 years old, with 16 years of education;

63% were female. The testing included the revised Weschler Adult Intelligence Scale (WAIS-R) digit span, mental arithmetic, digit symbol substitution, freedom from distractibility, and controlled oral word association as measures of frontally mediated cognition.

At baseline, carriers performed slightly better than noncarriers on the auditory verbal learning test, as well as



'Alzheimer's may have a preclinical phase that lasts for years' before onset of cognitive impairment.

DR. CASELLI

on short-term recall, long-term recall, and percent recall. However, by the end of the study period, carriers had declined significantly more than noncarriers in short-term recall as well as in mental arithmetic, digit symbol substitution, and freedom from distractibility—all frontal mediated cognitive domains.

"Aging is normally accompanied by modest declines in memory and executive skills, but in apo E4 carriers, this 'age effect' appears to be exaggerated," Dr. Caselli said in an interview. ■

Leuprolide Acetate Seems to Forestall Alzheimer's Decline

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

MADRID — Leuprolide acetate may help forestall functional decline in patients with mild to moderate Alzheimer's disease, Christopher W. Gregory, Ph.D., reported in a poster at the 10th International Conference on Alzheimer's Disease and Related Disorders.

The drug, most frequently used for prostate cancer, endometriosis, and precocious puberty, decreases levels of luteinizing hormone—an action that has been shown to decrease the rate of cognitive decline and amyloid accumulation in an Alzheimer's mouse model. Anecdotal evidence has suggested that leuprolide acetate also boosts cognition in some men taking it for prostate cancer, said Dr. Gregory, vice president of research for Voyager Pharmaceutical Corp.

"Our hypothesis is that elevations in luteinizing hormone levels, which are a result of normal aging, may contribute to several of the pathologic processes that foster the development of Alzheimer's" including promoting tau phosphorylation and amyloidogenic processing of the amyloid precursor protein, Dr. Gregory said in an interview. "Therefore, reducing luteinizing hormone levels may help to

improve the symptoms of Alzheimer's."

He presented the results of a phase II pooled data analysis in which 106 men and women with mild to moderate Alzheimer's received either leuprolide acetate (22.5-mg injections given every 12 weeks) or placebo for 48 weeks. About 75% of the patients were on acetylcholinesterase inhibitors, which were continued throughout the study.

After 48 weeks, compared with placebo patients, those in the active group retained significantly more function in both activities of daily living (mean change from baseline -5.4 placebo vs. -3.5 leuprolide) and global function (unchanged or improved from baseline, 34% placebo vs. 51% leuprolide acetate).

Leuprolide patients also experienced less cognitive decline than did placebo patients (about 2 points), although the difference was not statistically significant.

The results were encouraging enough for the Raleigh, N.C., company to launch two 56-week phase III trials of leuprolide implants vs. placebo. Each study will need 555 patients with mild to moderate disease. All patients must have been taking an acetylcholinesterase inhibitor for at least 120 days prior to baseline.

The conference was presented by the Alzheimer's Association. ■

More Data Confirm Protective Effect of Juice on Alzheimer's

MARY ANN MOON
Contributing Writer

Frequent drinking of fruit and vegetable juices substantially decreases the risk of Alzheimer's disease, reported Dr. Qi Dai of Vanderbilt University, Nashville, Tenn., and associates.

Results of several studies have suggested that the antioxidants and polyphenols in dietary fruits and vegetables may reduce the risk of Alzheimer's disease (AD) or delay its onset. Dr. Dai and associates hypothesized that intake of fruit and vegetable juices also might be protective. They tested their hypothesis using data from 1,836 subjects involved in the Kame Project, a large, population-based prospective study of Japanese Americans living in King County, Wash.

The subjects, aged 65 years or older at baseline (mean age 72 years), completed food frequency questionnaires and underwent periodic cognitive assessments. Over a mean of 6 years of follow-up, 81 incident cases of AD were diagnosed.

The risk of developing AD declined with increasing consumption of fruit and vegetable juices. Subjects who drank juice three times a week or more had a hazard ratio of 0.24, compared with those who drank juice less often than once a week.

This protective effect was seen in subjects with all different levels of education, physical activity, and fat intake (*Am. J. Med.* 2006;119:751-9).

As in previous studies, the antioxidant vitamins in dietary fruits and vegetables were found to be protective, but those in vitamin supplements were not.

Although tea was the beverage most often consumed, and tea is a rich source of some polyphenols, there was no relation between tea drinking and AD risk in this study. This finding agrees with those of two previous studies of tea drinking and AD. Wine is another potent source of antioxidants, and there was a small but statistically insignificant inverse association between wine or sake drinking and AD. The lack of statistical significance may be due to the small number of subjects (6%) who drank these beverages at least once per week, the researchers noted.

The protective effect of fruit and vegetable juices is being attributed to their antioxidant properties, but it is also possible that other characteristics such as anti-inflammatory properties are at work. Moreover, in addition to possessing antioxidant vitamins and polyphenols, juices may contain other components such as folate and minerals, which contribute to the protective effect, they added. ■