REVIEW ARTICLE

# PROGRESS IN CLINICAL NEUROSCIENCES: Cognitive Markers of Progression in Alzheimer's Disease

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**ABSTRACT:** The objective of this review is to summarize the literature on Alzheimer's disease progression utilizing cognitive batteries to track change over time. Studies published in English and obtained through PubMed searches (1983-2004) were included i) if they had a longitudinal design and followed probable Alzheimer's patients diagnosed by National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association or Diagnostic and Statistical Manual III/IV criteria, and ii) if the techniques used for serial assessment were well-established in terms of validity and reliability. Longitudinal studies examining Alzheimer's disease progression report highly variable annual rates of change in decline rate. It remains unclear if this reflects disease subgroups or stage-related rate of decline. In conclusion a combination of stage-appropriate cognitive tests such as the Mattis Dementia Rating Scale and the Severe Impairment Battery, along with appropriate statistical methods to account for individual variability in decline rates, can capture the progression of Alzheimer disease and may be useful in further investigation.

**RÉSUMÉ: Marqueurs cognitifs de la progression de la maladie d'Alzheimer.** Cette revue constitue un sommaire de la littérature sur l'utilisation de batteries de tests cognitifs pour suivre la progression de la maladie d'Alzheimer (MA). Les études publiées en anglais ont été identifiées par une recherche PubMed (1983-2004). Elles étaient incluses s'il s'agissait d'études longitudinales sur des patients atteints de MA probable, diagnostiquée selon les critères du National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association ou du Manuel diagnostique et statistique des maladies mentales III/IV; et si la validité et la fiabilité des techniques utilisées pour les évaluations successives étaient bien établies. Les études longitudinales sur la progression de la MA rapportent des taux annuels de progression très variables. Il n'est pas clair si cette observation est attribuable à l'évolution de la maladie chez des sous-groupes de patients ou à des taux de déclin en relation avec les stades de la maladie. ***Conclusions:*** Nous suggérons qu'une combinaison de tests cognitifs appropriés à différents stades de la maladie tels le Mattis Dementia Rating Scale et le Severe Impairment Battery, ainsi que des méthodes statistiques appropriées tenant compte de la variabilité individuelle du taux de déclin puissent évaluer la progression de la MA et pourraient être utiles dans les études futures.

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Progressive cognitive deterioration characterizes Alzheimer's disease (AD); but longitudinal studies following AD patients over time have revealed the complex nature and heterogeneity of AD disease progression. There are standardized neurological and neuropsychological criteria that help to diagnose probable AD[1-4] and neuroimaging tests that help to support the diagnosis[5-7] but there is no consensus on the best way to follow AD patients over time. A spectrum of cognitive tests, functional and behavioural scales and, more recently, neuroimaging techniques and biochemical markers, have been used by clinical investigators as markers of progression. This diversity has made it difficult to demonstrate consistent relationships between clinical characteristics and rate of progression and also to know which single measure or combination of measures is best to monitor individual patients. Previous reviews have compared progression measures[8-12] but the increased availability of longitudinal studies and advances in technical methods warrant summarizing the

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present literature to define what is known about AD progression, what the various methodological issues are[9,13] and how this knowledge should direct future research. In this review, the cognitive assessment tools that have been used to track change over time in AD are critically evaluated.

Accurately following the course of AD has become a clinical necessity not only because of an ever-increasing AD disease prevalence, now estimated to be 6% of the population over the age of 65, and 25% over the age of 85 in Canada[14] but also because of the advent of clinically available therapeutic interventions.[15,16] Understanding natural disease progression is imperative to determine treatment efficacy both in clinical treatment trials and within individual patients. Accurately defining subgroups or clinical disease stages that may differ in rate of progression, presumably reflecting different stages of expression of Alzheimer neuropathology, may be useful in predicting therapeutic response. A better understanding may also identify prognostic indicators that would provide valuable information for families and services managing AD patients.

This review of the current knowledge of AD progression assesses the clinical utility of cognitive testing batteries as markers of AD disease progression. Data on functional and behavioural scales are not included since these have been less well-studied.

## Pathophysiology of AD Progression

The hallmark histopathological findings in AD include amyloid plaques, neurofibrillary tangles derived from abnormally phosphorylated tau protein, loss of neurons and synapses, and local inflammation.[17,18] In antemortem studies, Braak and Braak have identified six stages of increasingly severe cortical destruction that exhibit a typical topographic progression through the brain based on identification of neurofibrillary tangles.[19-22] Prospective clinical-anatomical studies have demonstrated a linear correlation between the six stages of brain damage and cognitive decline.[23]

Studies of the neurochemistry of AD, using necropsy and receptor imaging, have established a number of neurotransmitter deficiencies and system dysfunction. However, it remains unclear if involvement of these systems arises as disease progresses into more brain regions or if involvement of different systems classifies pathological subtypes of AD.[24,25] Deficient cholinergic function is an invariant finding in autopsy studies[26,27] and is detectable by *in vivo* receptor imaging.[17,28-30] It has become a target for therapeutic intervention with some success.[15,16] Knowledge of these structural and biochemical deficiencies in AD and previously known brain-behaviour relationships provide a context for designing measures to monitor disease progression.

