Published in final edited form as:

J Neuropsychiatry Clin Neurosci. 2010 ; 22(2): 188–195. doi:10.1176/appi.neuropsych.22.2.188.

The impact of antidepressant treatment on cognitive functioning in depressed patients with Parkinson's disease

Roseanne DeFronzo Dobkin, PhD¹, Matthew Menza, MD^{1,2,3}, Karina L. Bienfait, PhD¹, Michael Gara, PhD^{1,3}, Humberto Marin, MD^{1,3}, Margery H. Mark, MD^{1,2}, Allison Dicke¹, and Alexander Troster, PhD⁴

¹ Department of Psychiatry at the Robert Wood Johnson Medical School

² Department of Neurology at the Robert Wood Johnson Medical School

³ UMDNJ-University Behavioral HealthCare

⁴ Department of Neurology, UNC- Chapel Hill

Abstract

Depression is associated with more rapid cognitive decline in Parkinson's disease (PD). The goal of this study was to examine the impact of the acute (8-week) and longer-term (24-week) antidepressant treatment on cognition in PD and to detail cognitive predictors of treatment response. Fifty-two depressed PD patients were enrolled in an NIH funded randomized-controlled trial of nortriptyline, paroxetine, and placebo. Neuropsychological testing was performed at baseline, and weeks eight and twenty-four. Higher baseline scores on measures of executive functioning, speed of processing, and verbal memory were associated with antidepressant response. Treatment responders did not exhibit larger gains in cognition than non-responders. Findings warrant replication.

Keywords

Parkinson's disease; depression; cognitive functioning

Parkinson's disease (PD) is the second most common neurodegenerative disease in the US, affecting over 1 million individuals. While the motor symptoms that define the illness, such as tremor, rigidity, and postural imbalance, have received a great deal of attention, the non-motor aspects of this condition are increasingly focused upon. Depression, one of the most prevalent non-motor complications in PD {1}, impacts as many as 50% of patients {2,3}. The

Address correspondence to: Roseanne D. Dobkin, PhD, Department of Psychiatry, UMDNJ, Robert Wood Johnson Medical School, D317, 675 Hoes Lane, Piscataway, NJ 08854, Phone: 732-235-4051, Fax: 732-235-3478, dobkinro@umdnj.edu.

Disclosure:

Roseanne DeFronzo Dobkin, PhD- Research Support: National Institutes of Health (NINDS).

Matthew Menza, MD- Research Support: National Institutes of Health (NINDS), Astra-Zeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Forest Laboratories, GlaxoSmithKline, Lilly, Pfizer, Sanofi-Aventis, Sepracor, Takeda Wyeth. **Consultant:** National Institutes of Health (NIMH, NINDS), GlaxoSmithKline, Kyowa, Lilly Research Laboratories, Pfizer, Sepracor, Takeda. **Speaker:** Sanofi-Aventis. **Stocks:** None. **Other Financial:** None

Karina Bienfait, PhD - None

Michael Gara, PhD - None

Humberto Marin, MD - Research Support: National Institutes of Health (NINDS), GlaxoSmithKline, Lilly, Sanofi-Aventis, Sepracor, Takeda. **Consultant:** Lilly Research Laboratories.

Margery Mark, MD- Research Support: Kyowa, Cephalon. **Speaker:** Allergan, Boehringer Ingelheim, GlaxoSmithKline, Valeant.

Allison Dicke - None

Alexander Troster, PhD- Research Support: Medtronic. **Consultant:** Medtronic, Advanced Neuromodulation Systems.

high prevalence of depression in PD is of great clinical significance as it has a documented negative impact on quality of life, self-care, family relationships, and physical disability {4, 5,6}.

Moreover, depression has been linked to more severe and more rapidly progressive cognitive decline in PD {7}. For example, difficulties with memory, attention, language, and executive functions have been frequently observed in PD and are often exacerbated by depression, especially when that depression is pronounced {8,9,10,11}. Of these various cognitive abilities, memory, and to a lesser extent language (i.e., verbal fluency and naming), appear to be the most severely affected by depression {2,3,8,9,10,12}. While these cognitive changes are independently detrimental to the patient's well-being {13} and have been found to predict non-response to psychopharmacological treatment in the aged {14,15,16}, they also further intensify the social, occupational, and functional impairment caused by both PD and depression.

