Target Symptoms and Outcome Measures: Cognition

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ABSTRACT: The Cognitive section of the Alzheimer's Disease Assessment Scale (ADAS-Cog) remains the most widely used cognitive measure in dementia trials although it does not assess attention, executive function, or agnosia. Designed for use in Alzheimer's disease (AD), it may not be ideal in assessing patients with other diagnoses. The ADAS-Cog differentiates between AD patients, patients with Mild Cognitive Impairment, and normal controls. It has been used in trials of drugs for vascular and mixed dementia and dementia with Lewy bodies. It is not clear that the ADAS-Cog is adequate for assessing cognition in frontotemporal dementia. Well-validated aphasia batteries, such as the Western Aphasia Battery, can be used to assess language. Brief tests of frontal function such as the Frontal Assessment Battery or the Executive Interview might be useful additions in frontotemporal dementia trials. The most widely used assessment tool for patients with advanced dementia is the Severe Impairment Battery. The domains tested are analogous to those assessed by the ADAS-Cog. The Mini-Mental State Exam and the Modified Mini-Mental State Examination are useful in stratifying patients for trial entry. Cognitive measures better tailored to the diseases in question are needed for non-Alzheimer dementias.

RÉSUMÉ: Symptômes cibles et critères d'évaluation de la cognition. La section sur la cognition de l'Alzheimer's Disease Assessment Scale (ADAS-Cog) demeure la mesure cognitive la plus utilisée dans les essais cliniques sur la démence, même si elle n'évalue pas l'attention, les fonctions exécutives ou l'agnosie. Cette échelle a été conçue pour être utilisée dans la maladie d'Alzheimer et n'est peut-être pas idéale pour évaluer les patients qui sont atteints d'autres pathologies. L'ADAS-Cog différencie les patients atteints de MA des patients ayant une atteinte cognitive légère et des témoins normaux. Elle a été utilisée dans les essais cliniques portant sur les démences vasculaires et mixtes et la démence à corps de Lewy. Il n'est pas certain que l'ADAS-Cog soit adéquat pour évaluer la cognition dans la démence fronto-temporale. Des batteries bien validées pour évaluer l'aphasie comme la Western Aphasia Battery peuvent être utilisées pour évaluer le langage. Des tests brefs de la fonction frontale comme la batterie d'évaluation frontale ou l'Executive Interview peuvent être ajoutés avec profit dans les études sur la démence fronto-temporale. L'outil le plus utilisé chez les patients qui ont une démence sévère est la Severe Impairment Battery. Les domaines évalués sont analogues à ceux qui sont évalués par l'ADAS-Cog. Le Mini-Mental State Exam et le Mini-Mental State Examination sont utiles pour stratifier les patients au début des études. Des mesures cognitives qui sont mieux adaptées aux maladies en question devront être développées pour les démences autres que la MA.

Impairment of cognition is an important deficit in dementia. Although behavioral and other problems may dominate in later stages of the illness, cognitive symptoms predominate in most patients with early dementia. Thus, treatments that alleviate, retard, reverse, or prevent cognitive decline are very much needed. Regulatory guidelines in several countries mandate an objective assessment of cognition as a primary outcome measure in antidementia drug trials.[1,2] Controversy over the utility of approved dementia therapies[3-5] highlights the need for measures of cognition that: 1. Are ecologically valid and have high face validity. 2. Can distinguish affected patients from normal controls. 3. Can assess a range of clinically relevant cognitive abilities. 4. Are sensitive to clinically relevant changes in cognitive abilities due to disease progression or to drug-induced improvement across a spectrum of dementing illnesses and disease severities. 5. Have high inter-rater and test-retest reliability. 6. Are convenient and timely to administer. 7. Can be used to assess patients from various linguistic and cultural backgrounds.