## Studies of Cognitive Progression

### Methodological Inclusion Criteria

The diverse methodological approaches to investigation of AD progression with respect to study design, patient selection, and outcome measures, have made it difficult to come to a general understanding of disease progression. For this reason, available literature was screened according to preset, minimal methodological requirements that included 1) use of accepted diagnostic criteria, 2) longitudinal design and 3) use of validated, reliable cognitive outcome measures.

#### *Use of accepted diagnostic criteria*

The widely accepted National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for the diagnosis of AD[1] have demonstrated good positive predictive value of 80-85% and reasonable intra- and inter-rater reliability,[31] but even when these criteria are used, subjects with other causes of dementia may be included in AD investigations.[32-34] This diagnostic uncertainty brings inherent variability to both patient selection and study outcome. The clinical diagnosis of AD can only be confirmed by biopsy (which is seldom warranted)[35] or postmortem, but following an AD cohort to this end requires funding and compliance over many years, a feat that has been accomplished in only a few series.[36,37] The reliability and validity of the NINCDS/ADRDA criteria were investigated using a computerized "dementia diagnosis system". The use of the computerized system significantly increased the specificity of the NINCDS/ADRDA diagnoses, which were shown to have moderate inter-rater reliability. The Diagnostic and Statistical Manual (DSM)-IV criteria had good validity for AD when compared with postmortem confirmation and also showed good inter-rater reliability. The results of this study showed that the forced use of decision trees through a computerized system enhanced the accuracy of the clinical diagnoses of dementia.[38] The pragmatic alternative and an inclusion criterion in this review was to ensure patients meet accepted diagnostic criteria for probable AD; therefore studies published in English and obtained through Pubmed searches meeting either the NINCDS/ADRDA or Diagnostic and Statistical Manual III/IV criteria were used for inclusion in this study.

#### *Longitudinal design*

Many descriptions of AD progression have been extrapolated from cross-sectional studies.[39-42] These studies often assume that mild dementia is equivalent to early, moderate to mid-stage and severe to long duration of disease. This assumption has not held true in longitudinal studies, in which some patients followed over long periods remain mildly demented.[36,43-45] A cross-sectional study design can also falsely classify factors as predictors of advancing disease when they are themselves actually measures of disease severity.[46] Longitudinal studies, on the other hand, offer particular challenges including nonrandom dropout, unequal follow-up times, correlated errors with repeated measure and other difficulties particularly with multivariate designs.[13,47,48] Nevertheless, a longitudinal design remains the only reliable method of clinically evaluating natural AD progression, and was the other major inclusion criterion for this review.

#### *Use of validated, reliable cognitive outcome measures to assess rate of change*

Within longitudinal studies, diversity in chosen endpoints has led to inconsistency of reported or inferred results. Some have included functionally discrete endpoints such as death, institutionalization, and urinary incontinence,[49-53] while others

use cognitive decline or cognitive test endpoints. Functional outcomes and scales are usually clinically relevant, but they can be influenced by many other factors such as social support or co-morbidity obscuring the true pathological process of AD. For this reason, recent studies and this review report annual rates of change (ARC) only of mental status evaluations, which is one way of gauging disease progression that is more specific and less variable as a measure of disease deterioration than clinical endpoints. This ARC value is most often calculated by dividing the difference of a specific test measure at two different times by the time interval between the testing points. Although this calculation standardizes measured values with variable follow-up, it also assumes linear change over the time intervals. This assumption, as we describe, may be stage dependent and may not be true for long intervals. More recent statistical approaches, for example, regression by least squares, have been used to address nonlinear change.[13] The sensitivity of a test measure to detect change over time is also a function of the range of the test measure. For example, some test measures may have floor effects in advanced stages of disease. In such cases, the ARC would actually reflect the limitation of the test measure rather than true AD progression.

Global rating systems such as the Clinical Dementia Rating (CDR)[54,55] and the Global Deterioration Scale[56] that have been used as endpoints in the past are not included in this review. Neither measure can be converted to ARC because they are non-parametric grading scales making them difficult to compare and analyze in longitudinal studies, although the sum of boxes on the CDR has made this measure more amenable to the study of longitudinal change.[57]

It is important to note that cognition alone provides only a partial insight into the full spectrum of changes that occur over time in AD. Some patients can have significant decline in day-to-day functional abilities that are not demonstrated on psychometric instruments, especially those that are relatively insensitive to executive functioning such as the Mini-Mental Status Examination (MMSE). Conversely patients with language loss may decline markedly on their cognitive tests but continue to do well in self-care activities. Nevertheless, cognitive functioning is a key domain assessed to diagnose dementia and monitor progression over time. A full understanding of decline over time must also include functional, behavioural and global outcomes. The purpose of this review, however, was to focus on changes in cognitive batteries commonly used to measure progression in AD.

