

EDITORIAL



Mild Cognitive Impairment — No Benefit from Vitamin E, Little from Donepezil

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In this issue of the *Journal*, Petersen et al. present the long-awaited results of a randomized, placebo-controlled trial of donepezil, a standard therapy for Alzheimer's disease, and the widely used antioxidant vitamin E as an early intervention for mild cognitive impairment — essentially the prodromal phase of Alzheimer's disease.¹ The implications of this study for primary care medicine and for public health are enormous. The clear-cut negative findings for vitamin E, which is widely used despite the dearth of evidence of its efficacy, are especially noteworthy. The findings for donepezil, on the other hand, are much less clear.

Mild cognitive impairment is conceived of as a transitional state between normal aging and dementia (or Alzheimer's disease in particular), one in which cognitive deficits are present but function is preserved. As such, it is inherently unstable and its upper and lower boundaries are difficult to delineate. In research such as that of Petersen et al., mild cognitive impairment is defined on the basis of subjective reports of memory loss, objective memory deficits (beyond those expected for age), and intact functional status,² whereas in clinical settings, the term is often used to describe patients who present with memory loss but do not have dementia. More recently, the amnesic subtype³ of mild cognitive impairment has been more carefully defined to identify a subgroup of such patients who have an increased risk of progression to Alzheimer's disease over time, and this is the subtype studied by Petersen and colleagues. Even when defined carefully, however, mild cognitive impairment is a heterogeneous category that includes some persons with the memory changes of normal aging, some with nonprogressive cognitive deficits, some with prodromal Alzheimer's disease, and

some with prodromal forms of other neurodegenerative dementias; only those on a course toward Alzheimer's disease are likely to benefit from Alzheimer's disease-specific interventions.

Because new treatments are expected to be better at preserving than restoring nerve function, early recognition of Alzheimer's disease and other neurodegenerative dementias — at the stage of mild cognitive impairment or even earlier, if current efforts at early detection are successful — is a major focus of current research. There is considerable evidence that the pathologic changes of Alzheimer's disease are already well established in the brain in a substantial fraction of those with a research diagnosis of mild cognitive impairment.⁴ Thus, intervention to prevent progression of mild cognitive impairment to Alzheimer's disease is probably more accurately viewed as early intervention.

Rather than wait for new agents, Petersen et al. carefully evaluated the ability of two standard treatments for established Alzheimer's disease to slow the progression from mild cognitive impairment to frank Alzheimer's disease. Donepezil is a widely used cholinesterase inhibitor with limited clinical benefits, which are often not detectable in individual patients⁵ and are sometimes equated to a delay in progression of approximately six months relative to placebo. Vitamin E was shown in a single high-quality trial (conducted by this same research group) to slow progression in patients with moderate-to-severe Alzheimer's disease.⁶ It is widely used for all types of patients with Alzheimer's disease because of its low cost and perceived safety (although the latter has recently been called into question^{7,8}). In addition, largely on the basis of theories of oxidative stress, *in vitro* work,⁹ and epidemiologic ev-

idence,¹⁰ vitamin E is widely used for the primary prevention of Alzheimer's disease among persons with normal cognition. However, this approach may soon change as the public adjusts to recent evidence that epidemiologically detected benefits of vitamin E for cardiovascular disease do not stand up to rigorous clinical testing⁷ and may even carry risks.^{7,8}

Published trials of treatments specifically for mild cognitive impairment have thus far been limited by their small sample sizes, brevity, predominantly industry funding,^{11,12} and uniformly negative results. Preliminary results from two as yet unpublished, large clinical trials of another commonly used cholinesterase inhibitor, galantamine, did not show a significant difference between galantamine and placebo in the rate of progression from mild cognitive impairment to Alzheimer's disease over a two-year period.^{13,14} Of note, the unexpected finding of an excess risk of death in the galantamine group in both trials recently led the Food and Drug Administration to issue a safety warning.¹⁵

The present trial represents a major step forward in the literature on trials of treatment for mild cognitive impairment. More than 700 subjects were enrolled, and they were followed for three years by a federally funded consortium of Alzheimer's Disease Centers with broad experience conducting Alzheimer's disease trials. The biggest news is the disappointing lack of efficacy of vitamin E in a well-powered trial that used the high doses previously shown to slow the progression of Alzheimer's Disease. Their detailed analysis of psychometric testing across a wide range of cognitive domains also showed no significant difference between vitamin E and placebo.

