Cognitive Effects of a Partial Agonist at the Alpha7 Nicotinic Acetylcholine Receptor in Mild Alzheimer's Disease

Susan De Santi[1], Saurabh Gupta[2]

[1]NYU School of Medicine, New York, NY, USA; [2]The Cognition Group, Newark, DE, USA

Abstract

Background: Assessing the effects of drug treatments on cognition in clinical trials of Alzheimer's disease (AD) has provided many challenges to researchers. Current FDA accepted cognitive assessment tools are limited and are, in many respects insensitive to detect change in short term studies. Given that there are many potential therapies emerging, the need for tools to assess cognition and detect change becomes urgent.

Methods: A randomized, parallel-group, double-blind, placebo-controlled study using several different doses of a partial nicotinic agonist or placebo in 60 male and female patients with probable AD was undertaken for 28 days. Cognition was assessed on Days 0, and 28 using the ADAS cog and the following Cogtest Computerized Tests (www.cogtest.com); Digit Span Forward and Backward, Auditory Number Sequencing, Word List Memory, Symbol Digit Substitution, Choice Reaction Time, Simple Reaction Time, and Tower of London. Cognitive data were converted to z scores, based on the Cogtest normative database. Individual tests and cognitive domains were examined.

Results: Using mixed linear models we found an interaction effect for the immediate memory domain (F=2.7, p<.05). The middle dose group significantly improved with treatment, p < .01. We explored this group in greater detail and compared them to placebo. We found that performance improved on trial 1 of the Word List Memory Test and digit span forward (p<.05). The ADAS cog showed no effect of treatment.

Conclusions: Cogtest is an instrument to detect treatment changes in cognition in short term clinical trials with mild AD whereas not such effect was seen with the ADAS cog. This study validates Cogtest as a sensitive tool in detecting treatment changes in safety and proof of concept studies in early AD.

Introduction

The amyloid hypothesis posits that AD is due to the neurotoxic effects of Aβ in the brain. Aβ accumulation affects neurotransmitters, such as acetylcholine (ACh). The number of, muscarinic and nicotinic cholinergic receptors are reduced in AD. Nicotinic acetylcholine receptors (nAChR) are involved in attention, memory, and cognition. Therefore, treatments targeting the nAChR should positively effect attention, memory, and cognition.

Aim:

To assess the neuro-cognitive effects of a partial agonist at the alpha7 nACh receptor, at four fixed doses in patients with probable AD compared to placebo and to compare its effect on verbal learning and overall cognition as assessed with ADAS cog versus Cogtest Word List Memory Test.

Hypothesis:

The partial agonist at the alpha7 nACh receptor, will
1: improve learning and memory in mild AD patients compared to placebo assessed using Cogtest and Cogtest change scores
2: and the ADAS cog change scores will be correlated.

Method:

Double- blind, parellel-group, randomized, placebo controlled study, where drug was administered tid for 28 days. The study was conducted on 60 medically stable male and female patients between 55 and 80 years of age with a diagnosis of probable AD and an MMSE score between 20 and 26.

Inclusion Criteria:
- adequate hearing, vision and language skills
- negative urine drug screen,
- stable living environment
- fluent in English
- AChE and memantine TX discontinued 30 days prior to randomization.

Exclusion criteria:
- active psychiatric, and neurological disease
- laboratory or ECG abnormalities etc.
- substance abuse
- nicotine use.

Study Protocol:
Cogtest was administered on Days 0, 14, 21 and 28 at 5 hours post AM dose.
ADAS-Cog was administered on days 0 to 28 .
Informed Consent was obtained prior to study participation.

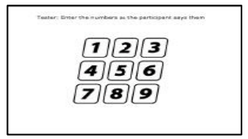
Baseline Demographics:

No significant group difference for
Age, F (4, 55) = .48, p = ns
Gender distributions, $\chi 2$ (4) = 2.3, p = ns,
Total ADAS cog score, 50 mg group scored significantly lower compared to 25mg, 75 mg, and 159 mg.

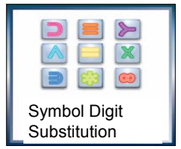
	25 mg n=12	50 mg n=12	75 mg n=12	150 mg n=12	Placebo n=12
Age	71.17 ± 4.9	69.75 ± 7.8	67.67 ± 7.2	68.75 ± 6.3	65.80 ± 7.1
% ♀	58%	75%	50%	50%	50%
ADAS Cog Total	9.67 ± 3.8	6.67* ± 2.0	11.08 ± 4.5	10.00 ± 3.9	8.76 ± 3.7

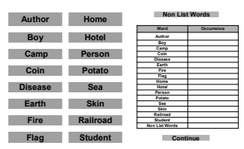
* p < .05 compared to 25mg, 75 mg and 150 mg

Auditory Number Sequencing



Auditory Digit Span





Word List Memory

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

Cogtest Battery:

Domains	Cogtest Test
Verbal Working Memory	Auditory Digit Span Backward Auditory Number Sequencing
Executive Function	Tower of London
Immediate Memory Auditory	Digit Span Forward Word List Memory (Total Recall Trial 1)
Declarative Memory	Word List Memory (Trial 1-5 and Trial to Trial Transfer) Word List Memory Delayed
Reaction Time	Simple Reaction Time Choice Reaction Time
Processing Speed	Symbol Digit Substitution

