Received: 14 November 2019 | Accepted: 3 February 2020 | Published online: 21 March 2020

DOI: 10.1002/dad2.12011

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

COGNITIVE & BEHAVIORAL ASSESSMENT

Cognitive composites in AD trials? Drinking the Kool-Aid and paying the price?

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Schneider and Goldberg (this issue) review several composite measures proposed as end points/outcomes in future clinical trials in preclinical, prodromal, and mild Alzheimer's disease (AD). However, these authors also point out the many problems with creating such composites and why they are unlikely to succeed in these future trials. Although I agree with the critical analysis presented by these authors, I fear that they provide little direction for the next step in the evolution of cognitive and functional outcomes.

Over the past 10 years, I have served as a rater for many clinical trials in AD. In nearly every one of them, I have administered the same limited battery of screening, baseline, and follow-up measures: MMSE, ADAS-Cog, CDR, and an occasional smattering of random add-on cognitive and functional measures. Despite unprecedented growth in biomarkers and treatment mechanisms in AD, I have seen very little advancement in the cognitive and functional outcome measures for these trials. Pharmaceutical companies, who sponsor these trials, have drunk the Kool-Aid, such that these companies feel that all AD trials need these same core measures. And these decisions have been reinforced by the professionals who advise them. Such decisions leave little room for innovation, which is the lifeblood of science.

Instead of building more composites or better composites, I would argue that it is time to completely re-examine outcome measures in these trials and push for progress. I offer two examples of such "out of the box" thinking (one that is completely self-serving and one that is not).

Schneider and Goldberg argue that one of the problems with existing composites is that they lack alternate forms, so may be susceptible to practice effects in longitudinal studies. However, over the past 15 years, I have been studying the potential importance of practice effects as a unique cognitive variable. There is a growing body of research that failure to show the expected practice effect is a poor cognitive sign in individuals at risk for dementia.[1–4] Specifically, individuals who demonstrate smaller-than-expected improvements on repeat testing are more likely to have brain amyloid deposition,[5] smaller hippocampi,[6] brain hypometabolism,[7] worse cognitive trajectories,[8] and poorer response to interventions.[9] If these studies are correct, then why do we continue to measure memory with Logical Memory Story A or ADAS-Cog Word Recall or some other static test?

Although the *sine qua non* of functional assessment has been the CDR for the past 30 years, it may have limits when applied to the mildest phases of AD (e.g., preclinical and prodromal AD). As such, there is a need to develop measures of daily functioning that can sensitively identify changes in these relatively intact individuals. One example of this is the Naturalistic Action Test (NAT),[10] which is a performance-based tool that requires a participant to actually complete the steps in daily activities (e.g., making instant coffee, packing a school bag). Overt and subtle errors in these daily activities, which involve attention, memory, and executive skills, may be able to distinguish between intact, mild cognitive impairment, and demented individuals.[11,12] The development and refinement of such performance-based tasks, like the NAT, have the potential to employ more meaningful outcomes in future clinical trials and still be acceptable to the U.S. Food and Drug Administration (FDA).

In addition to using innovation to advance our methods for evaluating cognition and daily functioning, Schneider and Goldberg point out the significant amount of overlap among the existing composite measures. For example, nearly every composite reviewed employed a list learning measure, most used at least one measure of orientation, and Digit Symbol/Coding was present in most composites. However, the current composites seem flawed for a few reasons. First, this process of developing a composite outcome seems backwards, as the tests that are already available are combined to see what best relates to some other outcome measures. Scientifically, a prospective, empirically driven composite would seem more fruitful (even if it does involve a certain level of ratiocination). Second, multiple composites have redundant measures within them. For example, the composites of repeatably battery for the assessment of neuropsychological status (RBANS), preclinical Alzheimer cognitive composite (PACC),

dominantly inherited Alzheimer network trials unit (DIAN TU), Alzheimer's prevention initiative composite (API), and Z-scores of attention, verbal fluency and episodic memory for non-demented older adults (ZAVEN) use both list learning and story memory tests. Such decisions seem based more on conceptual reasoning than on empirical support. Third, why would we expect any composite to be much different from any other one? That is, if they all are built with the same components, then they all probably perform quite similarly (with the same limitations).

As we move toward the future of clinical trials in AD, I concur with Schneider and Goldberg, who suggest that existing composites do not appear to be direction that we should be heading, despite the FDA's willingness to consider them. Rather, it seems more worthwhile to spend our energies identifying (or developing) unique cognitive and functional assessments that can be used across the spectrum for preclinical, prodromal, and mild AD trials. If we fail to deviate from the current path, then we will likely be paying the price for this decision for the foreseeable future.

REFERENCES

1. Goldberg TE, Harvey PD, Wesnes KA, Snyder PJ, Schneider LS. Practice effects due to serial cognitive assessment: implications for preclinical Alzheimer's disease randomized controlled trials. *Alzheimer's & Dementia*. 2015;1(1):103-111.
2. Hassenstab J, Ruvolo D, Jasielec M, Xiong C, Grant E, Morris JC. Absence of practice effects in preclinical Alzheimer's disease. *Neuropsychology*. 2015;29(6):940-948.
3. Jacobs DM, Ard MC, Salmon DP, Galasko DR, Bondi MW, Edland SD. Potential implications of practice effects in Alzheimer's disease prevention trials. *Alzheimers Dement (N Y)*. 2017;3(4):531-535.
4. Machulda MM, Pankratz VS, Christianson TJ, et al. Practice effects and longitudinal cognitive change in normal aging vs. incident mild cognitive impairment and dementia in the Mayo Clinic Study of Aging. *Clin Neuropsychol*. 2014;27(8):1247-1264.
5. Duff K, Foster NL, Hoffman JM. Practice effects and amyloid deposition: preliminary data on a method for enriching samples in clinical trials. *Alzheimer Dis Assoc Disord*. 2014;28(3):247-252.
6. Duff K, Anderson JS, Mallik AK, et al. Short-term repeat cognitive testing and its relationship to hippocampal volumes in older adults. *J Clin Neurosci*. 2018;57:121-125.
7. Duff K, Horn KP, Foster NL, Hoffman JM. Short-Term Practice Effects and Brain Hypometabolism: preliminary Data from an FDG PET Study. *Arch Clin Neuropsychol*. 2015;30(3):264-270.
8. Duff K, Lyketsos CG, Beglinger LJ, et al. Practice effects predict cognitive outcome in amnestic mild cognitive impairment. *Am J Geriatr Psychiatry*. 2011;19(11):932-939.
9. Duff K, Beglinger LJ, Moser DJ, Schultz SK, Paulsen JS. Practice effects and outcome of cognitive training: preliminary evidence from a memory training course. *Am J Geriatr Psychiatry*. 2010;18(1):91.
10. Giovannetti T, Libon DJ, Hart T. Awareness of naturalistic action errors in dementia. *J Int Neuropsychol Soc*. 2002;8(5):633-644.
11. Giovannetti T, Bettcher BM, Brennan L, et al. Characterization of everyday functioning in mild cognitive impairment: a direct assessment approach. *Dement Geriatr Cogn Disord*. 2008;25(4):359-365.
12. Seligman SC, Giovannetti T, Sestito J, Libon DJ. A new approach to the characterization of subtle errors in everyday action: implications for mild cognitive impairment. *Clin Neuropsychol*. 2014;28(1):97-115.

How to cite this article: Duff K. Cognitive composites in AD trials? Drinking the Kool-Aid and paying the price?. *Alzheimer's Dement*. 2020;12:e12011.
https://doi.org/10.1002/dad2.12011