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Predicting Progression in Parkinson’s Disease Using Baseline and 1-Year Change Measures

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Abstract

Background: Improved prediction of Parkinson’s disease (PD) progression is needed to support clinical decision-making and to accelerate research trials.

Objectives: To examine whether baseline measures and their 1-year change predict longer-term progression in early PD.

Methods: Parkinson’s Progression Markers Initiative study data were used. Participants had disease duration ≤2 years, abnormal dopamine transporter (DAT) imaging, and were untreated with PD medications. Baseline and 1-year change in clinical, cerebrospinal fluid (CSF), and imaging measures were evaluated as candidate predictors of longer-term (up to 5 years) change in Movement Disorders Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) score and DAT specific binding ratios (SBR) using linear mixed-effects models.

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INTRODUCTION

Understanding the progression of Parkinson’s disease (PD) is crucial to improve clinical management and to enhance therapeutic research. Offering patients accurate prognostic information at the time of diagnosis would inform patient decision making and physician management. Accurate baseline or early disease measures of longer-term outcomes in PD could improve trial efficiency by optimizing accuracy of sample size estimates, reducing required trial duration, and, when desired, informing selection criteria to allow for enrichment of the sample with participants who are at known risk of a given outcome.

An increasing array of possible predictors of PD progression can be explored. Several clinical predictors of motor progression in PD have been identified and replicated with high level of evidence, including age of onset [1] and greater degree of postural instability and gait disorder (PIGD) manifestations [1]. Other measures of motor and neuropsychiatric manifestations may be predictive of motor progression as well [1–3]. However, clinical measures of PD are subjective and fluctuate especially early-on in the disease course [4]. Thus, more objective measures of PD progression are needed, and multimodal models that incorporate both clinical measures and objective biomarkers are being pursued. The Parkinson Progression Markers Initiative (PPMI) study was established with the aim of identifying biomarkers of PD progression. PPMI is a multi-center longitudinal observational study of PD participants that were newly diagnosed and untreated at baseline, and a non-PD comparator group, as previously described [5]. Many groups have applied machine-learning techniques to PPMI data to explore multimodal models for PD diagnosis, subtyping, and modeling of progression [6–8]. While yielding interesting insights and promising results, replication and reproducibility of the models remain to be demonstrated. In addition, machine learning techniques have not yet provided clinically relevant predictive models, despite the integration of massive amounts of multimodal data. For example, in one study, machine learning was applied to 17,499 data points derived from clinical, genetic, imaging, and biofluid biomarker data from PPMI [7]. The best model accounted for 27% of the variation in motor progression, as measured by the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), a validated rating scale comprised of patient- and physician-assessed symptoms and examination findings. Thus, models that account for a greater proportion of the variance in outcome are needed. Much of the literature on predicting PD progression has focused on single measures at a baseline timepoint in longitudinal studies. Given the variability of PD across and within subjects, even early on in the disease, it would be of value to examine whether the short-term change of possible predictors improves the predictive utility of models of progression over the longer-term.

While many tools now exist to measure and define PD progression, change in MDS-UPDRS (or its predecessor UPDRS) remains the most commonly used clinical trial outcome. Among current potential objective measures of disease progression, dopamine transporter (DAT) ligand binding has emerged as a key outcome of interest. DAT binding and MDS-UPDRS motor scores have significant but weak correlation longitudinally [9], and they likely measure different processes and effects on functional outcome. The objectives of this analysis were to examine baseline predictors of change in total and motor MDS-UPDRS and DAT imaging over the first
5 years of PD diagnosis, and to assess the utility of adding the 1-year change of predictors into the predictive models.

METHODS

Sample

PPMI is a multicenter international prospective cohort study. Study aims and methodology have been published elsewhere [5] and are available on the PPMI website (http://www.ppmi-info.org/study-design). Briefly, PD participant enrollment criteria included (i) presence of 2 or more of the following: bradykinesia, rigidity, and resting tremor OR presence of either an asymmetric resting tremor or asymmetric bradykinesia (ii) disease duration from diagnosis of ≤2 years, (iii) dopamine transporter deficit on SPECT imaging. Participants could not be treated for PD or expected to need treatment within 6 months of enrollment. A comparator group of generally healthy individuals without PD (healthy controls, HC) were also enrolled. Enrollment criteria for the HC group were: (i) no significant neurologic dysfunction (ii) no 1st-degree relative with PD (iii) and a Montreal Cognitive Assessment (MOCA) score >26. At enrollment both PD and HC groups could not have contraindications to lumbar puncture or a diagnosis of dementia as determined by the investigator.

Only PD and HC participants with at least 1 post-baseline assessment for at least one outcome were included in this analysis. Data downloaded from www.ppmi-info.org/data on November 6, 2017 were used for this analysis.

Assessments

The following assessments were administered:

- Demographics: age at baseline, gender, education
- Body mass index: weight/height² (kg/m²)
- Motor severity: Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) [10] scores from the baseline and annual assessments during years 1–5 were considered for this analysis. A tremor score and postural instability gait disorder (PIGD) score were generated (see Supplementary Methods) [11]. Once participants started levodopa and/or dopamine agonists (dopaminergic therapy, DT), the MDS-UPDRS total/part III in

the relative OFF and ON medication states were considered separately. The “relative OFF” MDS-UPDRS part III score was obtained after subjects withheld levodopa or dopamine agonist for at least 6 hours. Other PD medications were not held for OFF testing. Previously published work has demonstrated that the duration of OFF did not appreciably influence the change in MDS-UPDRS score over time [9]; also see the Supplementary Materials). The ON MDS-UPDRS part III score was obtained 1 hour after administration of prescribed medications. For a given visit, when OFF testing was not obtained, the MDS-UPDRS OFF score was considered missing and only ON scores were considered.