## Cognitive Markers

Cognitive impairment is a cardinal clinical feature of AD, and since it is directly measurable by testing the patient, it could potentially provide an accurate index of the presence and severity of dementia. However, several important methodological issues raise questions about utilizing cognition to study AD progression. Even though a number of standardized mental status examinations have been developed, which have proven useful for documenting the presence and severity of cognitive impairment in an individual cross-sectionally, it is still not clear which cognitive rating scales would be best suited to assess AD longitudinally and track change over time. Ideally, the best way to evaluate a tracking tool would be to correlate scores on the tests with the severity of the neuropathology. Several studies have shown significant positive correlations between the presence of neuritic plaques or neurofibrillary tangles and the degree of premortem dementia measured by neuropsychological tests.[58-61] For instance, scores on the Blessed Information-Memory-Concentration test (BIMC) have been reliably validated against both the number of neuritic plaques and the levels of choline acetyltransferase in the postmortem brains of patients with AD.[58,62-64] Moreover, Iraizoz,[61] found a significant correlation between MMSE scores and neurofibrillary tangles within the Nucleus Basalis of Meynert. These scales might therefore be used to provide an index of the severity of the neuropathology of AD.

A number of cognitive batteries have been developed, which can be quickly administered and have proven content validity, test-retest reliability and allow calculation of ARC. These tests most widely used clinically give global cognitive scores. These include the MMSE;[65] the BIMC;[62] the Mattis Dementia Rating Scale (DRS);[66] Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog);[67] the Cambridge Mental Disorder of the Elderly Examination (CAMDEX);[68] the Consortium to Establish a Registry for Alzheimer's Disease (CERAD);[69] and the Severe Impairment Battery (SIB).[70] While many individual domain-specific tests have also been used in clinical neuropsychological assessments, these have varied in different studies; furthermore, there has been no consensus on which ones to use and the longitudinal change scores have been limited. This review, therefore, examined the MMSE, BIMC, DRS, ADAS-Cog, CAMDEX, CERAD and the SIB as instruments to track change overtime since these have been the most commonly used measures to study progression[71,72] (Table). The search terms used to identify the available literature included the following keywords: Alzheimer's disease, longitudinal design, follow-up, progression, cognitive markers, annual rate of change, Mini-Mental status examination (MMSE), Blessed Information-Memory-Concentration test (BIMC), Mattis Dementia Rating Scale (DRS), Alzheimer Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Cambridge Examination for Mental Disorders of the Elderly-the Cambridge Cognitive Examination (CAMDEX-CAMCOG), Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Severe Impairment Battery (SIB).

## Mini-Mental Status Examination

The MMSE is the most widely used test, followed by the BIMC and the ADAS-Cog when analyzed by Galasko et al.[12] The MMSE is divided into two sections, the first of which requires vocal responses and covers orientation, memory, and attention; the second part tests ability to name, follow verbal and written commands, write a sentence spontaneously and copy intersecting pentagons. The total maximum score is 30 with scores between 24 and 30 considered to be within normal limits; scores lower than 24 extend through the mild to moderate to severe cognitive impairment range, although education and age are taken into account in deriving individual cut-offs.[73] The test is a paper and pencil test and takes approximately ten minutes to administer with minimal training for any health care