The news about donepezil is not quite as disappointing. Although analysis of the primary end point of the study — the rate of progression to Alzheimer's disease within three years — was negative, the study does leave us with some hope. First, as the authors point out, they have shown that this difficult-to-define diagnostic category can be measured and studied, which is no small feat for a syndrome that was delineated less than a decade ago. Second, the rate of progression to Alzheimer's disease was somewhat lower in the donepezil group than in the placebo group during the first year of the study. Alas, by two years even this small effect had worn off. Two possible explanations come to mind: most of the subjects who were going to cross

the arbitrary threshold between mild cognitive impairment and Alzheimer's disease had already done so by 12 months, so no differences were detectable after this time, and there was reduced statistical power later in the study as the number of subjects at risk declined owing to death, withdrawal, and the development of Alzheimer's disease. However, the secondary analyses of the psychometric test results suggest that neither of these explanations is the case and, instead, that the benefits really did wear off. Although several of the psychometric tests showed statistically (although not necessarily clinically) significant differences early in the study (e.g., a fraction of an SD unit on a composite memory score), the results in the donepezil group were virtually identical to those in the placebo group after 12 months: the donepezil group really had caught up with the placebo group. The reason for the transient effect of the drug is unclear, and treatment trials for established Alzheimer's Disease offer few clues. The longest trial to date, which also lasted three years, also found that few of the differences between the placebo and donepezil groups persisted into the second half of the study.¹⁶ Neither study offers any insight into whether using donepezil in the mild cognitive impairment phase of the illness would have any effect on efficacy once Alzheimer's Disease is established.

What of the apparent differential effect between noncarriers and subjects who carried an apolipoprotein E (*APOE*) $\epsilon 4$ allele, a risk factor for Alzheimer's disease in the general population and thus for progression to Alzheimer's disease among those with mild cognitive impairment? As the authors suggest, their findings provide no support for recommending *APOE* testing in the evaluation of patients with mild cognitive impairment. In fact, a closer look at their data reveals no convincing evidence of a difference in treatment effect according to *APOE* $\epsilon 4$ carrier status: the effect of donepezil was similar among *APOE* $\epsilon 4$ carriers and noncarriers (hazard ratio for progression, 0.66, as compared with 0.80 for the entire cohort, with overlapping confidence intervals). These numbers suggest that the observed difference in significance may have been due to analogous differences in statistical power, since Alzheimer's disease developed in about twice as many *APOE* $\epsilon 4$ carriers (who are more likely to be on a course toward Alzheimer's disease), as noncarriers within the three years after enrollment.

What lessons does the study by Petersen et al. offer clinicians and their patients with mild cognitive symptoms? First, symptoms of memory loss in older persons should be taken seriously, since they may represent the beginning of Alzheimer's disease, and — once more effective early interventions are available — it will be critical to ask patients about these symptoms and learn to recognize them as early as possible. Second, at least one standard Alzheimer's disease therapy, donepezil, may offer some benefit, but any such benefit is quite limited and apparently transient. Last and most important, this study puts to rest the hope that early intervention with vitamin E can delay the onset of Alzheimer's disease, joining a group of recent trials of vitamin E with disappointing results.¹⁷

Despite these largely negative results, the bigger picture remains hopeful. Clinical studies of a wide variety of agents aimed at halting or even reversing the advance of pathologic brain lesions in Alzheimer's disease are under way. There is every reason to expect that at least some of these agents will prove effective and can be deployed early in the hope of stopping the disease process while function remains intact.

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