EDITORIAL

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Vitamin E, Memantine, and Alzheimer Disease

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The report by Dysken et al[1] in this issue of *JAMA* raises interesting issues about drug therapy for Alzheimer disease (AD) and emphasizes the importance of closely following this rapidly evolving field. In this randomized clinical trial, older veterans (97% men) with AD and Mini-Mental State Examination (MMSE) scores of 12 to 26 who were receiving acetylcholinesterase inhibitors were assigned to 1 of 4 treatment groups: receiving synthetic vitamin E (alpha tocopherol, 2000 IU/d); memantine, 20 mg/d; both agents; or placebo.

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As in almost all trials of therapy in AD, death was frequent (128 of 613 study participants), medication adherence was moderate, and loss to follow-up was greater than optimal, reflecting the practical challenges in conducting randomized trials among people with this disease of older age.

The primary trial outcome was score on the Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory; secondary outcomes included scores on the MMSE and the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog). Compared with individuals assigned to placebo, those assigned to vitamin E alone experienced 3.15 units less decline on the ADCS-ADL Inventory, a fairly modest 19% reduction that was statistically significant (P = .03) and may well be meaningful as the authors suggest. The groups assigned to memantine or the combination did not differ significantly from those assigned to placebo on the primary outcome, and none of the groups assigned to active interventions differed from the placebo group on the cognitive outcomes (MMSE and ADAS-cog).

The results seem especially pertinent to the use of combinations of agents to treat AD. Combination therapy for AD has substantial appeal because agents currently available for treating AD offer on average only modest therapeutic benefits, and some have bothersome adverse effects. Achieving greater benefit without more adverse effects by using medications in combinations, especially agents with different presumed mechanisms of action, is a reasonable goal. In this trial, differences among the randomly assigned groups were assessed among study participants receiving nonrandomly assigned acetylcholinesterase inhibitor therapy at entry (donepezil, 65%; galantamine, 32%; or rivastigmine, 3%).

For memantine therapy in this context, the trial results are not encouraging. Memantine is approved by the US Food and Drug Administration for use in moderate to severe AD. Use in individuals with milder AD may be widespread[2] despite little evidence suggesting the agent is beneficial at this level of disease severity.[3] This trial by Dysken et al of treating mild to moderate AD does not provide any new data to support its use because the comparison of the group assigned to memantine with the group assigned to placebo suggested no differences in either the primary ADCS-ADL outcome or in the secondary cognitive outcomes. The negative interaction between alpha tocopherol treatment, which was significantly beneficial alone, and memantine treatment in predicting the primary trial outcome is of concern and deserves further investigation. No formal comparison of the primary outcome was reported between the group assigned to alpha tocopherol alone and the group assigned to the combination of alpha tocopherol and memantine; the statement in the "Discussion" that "... the combination of alpha tocopherol and memantine had less effect than either alpha tocopherol alone or memantine alone" is difficult to support in the absence of such a comparison with significance testing.

For vitamin E, the results of this trial are more encouraging because of the significant difference from the placebo group observed for the primary outcome and the absence of severe adverse effects. A previous trial[4] among individuals with moderate to severe AD found delayed disease progression with 2000 IU/d of alpha tocopherol both alone and in combination with selegiline. The results of a trial[5] of vitamin E therapy among people with mild cognitive impairment were null; however, so were the results of trials[6,7] examining the effects of vitamin E on cognitive function among people with normal cognition. These null results emphasize that the findings of these 2 trials should not be extrapolated to use of vitamin E at different dosages, among people with different AD severity levels, or in combination with different agents than the ones examined in either of these 2 trials[1,4] reporting beneficial results. Different situations will require future direct empirical testing. Caution that the adverse effect profile of vitamin E may be greater than seen in these 2 trials is also warranted in view of the findings of a meta-analysis[8] of 19 randomized trials that vitamin E in doses greater than 400 IU/d was associated with increased all-cause mortality. Other possibly productive directions for future AD trials to explore include other dosage levels of alpha tocopherol and use of other tocopherols or combinations of tocopherols as therapeutic agents.

Major AD treatment trials like this one use functional ability, especially as assessed by the ADCS-ADL Inventory, as an outcome with increasing frequency. The use of functional ability measures for this purpose overtly or tacitly uses impairment in functional ability as though it were solely a consequence of AD progression. Such impairment, however, is not specific to AD but occurs frequently among older people as a consequence of many conditions.[9] Some aspects of this trial highlight the nonspecificity of the link between AD and functional decline. First, the results of the secondary cognitive out-

comes, MMSE and ADAS-cog, were null for all treatment groups; this can be viewed both positively (functional ability may be a more sensitive measure of AD progression and nonsignificant trends in the same direction were seen for these secondary cognitive outcomes) or with concern (the lack of specificity of functional ability and the perception that cognitive decline is the essence of AD). Second, the significant difference in the primary outcome, ADCS-ADL score, was not confirmed by significant differences in the secondary outcomes that might reflect functional ability, such as scores on the Caregiver Activity Scale (CAS) and the Dependence Scale, although there was nonsignificant change in the same direction for CAS score. Third, the mechanism of action of vitamin E in AD is uncertain. Much attention is focused on its antioxidant properties, but this mechanism is not specific for AD. Although these considerations do not lessen the significance of the difference found between the group randomized to vitamin E and the group randomized to placebo for the primary outcome, this difference would have been more convincing if also supported by parallel improvements in the relevant secondary outcomes and by a vitamin E mechanism of action more specific to AD.

Many features of the trial by Dysken et al reflect the best in trials of AD therapy, especially its size, duration, and separation from commercial motivation. However, as with almost all previous AD trials, the therapeutic effect seen was modest and more relevant to AD symptoms and consequences than to reversal of the disease process. The importance of treating patients with AD is clear, but finding the best balance between treatment and prevention efforts is challenging for this grim disease affecting millions of people from all developed countries.[10] Few would doubt the wisdom inherent in Rose's humanitarian justification[11] for prevention: "It is better to be healthy than ill or dead." Considering the difficulties inherent in trying to treat rather than prevent very high-prevalence diseases and the limitations thus far of the therapeutic efforts for people with AD, shifting to more emphasis on prevention seems warranted.

ARTICLE INFORMATION

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