Detecting Pro-cognitive Effects in Clinical Drug Trials: Case Studies from Alzheimer's Disease

PEER REVIEWED

Problems with the Status Quo

There has been turmoil in the world of Alzheimer's disease (AD) clinical drug trials over the past couple of years. Not too long ago we believed we had a good handle on the pathology that underlies brain cell death in this devastating disease – and better yet, drugs that could remove the pathological hallmarks. As well as compounds intended to modify the course of the disease, we also had a crop of drugs that might offer symptomatic relief. Unfortunately the promise of these new compounds has not been realised and we have instead witnessed a succession of failures, of which Neurochem's 'Alzhemed', Lilly's 'Semagacestat' and Pfizer's 'Dimebon' have been just the most high profile examples. Alzheimer's disease remains a major area of unmet need, and there is still plenty of enthusiasm amongst drug developers to continue research in this indication. The failures of the past two years have focused attention on not just the disease mechanisms, but also the instruments used to measure drug effects, particularly with respect to the assessment of cognition, the hallmark deficit of AD.

For the past 20 years the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) has been a feature of almost all late-phase development trials, and often included in exploratory studies where the ambition has been to establish Proof of Concept (PoC). However, it has long been recognised that the ADAS-cog, like many of the tests borrowed from clinical psychology, is an imperfect means of measuring cognition in clinical drug trials (1). A key issue in this context is the instrument's tendency to confounding factors such as practice, familiarity and learning effects. Further, a lack of placebo decline, likely the result of practice, has long confounded our best intentions to test for beneficial drug effects. In spite of this, the drug development community has persevered with the ADAS-cog. In fairness the practice effect is not solely an issue for the ADAS-cog, but also for other measures used in AD trials, and more generally across central nervous system (CNS) drug research. Two reasons are usually proffered to account for continued use of the ADAS-cog. The first is a dogmatic belief that regulators require use of the ADAS-cog. However, recent statements from both the FDA and EMA confirm that it is not a requirement. Second, the ADAS-cog has a reputation of being a 'gold standard', largely, it would seem, based on the fact that marketing approval for many of the so far registered AD drugs was gained on the basis of significant differences between treatment and placebo patients on this measure. However, many recent study results have undermined the utility of this measure, and in the following section we will discuss its inadequacy with particular relevance to issues of patient capacity and compliance.

Issues of Patient Capacity and Compliance

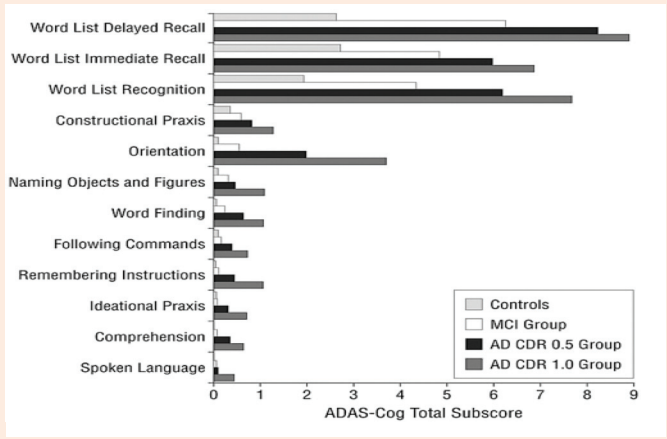
A key issue in the cognitive assessment of patients with Alzheimer's disease is the selection of appropriate measures with which to assess individuals at different stages of disease severity. Trials have routinely been stratified to focus on patients of different severity and the Mini-Mental State Examination (MMSE) is the most commonly employed staging instrument. The 0-30 point MMSE continuum is typically divided to yield mild (20-30), moderate (12-20) and severe (<12) groups and separate trials of i) mild-to-moderate and ii) severe stage patients have been commonplace. Common also is the selection of different cognitive tests, with the Severe Impairment Battery (SIB) being employed for use with severe patients. This is in recognition of the fact that they would find the measures employed in studies of mild-to-moderate patients so challenging that would likely perform at

'floor' levels. Interestingly this concern, and that of 'ceiling' effects, is also an issue with the use of the ADAS-cog in mild-to-moderate patients. Figure 1, reproduced from Grundman et al. (2), illustrates both of these phenomena. This figure shows that performance on verbal memory tests from the ADAS-cog is close to floor in the 'questionable dementia' (CDR=0.5) and Mild (CDR=1.0) AD groups. Ceiling effects are evident on many of the remaining subtests, typically those measuring praxis and language skills. Floor performance has also been seen on aspects of an alternative mild-to-moderate AD assessment, the Neuropsychological Test Battery (NTB), particularly on the delayed recall memory measures (3). Adoption of the NTB, coupled with the desire to employ all possible means of capturing cognitive effects, has led to AD trial protocols including a number of cognition assessments. The inclination to employ comprehensive cognitive measurement is understandable, but a legacy of this approach is that the time taken to administer the ADAS-cog, NTB and CDR can extend to more than three hours of assessment. This represents a considerable burden of testing. Levels of refusal to continue, and anecdotal accounts of fatigued and frustrated patients, suggest that for a significant number of trial participants such testing regimes are overly taxing. Little empirical evidence exists regarding the tolerance levels for testing of patients with AD. However, it seems likely that tolerance will be idiosyncratic and probably linked to disease severity. Our own inclination is to aim for a maximum total testing time per patient of approximately 30 minutes per visit.

