Assessing Change in Cognitive Function in Dementia: The Relative Utilities of the Alzheimer’s Disease Assessment Scale – Cognitive Subscale and the Cognitive Drug Research System

Keith A. Wesnes

Cognitive Drug Research Ltd., Goring-on-Thames, and Human Cognitive Neuroscience Unit, Northumbria University, Newcastle upon Tyne, UK; Brain Sciences Institute, Swinburne University, Hawthorn, Vic., Australia

Abstract

This paper considers the suitability of the Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-cog) as the gold standard in registration trials of treatments for Alzheimer’s disease. Working groups have recommended replacing the ADAS-cog if suitable automated alternatives can be found. This paper makes the case for the Cognitive Drug Research (CDR) computerised cognitive assessment system, as an example of a suitable instrument to replace the ADAS-cog. The CDR system has been widely used in dementia work for 20 years and shows good correlations to the ADAS-cog, while additionally assessing the domains of attention, working memory, information processing and retrieval speed of information held in memory. The utility of the system in evaluating and differentiating the major dementias will be described, as well as its ability to track deterioration over time. Its validation as a core measure of cognitive dysfunction in the dementias will be described, as will work showing that various CDR measures relate closely to activities of daily living. The sensitivity of the CDR system to anticholinesterases will be described in Alzheimer’s disease, dementia with Lewy bodies and Parkinson’s dementia. Finally, the CDR system has a large normative database which allows treatment effects in dementia to be put into an unambiguous clinical perspective.

While the Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-cog) is widely accepted as the gold standard in registration trials of treatments for Alzheimer’s disease (AD), there is no regulatory mandate for this. The strengths of the ADAS-cog are its history of use and ability to assess important aspects of cognition such as memory. However, these are overshadowed by its numerous weaknesses [1], which include: the subjective nature of several of the assessments; the fact that it fails to assess several core deficits of AD including attention, information processing and speed of retrieval of information held in memory; the absence of formal parallel forms; the time taken to administer it; the specialist training required for administrators; its relative insensitivity, and its failure in many recent trials to reliably identify...
declines over 6-month treatment periods in placebo-treated patients, which makes it unsuitable for drugs targeted at basic disease-modifying mechanisms.

In 1997, the International Working Group on Harmonisation of Dementia Drug Guidelines published a position paper on objective testing in dementia trials [2]. The group recommended that besides memory, domains which should be assessed in future trials should include attention and information processing. Further, they recommended that computerised procedures should be used together with the established procedures in the field (e.g. the ADAS-cog) so that the comparable utility and sensitivity of the two types of testing could be identified. If clear advantages of computerised procedures were demonstrated, computerised procedures could supersede existing methods.

The Cognitive Drug Research (CDR) system is a laptop-based set of cognitive tests which has been in use in worldwide clinical trials for over 20 years. As recommended by Ferris et al. [2], the verbal or numeric test stimuli are presented on the computer screen in large clear fonts, and the patient does not respond via the keyboard, instead responses are made via a response box containing a NO and a YES button. The system comprises tests of attention (simple and choice reaction time, digit vigilance), working memory (spatial and articulatory) and episodic memory (word recall and recognition, picture recognition). The administrator reads preset instructions for each task to the patient, and only initiates the test when sure the patient is ready and understands what to do. The system automatically selects the appropriate parallel forms of the tests each time the patient is assessed, and the data are recorded automatically on encrypted files. The CDR system has been extensively validated in the dementias [3]. It has shown good test-retest reliability, excellent criterion validity, discriminant validity and construct validity [3, 4]. The establishment of the construct validity of the system identified five core domains of cognitive function that the system assesses – the abilities to focus and sustain attention, hold information in working memory and episodic memory, and the time taken to retrieve information from memory. It can identify significant cognitive deficits in untreated patients over 6 months in core domains of attention and speed of retrieval of information held in memory, and over only 3 months in the ability to store, retain and retrieve information in verbal and pictorial episodic secondary memory [5]. It can be administered by non-specialists, has more than 20 parallel forms, over 45 language versions, takes only 25–30 min to complete and is compliant with regulatory requirements such as 21 CFR Part 11. The system thus has the utility the ADAS-cog lacks to reliably track performance changes over hours, days or weeks. The domain scores of the system have been validated by factor analysis [4] and have been shown to correlate with cerebrospinal fluid levels of tau and Aβ42. Importantly, attention measures from the CDR system have been demonstrated to have strong predictability for the ability to conduct the activities of daily living in demented patients, particularly in comparison to the ADAS-cog [6]. Further, the ability of the system to measure separate cognitive domains gives it two important advantages over the ADAS-cog. Firstly, it has enabled the CDR system to demonstrate differences in the cognitive profile of impairments in various dementias including AD, vascular dementia, dementia with Lewy bodies, Parkinson’s dementia and Huntington’s disease [7–9]. Secondly, it enables treatment-induced benefits to particular domains, e.g. attention, to be identified. Another advantage of a computerised system is the enormous benefits to data management, particularly in large international trials. A disadvantage of any computerised system in contrast to the ADAS-cog is that clinicians are very familiar with the ADAS and are often skeptical about automated tests.

The sensitivity of the CDR system to improvements in cognitive function has been demonstrated in AD patients with donepezil, valnacrine, galantamine, tacrine and S-12024 [10]. In one trial, benefits with galantamine started to appear after 4 weeks [11]. In both dementia with Lewy bodies [4, 12] and Parkinson’s dementia [13, 14], improvements have been seen with both rivastigmine and donepezil [15]. The use of the CDR system in pivotal trials in dementia with Lewy bodies and Parkinson’s dementia has drawn favourable editorial comments in both the Lancet [16] and New England Journal of Medicine [17].

In terms of establishing effect sizes and clinical relevance, the CDR system has the huge advantage over the ADAS-cog of having a large normative database of over 6,000 healthy volunteers from 18 to 87 years of age. It is thus possible to identify the actual magnitude of cognitive impairment in patients prior to treatment, and thus to determine how much patients are moved by treatment towards being normal for their age [10]. Thus in AD, 12 weeks’ treatment with galantamine has shown the ability to move the patients 30% closer towards being normal for their age [11]. In dementia with Lewy bodies, rivastigmine moved the patients approximately 50% towards being normal for their age on a core measure of attention [4], while in Parkinson’s dementia, rivastigmine moved...
Assessing Change in Cognitive Function in Dementia

The CDR system thus has the utility, reliability and practicality to be included in any trial design in the dementias. Its sensitivity in relatively small trials makes it extremely useful in phase II trials and of course in pivotal trials. Finally, its ability to predict the activities of daily living and the opportunity to fully identify the clinical benefit of treatment by determining exactly how much patients are moved towards being normal for their age makes it the natural successor to the ADAS-cog. It is now being included in a range of high-profile trials, particularly those with nicotinic agonists, and these are expected to confirm its suitability as a primary outcome measure in dementia research.

References