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

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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 assessments 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, and Tower of London. Cogtest battery was -scored against 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).

Conclusion: Cogtest is an instrument to detect treatment changes 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 holds 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, as well as their specific subtypes, is 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, parallel-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 = n.s.

Gender distributions, χ2 (4) = 2.3, p = n.s.

Total ADAS cog score, 50 mg group scored significantly lower compared to 25mg, 75 mg, and 159 mg.

<table>
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<th>Age</th>
<th>25 mg n=12</th>
<th>50 mg n=12</th>
<th>75 mg n=12</th>
<th>150 mg n=12</th>
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<td>71.17</td>
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<td>68.75</td>
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<td>75%</td>
<td>50%</td>
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<table>
<thead>
<tr>
<th>ADAS Total</th>
<th>9.67</th>
<th>6.87</th>
<th>5.71</th>
<th>5.67</th>
<th>7.86</th>
<th>10.00</th>
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</table>
| p < .05 compared to 25mg, 75 mg and 150 mg

Cogtest was administered on days 0 to 28. Informed Consent was obtained prior to study participation.

Statistical Procedures:

- Comparison was performed 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 and 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 < .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 Transfer Digit Substitution, Tower of London, Choice Reaction Time (p < .01)

Conclusions:

- Cogtest was positively affected after 28 days of treatment with the partial agonist.
- Immediate memory, executive function, processing speed and neuropsychological composite score improved over time on the mixed linear model.
- Immediate and Verbal memory were the domains that showed improvement compared to placebo.
- 75 mg of the partial agonist was the dose that most positively affected cognition.

- Cogtest Trial 1 of WLM showed group effects over time, whereas the ADAS-cog Verbal Recall did not.

References:


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