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Parkinson's Disease Severity and Use of Dopaminergic Medications

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Abstract

Background—The effects of dopaminergic therapy in Parkinson's disease (PD) can vary depending on the class of medication selected.

Objective—The aim of this *post hoc* study was to determine if the class of dopaminergic therapy correlated with disease severity in persons with early, treated PD.

Methods—A non-parametric global statistical test (GST) was used to assess the status of participants treated with dopamine agonist (DA) monotherapy, levodopa (LD) monotherapy or combined LD and DA therapy on multiple PD outcomes encompassing motor, cognitive, psychiatric and autonomic function, as well as disability and quality of life.

Results—The outcomes measured at the beginning of the study showed lower disease burden for participants on initial DA monotherapy compared to those taking combined LD and DA therapy after controlling for age, education, taking cogmeds and amantadine.

Conclusion—This observation suggests that clinicians treating early PD patients favor combined LD and DA therapy in patients with more disabling features over DA monotherapy. As such, studies of PD progression in treated PD patients may be affected by the class of symptomatic dopaminergic therapy.

1. Introduction

Factors influencing the selection of the initial dopaminergic therapy in early Parkinson disease (PD) are not well understood and likely multifactorial. Studies comparing levodopa (LD) and dopamine (DA) agonist monotherapy in previously untreated PD indicate that initial LD monotherapy is more effective in reducing motor symptoms and disability, whereas initial DA monotherapy is associated with less wearing off and a lower risk of developing dyskinesia. [1,2,3,4] The relationship of the initial dopaminergic treatment choice and the severity of early PD symptoms for those starting therapy independent of a randomized study is unknown.

The NET-PD (National Institute of Neurological Disorders and Stroke Exploratory Trials in PD) Long-term Study-1 (LS1, NCT00449865) was a multicenter, double-blind, randomized clinical trial of potential disease-modifying efficacy comparing creatine to placebo. [5] To be eligible, subjects were required to have the diagnosis of PD within 5 years and also to be taking dopaminergic therapy for more than 3 months but less than 2 years of study enrollment. Dopaminergic therapy choices for LS1 participants were made both by community providers and movement disorders specialists. LS1 was the largest clinical trial of its type, and participating centers spanned 43 population centers of the United States and two sites in western Canada.

A *post hoc* analysis of the baseline data from LS1 subjects offers an opportunity to answer the question whether the class of dopaminergic therapy at baseline is associated with disease severity. Multiple clinical rating scales were utilized, encompassing both motor and non-motor components. Since prior studies of motor disability and quality of life in PD have shown greater efficacy of LD compared to DA, we sought to determine whether the type of

dopaminergic therapy taken by LS1 participants is associated with nine broadly-based outcomes of PD severity.

2. Methods

2.1 LS1 Inclusion and Exclusion Criteria

A total of 1741 participants were enrolled in the LS-1 study over a 3-year period (March 13, 2007-May 28, 2010). Subjects were required to be taking dopaminergic therapy (levodopa and/or dopamine agonist) for at least 90 days but not more than 2 years. At baseline, early-stage PD participants were asked to recall all medications taken during the prior 180 days (recall window). Prior to beginning this *post hoc* analysis, we excluded 140 participants from the LS1 cohort on account of the following: 3 not taking any dopaminergic therapy at baseline, 65 initiating dopaminergic treatment outside the specified window, 32 with predefined criteria of excessive disease severity or misdiagnosis, and 25 with missing covariate data. Excessive disease severity was defined as any of the following: (1) motor dysfunction inconsistent with mild PD (Unified Parkinson's Disease Rating Scale [UPDRS] >60 total or >50 on Part III), (2) poor functional status (Schwab and England <60 or Parkinson's Disease Questionnaire-39 [PDQ39>50]), or (3) poor cognitive performance (Symbol-Digit Modality [SDM] <10). Thus, 1601 participants (92% of total LS1 participants) were eligible and included in this analysis.

2.2 Global outcome measure

A global statistical test (GST) was employed to evaluate a global outcome measure of PD severity, incorporating nine assessment scores felt to correlate with disease severity: (i) total UPDRS, (ii) PDQ39, (iii) Scales for Outcomes of Parkinson disease – Cognition (SCOPA-COG), (iv) SDM total correct responses, (v) Beck Depression Inventory (BDI), (vi) sleep disturbances (e.g. insomnia or hyper-somnolence), (vii) anorexia, nausea or vomiting, (viii) thought disorder (e.g. question 2 of the UPDRS I and question 33 from the PDQ39) and (ix) orthostatic hypotension. To facilitate the GST analysis coding was reversed for SCOPA-COG and SDM, making higher numerical values represent worse severity for all outcome measures. Summary statistics of these individual scores are presented without reversing their coding.

2.3 Orthostatic hypotension

To provide a sensitive method to identify mild dysautonomia, the presence of any of these four criteria was used to define orthostatic hypotension: (i) > 13 mmHg decline in mean arterial pressure (MAP) from sitting to standing, (ii) > 20 mmHg decline in systolic pressure, (iii) >10 mmHg decline in diastolic pressure or (iv) an affirmative answer to question 11 of the UPDRS IV (presence of symptomatic orthostasis).