Despite the deleterious impact of depression in PD (dPD), there are few well-designed treatment outcome studies that can guide clinical care. Moreover, few studies have investigated the impact of antidepressant treatment on the various aspects of cognitive functioning in PD, or the extent to which cognition affects antidepressant treatment response in this population {17,18}. In an NIH-funded, randomized, double-blind trial of nortriptyline, paroxetine and placebo for the treatment of dPD, we have recently demonstrated that nortriptyline was superior to placebo for the acute treatment of depression over an 8- week period {19} and that both active drugs were superior to placebo for the prevention of relapse over a 24-week period {20}. The purpose of this paper is to describe the neuropsychological findings obtained after the acute and longer-term treatment of depression in this randomized controlled trial, and to detail cognitive predictors of treatment response.

Method

Overview

This randomized controlled double-blind trial of nortriptyline, paroxetine, and placebo had 2 phases; an 8-week acute treatment phase and a 4 month extension phase. In the acute treatment phase, clinical response was defined a priori as a 50% reduction in baseline to endpoint score on the Hamilton Depression Rating Scale (HAM-D) {21}. However, patients were eligible to enter the extension phase of the study if they were rated at least minimally improved on the Clinical Global Impression Improvement Scale {22} (i.e., CGI-I rating of 1, 2, or 3) at the end of the acute treatment phase and wished to continue with blinded treatment. The results of neuropsychological testing obtained across both phases of this trial are detailed below. The study had the full approval of UMDNJ-Robert Wood Johnson Medical School IRB. All patients signed a statement of informed consent prior to the initiation of any study procedures.

Participants

Patients were recruited from the movement disorders clinic at Robert Wood Johnson Medical School, the New Jersey Chapter of the APDA, and local print media. All participants received free study medication and evaluation sessions, and \$20 for each completed study visit.

Fifty-two patients (27 male, 25 female; age 35–80) with a confirmed diagnosis of PD based on research criteria {23} and a primary diagnosis of major depression or dysthymia based on the Structured Clinical Interview (SCID) {24} for the Diagnostic and Statistical Manual of Mental Disorders 4th ed. (DSM-IV) {25} were enrolled in the acute phase of the treatment trial. Patients with cognitive impairment (MMSE {26} less than 26), “off time” greater than 50% of the day, any comorbid DSM-IV Axis I diagnosis other than an anxiety disorder, or who

had failed two or more adequate trials (dose and length) of an approved antidepressant were excluded from participation. Using additional psychotropic medications other than the study drug was prohibited. Patients maintained a stable dose of their PD medication throughout the trial. All evaluations were completed in the “on” state.

Thirteen additional patients signed consent but did not qualify for participation due to failure to meet the inclusion/exclusion criteria described above. Of the 52 patients who were enrolled, 20 met the a priori criteria for entry into the extension phase of the study (i.e., CGI-I of 1, 2, or 3) and chose to continue blinded treatment.

Measures

Cognition was assessed with a battery of neuropsychological tests designed to evaluate the aspects of cognitive functioning that may be affected in PD. These included the forward and backward digit span subtests of the Wechsler Adult Intelligent Test-Third Edition (WAIS-III) {27}, which assesses auditory attention; the word list recall and recognition subtests of the Wechsler Memory Scale-Third Edition (WMS) {28}, which measure verbal memory; the Boston Naming Test (BNT) {29} and verbal category fluency test (animal naming) which assess different aspects of language; and the Stroop Color-Word test {30}, a measure of both processing speed and executive function (i.e., set switching).

Measures of depression (HAM-D; CGI-I), anxiety (Hamilton Anxiety Rating Scale-HAM-A {31}), sleep (Pittsburgh Sleep Quality Index- PSQI {32}), quality of life (Medical Outcome Study Short Form - SF-36 {33}; Parkinson's Disease Questionnaire- PDQ-8 {34}), and motor functioning (Unified Parkinson's Disease Rating Scale- UPDRS {35}) were also administered over the course of the trial.