**Table: The annual rates of change (ARC) in specific cognitive scores.**

| Measure | Study (First author et al, year) | n | Interval period ( months ) | *ARC points/yr (SD/SEM) |
|---|---|---|---|---|
| **MMSE** | Aevarsson, 2000[98] | 494 | 36 | 2.8 |
| Mini-Mental | Becker, 1988[77] | 44 | 12 | 0.8 |
| Status Examination | Burns, 1991[43] | 110 | 12 | 3.5 |
| | Corey-Bloom, 1993[79] | 928 | 12 | 3.1 (3.86) |
| | Galasko, 2000[13] | 299 | variable | 3.48-3.76 **[.20]** |
| | Haxby, 1992[88] | 16 | 2.7 to 6.8 years | 4.4 (2.5 -3.6) |
| | Hogan, 1994[82] | 553 | 6 | 2.9 **[0.12]** |
| | Knopman, 1994[80] | 62 | 4,6,10,12 weeks | 2.8 |
| | Morris, 1993[92] | 373 | 12 | 3.9 (3.7) |
| | Mortimer, 1992[81] | 65 | 6 | 4.46 |
| | Salmon, 1990[78] | 55 | 12 | 2.8 (4.3) |
| | Teri, 1990[64] | 106 | variable | 2.8 **[0.45]** |
| | Uhlmann, 1986[75] | 156 | 12 | 2.2 to 3.9 (5) |
| | Yesavage, 1988[86] | 30 | variable | 4.4 (4.8) |
| **BMIC** | Corey-Bloom, 1993[79] | 928 | 12 | 3.1 (4.96) |
| Blessed Information- | Katzman, 1988[63] | 161 | 12 | 4.4 (3.5) |
| Memory-Concentration | Locascio, 1995[102] | 123 | 6 to 24 | 3 |
| | Lucca, 1993[99] | 56 | 3,6,12 | 2.6 (4.9) |
| | Ortof, 1989[101] | 54 | variable | 4.1 (3.6) |
| | Piccini, 1995[45] | 31 | 6 (variable) | 4.4 (3.2) |
| | Salmon, 1990[78] | 55 | 12 | 3.24 (3.03) |
| | Stern, 1994[89] | 111 | 6 to 96 | 2.2 (3.2) |
| | Thal, 1988[100] | 40 | 3 to 6 | 4.5 **[0.5]** |
| **DRS** | Becker 1988[77] | 86 | 12 | 21.9 |
| Mattis Dementia | Galasko, 2000[13] | 299 | variable | 13.7-14.8 **[0.72]** |
| Rating Scale | Haxby, 1992[88] | 16 | 2.7 to 6.8 years | 18 to 21 (11-22) |
| | Helmes, 1995[36] | 29 | 3.5 years | 43.2 |
| | Locascio, 1995[102] | 123 | 6 to 24 | 11.38 |
| | Salmon, 1990[78] | 51 | 12 | 11.38 (11) |
| **ADAS** | Knopman, 1994[80] | 62 | 4,6,10,12 weeks | 8 |
| Alzheimer Disease Assessment | Kramer-Ginsberg, 1988[109] | 60 | 6 | 9.32 (9.7) |
| Scale – Cognitive Section | Stern, 1994[89] | 111 | 6 to 96 | 9 to 11 |
| **CAMCOG** | Burns, 1991[43] | 110 | 12 | 12.3 |
| Cambridge Examination for | Forstl, 1996[121] | 55 | 24 | 28 |
| Mental Disorders of the Elderly – | Haupt, 1991[122] | 73 | variable | 11.8 (10) |
| the Cambridge Cognitive Examination | | | | |
| **SIB** | Wild, 1998[125] | 33 | 4 to 26 | 17.1 |
| Severe Impairment Battery | | | | |

n=sample size included in the calculation of the ARC. The interval period is the time elapsed between test dates.
The average ARC is stated (+/- STD or Standard Error of the Mean [SEM]).
Note that the SD is in plain font and the SEM in bold font.

professional.[74] A number of investigators have reported average ARCs of approximately 2 to 3 points for the MMSE.[64,75-82] The MMSE has excellent test-retest reliability[65,77,83-85] and correlates with other instruments used for cognitive testing such as the BIMC and the ADAS-Cog.[78,84,86] Specific issues have arisen regarding generalizability across disease stages and the pattern of change (linear versus nonlinear). It has been shown that the MMSE is equally sensitive to change in both the mild to moderate and moderate to severely demented Alzheimer patients and shows an overall ARC of 2.81.[78] In contrast, other studies have shown that the drop in MMSE scores over time is nonlinear.[87-92]

A finding consistent in all these studies is that progression rates of AD are highly variable between subjects, and that the ARC of mental status scores for an individual in the first year



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generally does not predict decline in the next year. These differences could be due to variations in cohort characteristics. Moreover, a number of investigators have reported that patients may enter periods of "plateau" during which their performance on mental status examinations remains stable.

Nonetheless, studies have shown that progression rates in AD show some predictability in that patients who begin with progression rates that are more rapid than average (greater than or equal to 5 MMSE points per year) continue to experience faster, clinically significant decline than patients who begin at slow or average rates.[87] Specifically in this study, patients were predicted to be slow, intermediate and rapid progressors based on the initial MMSE scores. Longitudinal follow-up revealed different time intervals to clinically meaningful deterioration, with the slow progressors taking the longest time, the rapid progressors declining the fastest and the intermediate progressors in between.[87] Other studies looking at the predictors of progression of AD have also indicated that an important predictor of progression is the severity of the cognitive impairment at onset.[92-95]

Another clinic-based study with frequent testing over an extended period of time clearly showed that the rate of decline in MMSE varied with disease stage.[88] However, in an earlier investigation, the MMSE scores could not predict progression in a group of mildly demented subjects followed for 30 months.[96] In fact, the reliability of the estimates of change may depend primarily upon the length of time of observations, and not on the number of observations made;[97] the rate of change determinants in this study were less reliable when the observation period was less than one year. The MMSE also showed a moderate floor effect and slight ceiling effect depending on the initial MMSE score.[13] Hence, despite all the inconsistencies in the literature, most studies do indicate that progression rates, to some degree, depend on the severity of cognitive impairment as indicated by the MMSE score at onset.

There may also be differences in the clinical setting of the studies, in patient demographics and comorbidities that could affect the rate of change. In order to determine whether longitudinal referral clinic and community-based population studies were equivalent in their progression rates, they were separately scrutinized. Although the majority of studies have been conducted in a referral clinic population, one large study conducted in a community setting (n=494) showed that dementia patients had a mean annual decline of 2.8 points per year,[98] which is quite comparable to the ARC reported in referral clinic studies. The study population setting, therefore, appeared to account for relatively minor differences in the ARC.