- Functional abilities: Modified Schwab and England Activities of Daily Living Scale (S&E) was administered at baseline in PD and HC groups and annually in the PD group.
- Cognition: Montreal Cognitive Assessment [12]. Baseline and annual assessments during years 1–5 in the PD and HC were considered for this analysis.
- Psychiatric symptoms: 15-item Geriatric Depression Scale [13] and State and Trait Anxiety Scale [14] were administered. Baseline and annual assessments during years 1–5 were considered for this analysis.
- Autonomic: Scales for Outcomes in PD-Autonomic (SCOPA-AUT) [15] was administered. Blood pressure and heart rate were measured in supine position and standing position. Baseline and annual assessments during years 1–5 were considered for this analysis.
- Sleep/Sleepiness: Epworth Sleepiness Scale (ESS) and REM Sleep Behavior Disorder Questionnaire (RBDSQ) were administered. Baseline and annual assessments during years 1–5 were considered for this analysis.
- Imaging: DAT SPECT scan was performed using the radionuclide ligand DatScan™ as previously described [5] at baseline in the PD and HC group and subsequently at years 1, 2, and 4 only in the PD group. Mean striatal specific binding ratio (SBR; average of putamen and caudate SBR on right and left) and mean putamen SBR were the DAT measures of interest in this analysis.
- PD therapy: PD medication intake was captured in logs. Time to PD medication was ascertained as previously described [16]. Levodopa
equivalent daily dose (LEDD) were calculated as previously described [17].

– Biofluid biomarkers: cerebrospinal fluid (CSF) was collected via lumbar puncture at baseline, 6 months, annually thereafter. β-amyloid 1–42 \([\text{A}\beta 1-42]\), total tau \([\text{T-tau}]\), tau phosphorylated at threonine 181 \([\text{P-tau181}]\), and unphosphorylated α-synuclein \([\alpha-\text{Syn}]\) were measured as previously described [18].

**Analysis**

**Outcome measures of progression**

Three main outcome measures of progression were selected for examination:

1. Absolute change in total MDS-UPDRS score (sum of parts I–III)
2. Absolute change in the MDS-UPDRS part III motor subscore and
3. Percent change from baseline in DAT measures (mean striatal SBR and mean putamen SBR).

Once participants began DT, the MDS-UPDRS part III score was measured in the ON and OFF state, as defined above, and OFF and ON total and part III subscores were considered as outcome measures in separate statistical models (see below).

**Selection of predictors**

The primary objective of this analysis was to identify variables for which the baseline and 1-year change predict longer-term change in PD. All putative clinical, imaging, and biofluid measures collected in PPMI that could be baseline predictors of change and had the possibility to change over time were included (thus, we did not examine genetic predictors). The exceptions were age, gender, and disease duration at baseline, all of which were included in all models to mitigate any potential confounding between identified predictors and the outcome.

Variables were selected as candidate short-term change predictors (STP) if they met the following criteria:

1. Significant difference in change from baseline to 1 year in the PD group vs. the HC group (for variables measured in both groups at these time points; this step was necessary in order to focus on STP specific to PD and not those that change in the course of “normal aging”) and
2. Significant change in the PD group from baseline to 1 year

An exception to these criteria was made for S&E and DATscan SPECT since these were only performed longitudinally in the PD group. These measures were selected as STP if they changed significantly in the PD group over 1 year.

For selection of the STP, significant change was defined statistically as \(p < 0.05\), using two-sample \(t\)-test, Wilcoxon signed rank sum, or McNemar’s test as appropriate.

**Model building**

As mentioned, data were limited to PD subjects with at least 1 annual follow-up \((n = 413)\). Baseline characteristics were summarized using descriptive statistics. The analysis was conducted in 4 steps.

Step 1: Each outcome was modeled from baseline to last follow-up (up to year 5) with linear and non-linear time models and a variety of covariance structures (see Supplementary Material; Supplementary Table 1). The optimal model fit for the MDS-UPDRS and mean striatum outcomes was a linear time model with a random intercept and slope and an unstructured covariance structure. The optimal model for mean putamen was a linear time model with a random intercept and an unstructured covariance structure.

Step 2: Next, associations between the outcomes and baseline predictors were examined by fitting pseudo-univariate models including the predictors of interest with a model adjusted for the baseline value of the respective outcome. The term pseudo-univariate (as opposed to univariate) is used to denote that baseline age, gender, and baseline disease duration were forced into the backwards selection model along with the baseline outcome value (regardless of their \(p\)-value). All baseline predictors that had a \(p\)-value < 0.20 were next included in a multivariate model. The multivariate linear mixed-effects model was reduced to a final model using backwards selection where predictors with \(p\)-values > 0.10 were eliminated.

Step 3: After the best-fit models were constructed with the baseline predictors, we next incorporated the STP variables. To examine whether the STP add any additional predictive ability to the model, above that of only baseline predictors, we adjusted all STP models for the significant baseline predictors identified in step 2, along with baseline age, gender, baseline disease duration, and the baseline outcome value. For the models examining STP, change in the key outcomes was measured from year-2 to last follow-up (up to year 5). Thereby, associations between the key
outcomes (starting at year 2 to last follow-up) and STP were tested. All STP with a $p$-value <0.20 were included in a multivariate model. Backwards selection was performed on the multivariate model using a 0.10 significance level.

Step 4: In order to compare the amount of variation explained by the addition of the STP, a method by Seyla et al. [19] was used to compute a coefficient of variation, $R^2$, for each of the final multivariate models. The $R^2$ was calculated by computing the proportion of the variance accounted for by the predictors:

$$R^2 = \frac{V_{null} - V_{full}}{V_{null}},$$

where $V_{null}$ is the residual variance of a model with only random effects and $V_{full}$ is the residual variance of a model with predictors and random effects. To ensure the reduction in variance was only due to the predictors, the variance explained by the random effects was held constant at that of the final STP models. For comparison, it was also necessary to model the outcomes over the same time points and with equal sample sizes to the final STP models.

To evaluate the replication stability of selected predictors in our models we performed cross-validation. The data were randomly split in two folds without replacement to form a training and a test data set. The training data set was fit with pseudo-univariate models and backwards selection was performed with the test data set. The same model building was performed in each step as described above. The number and percent of times the predictor was in the final backwards selection model was reported out of 1000 iterations [20, 21]. Higher selection percentage (SP) indicates more validity of the predictor. The fold assignment was varied at each iteration so that the pseudo-univariate and multivariate models were fit on a different subset of the data each iteration. Within each iteration, the same grouping was used when fitting each pseudo-univariate model for the various predictors. Selection frequencies are not reported for variables forced into the multivariate models since they are not considered in the backwards selection algorithm.

