

Cogtest is More Sensitive than the ADAS-cog in Detecting Change in Clinical Trials of Early Alzheimer's Disease

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Abstract

Background: The ADAS-cog is frequently used in clinical trials of Alzheimer's disease (AD) as the primary end point. The ADAS-cog is a standard 11-item instrument devised to assess the severity of cognitive impairment in patients with AD. Scores on the separate items are summed to provide a total score indicative of overall cognitive status. The total score range is 0 to 70 points, with a higher score indicating a worse state of disease progression.

The Word List Memory Test (WLMT) in the Cogtest Library is an auditory verbal recall test. Subjects have to recall as many as possible of 16 words that have been auditorily presented by the computer. On the second trial, the computer repeats only those words that the subject has not recalled and the subject is then asked to try to recall all 16 words again. Following each presentation the examiner records the subjects' responses on a touch screen, enabling immediate and automatic scoring. This process is repeated up to 5 times in total.

Methods: In a randomized double blind placebo controlled study of AD, the ADAS-cog was carried out at baseline and Day 28. We compared the performance on the list learning portion of the ADAS-cog to that of the WLMT. Both tests examine immediate and delayed memory performance, however, the administration and scoring procedures discriminate the two types of tests. We compared the list learning portion of the ADAS-cog with the first trial of the WLMT.

Results: Using a t-test, change from baseline to day 28 of the treatment groups combined was compared to that of the placebo group on each of the tests. There was a significant difference for the change from baseline for the first trial of the Word List Memory Test,

$t(1,55) = -2.6, p = .01$ but not for the list learning test from the ADAS-cog, $t(1,56) = 1.3, p > .10$.

Conclusions: This study provides evidence that tests from the Cogtest computerized library may be sensitive in proof of concept and Phase II treatment studies of AD even when there is no signal expected on the ADAS-cog.

Introduction

Alzheimer's disease (AD), the most common form of dementia, is a chronic, severely debilitating neuro-psychiatric disorder in which individuals demonstrate progressive inexorable deterioration of cognitive abilities over time. Several pharmacological treatments are available or currently being investigated to determine if cognition can be improved in AD. The Alzheimer's Disease Assessment Scale (ADAS) was designed to evaluate the severity of cognitive and non-cognitive behavioral dysfunctions characteristic of persons with Alzheimer's disease. Its cognitive subscale, the ADAS-cog, measuring disturbances of memory, language, praxis, attention and other cognitive abilities, often referred to as the core symptoms of AD (Rosen et al., 1984), is the most popular cognitive testing instrument used in clinical trials and often constitutes the primary outcome measure.

In a pharmacological study of mild AD which used both Cogtest and the ADAS-cog we attempted to determine the sensitivity of Cogtest's Word List Memory test (WLMT) compared to the ADAS-cog test in detecting cognitive change. Both tests examine verbal memory performance, however, the administration and scoring procedures differ between the two tests. Cogtest's WLMT is a selective reminding test with 5 learning trials of 16 words. On each trial words that were not remembered on a previous trial are selectively reminded. Following each trial the examiner records the subjects' responses on a touch screen, enabling immediate and automatic scoring. The total number of words on each trial is captured by the computer and variables for analysis are automatically computed. These include Total Learning over all trials and Percentage trial to trial transfer among others. A delay trial is administered after approximately 20 minutes. The ADAS-cog test presents all words on each of 3 learning trials. The total score constitutes the average of the total number of words not recalled over the 3 trials. Scoring is reversed in the ADAS-cog and errors are scored, not correct responses. The delay trial was not administered in the study.

Methods

Verbal memory using list learning was examined in 60 male and female patients with probable AD between 55 - 80 years of age. The study was a randomized, parallel-group, double-blind, placebo-controlled study of 4 fixed doses of a partial agonist at the alpha7 nACh receptor (25 mg tid, 50 mg tid, 75 mg tid, and 150 mg tid) or placebo with 28 days of consecutive dosing.

Patients with MMSE score between 20 and 26 at screening were enrolled in the study. The ADAS-cog was administered on Days 0 and 28 and the Cogtest Battery was administered on Days 0, 14, 21 and 28 at 5 hours post AM dose. Here we examine baseline and day 28 performance. All patients signed an informed consent form.