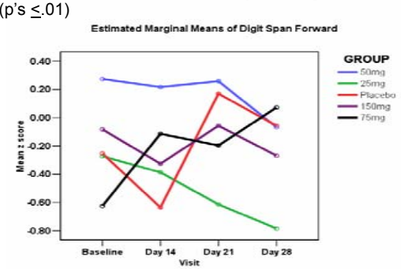
Alzheimer's disease Assessment Scale-Cognitive Subscale
The ADAS-Cog is a standard 11-item instrument devised to assess the severity of cognitive impairment in patients with AD (Rosen, et al., 1984). Scores on the separate items were summed and provided a total score indicative of overall cognitive status. In the ADAS-cog errors are scored not correct responses, so a higher score would indicate greater cognitive impairment.

Statistical Procedures:

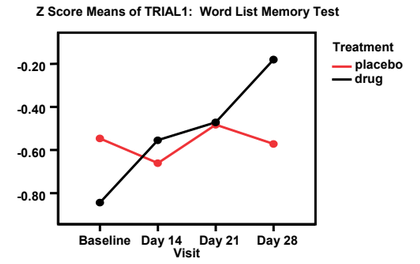
- Cogtest Battery was z-scored against the Cogtest Normative Database.
- Z-scores were used in Repeated Measures ANOVA comparing dose and placebo effects.
- Random effects models were used to examine cognitive performance over the entire study period with baseline performance covaried from the model.
- Raw scores were used in comparisons of ADAS cog total Score with Cogtest Neurocognitive Composite Score and ADAS cog Verbal recall with Cogtest Word List Memory test

Results:

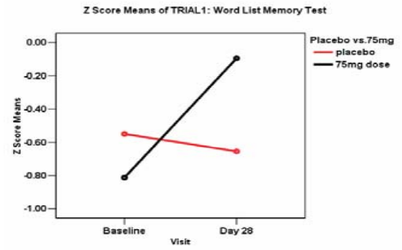
All Group Comparisons: Using the random effects model there was a significant time by treatment interaction, F (4, 50) = 4.03, $p \leq .01$ for the **Auditory Digit Span Forward** (Immediate Memory). The slope for the 75 mg group significantly improved with treatment, $p < .01$. **Within group Effects:** All groups showed improvement over time on WLM Trial ,Symbol Digit Substitution, Tower of London, Choice Reaction Time (p's $\leq$.01)



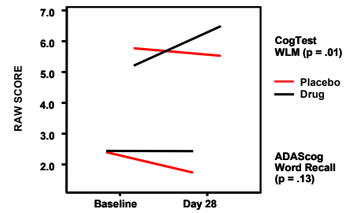
Results from All Treatment Groups Combined vs Placebo
All treatment groups were combined (drug group) and compared to the placebo group. **Trial 1 from the Word List Memory Test**, a measure of immediate memory, showed significant within group effects using a rANOVA, F (1,53) = 4.7, p < .05, as well as a significant interaction effect, F (1,53) = 3.9, p = .05. As can be noted from the graph below, the placebo group's performance begins and ends at the same point time, whereas the drug group's performance improves steadily throughout the study period. **Within group effects:** All groups showed improvement over time on Symbol Digit Substitution, Tower of London, Choice Reaction Time, and Simple Reaction Time (p's<.05).



Results from 75 mg vs Placebo: An significant improvement was seen in the 75 mg group compared to placebo for **Trial 1 from the Word List Memory Test** and **Auditory Digit Span Forward**, (p's $\leq$ .05). A trend toward improvement was noted for WLM Delayed Recall, *and trial to trial transfer* (p's =.10). **Within Group Effects**: Both groups showed improvement over time on Tower of London (p<.01) and Symbol Digit Substitution (p<.05)



Cogtest shows significantly more change than ADAS-cog



Conclusions:

- Cognition was positively affected after 28 days of treatment with the partial agonist.
- Immediate memory, executive function, processing speed and neurocognitive composite score improved over time on the mixed linear model.
- Attention and Verbal Memory were the domains that showed improvement with treatment compared to placebo.
- 75 mg of the partial agonist was the dose that most positively affected cognition.
- Cogtest Trial 1 of WLMT showed group effects over time, whereas the ADAS-cog Verbal Recall did not.

References:

- Hardy, J.A., Higgins, G.A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science* 256:184–185.
- Lorenzo, A., Yankner, B.A. (1994) Beta-amyloid neurotoxicity requires fibril formation and is inhibited by congo red. *Proc Natl Acad Sci USA*. 91:12243–12247..
- Narahashi, T., Marszalec, W., Moriguchi, S. (2003). Unique mechanism of action of Alzheimer's drugs on brain nicotinic acetylcholine receptors and NMDA receptors. Life Sci. 74(2-3):281-91.
- Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. American Journal of Psychiatry 141: 1356-64, 1984.
- Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: Measurement, rate and predictors of cognitive deterioration. American Journal of Psychiat

Presented at the International Conference on Alzheimer's Disease (ICAD) 2008, July 26th to 31st, Chicago.

The Cognition Group
advancing CNS research