RESULTS

413 PD and 185 HC participants were included in this analysis (Table 1). Mean age was 61.69 (SD 9.77) years and 61.01 (SD 11.16) in the PD and HC groups respectively. 339 (82.08%) were enrolled at US sites and 74 (17.92%) at non-US. Other baseline and year 1 characteristics of this cohort are shown in Table 1. Summary statistics for each of the outcome measures are shown in Table 2.

Median follow up time for the PD group was 60 months. 375 participants (91%) of the sample had at least 3 years of follow-up.

Pseudo-univariate relationships between each baseline predictor and the outcome measures are shown in Supplementary Table 2, as are the relationships for these variables with the outcome measures examined in the final models (after backwards selection was applied as per step 2 of the model building, as described above). The selection frequencies from the cross-validation are also shown in Supplementary Table 2.

**Multivariate models of baseline predictors of long-term change in MDS-UPRDS**

Table 3 (Supplementary Table 2) shows significant ($p \leq 0.10$) baseline predictors of change from baseline of total MDS-UPRDS score in the OFF state. These were baseline disease duration, MDS-UPDRS total score in the OFF state, male gender, CSF amyloid-$\beta_{1-42}$ (SP = 28.6%), mean striatum SBR (SP = 16.1%), orthostatic SBP (SP = 0.1%), and SCOPA-AUT (SP = 1.2%).

Baseline MDS-UPDRS total score in the ON state, male gender, CSF amyloid-$\beta_{1-42}$ (SP = 7.5%), MoCA score (SP = 1.4%), and SCOPA-AUT score (SP = 0.70%) were significant predictors for the model examining total MDS-UPRDS score in the ON state.

When the change from baseline in the part III subscore of MDS-UPDRS in the OFF state was examined as the outcome, significant predictors were baseline disease duration, baseline MDS-UPDRS part III subscore in the OFF state, US site (SP = 25.4%), baseline CSF amyloid-$\beta_{1-42}$ (SP = 10.9%), and baseline mean striatum SBR (SP = 7.2%).

When the change from baseline in the ON state part III subscore was the outcome, baseline disease duration, baseline MDS-UPDRS part III subscore in the ON state CSF amyloid-$\beta_{1-42}$ (SP = 0.8%), and US site (SP = 20.9%) continued to be significant. Baseline mean striatum SBR was no longer significant and baseline Epworth sleepiness scale score became significant (SP = 0.5%) (in comparison to the model for which the OFF state part III subscore was the outcome).
Table 1
Baseline and 1-year values of clinical, biofluid biomarker, and imaging variables in the PD group and HC groups. NC, not collected as per study protocol; BMI, body mass index; CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; GDS-15, 15-item Geriatric Depression Scale; PIGD, postural instability gait disorder; MoCA, Montreal Cognitive Assessment; RBDSQ, REM Sleep Behavior Disorder Questionnaire; SBR, specific binding ratio; SCOPA-AUT, Scales for Outcomes in Parkinsons—Autonomic; SBP, systolic blood pressure

| Variable | PD group (N=413) | | HC group (N=185) | p-value for significance of difference:
|-----------|-----------------|----------------|-----------------|-------------------|
|           | BL* 1 year*     |                 | BL* 1 year*     | from BL to 1 year, PD vs HC from BL to 1 year in PD group |
| H&Y score (N) | H&Y 0:0         | H&Y 0:1        | H&Y 0:182       | H&Y 0:178        |
|           | H&Y 1:191       | H&Y 1:99       | H&Y 1:2         | H&Y 1:3          |
|           | H&Y ≥2:232      | H&Y ≥2:233     | H&Y ≥2:0        | H&Y ≥2:4         |
|           | Missing: 0      | Missing: 80    | Missing: 1      | Missing: 0       |
| BMI (kg/m²) | 27.1 (4.6; 16.9–43.8; 3) | 26.8 (4.6; 16.7–44.2; 40) | 26.9 (4.4; 17.5–42.3; 1) | NC                  |
|           | 93.2 (5.9; 70–100; 0) | 90.5 (6.7; 70–100; 20) | NC               | 27.18 (4.9; 18.0–45.4; 1) |
| Schwab and England total score (S&E) | 93.2 (5.9; 70–100; 0) | 90.5 (6.7; 70–100; 20) | NC               | 27.18 (4.9; 18.0–45.4; 1) |
| Tremor score | 0.5 (0.3; 0–1.8; 19) | 0.6 (0.4; 0–2.7; 33) | 0.0 (0.1; 0–0.6; 1) | 0.1 (0.1; 0–0.6; 1) |
| PIGD score | 0.2 (0.2; 0–1.4; 1) | 0.3 (0.3; 0–1.8; 79) | 0.0 (0.1; 0–0.8; 1) | 0.0 (0.1; 0–0.6; 1) |
| GDS-15 Total Score | 2.3 (2.4; 0–14; 0) | 2.6 (2.9; 0–15; 18) | 1.3 (2.1; 0–15; 0) | 1.4 (2.4; 0–15; 0) |
| SCOPA-AUT Total Score | 9.4 (6.2; 0–39; 8) | 10.9 (6.4; 0–45.23) | 5.8 (3.7; 0–20; 2) | 5.8 (4.4; 0–22; 2) |
| STAI Score | 65.2 (18.2; 40–137; 1) | 65.2 (18.7; 40–142; 18) | 57.0 (14.1; 40–105; 0) | 56.2 (16.7; 40–128; 0) |
| ESS total score | 5.7 (3.4; 0–20; 0) | 6.1 (4.0; 0–21; 18) | 5.6 (3.4; 0–19; 1) | 5.4 (3.2; 0–16; 1) |
| RBDSQ total score | 4.1 (2.7; 0–12; 3) | 4.1 (2.8; 0–13; 20) | 2.8 (2.2; 0–11; 0) | 2.8 (2.3; 0–11; 0) |
| Orthostatic SBP change | 4.7 (12.7; –31–72; 1) | 3.9 (13.1; –32–58; 20) | 1.9 (12.3; –47–41; 0) | 1.6 (10.5; –26–30; 0) |
| Mean striatum SBR | 1.41 (0.39; 0.31–2.64; 3) | 1.24 (0.4; 0.2–2.7; 45) | 2.6 (0.6; 0.98–4.2; 1) | NC |
| Mean putamen SBR | 0.8 (0.3; 0.2–2; 3) | 0.7 (0.3; 0.0–2.3; 45) | 2.14 (0.5; 0.6–3.9; 1) | NC |
| MoCA | 27.1 (2.3; 17–30; 3) | 26.3 (2.8; 15–30; 21) | 28.2 (1.1; 26–30; 0) | 27.3 (2.2; 20–30; 0) |
| CSF amyloid-β_{1–42} | 849.10 (320.8; 238.8–1664.0; 68) | 818.20 (310.3; 249.5–1645.0; 116) | 899.54 (333.2; 239.1–1632.0; 36) | 930.9 (318.9; 312–1611; 52) |
| CSF Total-Tau | 168.9 (57.0; 80.9–467.0; 55) | 169.1 (58.4; 82.2–388.7; 99) | 192.3 (79.2; 82.0–580.8; 23) | 200.4 (83.1; 82.4–600.1; 37) |
| CSF Phos-Tau_{181} | 14.9 (5.2; 8.0–40.1; 82) | 14.9 (5.3; 8.2–34.3; 127) | 17.6 (8.5; 8.2–73.6; 32) | 18.2 (9.0; 8.3–80.1; 44) |
| CSF α-Synuclein | 1494.3 (672.1; 432.4–5256.9; 45) | 1425.5 (619.3; 420.0–3685.3; 88) | 1709.3 (761.2; 488.6–4683.1; 19) | 1778.9 (788.4; 517.1–4388.6; 32) |