The Cognitive section of the Alzheimer's Disease Assessment Scale (ADAS-Cog)[6,7] remains the most widely used instrument for measuring cognitive deficits in dementia drug trials. Unlike

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some scales that have been adapted to the task, the ADAS was originally conceived as a tool to measure treatment efficacy. The ADAS-Cog is an 11 item test scored out of 70, higher scores indicating more severe impairment. It takes 20 to 50 minutes to administer. Memory, orientation, language, construction, and praxis are assessed. Attention, executive function, and agnosia are not specifically addressed. Designed for use in Alzheimer's disease, the scale may not be ideal in assessing patients with other diagnoses such as frontotemporal dementia. The ADAS-Cog has been translated into several languages and appears to give quite comparable results in a number of languages.[8]

The ADAS-Cog has been shown to be useful in differentiating patients with Alzheimer's disease (AD) from normal control subjects[7] and in distinguishing between patients with different levels of dementia severity.[9,10] Inter-rater reliability is good with reliability coefficients for individual items on the ADAS reported to range from 0.669 to 1.0.[11] On the ADAS-Cog portion of the battery, the inter-rater reliability coefficient was 0.989 and the test-retest reliability coefficient 0.915.[11] In the same report, a small number of patients with Alzheimer's disease scored significantly higher (i.e. worse) on the ADAS-Cog when re-tested at 12 and 18 months whereas the performance of normal controls did not change.

Doraiswamy et al[12,13] found that baseline ADAS-Cog score was inversely correlated with level of education in Alzheimer's drug study participants. It has been estimated that patients with AD worsen by about eight points annually on the ADAS-Cog[14] but the rate of decline is not linear across disease severity. Floor and ceiling effects are important. For example, in a study of 151 patients with Alzheimer's disease of varying severities, Schmeidler et al[15] found that patients with moderate or severe AD deteriorated significantly more on the ADAS-Cog over 12 months than did patients with mild or very severe disease. Whether this phenomenon reflects the mode of progression of the disease itself or is a limitation of the ADAS-Cog, it needs to be taken into consideration in study design. Doraiswamy et al[16] also found that in a study of 26 weeks duration, probably approaching the minimum study length expected to demonstrate significant worsening in ADAS-Cog scores,[17] patients with moderate dementia had significantly greater ADAS-Cog deterioration than did those with mild disease. These investigators also pointed out that, in a study as short as six months, measurement error contributes substantially to the variance seen in ADAS-Cog scores. This makes the use of this tool problematic in brief trials.

Since several potentially relevant areas of cognition such as attention, concentration, working memory, executive function, and agnosia are not measured well by the ADAS-Cog, Mohs et al[18] investigated some possible additions and found that a letter and digit cancellation task was sensitive across a wide range of dementia severities. A word learning task with delayed recall and a maze task were impaired even in those with mild AD and thus may be useful additions in the study of patients with early dementia or Mild Cognitive Impairment (MCI).

The ADAS-Cog has also been used successfully to differentiate between patients with Alzheimer's disease, patients with MCI and normal aged controls.[19] It was also used in a recent study of donepezil for MCI[20] although other instruments such as

the Montreal Cognitive Assessment[21] have also been developed specifically for use in MCI and have been shown to have high specificity and sensitivity. Although the ADAS-Cog was developed to study patients with Alzheimer's disease, it has been used in trials of drugs for vascular dementia as well as mixed Alzheimer's/ vascular dementia.[22-24] As there are different subtypes of vascular dementia with different patterns of cognitive impairment,[25] a group of patients with vascular dementia is likely to be even more heterogeneous cognitively than a population with Alzheimer's disease. Vascular dementia is also apt to decline in a less linear fashion than Alzheimer's disease does. Since there are differences between the profile of cognitive deficits seen in AD and vascular dementia,[26,27] instruments that test attention, concentration, working memory, and executive function might be added to the ADAS-Cog for use in vascular dementia.