Procedure

Preliminary screening was conducted by telephone. Appropriate individuals were scheduled for an in-person evaluation where a detailed medical and psychiatric history was obtained via clinical and semi-structured interviews (SCID), a motor exam was performed (UPDRS), and baseline assessments of depression and anxiety were administered (HAM-D, HAM-A). Patients also completed a packet of self-report measures (PSQI, PDQ-8, SF-36) and a battery of neuropsychological tests (MMSE, Digit Span, recall and recognition subtests of the WMS, Stroop, animal naming, and BNT).

Eligible individuals were randomized, in variable length blocks, to receive equivalent-appearing nortriptyline, paroxetine CR or placebo. Dosing was flexible (based on ranges typical for a geriatric population) and decisions on dose were made at each visit based on efficacy and tolerability, or between visits if the patient was having troublesome side effects (i.e., dry mouth, insomnia). The minimum to maximum doses of study drug were as follows: paroxetine CR 12.5 mg to 37.5 mg; nortriptyline 25mg to 75 mg; placebo 1–3 pills. All patients were instructed to take a single daily dose of the study medication in the evening. All study personnel were blind to group assignment. Neuropsychological testing, and the assessments of depression, anxiety, motor function, sleep, and quality of life were re-administered at the end of the acute (week 8) and extension phases of the study (week 24).

Results

Data was analyzed using SPSS version 15 for Windows. All tests were two-tailed. Data analysis included all patients who had a baseline and at least one follow-up neuropsychological assessment. The results presented below detail the impact of successful antidepressant treatment on cognition in PD, and cognitive predictors of treatment response. The impact of

antidepressant treatment on mood, quality of life, and motor functioning are detailed elsewhere { 19, 20}.

Fifteen patients (28.8%) were treatment responders (>50% reduction from baseline to week 8 HAM-D) while 37 patients (71.2%) were classified as non-responders. In addition to comparing the impact of treatment response and non-response on cognition, several additional between group comparisons are reported below. In all of these analyses, the most impaired subgroup or quartile (i.e., highest scores for depression or disease severity; lowest score for memory or executive function) is compared to the rest of the sample. We chose this grouping so that the whole sample could be included in the analyses and because we were most interested in understanding the differences between patients with more severe levels of disease pathology versus those with lower levels of symptomatology.

Baseline Data

Of the 52 patients enrolled in the trial, 48 had a diagnosis of major depression. Two patients were diagnosed with double depression (dysthymia in addition to major depression), while 2 had only dysthymia. Eighty percent of the cases of major depression were recurrent in nature. The mean age of the sample was 62.2 (SD=8.7), the mean duration of PD was 6.6 years (SD=5.9), the average age of onset was 56 (SD=9.5), and the mode of the sample with regard to stage of illness (Hoehn-Yahr scale) was 2. The average dose of medication was 28.4 mgs for paroxetine CR, 48.5 mgs for nortriptyline (with a mean nortriptyline level of 74.88) and 2.7 pills for placebo.

Mean baseline scores on neuropsychological measures of attention, memory, and language all fell within the average range in this sample. The sample as a whole scored well below average on the Word and Color subscales (speed of processing) of the Stroop test. Because patients were so impaired in these areas, no Stroop effect was observed (i.e., mean scores on Color-Word, the executive function portion of the task, were higher than mean scores on the Word and Color subscales). See Table 1. In addition, one-way ANOVAs indicated that there were no significant differences between drug groups on any of the baseline neuropsychological measures (p values range from .17 to .98).

