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Choice of dopaminergic therapy among early, mild Parkinson disease subjects in North America ☆

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ABSTRACT

The choice of dopaminergic therapy in early Parkinson disease (PD) is an important clinical decision, yet factors influencing this decision have not been extensively studied. We sought to investigate the factors that may be associated with the choice of dopaminergic therapy at the NINDS Exploratory Trials in PD (NET-PD) Long-Term Study-1 (LS1). NET-PD LS1 was a clinical trial of creatine versus placebo in participants with early, mild PD on stable doses of dopaminergic therapy. Baseline data from 1616 out of the 1741 participants were evaluated using univariable and multivariable logistic or generalized logit regression analyses for available factors associated with the choice of dopaminergic therapy. The dopaminergic therapy choice was determined as: (i) therapy that subjects recalled taking 180 days before the study; (ii) therapy at baseline; and (iii) the longest duration of therapy reported by participants. Younger age, higher education level, longer length of time since PD diagnosis and use of an adjunctive, non-dopaminergic or monoamine oxidase inhibitor medication were associated with more frequent use of dopamine agonist compared to levodopa or combination therapy.

1. Introduction

The selection of the dopaminergic therapy in early Parkinson disease (PD) is an important clinical decision, yet the factors that influence this decision have not been studied in detail. The NINDS Exploratory Trials in PD (NET-PD) Long-term Study-1 (LS1) was a multicenter, double-blind randomized clinical trial designed to determine the disease modifying efficacy of creatine [1]. Eligible subjects were required to have been diagnosed with PD within 5 years and to be on levodopa or a dopamine agonist therapy, herein defined as "dopaminergic therapy", for more than 3 months but less than 2 years [2].

The rationale for these entry criteria was to enroll stably treated participants with early PD who were at or near their maximum symptomatic benefit from dopaminergic therapy that could still benefit from disease-modifying therapy [3]. The choices for initial and early symptomatic therapy for PD occurred before study enrollment and were not determined by the study protocol or necessarily directed by the study investigators. The choices of therapy in this cohort of early, mild PD subjects, therefore, reflect contemporary community practice. Given the large sample size and relatively broad inclusion criteria, LS1 provides a unique opportunity to investigate factors that might have influenced the choice of dopaminergic therapy.

Previous studies have evaluated the initial choice of dopaminergic therapy, but have had notable limitations including evaluating cohorts for whom initial therapy was selected prior to the release and marketing of newer dopamine agonists and small sample sizes [4,5]. In some of these published studies, selection of the dopaminergic therapy occurred after study enrollment (e.g., DATATOP, QE2, NET—PD FS1 and FSTOO) and was largely determined by study investigators with subspecialty expertise in PD management [6–9]. In contrast, the selection of the dopaminergic therapy for management of early PD (i.e., within 5 years of

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diagnosis) participants in LS1 occurred before study enrollment and was not directed by study investigators. Treatment choices for LS1 participants were often made by practicing providers in the community encountering a broad range of patients with early and mild PD, who were then enrolled into LS1 using minimal inclusion and exclusion criteria. As such, the factors influencing the choice of dopaminergic therapy for LS1 participants are likely to be relevant to the general population of *de novo* PD subjects seen in community practice.

Factors available for analysis that could affect the early choice of dopaminergic therapy for LS1 study participants included age, gender, race/ethnicity, education, health insurance status, handedness, family history of PD, medical history, duration of PD since diagnosis, use of monoamine oxidase inhibitors and use of non-dopaminergic adjunctive symptomatic medications, and medical comorbidities. We hypothesized that younger age, availability of health insurance, and lower medical comorbidities would be associated with the choice of a dopamine agonist in the early management of PD. Factors associated with the dopaminergic therapy being taken at the time of study enrollment were also evaluated. Finally, we assessed the stability of the category of dopaminergic therapy over the pre-enrollment period by identifying the longest duration of dopaminergic therapy reported by participants over the period of time from initiation of dopaminergic treatment to their screening visit.

