Neither vitamin E nor donepezil delays progression from amnestic mild cognitive impairment to Alzheimer’s disease in the long term


Q Do vitamin E or donepezil delay the clinical diagnosis of Alzheimer’s disease in people with the amnestic form of mild cognitive impairment?

METHODS

- **Design**: Randomised controlled trial.
- **Allocation**: Unclear.
- **Blinding**: Double blind.
- **Follow up period**: Three years.
- **Setting**: Sixty nine sites in the United States and Canada; March 1999 to January 2004.
- ** Patients**: 790 people aged 55–90 years, with amnestic mild cognitive impairment of a degenerative nature. Other inclusion criteria: Clinical Dementia Rating of 0.5; Mini-Mental State Examination score 24 to 30; impaired memory; and Logical Memory delayed recall score about 1.5 to 2 standard deviations below education adjusted norm.
- **Intervention**: Donepezil (10 mg daily) plus placebo vitamin E; vitamin E (2000 IU daily) plus placebo donepezil; or placebo vitamin E plus placebo donepezil for three years. All participants received a daily multivitamin tablet that contained 1.5 IU of vitamin E.
- **Outcomes**: Possible or probable Alzheimer’s disease (National Institute of Neurological and Communicative Diseases and Stroke, and the Alzheimer’s Disease and Related Disorders Association clinical criteria); adverse events.
- **Patient follow up**: 68% completed the study, 97% included in analyses.

MAIN RESULTS

Compared with placebo, neither vitamin E nor donepezil altered the probability of progression to Alzheimer’s disease after three years (vitamin E v placebo: HR for progression 1.02, 95% CI 0.74 to 1.41; donepezil v placebo: HR for progression 0.80, 95% CI 0.57 to 1.13). However, there was some indication that donepezil slowed progression to Alzheimer’s disease over the first two years compared with placebo (p = 0.03). Donepezil increased adverse events compared with placebo (diarrhoea, muscle cramps, insomnia, nausea, abnormal dreams: p < 0.01; loose stools, vomiting, arthritis: p < 0.05).

CONCLUSIONS

Neither vitamin E nor donepezil were associated with a lower rate of progression to Alzheimer’s disease after three years for people with mild cognitive impairment, although donepezil may lower rate of progression in the shorter term.

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Commentary

The paper by Petersen et al presents the results of a large, carefully conducted, three year clinical trial to examine whether vitamin E or standard Alzheimer’s therapy (the cholinesterase inhibitor donepezil) delays the progression from mild cognitive impairment (MCI) to Alzheimer’s disease (AD). Because MCI likely represents the prodromal phase of AD, when significant neuropathology is already present, this trial is probably best viewed as a secondary prevention trial. Extensive in vitro evidence supported a potential role for vitamin E in AD prevention, although a wide variety of epidemiological studies suggested that it was protective against AD, and a single clinical trial in established AD suggested that it delayed progression.

Alas, the results of the present trial were disappointing. Vitamin E showed no benefit whatsoever, one in a string of negative results for the antioxidant vitamin in the past year. Donepezil showed modest benefits at one year, but the difference between the treatment and placebo groups was gone by the three year end point. The results were somewhat more promising in a post hoc analysis of a subset defined by the AD risk factor gene APOE 4, but this likely represents a difference in statistical power (because more such individuals developed AD) than a true pharmacogenomic difference. Overall, the modest and time limited benefits of donepezil are consistent with AD treatment studies — not surprisingly, because many investigators believe that MCI represents the early stage of AD.

Taken together with other recent negative findings about vitamin E, the present results are likely to discourage the use of vitamin E for prevention of progression in MCI, but do not speak to the larger question of whether vitamin E taken earlier, before the onset of neuropathological changes, might be helpful in the primary prevention of AD. For donepezil, the results are less clear, and there is no consensus as to whether it makes sense to continue to offer the drug to individuals with mild cognitive symptoms.

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