### Blessed Information-Memory-Concentration

Similar to the MMSE, a wide individual variability in rates of progression have been shown in patients with AD when assessed with the BIMC.[63,99] The BIMC consists of many of the most commonly used mental status questions examining the areas of personal orientation, recall of remote memories both personal and nonpersonal and includes a name and address to be learned for recall five minutes later. The concentration section consists of three items: months backwards, counting from one to 20 and backward from 20 to one. The maximum score is 37. The test is a paper and pencil test and takes approximately thirty minutes to administer with minimal training for any health care professional. A generally linear decline in mean scores on the BIMC has been reported with annual rates of decline ranging from 3 to 4.4 points in both referral clinic[43,99-101] and community-based populations.[63] In studies matched for variables of disease severity within a mild to moderate spectrum, the scores on the BIMC worsened steadily at a predictable rate, and this decline was independent of the level of impairment noted at the initial measurement.[102] However, the ARC in the error score was reduced when the results were extended to severely demented stages of the disease due to a ceiling effect of the test, in which higher scores indicate worse performance.[63,78] One could argue that since the rate of change of the BIMC test does not differ between early-onset and late-onset AD, it may be useful as a single measure over the spectrum of disease progression. However, both variability in rate of change over time and a ceiling effect on the BIMC were clearly demonstrated in a relatively large study of 123 AD subjects, even though it was found to be one of the most sensitive measures to follow these patients over a relatively short mean follow-up time of 1.8 years.[102] Hence, despite its validity based on clinico-pathological associations, it remains unclear if the utility of the BIMC for tracking AD progression is limited to mild-moderate stages or over relatively short time periods.[102]

### Dementia Rating Scale

Unlike the BIMC and MMSE, which were initially developed as screening tests, the Mattis DRS[66] has a broader range and thus has remained more sensitive to change in early and more advanced disease. The DRS may still be applicable even in the later stages of the disease because it includes a wider range of items that vary in degree of difficulty. Moreover, in a direct comparison of the MMSE with the DRS, it was shown that the sensitivity of the DRS to progression increased with the degree of dementia and was superior to change in the severely demented patients when compared to the MMSE.[78,88]

The DRS was developed as a more detailed instrument, systematically testing cognitive areas of initiation, memory, attention, conceptualization, and construction. The maximum total score is out of 144 with higher scores meaning better performance. It is a paper and pencil test taking approximately 20 to 25 minutes to administer with training, preferably by a neuropsychologist.[103] It is a clinically valid[104] and widely available psychometric test that can be administered by trained psychometrists and other health care professionals, without requiring ongoing supervision from a neuropsychologist. It requires some equipment such as stimulus cards for the initiation/perseveration, memory, conceptualization and construction subscales. In one series, moderately severe patients had a mean change of 3.24 points on the BIMC, 2.8 on the MMSE, and 11.38 on the DRS per year, but only the DRS was sensitive enough to document decline in the second year.[102] It is more strongly weighted for executive function tasks than the MMSE or the ADAS-Cog, which may explain its sensitivity to change over a greater range of cognitive impairment.[105] Even though the DRS has an extended range, individual variability still limits the utility of comparing an individual's DRS score

changes to a group mean rate of change unless factors such as stage of illness are taken into account. Moreover, AD patients with significant aphasia are particularly impaired on semantic fluency tasks, which require the retrieval of information from semantic memory.[106,107] This poor performance on language subtests, further underlines the hazards of comparing an individual's DRS score change to a group mean rate of change.

To address the issue of individual and disease stage variability, Helmes et al[36] used a modified version of the DRS to study 29 AD patients for an average of 3.5 years prior to autopsy confirmation. Frequent testing allowed them to plot individual rate of change curves, and when patients were in a declining stage of their illness there was a fairly tight average rate of decline of 16.8% per year. This declining stage was not clearly defined by the duration of illness. Haxby et al[88] used regression models and found annual rates of deterioration of approximately 15% on both the MMSE and DRS when AD patients were in their declining phase. Statistical analysis using multivariate regression models in which outcome variables are the rate of cognitive decline for each patient, have been used to overcome assumptions of linearity of decline and can incorporate individual variability when using MMSE and DRS.[13] More specifically, Galasko and colleagues[13] applied several repeated measures analysis methods to the MMSE and the DRS to compare their longitudinal properties and assess how well either instrument captured change. Outcome variables (each patient's rate of cognitive decline) and intercepts were calculated using least squares and best linear unbiased predictors. Potential predictors of rates of change (level of dementia, severity, and subtypes of dementia) were examined using multivariate linear regression analysis. They found that the MMSE not only had more noise than the DRS, but also showed a moderate floor effect and a slight ceiling effect, depending on the initial MMSE score, whereas these effects were less prominent for the DRS. In multiple linear regression models looking at predictors of change, the MMSE was less useful than the DRS. Moreover, in the DRS data, predictors showed statistically stronger effects and explained a greater proportion of the variance than did similar models using the MMSE data. Others have modeled patterns of decline using the MMSE, allowing for between-patient variability through a random effects model and adjusting for uncertainty in age of disease onset.[108] These studies demonstrate that more sophisticated statistical approaches can be used to better account for the individual variability in cognitive decline.

