Cognitive Effects of Safinamide in Early Parkinson's Disease (PD) Patients

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ABSTRACT

Objective: This study evaluated the cognitive effects of 100 and 200 mg/day doses of safinamide, a new anti-PD agent that combines selective, reversible MAO-B and glutamate release inhibition, compared to placebo as an add-on therapy in non-fluctuating, early idiopathic PD patients receiving a stable dose of a single DA-agonist.

Background: PD affects several cognitive domains even in patients with early disease. The most severe areas of impairment are reaction time, working memory and executive functions.

Methods: A subset of 151 PD patients performed the Cogtest battery as a part of a phase III 24-week randomised placebo controlled trial. The test included Auditory Number Sequencing (ANS), Spatial Working Memory (SWM), Strategic Target Detection (STDT), Tapping Speed, Simple Reaction Time and Choice Reaction Time.

Results: Data were converted to z-scores based on healthy control data from Cogtest database. Changes from baseline to endpoint were assessed with repeated measures analysis of variance. Cogtest found impairments across several cognitive domains and in executive function in these patients. At baseline, no patients were cognitively intact, while >50% were impaired in 1 of the domains. Using LOCF method, statistically significant effects of safinamide were found (vs placebo) for executive function as measured by the STDT (p=0.037) and working memory indexed by ANS (p=0.035). A trend level difference was found in SWM (p=0.079). Also, cognitive effects were seen as early as 12 weeks after starting safinamide.

Conclusions: Significant deficits in multiple cognitive measures, most notably in executive function, were found in patients with early idiopathic PD on DA-agonists. Improvements in executive function and working memory were observed with safinamide, with a trend for improvements in spatial working memory. These data suggest cognitive deficits are prevalent even in treated PD patients. Cognitive impairments are a clinically relevant, yet understudied aspect of PD, which improved with addition of safinamide to a DA-agonist, suggesting safinamide possesses actions beyond DA enhancement. New trials will investigate safinamide cognitive effects.

INTRODUCTION

Parkinson's disease (PD) is considered a disorder of motor function with a clinical presentation that includes rigidity, tremor, bradykinesia, akinesia, and postural instability. Cognitive impairments, however, are evident in PD with dementia being present in approximately 30% of the cases (Aarsland, et al. 2005). 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 (Vingerhotes, 2003). Levodopa treatment has been shown to improve motor performance, but its effect on cognition is more complex with improvement and impairment being observed (see Cools, 2006 for review). MAO-B inhibitors have also been shown to positively affect cognition. However, the effect on cognition of MAO-B inhibitors and DA-agonists in combination is not well understood. The purpose of this study was to examine the cognitive enhancing effect of 2 different dosages of safinamide. 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.

METHODS

123 patients, between 30-80 years of age, diagnosed with idiopathic PD of less than 5 years duration, received 24 weeks of either 100mg of safinamide (n=41), 200mg of safinamide (n=38) or placebo (n=44) in this double-blind, parallel-group, randomised, multi-centre, multi-national, Phase III trial. Safinamide was an add-on therapy to a single dopamine agonist dose stabilized for at least 4 weeks prior to study entry. Patients were excluded from the study if they were of child bearing potential, fulfilled DSM IV criteria for drug abuse, had clinically significant gastrointestinal, renal, hepatic, endocrine, pulmonary or cardiovascular disease. All patients were safinamide naive at study entry. Cognitive assessments of working memory, executive function, simple motor speed, were administered at baseline, and again after 12 and 24 weeks of treatment. All patients signed an IRB approved consent form.

Cognitive Assessment

Cognitive function was assessed with *COGTEST*, a computerized neuro-cognitive test battery (Cogtest, Inc. Delaware, USA) 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.
Cognition was assessed in all subjects who completed the computerized *Cogtest* battery (www.cogtest.com) at each time point. The cognitive measures were selected based on the following criteria:

- Key domains impaired in PD including executive function, working memory, attention, and processing speed;
- Measures that correlated with progressive dopaminergic neuronal loss,
- Measures consistent with efficacy measures in PD trials;
- Robust test/retest reliability;
- Administration time less than 30 minutes;
- Culture free measures.

Cognitive Measures:

- **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 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 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.
- **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.
- **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 sec; 5 trials for each hand.
- **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.
- **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

To evaluate the effect of safinamide on cognition, we compared performance at the end of 12 weeks, and at the end of 24 weeks to performance at baseline. 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. Repeated ANOVA models were used to examine within group comparisons for time-points from baseline to 12 and baseline to 24 weeks. 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:	Safinamide low grp	Safinamide high grp	Placebo grp
Age	55 ± 10.3	58.4 ± 11.1	60.2 ± 10.9
Gender:			
% Male	59	66	57
% Female	41	34	43
Ethnicity:			
% Native American Indian	4	2	2
% Asian	43	33	43
% White	53	65	55
Region:			
% Europe	37	42	37
% India	43	31	43
% South America	20	27	20

Executive Function:

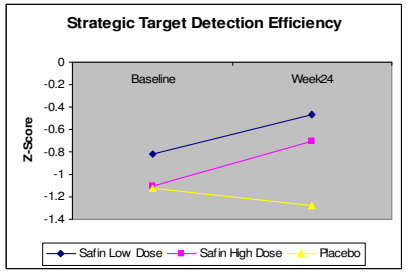
Significant (p=0.03, LSD) group (safinamide low dose vs placebo) differences were seen for the efficiency at which the subject's response (touching the target) approached the position of the target on the screen. This variable is a cumulative measure over all trials of the distance between the screen touch and the actual position of the target.

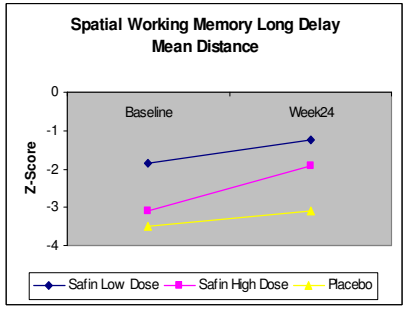
Spatial (visual) Working Memory:

When a 12 sec time delay between target presentation and response was presented, the High dose safinamide group showed an improvement of 1.3SD between baseline and 24 weeks (p = .07).

Auditory Number Sequencing:

Low dose group was superior to high dose (p= 0.03 LSD), while the low dose and placebo were not different.





CONCLUSIONS

In this study of PD patients who were on DA-agonists, improvement in cognition was seen in tests of executive function and working memory, deficits that are central in PD. It is extremely encouraging that in this sample, cognition was carried out on a sub-sample of patients in an exploratory manner but produced these results. It is also noteworthy that these cognitive improvements were seen without any increase in any adverse events compared to placebo.

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