Cognitive Assessment

Cogtest provided a customized computerized cognitive test battery (Cogtest, Inc. DE) designed for use with a variety of clinical populations and in clinical trials. The Cogtest platform allows for accurate recording of reaction times and enhanced standardization of administration relative to conventional paper-pencil tests.

The Cogtest Battery in the study included 7 tests - Auditory Digit Span, Auditory Number Sequencing, Word List Memory, Symbol Digit Substitution, Choice Reaction Time, Simple Reaction Time and the Tower of London Test. We examined the Word List Memory Test.



Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog): a specially designed paper pencil test with 11-items devised to assess the severity of cognitive impairment in patients with AD. We examined performance on the list learning portion of this test.

Baseline Demographic Results

	25 mg n=12	50 mg n=12	75 mg n=12	150 mg n=12	Placebo n=12
Age	71.17 ± 4.9	69.75 ± 7.8	67.67 ± 7.2	68.75 ± 6.3	65.80 ± 7.1
% ♀	58%	75%	50%	50%	50%
ADAS Cog Total	9.67 ± 3.8	6.67* ± 2.0	11.08 ± 4.5	10.00 ± 3.9	8.76 ± 3.7

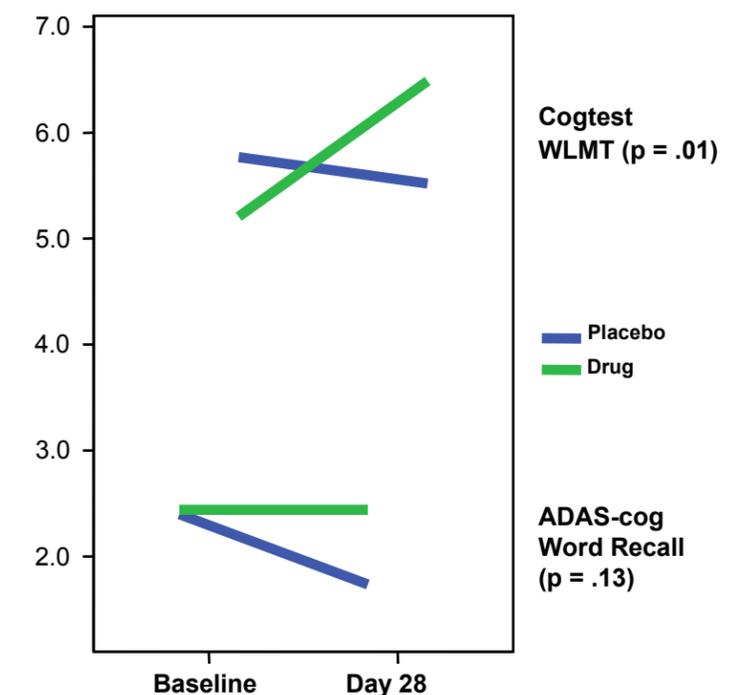
* $p < .05$ compared to 25mg, 75 mg and 150 mg

Statistical Analysis

Raw scores from the WLMT and the ADAS-cog were used in these analyses. Using a t-test, change from baseline to day 28 for the treatment groups combined was compared to that of the placebo group on each of the tests.

Results

There was a significant difference for the change from baseline for trial 1 of Cogtest's WLMT, $t(1,55) = -2.6, p = .01$ but not for the list learning test from the ADAS-cog, $t(1,56) = 1.3, p > .10$. No significant group difference was seen for learning over trials 1-3, $t(1,55) = -.10, p > .10$ or trials 1-5, $t(1,55) = -1.5, p > .10$ in the WLMT.



Performance on the list learning portion of the ADAS-cog compared to that of the first trial of Cogtest's Word List Memory Test

Conclusion

Verbal Memory assessed using the Word List Memory Test from the Cogtest library was more sensitive than the verbal recall section of the ADAS-cog in separating treatment and placebo groups with mild AD.

References

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. American Journal of Psychiatry 1984; 141: 1356-64.

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