*Values shown are mean (SD; range (min–max); number missing) for all continuous variables. **Hoehn and Yahr was the only variable examined as a categorical variable. The count in each stage followed by the number missing is indicated (H&Y 0:1; ≥2; missing). Change is defined as change from 1 or 2 to >2. Comparison between the PD and HC group was not possible due to the small number of HC participants with H&Y >0 at any time points.
Table 2

| Outcome | BL | ∗ | Change from BL to Year 1 | ∗∗ | Change from BL to Year 2 | ∗∗ | Change from BL to Year 3 | ∗∗ | Change from BL to Year 4 | ∗∗ | Change from BL to Year 5 |
|---------|----|---|--------------------------|---|--------------------------|---|--------------------------|---|--------------------------|---|--------------------------|
| MDS-UPDRS Total Score Off | 32.2 (13.1; 7–70; 1) | 7.5 (11.6; –35–78; 1) | 10.4 (13.5; –35–78; 1) | 14.3 (15.6; –35–78; 1) | 19.1 (16.5; –20–84; 1) | 20.9 (17.7; –11–11; 250) | 20.9 (17.7; –11–11; 250) | 20.9 (17.7; –11–11; 250) | 20.9 (17.7; –11–11; 250) | 20.9 (17.7; –11–11; 250) |
| MDS-UPDRS Total Score On | 32.2 (13.1; 7–70; 1) | 5.4 (12.7; –38–60; 1) | 7.0 (13.4; –33–60; 1) | 9.8 (16.6; –40–79; 1) | 11.9 (10.0; –35–54; 1) | 15.2 (9.4; 24–111; 200) | 15.2 (9.4; 24–111; 200) | 15.2 (9.4; 24–111; 200) | 15.2 (9.4; 24–111; 200) | 15.2 (9.4; 24–111; 200) |
| MDS-UPDRS III Score Off | 20.9 (8.9; 4–51; 0) | 4.5 (10.9; –31–34; 0) | 6.3 (13.3; –31–34; 0) | 8.8 (19.0; –33–41; 0) | 11.6 (16.6; –33–41; 0) | 16.5 (21.6; –31–34; 0) | 16.5 (21.6; –31–34; 0) | 16.5 (21.6; –31–34; 0) | 16.5 (21.6; –31–34; 0) | 16.5 (21.6; –31–34; 0) |
| MDS-UPDRS III Score On | 20.6 (8.9; 4–51; 0) | 2.5 (11.0; –25–34; 0) | 4.5 (10.9; –31–34; 0) | 8.8 (19.0; –33–41; 0) | 11.6 (16.6; –33–41; 0) | 16.5 (21.6; –31–34; 0) | 16.5 (21.6; –31–34; 0) | 16.5 (21.6; –31–34; 0) | 16.5 (21.6; –31–34; 0) | 16.5 (21.6; –31–34; 0) |
| Putamen SBR | 0.82 (0.3; 0.2–2.2; 3) | –13.4 (11.2; –31–141; 2–4) | –25.6 (11.2; –31–141; 2–4) | –41.2 (21.5; –86.7–167; 2–4) | –67.1 (18.6; –83.5–146; 2–4) | –92.7 (16.8; –83.5–146; 2–4) | –92.7 (16.8; –83.5–146; 2–4) | –92.7 (16.8; –83.5–146; 2–4) | –92.7 (16.8; –83.5–146; 2–4) | –92.7 (16.8; –83.5–146; 2–4) |
| Striatum SBR | 0.4 (0.3; 0.2–2.2; 3) | –11.2 (15.1; –31–99; 1) | –23.5 (15.1; –31–99; 1) | –34.1 (25.1; –51–99; 1) | –45.6 (15.1; –51–99; 1) | –58.1 (15.1; –51–99; 1) | –58.1 (15.1; –51–99; 1) | –58.1 (15.1; –51–99; 1) | –58.1 (15.1; –51–99; 1) | –58.1 (15.1; –51–99; 1) |

In all models examining change from baseline in the MDS-UPDRS and its part III subscore as an outcome the proportion of variance in the outcome accounted for by the predictors in the model did not exceed 15% for the OFF scores, and for the ON state scores was <5%.

**Multivariate models of baseline predictors of long-term change in DaTscan binding measures**

When percent change from baseline in mean putamen SBR was examined as the outcome, baseline CSF amyloid-β_{1–42} (SP = 12.70%), mean putamen score (SP = 97.80%) and RBDSQ (SP = 56.00%) were the only predictors (Table 3; Supplementary Table 2). In contrast, when percent change from baseline in mean striatal SBR was the outcome, both baseline RBDSQ (SP = 85.30%) and baseline S&E (SP = 9.50%) were significant clinical predictors, as were baseline CSF amyloid-β_{1–42} (SP = 9.80%) and baseline mean striatum SBR (SP = 65.40%). 29% and 36% of the variance in change in putamen and striatal DAT binding respectively was accounted for by these baseline predictors.

