Comment: MCI trials—Categorical “square pegs” in dimensional “round holes”?

Given repeated disappointments from trials of treatments for Alzheimer disease (AD), one hoped for better results from upstream interventions at the mild cognitive impairment (MCI) stage. However, results there have been almost as bleak. A new report¹ considers explanations for the latter: varying participant selection, observation methods, and outcomes assessment. Cleverly, the authors avoided differences in efficacy of various treatments by considering only the trials' placebo-assigned control groups. This design permitted inclusion of the Alzheimer's Disease Neuroimaging Initiative (ADNI) MCI cohort, assembled similarly to that of the Alzheimer's Disease Cooperative Study (ADCS).

The findings are sobering. They highlight difficulties in trial design within a clinical diagnosis, MCI, that is increasingly understood as a slice in time, without natural boundaries, in the evolution of AD. The article's figure 2 shows marked variability in the various trial cohorts' Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog) scores at baseline. Importantly also, ADAS scores for all trial cohorts except the ADCS and ADNI trials declined over time, suggesting that familiarity or practice effects may have obscured disease-related cognitive decline. As for outcomes, randomization and masking may protect against bias, but imprecision in diagnosis (owing again to lack of natural boundaries) may still have diluted treatment effects.

Figure 3 suggests a rapid exaggeration in symptoms at the first follow-up examination. Such a phenomenon could reflect selective enrollment of persons with near-normal Mini-Mental State Examination scores who were, in fact, sicker than their entry scores suggested. One might wonder about laxity of some clinics that were reimbursed on a per-person-enrolled basis. After this first follow-up, symptom progress appears haphazard. This suggests there was not much disease-related decline thereafter for the treatments to mitigate.

What to do now? Creation of a category for the slice in time that is MCI, while useful clinically, can be problematic for trial design. Even so, the longitudinal performance declines among the ADCS and ADNI cohorts suggest that strict criteria and meticulous methods can offer a target for disease-modifying interventions. Addition of more objective endpoints (various biomarkers, perhaps even multiple) may also help.² By contrast, functional difficulty, while of fundamental clinical importance, may be problematic as a trial outcome, since its variable origins may obfuscate real treatment effects. If only we understood better the true nature of AD—not just its features or manifestations or tautological animal models—we might have better luck assessing treatments that modify its progression.

1. Petersen RC, Thomas RG, Aisen PS, et al. Randomized clinical trials in mild cognitive impairment: sources of variability. *Neurology* 2017;88:1751–1758.
2. Leoutsakos JM, Gross AL, Jones RN, Albert MS, Breitner JCS. Alzheimer progression score: development of a biomarker summary outcome for AD prevention trials. *J Prev Alz Dis* 2016;3:229–235.

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trials required the clinical diagnosis of dementia with review by a central committee, and other trials used progression to CDR 1 as the endpoint. It is clear that participants can progress from MCI to dementia while still at the CDR 0.5 stage, and consequently, variability can be introduced by the nature of the endpoint.

Clinical trials designed to involve participants at the MCI due to AD stage can be improved. Clearly, through the use of AD-specific biomarkers, the clinical characteristics of the participants can be stratified and a more homogeneous group of participants can be enrolled. If the intervention is targeted at amyloid, amyloid positivity on PET scanning or CSF Aβ42

levels can be used to select participants. It is uncertain as to whether these biomarkers will overcome some of the other sources of variability encountered in the trials described, but that is a distinct possibility. The implementation of continuous outcome measures rather than clinical states may improve performance of trials, but clinical meaningfulness needs to be established. However, attention to other factors such as *APOE4* carrier status, language, culture, and comorbidities still needs to be entertained in designing trials in this state of the disease. Finally, these factors are not peculiar to trials of MCI due to AD but have implications for other chronic disorders of a gradually progressive nature. Several important lessons have been derived from analyzing the previously conducted trials.

AUTHOR CONTRIBUTIONS

Dr. Petersen: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data. Dr. Thomas: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data. Dr. Aisen: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data. Dr. Mohs: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data. Dr. Carrillo: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data. Dr. Albert: obtaining data, reviewing data, reviewing manuscript.

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