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?

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,4 a wide variety of epidemiological studies suggested that it was protective against AD,5 and a single clinical trial in established AD suggested that it delayed progression.6

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.7–9 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.10 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 studies11—not surprisingly, because many investigators believe that MCI represents the early stage of AD.12

Taken together with other recent negative findings about vitamin E,7–9 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.

Deborah Blacker, MD, ScD
Department of Psychiatry, Mass General Hospital/ Harvard Medical School, Boston, MA, USA

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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