Dementia with Lewy bodies (DLB) is clinically differentiated from AD more by history and general neurological examination than by cognitive differences. However, it has been reported that patients with DLB may perform more poorly on visual memory, attentional, visuoperceptive and visuoconstructive tasks as well as on tests of reaction time.[28-33] The ADAS-Cog has also been used to assess response to medication in patients with DLB[34] and in patients with Parkinson's disease and dementia.[35]

The pattern of cognitive impairment seen in frontotemporal dementia (FTD) is quite distinct from that seen in Alzheimer's disease. Patients with FTD may have very prominent language impairment and difficulty with word list generation and tests of executive function while performing better than AD patients on tests of memory and visuospatial abilities.[35-37] However, a recent study strongly suggests that behavioral tests are more useful than cognitive tests in distinguishing between FTD and AD.[38] It is not at all clear that the ADAS-Cog would be an adequate instrument to fully capture cognitive decline or improvement in an FTD drug study. There are a number of well-validated aphasia batteries that can be used to assess language impairment.[39] One of these, such as the Western Aphasia Battery,[40] might prove invaluable in following patients with progressive nonfluent aphasia or semantic dementia. Brief tests of frontal function such as the Frontal Assessment Battery[41,42] or the Executive Interview (EXIT25)[43,44] might be considered as additions to the ADAS-Cog in treatment efficacy trials in frontotemporal dementia. Each has been shown to be valid in differentiating between AD and FTD[42,43,45-47] but this is certainly an area that requires further development.

The floor effect of the ADAS-Cog has resulted in adoption of other tests that can measure cognitive change in patients with more advanced dementia. The most widely used assessment tool for patients with advanced dementia is the Severe Impairment Battery (SIB).[48,49] The SIB takes about 20 minutes to administer. It consists of 40 simple one-step commands with gestural cues (e.g., "Please sit here.") and provides a score out of 100. Subtests examine attention, orientation, language, memory, visuospatial ability, and construction. One advantage of the SIB in providing consistency in dementia studies across various disease severities is that the domains tested are analogous to those assessed by the ADAS-Cog. The SIB appears to be reliable and valid and it has been shown to be a useful tool in following deterioration in severe dementia.[50,51] It has been used

successfully in drug studies for patients with moderate to severe dementia.[52-54]

The Mini-Mental State Exam (MMSE)[55] is a 5 to 15 minute screening test of cognition that briefly assesses orientation, memory, attention, naming, comprehension, and construction. It warrants mention in any discussion of cognitive assessment of dementia because of its ubiquity and familiarity as a clinical screening instrument for dementia. The MMSE provides a score out of 30 with lower scores indicating more severe impairment. Although it is often used to classify severity of dementia, a ceiling effect in very mildly impaired patients and a floor effect in those with severe dementia are limiting factors.[56,57] A typical annual rate of change in Alzheimer's disease is about three points but this varies across the time course of the illness.[58-60] Scores are affected by age and level of education.[61] The Modified Mini-Mental State Examination (3MS),[62] developed in an attempt to overcome some of the shortcomings of the MMSE, added four items and introduced a graded scoring system to give scores out of 100. The 3MS assesses word fluency, abstraction, simple naming, and the effect of cuing. Normative data are available.[63,64] High inter-rater variability makes use of the 3MS as an outcome measure problematic in drug studies.[65] Although the MMSE has been included as an outcome measure in some dementia drug trials[4,66,67] its main use in pharmaceutical trials is likely to continue to be as a criterion for patient inclusion in trials.

New tools such as computerized assessments hold promise for evaluation of patients with MCI[68] and dementia.[69]

The ADAS-Cog remains the most widely-used cognitive outcome measure in dementia trials and it is likely to remain so, particularly for patients with Alzheimer's disease, largely due to long experience with its use for this purpose. The SIB will continue to prove useful in the study of patients with more advanced dementia. The MMSE and 3MS remain useful for stratification of patients for entry into trials. However, measures of cognition better tailored to the diseases in question will be required for the development of treatments for non-Alzheimer dementias. The ADAS-Cog with some added items would be useful in assessing patients with vascular disease. The ADAS-Cog seems a reasonable tool for measuring treatment efficacy in DLB but a tool better suited to the task will be needed to study patients with FTD.

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