Baseline cognition, depression, and duration of PD—Exploratory t-tests were conducted to compare the neuropsychological test results of patients who scored in the top quartile for depression (i.e., most depressed; HAM-D >22) to those with ratings in the bottom three quartiles (HAM-D range of 10–21). While there was no significant difference between patients with higher versus lower depression on the MMSE ($p=.89$), patients with higher levels of depression performed significantly worse on baseline measures of language (Boston naming, $t(49)=-2.35$, $p=.02$; category fluency, $t(49)=-3.32$, $p=.002$) and memory (recall, $t(49)=-1.97$, $p=.05$; delayed recall, $t(49)=-2.20$, $p=.03$) compared to those with less severe depression ratings.

Exploratory t-tests also indicated that longer (top quartile 10–20 years) vs. shorter (bottom 3 quartiles 1–9 years) duration of PD was associated with poorer performance on both the Word subscale of Stroop (speed of processing; $t(49)=-2.87$, $p=.006$) and composite Stroop test score (speed of processing and executive functions [attention/response inhibition]; $t(50)=-2.05$, $p=.05$). However, there was no significant difference in baseline depression scores between patients who had PD for a longer vs. shorter period of time ($p=.81$). In addition, no significant difference in baseline depression was found between those who scored highest (top quartile) versus lower (bottom 3 quartiles) on the measures of disease severity (UPDRS total and motor subscale scores, $p=.59$ and $.10$, respectively).

Baseline cognition and response to treatment—Exploratory t-tests indicated that treatment responders (> 50% reduction in baseline to week 8 HAM-D score) had significantly higher baseline scores (i.e., were less impaired) on measures of speed of processing/executive functioning (Stroop composite score, $t(50)=2.80$, $p=.007$; Stroop Word, $t(49)=2.45$, $p=.018$; Stroop Color, $t(49)=2.53$, $p=.015$; Stroop Word-Color, $t(49)=1.89$, $p=.07$) and memory (composite score reflecting word list recall, delayed recall, and recognition, $t(50)=2.05$, $p=.046$; individual memory subscales ns).

Acute Phase of Treatment

Neuropsychological predictors of acute treatment response—Because patients who were treatment responders in the acute phase had significantly higher baseline scores on measures of both speed of processing/executive functioning and memory, we used logistic regression to examine if higher (top three quartiles; better performance) vs. lowest (bottom quartile; poorest performance) scores in these cognitive domains were predictive of treatment response, when considering potential confounding variables. When controlling for baseline depression (HAM-D), age, duration of PD, and the effect of drug (also a significant predictor), a “higher” Stroop composite score at baseline remained a significant predictor of treatment response (Wald $\chi^2(1)=4.07$, $p=.04$; OR=10.96). A “higher” baseline composite memory score (Wald $\chi^2(1)=.478$, $p=.49$, OR=1.81) however, was not a significant predictor of treatment response when controlling for the aforementioned variables. See Table 2.

Effect of depression treatment response on cognition—Repeated Measures ANOVA indicated that there were no significant group (responder status; > 50% reduction in baseline to week-8 HAM-D score) by time interactions on any of the neuropsychological measures in the acute treatment phase (p values range from .10 to .889). Therefore, depression “responders” did not demonstrate larger improvements in cognition than non-responders. In addition, there was no correlation between change in patients’ HAM-D scores and change in their performance on any neuropsychological measure between baseline and week 8 (p values range from .55 to .78). Extension Phase of Treatment Because only twenty patients entered the extension phase of the study, there was not sufficient power to examine neuropsychological predictors of long-term treatment response or to compare differences between responders and non-responders in this phase of treatment. However, we did examine the impact of longer-term treatment of depression on cognition for all patients who met the criteria to enter the extension phase of the study (at least minimally improved on the CGI-I after 8 weeks of treatment). Results of Repeated Measures ANOVA suggested that patients who entered the extension phase of the study demonstrated significant improvements in verbal memory (composite score, $F(2,17)=7.93$, $p=.004$; word recall, $F(2,16)=9.12$, $p=.002$; word recognition, $F(2,16)=5.50$, $p=.02$; word delayed recall, $F(2,16)=6.09$, $p=.01$), and one test of language (BNT, $F(2,16)=6.37$, $p=.009$) over the course of the study. Planned contrasts indicated that significant improvements in the verbal memory composite score ($F(1,18)=16.70$, $p=.001$) and immediate recall ($F(1,17)=16.97$, $p=.001$) were evident by the end of the acute phase and maintained throughout the end of the extension phase (composite, $F(1,18)=7.72$, $p=.01$; recall, $F(1,17)=6.26$, $p=.023$). Gains specific to delayed recall ($F(1,17)=12.36$, $p=.003$) and recognition ($F(1,17)=11.40$, $p=.004$) were observed at week 8, but week 24 scores on these domains were not significantly different from baseline (.10 and .15, respectively). Improvements on the Boston Naming Test, however, were not apparent until the extension phase of the study ($F(1,17)=13.05$, $p=.002$) (i.e., no change between baseline and week 8, but significant change noted between baseline and week 24). No notable changes were observed in a second test of language (verbal fluency-animal naming, $p=.257$), or measures of attention (digit span, $p=.386$) or executive function (Stroop, p values range from .258 to .692).