**Short-term changes in candidate predictors**

Table 1 shows the change from baseline to year-1 in all considered variables. Candidate STP that met criteria for consideration in the multivariate models were: BMI, S&E, tremor score, PIGD score, SCOPA-AUT Total Score, ESS, CSF α-synuclein, mean striatal SBR, and mean putamen SBR.

Univariate relationships between STP and the outcome measures are shown in Supplementary Table 3 (1-year-changes (1-yr-Delta)), as are the relationships for these variables with the outcome measures in the final models (after backwards selection was applied as per step 3 of the model building, as described above). The selection frequencies from the cross-validation are also shown in Supplementary Table 3.

**Multivariate models of short-term change predictors of longer-term change in MDS-UPDRS**

Table 4 (Supplementary Table 3) shows results of the multivariate mixed models examining predictors of change in key outcomes (from year 1 to last annual follow-up), but including the 1-yr-Delta of the STPs, as well as the baseline variables significantly associated with the key outcomes. Importantly, after
Table 3

Final results of mixed models examining baseline predictors of outcomes. Only variables associated with the outcome at a p-value of ≤0.10 are listed here. For the full model, see Supplementary Table 2. BMI, body mass index; CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; PIGD, postural instability gait disorder; MoCA, Montreal Cognitive Assessment; RBDSQ, REM Sleep Behavior Disorder Questionnaire; SBR, specific binding ratio; SCOPA-AUT, Scales for Outcomes in Parkinsons—Autonomic; SBP, systolic blood pressure

| Outcome | Predictor (All baseline values) | Multivariate Effect Estimate β (95% CI) | Multivariate p-value | Multivariate Adjusted R^2 |
|---------|--------------------------------|----------------------------------------|---------------------|--------------------------|
| MDS-UPDRS Total Score OFF - Change from Baseline | Disease duration | 0.1596 (0.0204, 0.2988) | 0.0246 | 0.1383 |
| N = 373 | Gender (Male) | 1.9042 (0.0550, 3.7535) | 0.0436 | |
| | CSF amyloid-β$_{1-42}$ | -0.0031 (-0.0058, -0.0005) | 0.0217 | |
| | Mean striatum SBR | -2.5317 (-4.8456, -0.2179) | 0.0320 | |
| | SBP | -0.0779 (-0.1468, 0.0090) | 0.0267 | |
| | SCOPA-AUT | 0.1413 (-0.0174, 0.3000) | 0.0809 | |
| | MDS-UPDRS Total Score ON - Change from Baseline | MDS-UPDRS total score in ON | -0.1990 (-0.2721, -0.1260) | <0.0001 | 0.0533 |
| N = 374 | CSF amyloid-β$_{1-42}$ | -0.0028 (-0.0054, -0.0001) | 0.0407 | |
| | Gender (Male) | 1.6797 (-0.1650, 3.5244) | 0.0743 | |
| | MoCA | -0.3482 (-0.7439, 0.0474) | 0.0844 | |
| | SCOPA-AUT | 0.1487 (-0.0105, 0.3079) | 0.0671 | |
| MDS-UPDRS Part III Score OFF - Change from Baseline | Disease duration | 0.1377 (0.0405, 0.2349) | 0.0055 | |
| N = 382 | Clinical Site (US) | 1.1952 (0.2462, 3.5841) | 0.0246 | |
| | CSF amyloid-β$_{1-42}$ | -0.0021 (-0.0039, -0.0002) | 0.0284 | |
| | Mean striatum SBR | -1.6005 (-3.1793, -0.0218) | 0.0469 | |
| | MDS-UPDRS Part III Score ON - Change from Baseline | MDS-UPDRS part III score ON | -0.1849 (-0.2567, -0.1131) | <0.0001 | 0.1156 |
| N = 385 | Clinical Site (US) | 1.9541 (0.3446, 3.5636) | 0.0174 | |
| | CSF amyloid-β$_{1-42}$ | -0.0019 (-0.0038, -0.0001) | 0.0417 | |
| | ESS | -0.1572 (-0.3351, 0.0207) | 0.0833 | |
| | SCOPA-AUT | 0.1487 (-0.0105, 0.3079) | 0.0671 | |
| Mean putamen SBR - % Change from Baseline | CSF amyloid-β$_{1-42}$ | 0.0055 (-0.0001, 0.0111) | 0.0526 | 0.2870 |
| N = 352 | Mean putamen SBR | -17.1848 (-23.6240, -10.7457) | <0.0001 | |
| | RBDSQ | -1.0837 (-1.7730, -0.3945) | 0.0021 | |
| Mean striatum SBR - % Change from Baseline | CSF amyloid-β$_{1-42}$ | 0.0039 (-0.0003, 0.0081) | 0.0708 | |
| N = 351 | Mean striatum SBR | -6.2020 (-9.7532, -2.6508) | 0.0007 | 0.3563 |
| | Modified Schwab & England (S&E) | 0.2417 (0.0037, 0.4797) | 0.0466 | |
| | RBDSQ | -1.0030 (-1.5268, -0.4793) | 0.0002 | |

1Age, gender, disease duration, and the baseline value of the outcome were forced into each model.

adjustment for the short-term change in total MDS-UPDRS OFF score, many of the significant baseline predictors noted above (CSF amyloid-β$_{1-42}$, mean striatum, baseline SBP, baseline SCOPA) become non-significant. In the final model, change from baseline in total MDS-UPDRS score in the OFF state was significantly associated with baseline disease duration, male gender, baseline MDS-UPDRS score in the OFF state, and 1-yr-Δ in total MDS-UPDRS score in the OFF state (SP = 99.90%).

