Received: 3 November 2019 | Accepted: 3 February 2020 | Published online: 13 April 2020

DOI: 10.1002/dad2.12009

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

COGNITIVE & BEHAVIORAL ASSESSMENT

Commentary: Composite cognitive and functional measures for early stage Alzheimer's disease trials

John E. Harrison[1,2,3]

[1]Metis Cognition Ltd, Park House, Kilmington Common, Wiltshire, UK

[2]Alzheimer Center, AU Medical Center, Amsterdam, The Netherlands

[3]Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

Correspondence
John E. Harrison, Principal Consultant, Metis Cognition Ltd., Park House, Kilmington Common, Wiltshire, BA12 6QY, UK.
Email: john@metiscog.com

Abstract

In this commentary I consider the issues raised in Schneider and Goldberg's review of composite cognitive and functional measures. I find much to agree with in their commentary and especially their concerns regarding satisfactory psychometric validation of composite measures. I endorse also their provision for analysis by cognitive domain, backed by the use of statistical methods for grouping test variables. The authors helpfully mention the possibility that treatment effects may be peculiar to specific domains of cognitive function. I develop this view and argue for exploratory studies of new therapeutic interventions to include broad assessments of the cognitive domains known to be compromised in early Alzheimer's disease. I suggest that the results of exploratory studies be used to help identify target domains for confirmatory studies. Finally, I note that computerized cognitive composite assessments have often been validated in the fashion that the authors recommend for composite measures.

1 | COMMENTARY

In this issue, Schneider and Goldberg ("the authors") offer us a timely and helpful view of the composite measures that have proliferated in the Alzheimer's disease (AD) field.[1] In their review, the authors consider 11 composite measures derived from an extant literature search. This is an entirely reasonable approach, but it is important to note that their search strategy did not identify established computerized assessments, such as the Cognitive Drug Research and CogState systems, the results from which are sometimes reported as composite scores.[2] Furthermore, the review excludes composites that are under development but which have not yet been reported in the context of clinical trial results. This includes the Cognitive Functional Composite (CFC) that has been validated as part of the Catch-Cog trial initiative.[3]

The authors offer a balanced and critical review and list a number of positive aspects to assessment by composite. They identify factors such as reduced impact of range restrictions, improved temporal reliability, and a solution to the issue of statistical multiplicity. They helpfully also identify some important possible challenges when using composite measures. The first issue they raise is whether human cognition can be usefully thought of as a single construct. The authors helpfully remind us that a wealth of neuropsychological, psychopharmacological, and experimental psychological evidence exists with which we can dissociate a variety of cognitive domains. Furthermore, they rightly point out that composite scores "might dilute a specific impairment or a treatment response to said cognitive impairment" (p.??). This is an excellent point and is why I have argued often and repeatedly for analysis by cognitive domain.[4-6] From my perspective, the challenge to adopting this approach has been a historic desire by sponsors to analyze the unitary construct "cognition." However, in the event of a positive effect on a global measure, there is often interest in seeking to determine which domains benefited from treatment. A good recent example of this has been investigations into the use of vortioxetine in patients with major depressive disorder.[7,8]

Global cognitive measures are most often the preferred approach for drug developers. However, it is my recent experience that sponsors are tending to a preference for "target engagement." Sometimes the target domain is suggested by the mechanism of the compound's pharmacological action. A second approach has been to test a range of cognitive domains to determine which domain, or domains, is impacted by treatment. A recent example of the latter approach has been Probiodrug's development program for their glutaminyl cyclase inhibitor PQ912.[9] However, there is further precedent from other earlier studies of compounds such as rilapladib (SB659032)[2] and the H3 receptor antagonist GSK239512.[10] This seems to me a principled approach to understanding treatment effects in exploratory development stages and then seeking to replicate the observed effect in confirmatory studies. A preference for testing by domain is commonly expressed by expert groups, including the European Task Force for Alzheimer's Disease and the Special Advisory Group for Clinical and Cognitive Outcomes of the EPAD initiative.[11,12] Note also that in other indications, such as cognitive impairment associated with schizophrenia, a domain-based approach has been widely accepted.[13]

A key question arising from the assessment of cognitive domains is the basis for combining tests into scientifically defendable constructs. Tests are often grouped according to our understanding and interpretation of the cognitive domains indexed by the paradigm employed. Thus visual and verbal memory measures are typically grouped as tests of episodic memory and classic simple and choice reaction time tasks as tests of attention, and so on. The authors suggest that such grouping exercises "should be backed by a factor analysis or structural equation modeling, not an assertion" (p.??). I concur strongly with their view and note that for the CFC and for most computerized testing systems this has been addressed.

Throughout the commentary, the authors note with regret that "Most composite reports have not been overly disciplined in presentation of important psychometric data" (p.??). They also helpfully list U.S. Food and Drug Administration (FDA) criteria covering reliability, construct validity, ability to detect change, and so on. Again I concur entirely with their view and have often made the same argument.[6,14] Often such data are available for individual tests contributing to composites. However, it is important to establish the psychometric characteristics of the composite and to check that individual test characteristics are preserved when used in concert. In their Table 2, the authors dichotomize the derivation of composites into those constructed from considerations of perceived need regarding cognitive domain coverage (rational) and those selected on the basis of sensitivity to change (sensitivity). My view is that sensitivity is a sensible selection approach, so long as key cognitive domains are covered. However, once the assessment measures are identified, their combined use must be validated in a study designed to determine key psychometric characteristics and a statistical justification for grouping tests into cognitive domains. Not unusually, individual cognitive tests are appropriated from clinical assessments, often because the paradigm has shown sensitivity to the presence of impairment. However, these measures are often not designed for longitudinal assessment and so are prone to repeated assessment effects, including improvement through practice. This is a key reason that assessment of temporal reliability, as well as the use of genuinely parallel alternate forms, is crucial. I note also that there has been consensus on these issues among key opinion leaders for more than two decades.[15]

The inclination to create novel assessments for indexing cognitive change is presumably driven by widespread dissatisfaction with the Alzheimerωs Disease Assessment Scale - Cognitive subscale (ADAS-Cog).[16-18] I share this dissatisfaction, but like the authors I am keen to ensure that new assessments meet current best practice with regard to reliability, validity (especially cognitive domain coverage), and sensitivity. I believe that the AD therapeutic development community would be best served by taking a more targeted approach to cognitive evaluation and that analysis by cognitive domain, rather than by global cognitive composite, will ultimately better inform our endeavors.