Effect of Drug on Cognition- Acute and Extension Phase

Repeated Measures ANOVA indicated that there were no significant group (drug) by time interactions on any of the neuropsychological measures in either the acute (p values range from .10 to .89) or follow-up period (p values range from .15 to .90). Therefore, neither paroxetine, nortriptyline, nor placebo were associated with either an improvement or worsening of cognitive functioning in either short or longer-term treatment.

Discussion

This is one of few studies to examine the impact of antidepressant treatment on cognition in patients with Parkinson's disease and depression. Overall, results indicated that higher baseline scores on measures of speed of processing and executive functions (Stroop) predicted acute treatment response, even when controlling for confounding factors such as age, duration of PD, baseline depression, and the effect of drug (with nortriptyline superior to placebo for the acute treatment of depression as detailed elsewhere {19, 20}). However, while these aspects of cognitive functioning appeared to predict short-term treatment response in this population, no area of cognition was found to improve as a result of successful antidepressant treatment after the end of the 8-week acute phase. Patients who demonstrated "response" to antidepressant treatment scored higher on baseline measures of cognition (i.e., verbal memory, speed of processing, executive functioning), compared to patients who did not respond, but their scores did not improve over the course of treatment. Moreover, neither paroxetine nor nortriptyline appeared to have negative effects on cognition in the context of short (8 weeks) and longer-term (24 weeks) antidepressant treatment. Finally, consistent with past cross-sectional studies {8,9,10,11,12}, more severe depression was associated with poorer performance on baseline tests of memory and language and no Stroop effect was observed {36,37}.

There are few studies with which to compare these results in PD. In one of the limited studies conducted within the dPD population, Weintraub et al. also found higher baseline scores of verbal memory to be associated with increased rates of treatment response with escitalopram, and that treatment "response" was not associated with any type of improvements across a variety of cognitive domains {17}. However, in contrast to our study, these authors did not find an effect for either baseline psychomotor speed or executive functions on treatment outcome. Yet, the small sample size and limited rates of response in Weintraub et al.'s study make it difficult to aggregate these findings. In addition, dopamine agonists, such as pramipexole, have been shown to have negligible effects on working memory and attention in dPD, despite their potential antidepressant effects {18}.

Several of our findings are also consistent with the geriatric depression literature. For example, speed of processing, verbal memory, and executive functions have been found to be predictive of antidepressant treatment response in several studies in the aged {14,15,16}. While research concerning change in cognitive status is mixed, some studies have indicated that efficacious antidepressant treatment is not associated with cognitive gains in the elderly {38,39,40}. Furthermore, one study found that older patients with little cognitive impairment prior to treatment did not experience cognitive gains following antidepressant therapy whereas patients who were more impaired did exhibit improvements following treatment {40}.

Therefore, one possibility for our finding that responders did not improve more than non-responders on neuropsychological measures after acute treatment may be the fact that patients did not demonstrate gross impairments on the neuropsychological measures at baseline (with the exception of Stroop). This pattern of average baseline performance and lack of change over time is consistent with that observed by Rektorova et al. in their study investigating the efficacy of dopamine agonists on depression and cognition in PD {18}. It is also likely that both the

small sample size, the limited range of scores observed on many of the neuropsychological measures (potentially because the majority of our patients presented in the earlier stages of PD), and the mild to moderate levels of depression reported by the majority of the sample (as more severe depression has a greater deleterious impact on cognition {41}) restricted our ability to detect cognitive changes between responders and non-responders.