For the model examining change from baseline in total MDS-UPDRS score in the ON state as the outcome, significant predictors included baseline disease duration, baseline total MDS-UPDRS score in ON state, baseline SCOPA-AUT, baseline CSF amyloid-β$_{1-42}$, male gender, 1-yr-Δ in total MDS-UPDRS score in the ON state (SP = 99.90%), and 1-yr-Δ in SCOPA-AUT (SP = 34.40%). Compared to the model only containing the baseline predictors, MoCA was not a significant predictor.

When the long-term change from baseline in the part III subscore of the MDS-UPDRS in the OFF state was the outcome, baseline disease duration, male gender, baseline part III subscore of the MDS-UPDRS in the OFF state, 1-yr-Δ in part III subscore of the MDS-UPDRS (SP = 100.00%), 1-yr-Δ in BMI (SP = 2.10%), and 1-yr-Δ PIGD score (SP = 20.60%) were significant predictors.

Predictors of long-term change in part III subscore of the MDS-UPDRS in the ON state, on the other hand, included US site, male gender, baseline CSF amyloid-β$_{1-42}$, baseline part III subscore
Table 4

Final results of mixed models examining baseline and short-term change predictors of outcomes. Only variables associated with the outcome at a p-value of ≤0.10 are listed here. For the full model, see Supplementary Table 3. BMI, body mass index; CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; PIGD, postural instability gait disorder; RBDSQ, REM Sleep Behavior Disorder Questionnaire; SBR, specific binding ratio; SCOPA-AUT, Scales for Outcomes in Parkinsons—Autonomic; SBP, systolic blood pressure.

| Outcome Predictor | Multivariate Effect Estimate β (95% CI) | Multivariate p-value | Multivariate Adjusted R² |
|-------------------|------------------------------------------|----------------------|-------------------------|
| MDS-UPDRS Total Score Off - Change from Baseline | Baseline disease duration | 0.3506 (0.1457, 0.5554) | 0.0009 | 0.1763 |
| MDS-UPDRS Total Score Off from Baseline | Baseline MDS-UPDRS Total Score Off | -0.1986 (-0.3149, -0.0822) | <0.0001 | |
| N = 280 | Gender (Male) | 3.0569 (3.0140, 5.6877) | 0.0295 | |
| MDS-UPDRS Total Score On - Change from Baseline | Baseline disease duration | 0.2087 (0.0075, 0.4098) | 0.0421 | |
| MDS-UPDRS Total Score On from Baseline | Baseline CSF amyloid-β₁–42 | -0.0039 (-0.0077, -0.0002) | 0.0414 | 0.0943 |
| N = 329 | Gender (Male) | 4.0093 (1.3736, 6.6451) | 0.0030 | |
| MDS-UPDRS Part III Score Off - Change from Baseline | Baseline disease duration | 0.1558 (0.0152, 0.2965) | 0.0301 | |
| MDS-UPDRS Part III Score Off from Baseline | Baseline MDS-UPDRS Part III Score Off | -0.1690 (-0.2823, -0.0557) | 0.0036 | |
| N = 264 | Gender (Male) | 1.7635 (-0.1740, 3.7009) | 0.0743 | 0.1719 |
| MDS-UPDRS Part III Score On - Change from Baseline | Clinical Site (US) | 2.1511 (-0.1819, 4.4841) | 0.0706 | |
| MDS-UPDRS Part III Score On from Baseline | Baseline CSF amyloid-β₁–42 | -0.2610 (-0.3659, -0.1562) | <0.0001 | |
| N = 341 | Gender (Male) | 2.1375 (0.3268, 3.9482) | 0.0208 | 0.0755 |
| Mean putamen SBR - % Change from Baseline | Baseline RBDSQ | -0.8478 (-1.5740, -0.1216) | 0.0223 | |
| N = 313 | 1-yr-Δ Mean putamen SBR | 65.3565 (51.7328, 78.9803) | <0.0001 | 0.3580 |
| Mean striatum SBR - % Change from Baseline | Baseline Mean striatum SBR | 7.2315 (2.2679, 12.1951) | 0.0088 | |
| N = 302 | Baseline RBDSQ | -0.6229 (-1.2910, 0.0452) | 0.0645 | 0.4405 |
| 1-yr-Δ Mean striatum SBR | 45.9181 (35.9935, 55.8427) | <0.0001 | |
| 1-yr-Δ SCOPA-AUT | -0.3251 (-0.6948, 0.0446) | 0.0786 | |

¹Age, gender, disease duration, and the baseline value of the outcome were forced into each model.

of the MDS-UPDRS in the ON state, and its 1-yr-Δ (SP = 100.00%).

In all models that incorporated the STP variables, the percentage of variance in the outcome accounted for by the predictors in the model increased a few percentages as compared to the model without STP, though none exceeded 17.2%, and variance in the ON state outcomes continued to be largely unexplained by the models.

**Multivariate models of short-term change predictors of long-term change in DaTscan binding measures**

As shown in Table 4 (Supplementary Table 3), 1-yr-Δ in mean putamen (SP = 100.00%) and baseline RBDSQ score were predictors of long-term (from 1-year to last follow-up) percent change in mean putamen SBR from baseline. On the other hand, baseline mean striatum SBR, baseline RBDSQ, 1-yr-Δ in mean striatum SBR (SP = 100.00%), and 1-yr-Δ change in SCOPA-AUT (SP = 1.07%) predicted long-term (2-year to last follow-up) percent change in mean striatum SBR. In both models, CSF amyloid-β₁–42 was no longer significantly associated with the outcome. The predictors in the model accounted for 44.1% of the variance in percent change from baseline in mean striatum SBR.

**DISCUSSION**

This analysis examined clinical, imaging and biofluid predictors of progression in PD, assessed
clinically with total and motor subscore of the MDS-UPDRS and by imaging with DAT binding, to explore whether baseline and short-term (1-year) change in these measures can improve prediction of longer-term change in PD. There are three key findings. First, while a combination of baseline clinical, imaging, and biofluid biomarker measures consistently predicted change in MDS-UPDRS, the predictive value in the models was low, accounting for <15% of the variance in the outcome. Second, and in contrast, this multimodal model did account for a substantial percentage of the variance in DAT binding change. Third, combining the short-term change with baseline values of possible predictors improved the percentage of the variance in the outcome accounted for by the model especially for DAT binding.