### Alzheimer Disease Assessment Scale-Cognitive Section

Progression in AD has also been studied using the ADAS-Cog, the most widely used battery in clinical trials. In fact, the adoption of the ADAS-Cog in the early trials of cholinesterase inhibitors was based in part on the availability of longitudinal data that permitted calculation of sample size requirements. The ADAS-Cog consists of 11 tasks measuring disturbances of memory, language, praxis and orientation that are often referred to as the core symptoms of AD. Higher scores indicate greater severity of dysfunction with most errors scored on a scale of 1-5, for a possible total error score of 70. The test takes approximately 20 to 45 minutes to administer with appropriate training, preferably by a neuropsychologist,[103] trained psychometrists or other health care professionals can administer it without ongoing supervision by a neuropsychologist. Like the MMSE, it is a widely used test but takes more time to administer and requires some equipment such as word lists and objects for naming.

The ADAS has very high inter-rater and test-retest reliability when repeated over a one-month interval with an ARC from 9 to 11 points.[80,109] Moreover, it has the ability to differentiate clinically diagnosed AD patients from matched controls.[67,110] In one study (Gillen et al[111]), the large database of the CERAD was used to develop a "derived" ADAS-Cog score from the performance data. Two ADAS-Cog scores were derived. The first was based on clinically mapping the items on the ADAS-Cog to assessments that were done in the CERAD study. The second was based on correlating the ADAS-Cog to the MMSE. The results showed that the ADAS could be used to model the progression of an untreated population of patients with AD.

Furthermore, several notable findings emerged from a study looking at the patterns of decline on the total and item scores of the cognitive subscale of the ADAS-Cog in AD.[112] Subjects with greater dementia severity at baseline showed greater cognitive worsening over time in most domains. When subjects were stratified by baseline MMSE score, this difference was further highlighted and was consistent with the findings of Stern et al[89] who longitudinally evaluated total ADAS-Cog scores in 111 AD subjects. These findings were also consistent with the different rates of decline observed in mild versus moderate subgroups of patients in cholinesterase inhibitor trials.[113] In a study by Schmeidler et al,[114] 151 patients representing a broad range of severity were followed up over a 12-month period to identify individual measures that are likely to be sensitive at the different stages of the disease. It was shown that for individual items and total scores on the ADAS-Cog, the rate of change was greater for patients in the moderate and severe categories than for mild or very severe patients. Ceiling and floor effects could explain the slower rate of change in the very mild and severe patients.

Another study looking at clinical changes over a two-year longitudinal course showed the feasibility of measuring AD progression with instruments such as the ADAS-Cog over a fairly broad range of symptom severity.[109] Sixty AD and 39 control patients were followed for a period of one year. Of these, 25 AD patients and 19 controls were followed for an additional year. The results showed that Alzheimer and control subjects were significantly different at baseline and follow-up testing intervals on the ADAS total as well as on its cognitive and noncognitive subscales. Also, severity scores increased for AD patients in year 1 of follow-up testing, and continued to increase in year 2. When patients were stratified by baseline MMSE into very mild, mild, moderate, and severe dementia and compared to a group of elderly controls, it was found that all four groups of AD patients performed statistically worse than the elderly control group on all 11 ADAS cognitive subtest scores.[115] Moreover, although the best indicators of progression were the ADAS cognitive and the ADAS total scores, the differential rate of decline of the various ADAS subtests appeared to reflect not only the changing pattern of cognitive impairments as a function of severity, but also the limitations of some of the subtests.



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### Cambridge Examination for Mental Disorders of the Elderly-the Cambridge Cognitive Examination

The CAMDEX is a standardized instrument widely used in Europe especially developed to evaluate the presence, type and severity of dementia.[68,116] The cognitive part of the CAMDEX, the Cambridge Cognitive Examination (CAMCOG), is a paper and pencil test that takes approximately 25 minutes to administer with training, preferably by a neuropsychologist; trained psychometrists or other health care professionals can administer it without ongoing supervision by a neuropsychologist. The CAMCOG evaluates a broad range of cognitive functions at varying grades of difficulty and is derived from 60 items and has a maximum of 107 points with higher scores reflecting better performance.[68,117,118] However, due to floor effects, the overlap in test performance of the mild and moderate/severe groups is considerable, and consequently the contribution of the CAMCOG to the grading of dementia is limited.[68] Nevertheless, high test-retest reliability, the broad range of cognitive functions included, and relatively fewer ceiling effects, enhance its ability to detect mild degrees of cognitive impairment. This is a strength of the CAMCOG.[119] Moreover, the CAMCOG score has proven to have high sensitivity and specificity in the differentiation between organic and nonorganic cases and has been found to be highly correlated with the Blessed Dementia Scale.[68,119] A comparison of the CAMCOG, the MMSE and three clock drawing tests was performed in 52 patients with AD, 36 patients with vascular dementia, and 26 normal controls. It showed that the MMSE and the CAMCOG scores were highly correlated in the AD group. In a two-year follow-up study done by Nielsen et al,[120] it was shown that scores on four of the 14 CAMCOG items could be used as significant predictors of dementia two years before the patients fulfilled the diagnostic criteria for dementia. Logistic regression analyses showed that higher age, reduced recent and remote memory, low category verbal fluency and attentional deficiency characterized incipient dementia two years before the diagnosis was made.

