Overlap of Cognitive Deficits in Parkinson's Disease (PD) & Alzheimer's Disease (AD): Potential use of Safinamide

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ABSTRACT

Objective: We performed a comparison of the cognitive domains affected in AD and in early PD patients and also determined the potential benefits of safinamide in treating the cognitive deficits and the activities of daily living (ADL) of AD based on recent results from a trial in early PD patients.
Background: Cognition is impaired in early AD (perceptual speed, executive functioning, episodic and working memory) and early PD (reaction time, working memory and executive function). Comparisons using the same computerized cognitive battery have not been performed.
Methods: The Cogtest database on 225 AD patients from 3 prospective studies was compared to data from a Phase III double-blind placebo-controlled randomized 24-week trial evaluating safinamide, a selective reversible MAO-B and glutamate inhibitor, as add-on therapy to a single DA-agonist in 123 early PD patients. Auditory Number Sequencing(ANS), Spatial Working Memory(SWM), Strategic Target Detection (STDT), Tapping Speed, Simple Reaction and Choice Reaction Time were chosen. Data from AD and PD patients were converted to z-scores, based on healthy control data from Cogtest database and expressed in SD units.
Results: Deficits in AD patients compared to controls showed significant decrements (all p values <0.05) of z scores of processing speed(4.5SD), episodic(5SD) and working memory(4SD) and executive function(1SD). At baseline, all PD patients showed cognitive deficits in at least one domain and 50% had deficits in ≥2 domains. The domains affected were verbal working memory (3.5SD), finger tapping(1.5SD), spatial working memory(6.5SD) and executive function(1SD). Safinamide produced statistically significant benefits in executive function(STDT; p=0.037) and working memory (ANS; p=0.035) as well as in ADL(p=0.024).
Conclusions: Using Cogtest, cognitive deficits noted in early PD and AD overlapped in working memory and executive function. AD patients were impaired, in addition, in episodic memory. Safinamide's cognitive improvement in early PD patients on DA-agonists suggests that the mechanism of benefit may be non-dopaminergic. Based on the similarities in PD and AD, data suggest that safinamide may be of use in treating ADL and cognitive deficits of AD.

INTRODUCTION

Dementia of the Alzheimer's type is currently observed in 17 to 25 million people worldwide.[1,2] It is the major probable cause of dementia in the aged[2] and its incidence rises from about 5 percent in those aged 65 and over to about 25 percent in those aged 85 years and older.[2,3] With more people living well into old age, AD is a growing problem. Cognitive impairment is associated with neurodegenerative diseases. Alzheimer's (AD) and Parkinson's disease (PD) affect cognition, with both overlapping and separate cognitive domains affected early in each disease process[4]. Alzheimer's disease, a cortical dementia, is most often associated with impaired episodic memory, although perceptual speed, executive functioning, and working memory may be affected[4]. In early PD executive functioning and working memory are most often impaired but widespread frontal-lobe cognitive dysfunction with mild to moderate impairment in attention and memory, and slight visuo-spatial alterations present as well[5]. Approximately 30% of the cases with idiopathic PD develop dementia[6].
Computerized cognitive test batteries are gaining wide use in clinical assessment and clinical trials with neurodegenerative diseases. The purpose of this study was to use *COGTEST* to compare the cognitive domains affected in AD and in idiopathic PD. In addition, we show the benefit of safinamide in treating the deficits of cognition in early PD patients and will explore its effect in AD on cognition and activities of daily living (ADL).

METHODS

From The *COGTEST* database, 225 early AD patients from 3 prospective studies were selected and compared to data from a Phase III double-blind placebo-controlled randomized 24-week trial evaluating safinamide as an add-on therapy to a single DA-agonist in 123 early PD patients. Safinamide has a novel mode of action as a dopamine modulator (comprising both selective and reversible MAO-B inhibition and also blockade of dopamine reuptake) complemented by an effect on the glutamate pathway. All patients were between 30-80 years of age. PD patients were diagnosed within 5 years of the study. The AD patients were at the early stage and fulfilled NINCDS-ADRDA criteria[7]. Cognitive assessments of working memory, executive function, episodic memory and motor speed were administered to both groups. All patients signed an approved IRB consent form.

Cognitive Domains and Measures:

Episodic Memory

Word List Memory (WLM): The WLM is an auditory-verbal recall test. Subjects are asked 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 subjects have not recalled and subjects are then asked to try to recall all 16 words again. The process is repeated up to five times total and there is a 30 minute delay trial.