We found that a multimodal model consisting of baseline clinical, CSF, and imaging measures can predict motor progression. The clinical predictors varied somewhat depending on the outcome measure examined, which is not surprising considering that in treated patients, motor measures are impacted by the effect of the underlying treatment [9]. Generally, though, our results suggest that motor progression is greater among men (similar to other studies [2]). While clinical measures of autonomic dysfunction (blood pressure measures and/or questionnaire-based) were statistically associated with greater motor disease progression, the low percentage of selection of these variables in the cross-validation indicates that these results should be interpreted with caution. Lower baseline striatal DAT binding was also a consistent predictor of greater motor progression. Our findings add to the accumulating evidence that DAT binding may be a biomarker for PD disease progression [22–24]. It is of note that the Schwab and England did not predict motor progression, in contrast to more advanced cohorts [1]. Perhaps in earlier PD, DAT measures are a more sensitive correlate of disability, as compared to motor scores. Finally, lower CSF amyloid-β₁₋₄₂ predicted motor progression, though again here the low percentage of selection in the cross-validation raises caution in interpretation of this result. Having said that, in prior studies, CSF amyloid-β₁₋₄₂ has been associated with greater α-synuclein pathology in the cortex in advanced disease [25], suggesting a possible mechanism for this association. It would be of interest to examine the relationship between CSF amyloid-β₁₋₄₂ and subcortical α-synuclein pathology in earlier PD disease stages, but our current data do not permit such an analysis.

When DAT binding measures were examined as the outcome, perhaps not surprisingly, baseline DAT binding measures predicted the change in DAT binding, with a large effect size. Of interest is that higher REM sleep behavior disorder (RBD) questionnaire scores predicted greater decline in DAT binding, and the cross-validation analysis adds strength to this observed effect. This is consistent with the possibility that RBD is a marker of worse disease severity in PD, likely due to more widespread neurodegeneration [26, 27].

In general, adding the short-term changes in the predictors, rather than using just the baseline values of those predictors, improved modeling of the outcome, especially for DAT binding. The short-term change of the outcome of interest was selected >99% of the time in the cross-validation. These findings are in line with the idea that, given the clinical variability of PD, single baseline cross-sectional clinical measures are likely not as useful as longitudinal in predicting longer clinical trajectory. Our results indicate that clinical and DAT binding trajectory may be identifiable early on in the PD diagnosis, and the trajectory exhibited early in disease may reflect longer-term change. The utility of incorporating short-term changes as entry criteria into PD clinical trials has not been examined. However, an example from another neurodegenerative disease, ALS, illustrates its potential utility. In a trial of the agent edaravone as a modifier of disease progression in ALS, short-term change, over a 12-week period, in a functional outcome score was used to identify patients who progressed either too rapidly or not at all. These patients were excluded from the trial as it was felt that evaluation of the effect of edaravone in these subgroups would not be useful [28].

Several limitations of this study warrant mention. The definition of “OFF” in PPMI, requiring holding of only levodopa or dopamine agonists for 6 hours, makes it challenging to extricate the effect of PD medications on the results. In addition, while overall retention in the PPMI cohort has been high, there are some missing data longitudinally, and this many influence the results. Furthermore, there is some diagnostic accuracy in early PD, such that some patients may have had alternate disorders marked by parkinsonism and abnormal DAT imaging, including the more severe neurodegenerative parkinsonian syndromes. The number of cases with a revision of
clinical diagnosis was low. However, additional undetected misdiagnosed cases may have been included in the sample. Future analyses using PPMI brain bank data will help investigate this possibility in the future.

The results of this analysis might be considered in the context of an FDA regulatory guidance on accelerated drug approval for serious conditions [29] suggesting the concept of intermediate clinical outcomes as measures that are “considered reasonably likely to predict long-term benefit” (page 18). For example, could baseline plus short-term changes in MDS-UPDRS be considered a candidate intermediate clinical outcome in studies of diseases modifying therapies with the caveat that long term benefit would need to be proven? This approach therefore holds the promise of improving the efficiency and possibly shortening PD clinical trial duration. In terms of the clinical applicability of our results, if future work validates the predictors we have identified in independent cohorts representative of the general PD population, they may translate into clinical tools for prognostication.

Our results show that baseline and short-term change in measures of motor disability (MDS-UPDRS) are the strongest predictors of longer-term change in this clinically relevant metric and that baseline and one-year change in striatal DAT binding are predictors of longer-term change in this imaging measure. These findings if replicated, suggest baseline combined with short-term change in PD predictors may have value as proxies for longer-term change in PD. These data may be considered in study design strategies of PD clinical trials as tools to either gain an early signal of a therapeutic intervention or to develop an outcome for an adaptive design.

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CONFLICTS OF INTEREST

None of the authors report conflicts of interest related to the research covered in this article.

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REFERENCES

[1] Post B, Merkus MP, de Haan RJ, Speelman JD, CARPA Study Group (2007) Prognostic factors for the progression of Parkinson’s disease: A systematic review. Mov Disord 22, 1839-1851; quiz 1988.

[2] Reinoso G, Allen JC Jr, Au WL, Seah SH, Tay KY, Tan LC (2015) Clinical evolution of Parkinson’s disease and prognostic factors affecting motor progression: 9-year follow-up study. Eur J Neurol 22, 457-463.

[3] Venuto CS, Potter NB, Dorsey ER, Kieburtz K (2016) A review of disease progression models of Parkinson’s disease and applications in clinical trials. Mov Disord 31, 947-956.

[4] Simuni T, Caspell-Garcia C, Coffey C, Lasch S, Tanner C, Marek K, PPMI Investigators (2016) How stable are Parkinson’s disease subtypes in de novo patients: Analysis of the PPMI cohort? Parkinsonism Relat Disord 28, 62-67.

[5] Parkinson Progression Marker Initiative (2011) The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol 95, 629-635.

[6] Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB (2017) Clinical criteria for subtyping Parkinson’s disease: Biomarkers and longitudinal progression. Brain 140, 1959-1976.

[7] Latourelle JC, Beste MT, Hadzi TC, Miller RE, Oppenheim JN, Valko MP, Wuest DM, Church BW, Khalil IG, Hayete B, Venuto CS (2017) Large-scale identification of clinical and genetic predictors of motor progression in patients with newly diagnosed Parkinson’s disease: A longitudinal cohort study and validation. Lancet Neurol 16, 908-916.