The natural course of cognitive performance in Alzheimer's disease was investigated in a two-year follow-up study using the CAMCOG.[121] It was seen that, on average, cognitive performance deteriorated by 28 points on the CAMCOG in the AD group. Other studies have shown a mean average decline of 12 points per year[43,122] and it was also seen that cognitive performance at the first examination was a significant predictor of performance at the follow-up examination. A cluster analysis of CAMCOG in 51 AD patients and 79 normal controls effectively separated normal from demented subjects. Four subgroups of AD patient were identified across a number of neuropsychological functions. The four subgroups of dementia of the Alzheimer type (DAT) patients differed more in level of impairment than for specific neuropsychological function. Stage specific patterns were noted with the higher functioning group exhibiting greatest losses in memory skills and the lowest functioning group in language skills.[123]

Schmand et al[124] divided the CAMCOG into a memory and a nonmemory section to test the hypothesis that the memory section was a better detector of AD and that the nonmemory section was a better predictor of the subsequent cognitive decline. Normal (N=169) and AD (N=155) participants were administered the CAMCOG initially and for three follow-up assessments over a period of at least three years. As expected, memory performance discriminated AD from normals better than the other tasks, whereas the nonmemory tasks better predicted subsequent cognitive decline. The decline on the nonmemory section was 5.5 points per year, while the corresponding decline on the memory tasks was much less noticeable, indicating a floor effect. Hence it may be best to use the memory and nonmemory sub scores separately, instead of the total CAMCOG score, for initial diagnosis and for measuring progression in AD.

### The Consortium to Establish a Registry for Alzheimer's Disease

The Consortium to Establish a Registry for Alzheimer's Disease[69] adopted a series of cognitive tests specifically aimed at the diagnosis and monitoring of AD in the participating US Alzheimer's disease centers.[117] The large, well-characterized CERAD sample was used to gain reliable information on rates of progression of cognitive impairment in probable AD. The neuropsychological test battery measures the primary cognitive domains including memory, language, and visuospatial deficits. Some of the tests included in the battery, such as word list recall, word list recognition and constructional praxis are also included in the ADAS-Cog. It is a paper and pencil test that can be administered by a trained examiner who meets a predetermined certification standard.[103] A least squares regression method was used to adjust for different levels of impairment and periods of observation. Rates of change on the Short Blessed test, MMSE, BIMC, CDR, and other cognitive measures were studied in 430 patients with probable AD for up to four years. It was seen that the rate-of-change determinants were less reliable when the observation period was one year or less, that dementia progression may be nonlinear when described by certain measures, and that simple change scores did not accurately characterize the rate of decline. It was also confirmed that the rate of progression in AD was determined by the severity of cognitive impairment, i.e., the less severe the dementia, the slower the rate of decline.[92]

### Severe Impairment Battery

An instrument commonly used to measure cognition in the advanced stages of AD is the SIB.[70] It contains 40 questions with a possible range of 0 to 100 points incorporating nine areas of cognitive function (social interaction, memory, orientation, language, attention, praxis, visuospatial ability, construction and orientation to name) and takes approximately 20 to 30 minutes to administer by a trained interviewer. It also requires common objects for questions on praxis and visuospatial ability. Items on the SIB are presented as single verbal or one-step commands that are enhanced with gestural cues. The maximum total score is out of a 100 with higher scores reflecting better performance. The ARC on the SIB for moderately and severely impaired patients have been reported to be 15.4 and 18.8 points per year (mean ARC of 17.1 points per year).[125] In a study by Schmitt et al[126] the SIB was examined in a one-year evaluation of change across a wide range of AD severity. The results suggested that the SIB is a reliable, valid and useful instrument for evaluating change in AD patients in the more severe stages of the disease, with initial

MMSE scores below ten, and is more sensitive to change in these patients.[126,127] Wild and colleagues[125] showed that patients with severe dementia can demonstrate rates of progression similar to patients who are moderately impaired if floor effects of the assessment instrument are minimized. The SIB is able to detect change in multiple cognitive domains. Moreover, it was shown that ARC in one year did not predict disease progression in the subsequent year even in the severe stage of the disease.[125] Similarly, when rates of change in subtest scores were compared, only the language subtest showed significant group differences, with the severely impaired group declining at a faster rate than those with MMSE scores above 11; however, when corrections for multiple comparisons were made, this difference was no longer statistically significant. According to Wild and colleagues, there is no slowing in the progression of the disease as the dementia becomes severe. Two other scales that have been used in the severe stages of AD include the Severe Cognitive Impairment Profile[128] and the Test for Severe Impairment Battery.[129] The SIB, however, has the most reliability and validity.[126] It is the only tool that has been evaluated for measuring longitudinal changes in cognitive functioning in advanced stages of AD and has been used in clinical trials.[130] However, it has limited utility in earlier stages of disease due to ceiling effects.

