NEUROPSYCHOLOGICAL AND CLINICAL ENDPOINTS IN PRECLINICAL AND EARLY AD: PRO NEUROPSYCHOLOGICAL & CLINICAL ENDPOINTS

Michael T. Ropacki
Janssen Research & Development, LLC, USA

Alzheimer's disease (AD) research is moving earlier in the disease course when treatments may have greater impact. When selecting measures and clinical endpoints investigators must consider the AD stage at baseline, study duration, expected AD progression over the trial, evidence supporting the measure's psychometric properties and sensitivity in this population, availability of normative data, as well as clinical meaningfulness of the results. However, there is a lack of consensus on which cognitive or functional endpoints should be used in the pre-dementia stages. Furthermore, many measures traditionally used in AD trials (e.g., ADAS-Cog) are insensitive in this stage of disease. Moreover, you would not expect this population to have impaired ADLs (e.g., toileting) measured by commonly used instruments like the Disability Assessment of Dementia (DAD).

When conducting studies with a preclinical AD/early MCI (eMCI) population, sensitivity and clinical meaningfulness issues are compounded because, in theory, there are only finite differences between healthy and affected individuals. To assist in this regard the United States Food and Drug Administration (FDA) recently published draft guidance for industry consideration when developing drugs for the treatment of early AD. This guidance discusses employing clinical measures that combine assessment of cognition and function, composite scales/scores and isolated neuropsychological measures. The challenge of moving earlier in the disease course is to find neuropsychological measures that are psychometrically validated, sensitive across the range of disease, devoid of floor and ceiling effects, not prone to practice effects, and applicable cross-culturally. In addition, these measures need to be feasible to implement, easy to administer and score, have low patient burden and good compliance, and provide clinically meaningful data.

Contrary to the hypothetical models proposed by Jack and colleagues, the scientific literature supports that certain cognitive domains (e.g., episodic memory, executive function) decline well before the diagnosis of MCI. Specifically, the rate of cognitive decline increases and is detectable 4-to-6 years before the diagnosis. In addition, there is supporting evidence from the Alzheimer's Disease Neuroimaging Initiative database that baseline measures of cognition were more robust predictors of conversion from MCI to AD than biomarkers. Overall, there are many challenges when conducting studies in preclinical and early AD, but at present the scientific evidence supports that measures of cognition move many years before the diagnosis of MCI and are better predictors of conversion.