In spite of the traditional scale deficiencies, versions of the ADAS-cog and NTB both routinely feature in studies of patients in the mild-to-moderate stages of AD. However, a recently published study has highlighted the virtues of what can be achieved with what we would view as more appropriate test use. Scheltens et al. (4) recently published the results of a 24-week trial of the medical food 'Souvenaid' on mild stage AD patient cognitive function. The sponsor of this trial selected a version of the NTB featuring tests of verbal memory and executive function (EF), but opted to analyse data for these two cognitive domains separately. Combined performance on two verbal memory tests drawn from the NTB was specified as the primary efficacy measure, and four tests of EF were combined to yield a secondary efficacy measure. The results of this study yielded a significant benefit for memory of Souvenaid use after 24 weeks. The decision to analyse treatment effects on memory and EF separately was in part based on previous evidence showing a pharmacological dissociation between these two cognitive domains. A previous study of the active immunotherapy AN1792-201 yielded significant effects on the statistically-derived memory factor, but not on the EF factor (5). In contrast, studies of the compound PBT2 have witnessed significant effects on the EF factor, but only trends on the memory score (6). As the effect of Souvenaid had previously been witnessed only on tests of verbal memory, it was decided to look for primary efficacy solely in this domain of function.

The above approach has in our view much to recommend it. As discussed, the inclination of many sponsors has been to employ the ADAS-cog based solely on a perception that from a regulatory perspective this measure is the preferred

Figure 1: Performance of Control, MCI and AD patients on ADAS-cog subtests (2)
This figure illustrates that compared to control study participants, the performance of individuals with Mild Cognitive Impairment (MCI) and patients with Alzheimer's disease (AD) on Word List tests and, to some extent, Orientation, is impaired. However, performance on the remaining subtests is at, or close to, ceiling.



cognition measure. However, representatives of the FDA have stated publicly that they have no particular expectation that trial sponsors will necessarily employ the ADAS-cog (7). The EMA have pointed out that there is no 'reference technique' (8) and have added the NTB as a candidate primary efficacy measure in recent revised guidelines for dementia drug development. Furthermore, a section of these guidelines reveals that cognitive domains such as attention and psychomotor speed are specified for investigation. Neither of these functions is indexed by the NTB or by the ADAS-cog, and so new measures will need to be employed to meet these requirements.

Many sponsors are seeking to treat patients as early as the prodromal phase of the disease, with the intention of halting cognitive decline and preventing conversion to a diagnosis of AD. Expert groups such as the European Task Force for Alzheimer's disease have focused on the need to measure cognitive function in domains such as episodic memory, working memory and executive function (9) in these early stage patients, but have made few specific recommendations concerning how appropriate tests should be selected. Our inclination is to be guided by best practice advice offered by Ferris et al. (10) and Harrison & Maruff (11), both of whom stress the need for tests to be sensitive, valid and reliable.

Next Steps

New challenges in dementia drug development will require the use of appropriate cognitive measures. Much can be learned from the extensive neuropsychological research that has been conducted in patients with Alzheimer's disease. However, in the context of clinical trial work, with the need for repeated patient assessment, the best measures of cognitive change may not necessarily come from the traditional canon of psychological testing. Instead the emphasis should be on the adoption of stable and validated measures of cognitive change, which can ideally also be used to address the issue of clinical relevance.

References

1. *Wesnes, K. & Harrison, J.E. The evaluation of cognitive function in the dementias: methodological and regulatory*

considerations. Dial. Clin Neurosci. 5, 77–88 (2003).

2. *Grundman, M.P.H., Petersen, R.C., Ferris, S.H. and the Alzheimer's Disease Cooperative Study. Mild cognitive impairment can be distinguished from Alzheimer's disease and normal aging for clinical trials. Arch Neurol. 61, 59-66 (2004).*
3. *Harrison, J. & Caveney, A. 10 years of the Neuropsychological Test Battery (NTB). PRO Newsletter 45, 21-4 (2011).*
4. *Scheltens, P., Twisk, J., Blesa, R., Scarpini, E., Von Arnim, C., Bongers, A., Harrison, J., Swinkels, S., De Deyn, P., Wieggers, R., Vellas, B., Kamphuis, P. Souvenaid improves memory in drug-naïve patients with mild Alzheimer's disease: Results from a randomized, controlled, double-blind study (Souvenir II). J Nutr Health Aging, 15(1), S13 (2011).*
5. *Gilman, S., Koller, M., Black, R.S. and the AN1792(QS-21)-201 Study Team. Clinical effects of A-beta immunization (AN1792) in patients with AD in an interrupted trial. Neurol, 64, 1553-1562 (2005).*
6. *Lannfelt, L., Blennow, K., Zetterberg, H., Batsman, S., Ames, D., Harrison, J., Master, C.L., Targum, S., Bush, A.I., Murdoch, S., Wilson, J. & Ritchie, C.W. Safety, efficacy, and biomarker findings of PBT2 in targeting A as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol, 7(9), 779-786 (2008).*
7. *Katz, R. Presentation at Alzheimer's Association Research Roundtable, Washington, April, 2008.*
8. *www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003562.pdf, visited on 4th November, 2011.*
9. *Vellas, B., Andrieu, S., Sampaio, C., Coley, N., Wilcock, G. and the European Task Force Group. Endpoints for trials in Alzheimer's disease. Lancet Neurol. 7, 436-50 (2008).*
10. *Ferris, S. et al. Objective psychometric tests in clinical trials of dementia drugs. Position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. Alz Dis Assoc Disord.11(S3), 34-8 (1997).*
11. *Harrison, J. & Maruff, P. Measuring the mind: assessing cognitive change in clinical drug trials. Exp Rev Clin Pharmacol. 1(4), 471-473 (2008).*

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