Progression From Mild Cognitive Impairment To Alzheimer's May Be Delayed By Drug, According To National Study

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In a study of people with mild cognitive impairment (MCI), those who took the drug donepezil were at reduced risk of progressing to a diagnosis of Alzheimer's disease (AD) during the first year of the trial, but by the end of the 3-year study there was no benefit from the drug. Vitamin E was also tested in the study and was found to have no effect at any time point in the study when compared with placebo.

These findings, from the Memory Impairment Study, are the first to suggest than any agent can delay the clinical diagnosis of AD in people with MCI. The effects of the drug measured in this study "did not provide support for a clear recommendation for the use of donepezil" generally to forestall the diagnosis of AD in people with MCI, the researchers stated in their report, but they did note the potential importance of the findings for some patients. The data, they said, "could prompt a discussion" between clinicians and patients on the possibility of donepezil therapy in certain cases.

The findings were reported in the April 14, 2005, online *The New England Journal of Medicine* by principal investigators Ronald Petersen, Ph.D., M.D., of the Mayo Clinic, Rochester, MN, Leon Thal, M.D., of the University of California, San Diego, and colleagues. The research was funded in part by the National Institute on Aging (NIA) and was conducted as part of the Alzheimer's Disease Cooperative Study (ADCS), a nationwide clinical trials consortium supported by the NIA, a component of the National Institutes of Health, U.S. Department of Health and Human Services.

Thal, who is director of the ADCS and chair of the UCSD Department of Neurosciences, said "these findings represent the first time that any intervention has had an effect in slowing progression for subjects with mild cognitive impairment."

"While the delay in progressing to Alzheimer's disease had a limited effect in this case, it comes at an early stage of memory loss, a critically important time for patients and families hoping that the disease can be held at bay," says Neil Buckholtz, Ph.D., chief of the Dementias of Aging Branch at the NIA.

As part of the study, the researchers examined the effect of donepezil and vitamin E on delaying diagnosis of AD among a subset of people with MCI with apolipoprotein E-4 (APOE-e4), the only known genetic risk factor for late-onset AD. While the overall rate of progression to AD was greater in this group, use of donepezil in the APOE-e4 subset was beneficial for up to 36 months in reducing the risk of an AD diagnosis. The researchers did not recommend APOE-e4 genotyping for people with MCI, suggesting more research would be needed to understand the mechanism of action of the drug and other factors.

Additional important factors in the study were the success in diagnosing MCI on a reliable basis in a multi-site study and the finding that MCI can be predictive of AD. A condition whose characterization in the medical community is relatively new, MCI is a transitional state that occurs between the cognitive changes of normal aging and the very early stage of AD. The amnestic subtype of MCI, the focus of this research, involves memory problems not severe enough to be classified as dementia. Previous studies have shown that approximately eight

in 10 people who meet criteria for amnestic MCI progress to AD within 6 years of diagnosis and that people with the APOE-e4 gene progress to AD more rapidly.

In this trial, donepezil and the antioxidant vitamin E were each compared to placebo to learn whether either treatment might delay or prevent progression to AD among people with MCI. Participants were randomized to three groups, one taking 2000 International Units daily of vitamin E, the second receiving 10 mg of donepezil daily, and the third on placebo. All participants also took daily multivitamins. The average age of the participants at baseline was 73 years.

Among the 769 study participants enrolled at 69 sites in the U.S. and Canada, 212 developed possible or probable AD within the 3-year study period. The overall rate of progression from MCI to AD for all three treatment groups combined was 16 percent per year. The study found that the group on donepezil's risk of progression to a diagnosis of AD was reduced by 58 percent one year into the study, 36 percent at 2 years, but there was no risk reduction at the end of the full 3 years of the study.

"These findings give me a great deal of hope," says Petersen. "We have not answered the question of whether donepezil reduces the underlying brain changes in Alzheimer's disease, but now we know that for some people, drug therapy did make a real, clinical difference. I think there will be real opportunities in the future to test other therapies for patients with MCI."

Donepezil, a cholinesterase inhibitor, is currently prescribed for mild to moderate stages of AD to improve memory and other cognitive functions. Cholinesterase inhibitors work by delaying the breakdown of the neurotransmitter acetylcholine in the brain. Acetylcholine helps communication between the nerve cells and is important for memory.

The trial received primary support from the NIA, with additional funding provided by Pfizer, Inc., and Eisai, Inc. Pfizer and Eisai also contributed the donepezil study medication, and vitamin E was provided by DSM Nutritional Products, Inc.

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