Understanding, Preventing, Diagnosing, and Treating Alzheimer's Disease: Delaying Progression from Mild Cognitive Impairment to Alzheimer's in a Clinical Trial

Among people with mild cognitive impairment, an NIH-supported study of donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first year of treatment, although the apparent benefit disappeared after the first year.

Lead Agency: National Institute on Aging (NIA)/National Institutes of Health (NIH)

Agency Mission:

- Support and conduct genetic, biological, clinical, behavioral, social, and economic research related to the aging process, diseases and conditions associated with aging, and other special problems and needs of older Americans.
- Foster the development of research and clinician scientists in aging.
- Communicate information about aging and advances in research on aging to the scientific community, health care providers, and the public.

Principle Investigator:

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Partner Agencies:

Pfizer, Inc.
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General Description:

Delaying Progression from Mild Cognitive Impairment to Alzheimer's in a Clinical Trial
Amnestic mild cognitive impairment (MCI), characterized by memory problems not severe enough to be classified as dementia, is considered to be a transitional state that occurs between the cognitive changes of normal aging and the very early stages of Alzheimer's disease (AD). Previous studies have shown that approximately 8 in 10 people who meet criteria for MCI progress to AD within 6 years of diagnosis and that people with the apolipoprotein E-ε4 (APOE-ε4) gene, the only known genetic risk factor for late-onset AD, progress to AD more rapidly.

The first NIH secondary AD prevention trial, comparing the effects of vitamin E and donepezil (Aricept®) in preventing AD in people diagnosed with amnestic MCI, was conducted at 69 sites across the United States and Canada. The investigators found that individuals who took donepezil were at reduced risk of progressing to a diagnosis of AD during the first year of the trial, but by the end of the three-year study there was no benefit from the drug. Vitamin E was found to have no effect on AD risk when compared with placebo. As part of the trial, the researchers examined the effect of donepezil and vitamin E on delaying diagnosis of AD among

a subset of people with APOE-ε4. While the overall rate of progression to AD was greater in this group, use of donepezil in the APOE-ε4 subset was beneficial for up to three years in reducing the risk of an AD diagnosis.

These findings are the first to suggest that an agent can delay the clinical diagnosis of AD in people with MCI. However, because too little is known about the effects of taking donepezil so early in the disease course on subsequent progression, the results, although promising, do not support a recommendation for the generalized use of donepezil to forestall the diagnosis of AD in people with MCI. Further studies are needed of donepezil and other therapies that may benefit patients at risk of developing AD.

Excellence: What makes this project exceptional?

This is the first study to demonstrate a benefit for any chemopreventive agent in the treatment of AD.

Significance: How is this research relevant to older persons, populations and/or an aging society?

As many as 4.5 million Americans ages 65 or over suffer from Alzheimer's disease (AD) and many more have mild cognitive impairment (MCI), AD's precursor condition. Approximately 80 percent of those who meet the criteria for amnestic mild cognitive impairment will have Alzheimer's disease within six years, and the presence of one or more apolipoprotein (*APOE*) ε4 alleles is associated with a more rapid rate of progression. Therefore, the ability to prevent or delay the development of AD among people with MCI is of tremendous public health importance.

Effectiveness: What is the impact and/or application of this research to older persons?

Although too little is known at present about donepezil's long-term effects to support a recommendation for its routine use to forestall the diagnosis of AD in people with mild cognitive impairment, these findings suggest that chemoprevention of AD is possible and provide hope that future clinical studies will lead to the development of effective drug interventions.

Innovativeness: Why is this research exciting or newsworthy?

These findings are the first to suggest that an agent such as donepezil can delay a diagnosis of AD among people with MCI, and they indicate that chemoprevention of AD is possible.