RESEARCH PAPER

What is the clinically relevant change on the ADAS-Cog?

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ABSTRACT

Objective To establish the minimal clinically relevant change (MCRC) on the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) for patients with mild Alzheimer's disease (AD).

Design Cohort study.

Setting 59 recruiting sites for the Alzheimer's Disease Neuroimaging Initiative.

Patients Outpatients with AD in the Alzheimer's Disease Neuroimaging Initiative.

Main outcome measures The authors applied anchor-based MCRC methodology comparing ADAS-Cog change against clinicians' judgement of clinically relevant worsening between baseline and 6 months in four domains: memory and non-memory cognitive performance; Clinical Dementia Rating Scale; and Functional Assessment Questionnaire. The analysis was repeated for the 6–12-month interval. To support these findings, the authors calculated distribution-based measures including half-baseline SD (1/2 SD) and SEM.

Results 181 patients (baseline ADAS-Cog score 18.5±6.4) had ADAS-Cog data at 0 and 6 months. Those undergoing clinically significant worsening on any of the four anchor questions (n=41–47) had an average ADAS-Cog change of 3.1–3.8 points. Similar results were found for the 177 patients with 6–12-month data. The average 1/2 SD for the baseline ADAS-Cog score was 3.2, and the SEM was 3.7.

Conclusions 3 points decline on the ADAS-Cog may be an appropriate MCRC for clinical trials of patients with early AD. However, further studies assessing the MCRC for improvement on the ADAS-Cog, using patient-based judgement as an anchor, and determining the minimal clinically relevant difference between change on two treatments are required.

Clinical trial registration number http://clinicalTrials.gov Identifier: NCT00106899.

The Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) is a principal-outcome measure for clinical trials in established Alzheimer's disease (AD).[1] However, statistically significant changes in ADAS-Cog scores may not equate to clinically relevant changes.[2] The minimal clinically relevant change (MCRC) on the ADAS-Cog often used in clinical studies to define responders varies between 3 and 5 points, with a change of ≥4 being recommended by a consensus committee of the FDA.[3]

An alternative to relying on consensus opinion is to determine the MCRC empirically. A number of methods have been proposed, including: (1) anchor-based techniques, which compare change against independent, clinically relevant indices,[4] and (2) distribution-based methods, based solely on the statistical characteristics of the outcome measure. The latter includes half baseline SD (1/2 SD)[5] and standard error of the mean (SEM).[6] These methodologies have been used to assess the MCRC for outcome measures in several disorders, including pain, osteoarthritis, Parkinson's disease[7] and some outcomes measures for AD.[8] However to our knowledge these methods have not been applied to the ADAS-Cog. We aimed to determine the MCRC of the ADAS-Cog in patients with mild AD using anchor-based methodology, calculating distribution-based results for comparison.

METHODS

All subjects were drawn from the Alzheimer's disease Neuroimaging Initiative, a multicentre public-/private-funded longitudinal study investigating adult subjects with AD, mild cognitive impairment and normal cognition (see supplementary material for further details). We included all patients with AD at baseline and ADAS-Cog data at 0 and 6 months; and for confirmation those with AD at 6 months with ADAS-Cog data at 6 and 12 months. Written informed consent was obtained, as approved by the relevant Institutional Review Boards.

All participants underwent baseline and periodic clinical and neuropsychometric assessments (http://www.adni-info.org). Ratings included the ADAS-Cog, a structured scale scored from 0 to 70, with higher scores indicating worse performance[1]; the Functional Activities Questionnaire (FAQ),[9] an interview-based disability measure scored from 0 to 20, with higher scores indicating more disability; the Clinical Dementia Rating Scale (CDR),[10] comprising a global staging of dementia with 5 stages: 0, 0.5 (mildly impaired), 1, 2, 3 (most impaired) and a severity score—the CDR sum of boxes—from 0 to 18; and a comprehensive neuropsychological test battery including tests of memory, naming and executive function.

At both the 6- and 12-month follow-up, clinicians were provided with the current and prior test results and asked to judge whether, compared with the prior assessment, there had been any clinically relevant worsening (yes/no) in a number of domains including the following four which were used as anchors: (a) memory, (b) non-memory cognitive function, (c) FAQ and (d) CDR.