## Conclusions

Clinical studies of AD progression using cognitive markers can be used to detect deterioration over time. However, each scale has technical or theoretical limitations in acquisition and/or sampling that make it less than ideal as a single marker of progression. Combining markers, however, could exploit individual strengths and hopefully compensate for these limitations. Cognitive rating scales that have a clear expected ARC may be best for evaluating interventional trials over a few years, but high individual variability in progression rates, and floor and ceiling effects make them less helpful in following individuals, as opposed to groups of individuals, throughout all disease stages.

Most longitudinal studies that rely on interactive cognitive testing to define disease state inevitably have subjects drop out at some point and become "untestable". For this reason, the most advanced stages of AD are poorly represented in clinical studies using cognitive measures. In general, all cognitive tests, regardless of extent of range ultimately have testing limits, but those with a more extended range are better able to track disease progression in AD subjects. Moreover, powerful statistical methods used to analyze repeated measures and to model change may provide a better estimate of rate of change than simple subtraction of scores.[108,131,132] Growth curve models, general linear mixed models and best linear unbiased predictors are some of the other ways used for estimating rates of cognitive change in longitudinal studies.[47,133-136] These models not only help model more than one outcome measure but also help understand their relationship over time.

The rate of decline is heterogeneous regardless of the measure used and this may reflect either subtypes of AD, intrinsic variability in biological factors contributing to decline and/or variability inherent in using clinical measures. Although there are studies that suggest that the age of onset, and the presence of certain distinguishing clinical features may predict rate of decline, lack of understanding of heterogeneity in decline rate impairs our ability to identify consistent predictors of decline. Heterogeneity in decline rate makes predictive factors associated with a specific subgroup or phase of decline difficult to distinguish in large group analysis. Alternatively those predictive factors that do show consistent trends towards significance may be an indication of the robustness of their relationship to progression despite individual variability. Measures of functional activity and caregiver burden may also provide indicators of decline,[137] and the addition of brain imaging biomarkers, for example, measuring brain volume loss, may provide correlative biological information, to supplement cognitive markers of decline.[138,139]

In summary, the most commonly used tests in North America include the MMSE followed by the ADAS-Cog and the DRS. The MMSE has been shown to be sensitive to change in the mild to moderate and moderate to severe stages of AD patients and is highly correlated with the BIMC and the ADAS-Cog. However, the sensitivity of the DRS is superior to change in more severely demented patients when compared to the MMSE and the ADAS-Cog. This suggests validity of these cognitive scales but also points to their limited useful range; that is, while the MMSE and the BIMC may be sensitive to change in the mild to moderate stages of the disease, the DRS may be able to measure change in the more advanced stages of the disease because it reaches a floor later than the MMSE, BIMC and the ADAS-Cog. Therefore, even though the MMSE may be the most widely and readily used test, the DRS may be a more sensitive tool to capture change across a greater disease spectrum. Furthermore, the DRS better assesses the domains of attention and executive functioning that are poorly sampled by the ADAS-Cog.[140] Daily functional and behavioural scales add another dimension to monitoring AD progression, but have not been included in this review because of the paucity of studies and because the ranking scales used make longitudinal comparison difficult. They contribute further heterogeneity to the decline rates.

Therefore, the selection of the appropriate cognitive test instrument in studying progression in cohorts of patients with AD is critical because longitudinal properties, floor and ceiling effects, and precision of estimates of change vary between instruments. The DRS has been shown to have many superior longitudinal properties compared to the MMSE, which appears to underscore the validity and robustness of the DRS in characterizing patterns of cognitive impairment across the AD spectrum. Precision (a measure of reliability), less noise, a more predictable course and less evident floor and ceiling effects have been shown for the DRS than the MMSE using multivariate regression analysis. However, it requires more training and more equipment to administer. The metric properties and longitudinal characteristics of cognitive tests and the statistical methods used are key factors in charting the progression of AD and providing a more robust and interpretable index of cognitive change. Hence a combination of the DRS and SIB may be used in assessing disease progression in AD through most of its course. Furthermore, statistical methods that take advantage of repeated test measures to calculate change thereby overcoming assumptions of linearity of decline and incorporating individual

variability, should be used to obtain reliable data and to interpret and capture the defining elements of AD progression.


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