[8] Nilashia M, Ahmadi OI, Shahmoradi L, Farahmand M (2018) A hybrid intelligent system for the prediction of Parkinson’s Disease progression using machine learning techniques. Biocybern Biomed Eng 38, 1-15.

[9] Simuni T, Siderowf A, Lasch S, Coffey CS, Caspell-Garcia C, Jennings D, Tanner CM, Trojanowski JQ, Shaw LM, Scibyl J, Schuff N, Singleton A, Kieburtz K, Toga AW, Mollenhauer B, Galasko D, Chahine LM, Weintraub D,
Foroul T, Tousn D, Poston K, Arnedo V, Frasier M, Sherrer T, Chowdhury S, Marek K. Parkinson's Progression Markers Initiative (2018) Longitudinal change of clinical and biological measures in early Parkinson's disease: Parkinson's progression markers initiative cohort. *Mov Disord* **33**, 771-782.

[10] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martín P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nenhuys D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N. Movement Disorder Society UPDRS Revision Task Force (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Mov Disord* **23**, 2129-2170.

[11] Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC (2013) How to identify tremor-dominant and postural instability/gait difficulty groups with the Movement Disorder Society Unified Parkinson's Disease Rating Scale: Comparison with the Unified Parkinson’s Disease Rating Scale. *Mov Disord* **28**, 668-670.

[12] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695-699.

[13] Weintraub D, Oehlberg KA, Katz IR, Stern MB (2006) Test characteristics of the 15-item geriatric depression scale and Hamilton depression rating scale in Parkinson disease. *Am J Geriatr Psychiatry* **14**, 169-175.

[14] Spielberger CD, Gorsuch RL, Lushene PR, Vagg PR, Jacobs AG (1983) *Manual for the State-Trait Anxiety Inventory (Form Y)*. Consulting Psychologists Press, Inc.; 1983., Palo Alto, CA.

[15] Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ (2004) Assessment of autonomic dysfunction in Parkinson’s disease: The SCOPA-AUT. *Mov Disord* **19**, 1306-1312.

[16] Simuni T, Long JD, Caspell-Garcia C, Coffey CS, Lasch S, Tanner CM, Jennings D, Kieburzt KD, Marek K. PPMI Investigators (2016) Predictors of time to initiation of symptomatic therapy in early Parkinson’s disease. *Ann Clin Transl Neurol* **3**, 482-494.

[17] Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson’s disease. *Mov Disord* **25**, 2649-2653.

[18] Kang JH, Irwin DJ, Chen-Plotkin AS, Siderowf A, Caspell C, Coffey CS, Waligorska T, Taylor P, Pan S, Frasier M, Marek K, Kieburzt K, Jennings D, Simuni T, Tanner CM, Singleton A, Toga AW, Chowdhury S, Mollenhauer B, Trojanowski QJ, Shaw LM, and the Parkinson’s Progression Markers Initiative (2013) Association of cerebrospinal fluid beta-amyloid 1-42, T-tau, P-tau181, and alpha-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. *JAMA Neurol* **70**, 1277-1287.

[19] Selva AS, Rose JS, Dierker LC, Hedeker D, Mermelstein RJ (2012) A practical guide to calculating Cohen’s f(2), a measure of local effect size, from PROC MIXED. *Front Psychol* **3**, 111.

[20] Altman DG, Andersen PK (1989) Bootstrap investigation of the stability of a Cox regression model. *Stat Med* **8**, 771-783.

[21] Chen CH, George SL (1985) The bootstrap and identification of prognostic factors via Cox’s proportional hazards regression model. *Stat Med* **4**, 39-46.

[22] Conrado DJ, Nicholas T, Tsai K, Macha S, Sinha V, Stone J, Corrigan B, Bani M, Mugiya P, Watson IA, Kern VD, Shevel-eva E, Marek K, Stephenson DT, Romero K, Critical Path for Parkinson’s (CPP) Parkinson’s Disease Modeling and Simulation Working Group (2018) Dopamine transporter neuroimaging as an enrichment biomarker in early Parkinson’s disease clinical trials: A disease progression modeling analysis. *Clin Transl Sci* **11**, 63-70.

[23] Nissen T, Malek N, Grosset KA, Newman EJ, Patterson J, Hadley D, Grosset DG (2014) Baseline [(123) I]-FP-CIT SPECT (DaTSCAN) severity correlates with medication use at 3 years in Parkinson’s disease. *Acta Neurol Scand* **129**, 204-208.

[24] Ramani L, Malek N, Patterson J, Nissen T, Newman EJ (2017) Relationship between [(123) I]-FP-CIT SPECT and clinical progression in Parkinson’s disease. *Acta Neurol Scand* **135**, 400-406.

[25] Irwin DJ, Xie SX, Coughlin D, Nevler N, Akhtar RS, McMillan CT, Lee EB, Wolk DA, Weintraub D, Chen-Plotkin A, Duda JE, Spindler M, Siderowf A, Hurtig HI, Shaw LM, Grossman M, Trojanowski QJ (2018) CSF tau and beta-amyloid predict cerebral synucleinopathy in autopsied Lewy body disorders. *Neurology* **90**, e1038-e1046.

[26] Postuma RB, Adler CH, Duggar BN, Hentz JG, Shill HA, Driver-Dunckley E, Sibagh MN, Jacobson SA, Belden CM, Sue LI, Serrano G, Beach TG (2015) REM sleep behavior disorder and neuropathology in Parkinson’s disease. *Mov Disord* **30**, 1413-1417.

[27] Boucetta S, Salimi A, Dadar M, Jones BE, Collins DL, Dang-Vu TT (2016) Structural brain alterations associated with rapid eye movement sleep behavior disorder in Parkinson’s disease. *Sci Rep* **6**, 26782.

[28] Abe K, Itoyama Y, Sobe G, Tsuji S, Aoki M, Doyu M, Hamada C, Kondo K, Yoneoka T, Akimoto M, Yoshino H, Edaravone ALS Study Group (2014) Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotoemporal Degener* **15**, 610-617.

[29] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (May 2014) Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, Procedural OMB Control No. 0910-0765.