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EDITORIAL

Cracking the therapeutic nut in mild cognitive impairment

Better nuts and better nutcrackers

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In this issue of *Neurology*®, the results of a 48-week trial of donepezil in patients with mild cognitive impairment (MCI) are reported.[1] Although the investigators found a statistically significant effect of donepezil on the modified Alzheimer disease (AD) Assessment Scale–cognitive (ADAS-cog), there was no benefit for donepezil-treated patients on the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB).

At face value, the lack of benefit of donepezil on the CDR-SB in patients with MCI over nearly 1 year refutes the presumption that donepezil should be effective in MCI because it was in mild to moderate AD. Two other studies with donepezil reached nearly the same conclusion,[2,3] and studies of the other cholinesterase inhibitors rivastigmine[4] and galantamine[5] also failed to show benefits in MCI.

However, inspection of the data in the current study[1] raises questions about the adequacy of the study design. The subjects with MCI in the study did not deteriorate. Over 48 weeks, the CDR-SB ratings dropped only 0.1 point. On the modified ADAS-cog, the placebo group actually improved 0.13 points. The trial used the same inclusion criteria as the AD Cooperative Study's (ADCS) 3-year MCI trial.[3] The study participants had less decline over 1 year than in the ADCS trial, but even in the ADCS trial, the amount of decline was small. More sensitive neuropsychological test batteries, as suggested by the authors,[1] would not have detected robust declines in a placebo group in the face of their net improvement on the ADAS-cog.

This study demonstrated how difficult it is to rely on clinical criteria alone to achieve the level of deterioration required to detect treatment differences. The operational criteria for MCI in clinical trials must be supplemented by biomarkers in order to maximize the number of subjects with progressive disease. For example, hippocampal atrophy,[6] low CSF amyloid-β/tau protein ratios,[7] and APOE ε4 genotype[3] have all been associated with higher rates of future worsening of function and cognition among persons with MCI. An international group has made a very similar proposal.[8] Even though APOE genotype had no impact on outcome in the current study, APOE genotype had a large impact on the rate of incident dementia in the ADCS MCI trial.[3] To be sure, there are several trade-offs with selective recruitment. Recruiting patients becomes more difficult and costly. Second, generalization to all patients with MCI becomes difficult. Yet, if there are identifiable subgroups of patients with MCI at low risk for deterioration, research recruitment and clinical practice both ought to reflect the appropriate selectivity.

Even with biomarker-enhanced recruitment, outcome measures for MCI therapeutic trials cannot follow the same regulatory formula that is used in mild to moderate AD. Because of the uncertainties of using surrogates such as MR volumetry as endpoints,[9] let us consider only clinical outcome measures here. Survival analyses using dementia as the endpoint have much appeal, but the variability inherent in the diagnosis of dementia in the clinical trial context is a weakness,[8] and in any case, such a design requires at least 2 to 3 years to perform. As shown by the current study,[1] detection of decline in daily functioning by a global measure may be difficult to document in MCI over only 1 year. Patients with MCI may still possess compensatory abilities that may mask genuine cognitive declines. If milestones like dementia onset or global instruments like CDR-SB are inadequate, there is only one alternative. Neuropsychological test batteries, when combined with targeted recruiting, are the only reliable way clinically to detect therapeutic effects in patients with MCI.

Unfortunately, there is currently a major barrier to the adoption of neuropsychological testing as a sole primary outcome measure. That is the regulatory concern that benefits on cognitive test scores in MCI

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or mild to moderate AD could be dissociated from clinically meaningful benefits in daily functioning. AD clinical trial experience has shown that benefits in cognitive test scores and clinician judgment of clinically meaningful change may be linked. In MCI, in contrast, such evidence is still lacking. In the short run, neuropsychological testing results could be dissociated from functional outcomes in persons with MCI, but given the tight linkage between cognition and function in mild AD, sustained benefits in neuropsychological test scores are highly likely to translate into clinically meaningful benefits in the long run.

Society desperately needs better therapies for AD, especially ones that are effective at the MCI stage of AD. To identify those therapies, better study designs are needed: a realistic approach to outcome measures together with a new approach to inclusion criteria for high-risk subjects with MCI.

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