Working Memory:

•**Auditory Number Sequencing (attention, working memory, executive function)**: Subjects hear a series of numbers (e.g. "9.. 3.. 6"; minimum=2 digits, maximum=8 digits) and are asked to repeat the numbers in consecutive order, from lowest to highest, requiring both working memory maintenance and manipulation.

•**Spatial Working Memory** (**visual working memory test).** A visual target is briefly presented on the screen and the subject must touch the target. A delayed condition is also presented. Here the visual target is briefly presented, followed by distracters which the subject must also touch. The subject is then asked to point to the spot where the target appeared. A delay period of 2 or 12 sec. between target presentation and response is randomized over trials.

Executive Function:

• **Strategic Target Detection Test** (**complex attention, executive function).** This test requires the subject to touch the target stimuli (shapes) directly on a touch screen. The participant must learn which target is correct by choosing one of the stimuli following computer-generated feedback.

Speed/Processing Speed

•**Tapping Speed (motor speed, manual dexterity):** Similar to the finger tapping test, subjects press a key as fast as possible with the index finger for 10 s; 5 trials for each hand are administered.

•**Simple Reaction Time** (**psychomotor speed, reaction time, attention**). The subject pressed the space bar as fast as they could when the visual stimulus (green ball) appeared on the screen.

Attention:

•**Choice Reaction Time** (**attention, vigilance**). The subject pressed a key at the right or left side of the keyboard corresponding to the side of the screen on which a red or green circle appeared. Following the presentation of a vertically and horizontally centered fixation point (crosshair) the circle occurred after a random delay time (varying between 750ms and 1500ms). The subject first completed a practice phase and after reaching a criterion level of 16/20, the test phase began and included 100 trials.

Statistical Analysis

Z scores, based on an age matched normative sample, were calculated for all measures except those obtained in the simple and choice reaction time tests. The Least Significant Difference (LSD) procedure was used for post hoc group comparisons. Statistical significance was declared at the .05 level (two-tailed).

RESULTS

Demographic Data	PD Grp. (n = 123)	AD Grp. (n = 225)	Norm Grp. (n = 50)
Age	57	77	64
Gender:			
% Male	60	40	52
% Female	40	60	48
Ethnicity:			
% Native American	2	0	N/A
% Asian	40	42	N/A
% White	58	58	N/A

Figure 1. AD performance compared to Normative Group

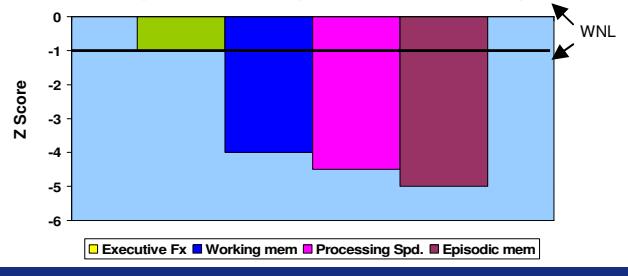


Figure 2. PD performance compared to Normative Group

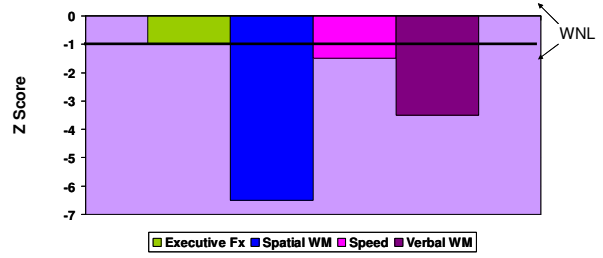
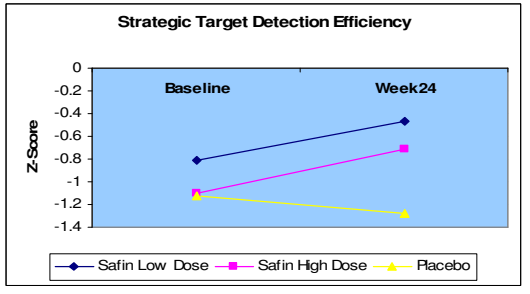


Figure 3. Performance Pre and Post Safinamide Treatment in PD



CONCLUSIONS

Cognitive domains, such as executive function and working memory are impaired in early PD before dementia is diagnosed and this impairment is as extensive as that seen in early AD. AD patients were impaired, in addition, in episodic memory. Safinamide's cognitive improvement in early PD patients on DA-agonists suggests that the mechanism of benefit may be non-dopaminergic. Based on the similarities in PD and AD, data suggest that safinamide may be of use in treating ADL and cognitive deficits of AD.

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