Analysis

We analysed data at screening/baseline and 6 months for all patients with AD at baseline; and 6–12 months for patients with a diagnosis of AD at 6 months for confirmation. Those with missing

Table 1 Subject demographics and baseline scores

	0–6 months	6–12 months*
n	181	177
Mean (SD) age (years)	75.2 (7.5)	75.8 (7.3)
Mean (SD) baseline Mini-Mental State Examination	23.4 (2.0)	22.7 (3.1)
Percentage with Clinical Dementia Rating Scale global score (0.5:1)	52:48	57:43
Mean (SD) baseline Alzheimer's Disease Assessment Scale-Cognitive score	18.5 (6.4)	17.8 (6.2)
Mean (SD) baseline Functional Assessment Questionnaire	12.9 (6.8)	12.2 (6.8)
Mean (SD) years of education	14.8 (3.1)	14.9 (3.1)
Gender (percentage male)	53.0	54.8
On acetylcholinesterase inhibitor (%)	86.2	96.1
Mean (SD) disease duration (years)	3.5 (2.5) (n=175)	4.0 (2.5) (n=174)

*Baseline at 6 months.

or incomplete data were excluded. Statistical analyses were carried out in STATA V.10.

Calculation of the minimal clinically relevant ADAS-Cog score change

We examined the mean ADAS-Cog score change and 95% CIs in patients with and without a clinically relevant change on each anchor question. As those judged to have clinically relevant change also included those with more than *minimal* clinically relevant change, the MCRC was judged to lie above the mean of the unchanged group and below the mean of the clinically changed group. Changes in all groups were compared with the baseline using t tests. We also calculated the ADAS-Cog change score in those who had deteriorated by one stage (0.5 to 1) on the CDR-global score and those who were unchanged (in addition to the clinical judgement of clinically relevant worsening on the CDR as one of the four anchor questions). We also calculated the effect size (ES=mean difference/baseline SD) and standardised response mean (SRM=mean difference/SD of change) of ADAS-Cog change. An ES or SRM of 0.5 has been proposed as appropriate for a MCRC, with an ES or SRM of 0.2 considered a small change and 0.8 a large change.[11]

To complement these anchor-based methods, we calculated two additional distribution-based measures: 1/2 SD for baseline ADAS-Cog scores; and SEM (SEM $=SD^*\sqrt{(1-\text{Cronbach's } \alpha \text{ coefficient})}$) based on the baseline ADAS-Cog scores.

RESULTS

Patient characteristics are shown in table 1. One hundred and eighty-one patients (baseline ADAS-Cog score=18.5±6.4) were included in the 0–6-month analysis; and 177 (baseline ADAS-Cog score=17.8±6.2) in the 6–12-month analysis. Changes in ADAS-Cog score over these intervals are shown in table 2.

For all four anchor questions for the 0-6 month interval, the mean ADAS-Cog change in those with clinically relevant change was 3.1–3.8 points. The mean changes in the clinically unchanged group were 1.9–2.0 points, with the upper 95% CI not exceeding 3. Very similar results were seen over 6–12 months. For both groups and time intervals, for all four anchor questions the change in ADAS-Cog was statistically significantly greater than zero. The ES for the clinically relevant change group was higher (0.4–0.6) than for the unchanged group (0.3), as was the SRM (0.6–0.7 vs 0.3). Those who deteriorated by one stage on the CDR-global scale had a mean change score of 3.98. Compared with the unchanged group, those changing stage on the CDR-global scale had substantially larger ES (0.70 vs 0.26) and SRM (0.83 vs 0.27) than those not changing, consistent with this change being more than an MCRC (table 3).

The SEM for the ADAS-Cog at baseline was 3.7. The 1/2 SD for baseline ADAS-Cog score was 3.0–3.6, with an average of 3.2. One-fifth of the SD at baseline (a small change) was 1.3, and four-fifths of the SD (a large change) was 5.3. Similar results were seen between 6 and 12 months (table 2).

Comparing individuals with/without a clinically relevant change in any of the domains, there were no reliable differences

Table 2 Change in Alzheimer's Disease Assessment Scale-Cognitive score compared with external anchors in patients with a diagnosis of Alzheimer's disease at baseline

			Change in Alzheimer's Disease Assessment Scale-Cognitive							
	Clinically relevant decline?	n	Mean	Lower 95% CI	Upper 95% CI	Median	p Value† versus baseline	Effect size	Standardised response mean	1/2 SD at baseline
Baseline to 6 months										
Neuropsychological testing (memory)	No	140	1.9	1.1	2.7	2.0	<0.001	0.3	0.4	3.1
	Yes	41	**3.8**	2.1	5.5	3.3	<0.001	0.6	0.7	3.4
Neuropsychological testing (non-memory)	No	134	1.9	1.1	2.6	2.0	<0.001	0.3	0.4	3.0
	Yes	47	**3.6**	1.9	5.3	3.7	<0.001	0.5	0.6	3.6
Functional assessment questionnaire	No	137	2.0	1.2	2.8	2.0	<0.001	0.3	0.4	3.2
	Yes	44	**3.5**	1.9	5.0	3.0	<0.001	0.5	0.7	3.3
Clinical dementia rating scale	No	135	2.0	1.3	2.8	2.0	<0.001	0.3	0.4	3.0
	Yes	46	**3.1**	1.5	4.8	3.2	<0.001	0.4	0.6	3.6
6–12 months*										
Neuropsychological testing (memory)	No	135	1.5	0.6	2.3	1.7	0.001	0.2	0.3	3.3
	Yes	39	**3.4**	1.7	5.1	2.0	0.000	0.3	0.6	4.9
Neuropsychological testing (non-memory)	No	124	1.2	0.3	2.1	1.7	0.007	0.2	0.2	3.4
	Yes	50	**3.6**	2.0	5.1	2.7	0.000	0.4	0.6	4.3
Functional assessment questionnaire	No	126	1.4	0.5	2.3	1.2	0.002	0.2	0.3	3.4
	Yes	50	**3.0**	1.5	4.4	2.7	0.000	0.3	0.6	4.5
Clinical dementia rating scale	No	127	1.6	0.7	2.5	1.7	0.001	0.2	0.3	3.9
	Yes	47	**2.7**	1.1	4.4	2.3	0.002	0.3	0.5	4.5