2.4 Dopaminergic Therapy Ascertainment

Study participants were classified into one of three groups depending on the dopaminergic therapy that they were receiving: (1) LD monotherapy, 2) DA monotherapy, or 3) combined therapy with LD and DA. All 3 groups could include participants taking adjunctive non-dopaminergic therapy. For this analysis “monotherapy” is intended to indicate participants

taking a single dopaminergic agent (DA or LD). Participants using DA monotherapy were used as the reference category for dopaminergic therapy exposure.

2.5 Covariates

Analyzed covariates included demographics, i.e., age, highest level of education, and body weight (kg); total levodopa equivalent daily dose (LEDD); concomitant medications and medications that were felt to likely impair cognitive performance (cog-meds). LEDD was determined by a modification of the method described by Tomlinson. [6] The complete list of reported medications was reviewed by three neurologists (JF, JG and ML) who identified cog-meds by class. Broad categories of cog-meds included: anticholinergics, antidepressants, antispasmodics, narcotics, and sedatives (See appendix.) Adjunctive symptomatic PD medications were also identified and analyzed by class including amantadine, COMT-I, MAO-I, and any other adjunctive medications, such as supplemental carbidopa.

2.6 Statistical methods

To evaluate whether the dopaminergic therapy taken by LS1 participants at baseline was associated with PD severity, we compared the mean summed ranks of the nine assessment scores between the three exposure variable levels (LD, DA, combined therapy) using the global O'Brien non-parametric statistical test. [7] Where the GST was significant, a crude analysis without adjustment for covariates using univariate testing of the individual outcomes was conducted at the two-sided nominal type-I error level of 0.05 via analysis of variance for continuous outcomes and chi-square statistics for the binary outcomes.

Two multivariable models were pre-planned to adjust for covariates: (i) one full model regressing the summed ranks of the GST on all the pre-planned covariates in addition to the exposure variable; and (ii) a reduced model obtained by limiting the covariates in the model that were not observed to be significant on simple linear regressions of each covariate on the summed ranks of the GST, using a p-value of <0.20. A partial F-test was used to compare between the pre-planned full and reduced model to select the final model. Parameter estimates with standard errors and p-values are reported for both models. Diagnostics methods (i.e. normality of the residuals, homogeneity of the variance) were conducted for the final model. Given that GST was significant in the final model for the exposure variable, adjusted testing of the individual outcomes was conducted at the two-sided nominal type-I error level of 0.05 using linear regression for continuous outcomes and logistic regression for binary outcomes.

3. Results

Table 1 describes the summary statistics (mean with standard deviations, or proportions) of each of the nine assessment scores as a total and by the dopaminergic therapy that participants were taking at baseline. The global O'Brien non-parametric rank sum F test was 6.17 with 2 and 1598 degrees of freedom ($p=0.0021$). There were statistically significant differences in the mean summed ranks of the nine assessment scores among the type of dopaminergic therapy taken by LS1 participants. Without adjusting for covariates, the

following results were observed: (i) the mean total UPDRS and the PDQ39 scores in the LD monotherapy group and the combined LD and DA group were higher (representing more severe symptoms) than that for DA group; (ii) cognitive measures (SCOPA-Cog and SDM) were slightly worse in the LD monotherapy and combined LD and DA groups compared to the DA monotherapy group and (iii) among the nine measures, only BDI, orthostatic hypotension and presence of thought disorder showed no difference with the type of dopaminergic therapy.

The full model analysis (Table 2) shows the association of the type of dopaminergic therapy on the summed ranks of the GST after adjusting for age, education, taking cog-meds, taking amantadine, taking other PD-adjunctive medications, LEDD, and weight. Age, education, taking cog-meds, and taking amantadine were statistically significant in the simple regression models and associated with the summed ranks of the GST using $p < 0.20$. The reduced model (Table 2) shows the association of the type of dopaminergic therapy on the summed ranks of the GST after adjusting for age, education, taking cog-meds and taking amantadine. The partial F-test statistic comparing the full versus the reduced model was 0.29 with 5 and 1587 degrees of freedom, indicating that the reduced model should be preferred. Although the reduced model did not reach normality of the residuals or homogeneity of the variance, we relied on the robustness of the regression model for departure from these assumptions given the large sample size. Use of combined therapy with LD and DA at baseline had higher summed ranks of the GST, i.e., more severe PD symptoms, compared to those taking DA monotherapy at baseline after controlling for age, education, taking cog-meds, and taking amantadine ($p=0.02$).

Adjusted testing of the individual outcomes was conducted on the reduced model: PDQ39 was the only one of the nine outcomes that was significantly different when comparing LD +DA therapy with DA monotherapy after adjusting for age, education, taking cog-meds, and amantadine.