CONFLICTS OF INTEREST

Dr Harrison reports personal fees from the following organizations during the conduct of the study; AbbVie, Alkahest, AlzeCure, Amgen, Aptinyx, AstraZeneca, Athira, Axon Neuroscience, Axovant, Biogen, BlackthornRx, Boehringer Ingelheim, Cognition Therapeutics, Curasen, DeNDRoN, EIP Pharma, Eisai, Eli Lilly, GfHEU, Heptares, Johnson & Johnson, Kaasa Health, Lundbeck, Lysosome Therapeutics, Merck, Neurocog, Neurodyn, Neurotrack, Novartis, Nutricia, Probiodrug, Regeneron, Roche, Rodin Therapeutics, Sanofi, Servier, Signant Health, Takeda, vTv Pharma & Winterlight Labs. In addition, Dr Harrison has a patent Cognition training system pending with MyCognition.

REFERENCES

1. Schneider LS, Goldberg TE. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. Composite cognitive and functional measures for early stage Alzheimer's disease trials. *Alzheimers Dementia*.
2. Maher-Edwards G, De'Ath J, Barnett C, Lavrov A, Lockhart A. A 24-week study to evaluate the effect of rilapladib on cognition and cerebrospinal fluid biomarkers of Alzheimer's disease. *Alzheimers Dement*. 2015;65:131-140.
3. Jutten RJ, Harrison JE, de Jong F, et al. A composite measure of cognitive and functional progression in Alzheimer's disease: design of the Capturing Changes in Cognition study. *Alz Dement*. 2017;3(1):130-138.
4. Harrison JE, Hendrix S. The assessment of cognition in translational medicine: a contrast between the approaches used in Alzheimer's disease and Major Depressive Disorder. In: Nomikos G, Feltner D, eds. *Translational Medicine in CNS Drug Development Handbook of Behavioral Neuroscience*, vol. 29. Amsterdam: Elsevier; 2019:297-308.
5. Harrison JE, Maruff P. Measuring the mind: assessing cognitive change in clinical drug trials. *Expert Rev Clin Pharmacol*. 1(4):471-473.
6. Harrison JE. Measuring the mind: detecting cognitive deficits and measuring cognitive change in patients with depression. In: McIntyre RS, ed. *Cognitive Impairment in Major Depressive Disorder*. Cambridge: Cambridge University Press; 2016:229-241.
7. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharm*. 2014;17(10):1557-1567.
8. Harrison JE, Lophaven S, Olsen CK. Which cognitive domains are improved by treatment with vortioxetine? *Int J Neuropsychopharmacol*. 2016;19(10):pyw054.
9. Scheltens P, Hallikainen M, Grimmer T, et al. Safety, tolerability and efficacy of the glutaminyl-cyclase inhibitor PQ912 in Alzheimer's

disease: results of a randomized, double-blind, placebo-controlled phase 2a study. *Alzheimers Res Ther*. 2018;10(1):107.
10. Grove RA, Harrington CM, Mahler A, et al. A randomized, double-blind, placebo-controlled, 16-week study of the H3 receptor antagonist, GSK239512 as a monotherapy in subjects with mild-to-moderate Alzheimer's disease. *Curr Alz Res*. 2014;11:47-58.
11. Vellas B, Andrieu S, Sampaio C, Coley N, Wilcock G. Endpoints for trials in Alzheimer's disease: a European task force consensus. *Lancet Neurol*. 2008;7(5):436-450.
12. Ritchie K, Ropacki M, Albala B, et al. Recommended cognitive outcomes in pre-clinical Alzheimer's disease: consensus statement from the European Prevention of Alzheimer's Dementia (EPAD) Project. *Alz Dement*. 2016;13(2):186-195.
13. Vingerhoets WAM, Bloemen OJN, Bakker G, van Amelsvoort TAMJ. Pharmacological interventions for the MATRICS Cognitive Domains in Schizophrenia: what's the evidence? *Front Psychiat*. 2013;4:157.
14. Harrison JE, Lam RW, Baune BT, McIntyre RS. Selection of cognitive tests for trials of therapeutic agents. *Lancet Psychiat*. 2016;8(8):1-13.
15. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alz Dis Assoc Dis*. 1997;11(suppl 2):13-21.
16. Hobart J, Cano S, Posner H, et al. Putting the Alzheimer's cognitive test to the test I: traditional psychometric methods. *Alz Dement*. 2013;9(1 suppl):S4-S9.
17. Sevigny JJ, Peng Y, Liu L, Lines CR. Item analysis of ADAS-Cog: effect of baseline cognitive impairment in a clinical AD trial. *Am J Alz Dis Dement*. 2010;25:119-124.
18. Harrison JE. Cognition comes of age: comments on the new FDA draft guidance for early Alzheimer's disease. *Alz Res Ther*. 2018:10;61.

How to cite this article: Harrison JE. Commentary: Composite cognitive and functional measures for early stage Alzheimer's disease trials. *Alzheimer's Dement*. 2020;12:1–3.
https://doi.org/10.1002/dad2.12009