Alternatively, it is possible that the neuroanatomical changes that characterize PD (i.e., degeneration of dopaminergic cells in the substantia nigra, dysfunction of cortico-striatal circuits instrumental in frontal brain functions, and presence of diffuse Lewy bodies {13}) are the main contributor to the cognitive deficits observed in this population. For example, because Stroop score, (predictive of treatment response), was associated with PD duration but not depression at baseline, poor Stroop performance may be more sensitive to PD than depression {42}. As a result, poor performance on this test may index more severe disease and widespread neuropathology, making treatment response less likely for this reason. For the same reason, and because poor performance on select cognitive tasks (such as Stroop) may not be related to depression, successful treatment of dPD may exert minimal impact on certain aspects of cognition (i.e., executive functions, speed of processing) as it cannot reverse the structural brain changes inherent in the disease process.

Limited conclusions may be drawn from the extension phase data given the small sample size and lack of power needed to make between group comparisons. Yet, it is interesting to note that improvements in language (i.e., naming) were not observed until the extension phase of the trial for patients who opted to continue with blinded treatment. This finding may suggest that longer term treatment of depression may lead to sustained improvement in this cognitive domain. However, in the absence of a comparison condition (all patients who entered the extension phase were at least partially improved, though not necessarily “responders”), interpretation of this finding is difficult and the role of practice effects, though thought to be small in PD {43}, can not be dismissed.

In conclusion, our findings suggest that higher baseline performance on measures of executive functioning, speed of processing, and verbal memory was associated with antidepressant treatment response in PD. However, “responder status” was not linked with any improvements or changes in cognitive status during the acute phase of treatment. Improvements in language noted during the extension phase must be interpreted with caution given the absence of a comparison condition. As this is one of few studies examining the impact of treatment of depression on cognition in PD, further research is needed to replicate these findings.

Acknowledgments

This study was supported by a grant from the National Institute of Neurologic Disorders and Stroke (NINDS) RO1NS043144. GlaxoSmithKline provided free paroxetine CR and matching placebo. Clinical Trials Registration: Clintrials.gov Identifier: NCT 00062738.

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Table 1

Means (T-scores) and Standard Deviations for Baseline Neuropsychological Measures

Measure	Mean	Standard Deviation
Digit Span	53.65	8.91
WMS Immediate Recall	46.16	11.52
WMS Delayed Recall	55.57	7.83
WMS Recognition	52.14	8.60
Boston Naming Test	48.49	15.10
Category Fluency	53.59	11.33
Stroop Word	34.96	14.31
Stroop Color	33.92	11.12
Stroop Color-Word	42.67	12.86

Table 2

Logistic Regression- Predictors of Treatment Response

	Wald χ^2	p-value	Odds Ratio
<u>Stroop</u>			
Baseline HAM-D	0.60	.44	
Age	1.07	.31	
Duration of PD	0.35	.55	
Drug **	7.84	.02	
(Paxil v. Placebo)	0.91	.34	.37
(Nortriptyline v. Placebo)	3.66	.06	5.14
Stroop Higher v. Lowest	4.07	.04	10.96
<u>Memory</u>			
Baseline HAM-D	1.70	.19	
Age	1.38	.24	
Duration of PD	0.25	.62	
Drug	7.69	.02	
(Paxil v. Placebo)	1.23	.27	.31
(Nortriptyline v. Placebo)	3.12	.08	4.16
Memory Higher v. Lowest	.48	.49	1.81

** Please note that drug is also a significant predictor of treatment response as detailed in prior publications (19, 20), with higher response rates noted amongst patients taking nortriptyline vs. placebo. Baseline Stroop score remained a significant predictor of treatment response even when controlling for this variable.