2. Materials and methods

2.1. Subjects

The LS1 protocols were approved by institutional review boards of the Clinical Trial Coordinating Center (University of Rochester) and the individual participating sites (NCT00449865). All participants provided written informed consent prior to participation. A total of 1741 participants were enrolled in the LS1 study over a 3-year period (March 13, 2007–May 28, 2010). At the screening LS1 study visit, subjects were asked to recall all medications taken during prior 180 days (recall window) [1,2]. Given the intent to determine factors associated with the choice of dopaminergic therapy at baseline (randomization date) in early, mild PD subjects, baseline LS1 participants was refined to focus on those participants who had typical early stage PD and who had initiated dopaminergic therapy for at least 90 days prior to baseline and less than two years prior to the screening visit. To this end, we excluded 32 participants who fit pre-specified criteria of non-homogeneity that suggested they had atypical or more advanced PD as follows: (1) Modified Ranking Scale >3, (2) Symbol Digit Modality Test Score < 10, (3) modified Schwab and England (S&E) scale <60, 4) PDQ39 quality of life scale ≥50, (4) a total functional capacity score of <5, (5) UPDRS total scale ≥60, and (6) UPDRS motor scale ≥50. Twenty-five participants were excluded because they had a missing data at baseline in at least one of the scores (i.e. UPDRS total, SCOPA-COG total, PDQ39 summary index, Symbol Digit Modality Test Score or Schwab and England(S&E) ADL). We also excluded 68 participants who did not meet eligibility criteria—three subjects were not taking any dopaminergic therapy at baseline, while eight started dopaminergic treatment >913 days prior to screening, 24 reported the longest duration of dopaminergic therapy as <90 days before baseline, and 33 participants were documented to have 1–90 days on dopaminergic therapy at baseline. With these refinements, 1616 participants (93% of total LS1 participants) were included for this secondary data analysis.

2.2. Dopaminergic treatment groups

For the purpose of this analysis, dopaminergic therapy was defined as taking either levodopa or a dopamine agonist, as this was an absolute LS-1 inclusion criteria. Notably, other therapies that could be considered indirect dopaminergic therapy (e.g., monoamine oxidase inhibitors) were not included as dopaminergic therapy for this analysis since their use was not required to participate in the LS-1 study. Use of non-dopaminergic medications or monoamine oxidase inhibitors (rasagiline, selegeline), however, were included as covariate factors. Study participants were classified into one of three groups depending on the treatment they were receiving: (1) levodopa, taken alone or with other antiparkinsonian medications except a dopamine agonist; (2) dopamine agonist, taken either alone or with other antiparkinsonian medications except levodopa; and (3) combined therapy with levodopa and a dopamine agonist. Three outcome scenarios were considered in this analysis based on variations in the method used to determine dopaminergic treatment group classification. Outcome 1, the initial dopaminergic therapy that participants recalled taking during the 180 days prior to their screening visit; outcome 2, the dopaminergic therapy that participants were taking at baseline; and outcome 3, the dopaminergic therapy with the longest duration of time that participants recalled taking before the 180 days preceding the screening visit. The total levodopa equivalent daily dose (LEDD) in milligrams, for dopaminergic therapy participants were taking at baseline was determined by a modification of the method described by Tomlinson [10]. LEDD was not determined for outcome 1 or 3 as the recall of specific doses may be unreliable and could not always be verified.

2.3. Covariates

Baseline data (socio-demographic factors, family history of PD, comorbidities, years since diagnosis of PD and number of adjunctive medications) were used to explore associations with the choice of dopaminergic therapy in early PD. Socio-demographic characteristics included age, gender, race (non-Hispanic, white, and other), being Hispanic, highest level of education, handedness (right, left, or mixed), and insurance status. Handedness was considered because it can affect the interval between onset of symptoms, seeking medical attention and diagnosis. Insurance status was determined using the baseline data query "For US residents only: How would you describe your current health insurance status" with categories of response being no health insurance, private insurance, Medicare, Medicaid, Military care, or other insurance. Participants with private insurance, Medicare, Medicaid, Military care, or other insurance were considered as having health insurance for the purpose of this secondary data analysis.

A family history of Parkinson disease was identified by probing whether their biological mother and father, any full or half siblings were known to have PD or parkinsonism. Medical comorbidities were determined by a modification of the Charlson comorbidity index [11, 12] without adjusting for age, which was already included as separate covariate. A summative comorbidity index was generated by assigned weighted numerical values for the limited set of comorbid disease categories determined at baseline. Participants with a history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, and diabetes without end-organ damage were given a weight score of 1. Participants with hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, tumor without metastases (years from diagnosis <5), leukemia, or lymphoma were given a weight score of 2. Participants with moderate or severe liver disease were given a weight score of 3 and those with a metastatic solid tumor or AIDS were given a weight score of 6. After reviewing the distribution of comorbidity scores at baseline, the categories of comorbidity scores were collapsed into participants without comorbidity (i.e., weight score = 0), participants with at least one comorbid illness (weight score = 1), and participants with multiple or severe comorbidities (weight score ≥ 2).

Symptomatic treatment with monoamine oxidase inhibitors and non-dopaminergic medications was neither required nor exclusionary for enrollment into the LS1 study. Accordingly, all three dopaminergic treatment groups included some subjects who were also taking monoamine oxidase inhibitors and/or non-dopaminergic symptomatic therapy, and others who were not. Reported use of medications other than