4. Discussion

The LS1 participants taking combined LD+DA therapy had more severe PD symptoms and worse cognitive function compared to those on DA monotherapy after controlling for age, education, taking cog-meds and taking amantadine. Although these results could suggest that participants taking DA monotherapy were more optimally treated than the other participants in LS1, there are several alternative explanations: (1) More severely affected PD patients may not adequately respond to DA monotherapy, and LD may have been added, (2) Clinicians may favor DA monotherapy for less severely affected patients, or (3) Clinicians may employ a strategy of combination therapy to avoid side effects generated by using a DA monotherapy at a higher dose. Determining which of these explanations is correct would require a randomized, head-to-head clinical trial of LD vs. DA vs. combined therapy with LD and DA. Although we cannot specifically address that question with this study, our data do support the interpretation that clinicians use combined therapy in more severely affected patients or dopamine agonist monotherapy in less severely affected patients. Why clinicians did not use LD monotherapy and DA monotherapy equally in less severely affected patients remains unknown. Furthermore, determining whether any particular dimension in the

PDQ-39, such as motor dysfunction, mood alterations, sensory dysfunction or caregiver strain, guided the overall observations could not be determined in this study.

Interestingly, although it might be expected that treating clinicians would select either LD monotherapy or LD and DA therapy in patients with greater disease burden, using the global outcome scale, we did not find a difference in the LD monotherapy group compared to the DA group. Instead, only the combined LD and DA group scored worse on severity of motor symptoms and cognition. This observation suggests that patients with early, mild PD taking combined LD and DA therapy may benefit from switching to either LD or DA monotherapy. Notably, this *post hoc* analysis is limited by the factors and outcomes available for analysis. In addition, the study population was not specifically recruited to address the relationship between symptomatic treatment and baseline outcome. Thus, unmeasured covariates, particularly disease features not fully captured by the outcome rating scales, and recruitment bias are potential confounding factors to consider.

More broadly, our observations suggest that clinical trials of subjects already taking dopaminergic therapy need to account for or balance the distribution of participants taking combination DA plus LD therapy and those taking monotherapy, particularly when disease severity and cognitive function are components of the outcome analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

PD	Parkinson's disease
UPDRS	Unified Parkinson's Disease Rating Scale
SBP	systolic blood pressure
DBP	diastolic blood pressure
MAP	mean arterial pressure
PDQ39	Parkinson's Disease Questionnaire -39
SDM	Symbol Digit Modality
BDI	Beck Depression Inventory
GST	Global Statistical Test
NINDS	National Institute of Neurological Disorders and Stroke
LS1	Long-term Study -1

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Highlights

- This is a post hoc study from the LS1 clinical trial.
- We examined a set of clinical metrics of more severe Parkinson's disease.
- Using a global statistic the metrics correlated with type of dopaminergic therapy.
- Subjects taking dopamine agonist monotherapy were less severe than their peers.
- This difference was maintained after adjusting for several covariates.

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Table 1

Summary statistics of the global outcome measure as a total and the dopaminergic therapy at baseline of LS1 participants.

Outcome	Levodopa (n=622)	Dopamine Agonist (n=691)	Levodopa and Dopamine Agonist (n=288)	Total (n=1601)
UPDRS Total (Mean(Std))	26.3(10.8)	24.6(10.0)	26.5(11.6)	25.6(10.7)
PDQ39 Summary Index(Mean(Std))	12.8(9.8)	11.9(9.0)	14.2(10.2)	12.7(9.6)
SCOPA-COG total(Mean(Std))	29.1(5.3)	31.3(5.0)	30.6(5.2)	30.3(5.3)
SDM (total correct responses) (Mean(Std))	41.6(12.0)	47.2(10.7)	45.2(10.9)	44.7(11.5)
BDI (Mean(Std))	6.9(5.2)	6.3(5.0)	6.8(5.2)	6.6(5.1)
Subjects with sleep disturbances (e.g. insomnia or hypersomnolence) (%)	31.7	37.9	40.6	36.0
Subjects with anorexia, nausea or vomiting (%)	12.1	8.8	13.9	11.0
Thought disorder (%)	42.3	33.0	37.8	37.5
Orthostatic hypotension (%)	26.0	22.0	25.0	24.2

Table 2

Association of the type of dopaminergic therapy taken at baseline on the sum of the ranks adjusting for covariates

	Full Model			Reduced Model		
	Parameter Estimate	**Standard Error**	**P-value**	**Parameter Estimate**	**Standard Error**	**P-value**
Dopamine Agonist versus Levodopa	28.13	107.30	0.79	36.92	94.79	0.70
Dopamine Agonist versus Levodopa and Dopamine Agonist	243.70	133.61	0.07	260.29	112.14	0.02
Intercept	8538.76	339.22	<.0001	8349.49	261.46	<.0001

Full model is adjusted by age, education, taking medications that were felt to likely impair cognitive performance, amantadine, COMT-I (Tolcapone, Entacapone, Stalevo), MAO-I (Rasagiline, Selegiline), other Adjunctive (Co-Q10, Carbidopa alone), levodopa equivalent daily dose at baseline and body weight.

Reduced model is adjusted by age, education, taking cog-meds and amantadine.