*In patients with a diagnosis of Alzheimer's disease at 6 months.
†Wilcoxon test. Mean values of ADAS-Cog change in the groups judged to have changed on the transition questions, which were used as the main criteria for judging the MCRC, are highlighted in bold.

Table 3 Alzheimer's Disease Assessment Scale-Cognitive change by Clinical Dementia Rating Scale global change

Interval	Global Clinical Dementia Rating Scale	n	Mean Alzheimer's Disease Assessment Scale-Cognitive change (SD)	Lower 95% CI	Upper 95% CI	Effect size	Standardised response mean
0–6 months	No change	118.0	1.64 (4.44)	0.83	2.45	0.26	0.37
	Change from 0.5 to 1	37.0	3.98 (4.82)	2.37	5.59	0.70	0.83
6–12 months	No change	135.0	1.60 (4.57)	0.82	2.38	0.25	0.39
	Change from 0.5 to 1	18.0	3.45 (5.26)	0.83	6.06	0.61	0.65

in baseline Mini-Mental State Examination, ADAS-Cog, FAQ score, gender or AChEI use. There was a consistent trend for individuals undergoing a clinically relevant change to have more years of education than those who did not. However, although this reached nominal statistical significance (at the $p<0.05$ level), this was no longer the case when a correction was made for multiple comparisons (supplementary table).

DISCUSSION

The ADAS-Cog is a validated and robust scale for measuring change in AD, and remains the regulatory standard outcome for AD trials. To date, however, decisions on the magnitude of change required to show a clinically meaningful change have principally been based on expert consensus. In this study, using several MCRC methodologies, we demonstrate that a 3-point change on the ADAS-Cog score is an appropriate MCRC for mild AD.

Anchor-based MCRC techniques based on memory, non-memory, disability and global function produced very consistent results: the mean ADAS-Cog change in those judged to have clinically relevant change was just over 3 points, with the remainder changing by approximately 2 points. The ES/SRM scores of the ADAS-Cog for those undergoing change were in the ranges typically considered to be appropriate for an MCRC (ie, 0.4–0.7), with values for those not undergoing a clinically significant change being smaller (0.2–0.4). Change by one stage on the CDR-global score was associated with an ADAS-Cog change of 4 points. However, this change is likely to represent more than just a *minimal* clinically relevant change, not only on clinical grounds but also as reflected by the relatively large ES and SRM scores (0.7–0.8). Distribution-based methods, which we undertook for comparison, provided broadly similar results, with the SEM of the ADAS-Cog being 3.7 and 1/2 SD 3.2.

Determining a cut-off for an MCRC is inevitably a balance: too low a level risks licensing a drug with borderline clinically relevant change, while an overly high MCRC risks not licensing a drug which may provide at least a minimally significant change to patients. On the basis of this study, we suggest that the current FDA requirement for a 4-point change may be too severe and that 3 points is likely to be the most appropriate whole number for an MCRC for patients with early AD.

There are a number of potential limitations of this study. These results are drawn from a relatively small natural-history study and reflect clinically relevant deterioration rather than stabilisation or improvement expected in a treatment trial. The MCRC may well differ in patients with different disease severities.[12] Importantly, MCRC calculations reflect average group changes and may not be appropriate to judge changes in individual patients. The MCRC is an important concept for planning and interpreting trials, providing reassurance that the effects of a drug are not only statistically, but also clinically, relevant. Future studies should examine the MCRC score based on patients' rather than clinicians' judgement. Analysis of data from positive clinical trials would also allow both for the MCRC for improvement rather than deterioration, and the related but different concept of minimal clinically relevant difference between changes in two treatment arms to be assessed.

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Competing interests None.

Ethics approval Provided by Local Review Boards of the ADNI participating centres.

Contributors Both authors contributed to the design, analysis and writing of the manuscript. Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators is available at http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Citations.html. The authors are grateful to Dr Ian Malone for help with data processing.

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