



ORIGINAL ARTICLE

Subtyping of Parkinson's Disease by Longitudinal Trajectories of Levodopa Equivalent Daily Dose

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ABSTRACT

Objective Clinical heterogeneity exists in the optimal timing and dosage of symptomatic treatments for Parkinson's disease (PD). This study aimed to cluster PD patients on the basis of longitudinal trajectories of levodopa equivalent daily dose (LEDD) and evaluate the clinical features and progression associated with these clusters.

Methods From the Parkinson's Progression Markers Initiative database, we enrolled 301 PD patients who were followed up for at least 3 years after the initiation of antiparkinsonian medications. On the basis of the longitudinal trajectories of the LEDD increment, the participants were classified into three clusters: slow-increment, initial-increment, and rapid-increment. The outcomes were initial and longitudinal changes in motor phenotype, on-time motor symptoms, and the efficacy of antiparkinsonian medications.

Results The initial-increment cluster exhibited the greatest symptomatic improvements following the administration of higher doses of LEDD, although the motor improvement per unit of LEDD was comparable across clusters. Longitudinally, motor phenotypes changed rapidly in the initial-increment cluster. The initial-increment cluster showed continuous worsening of on-time motor symptoms, with limited LEDD efficacy. In contrast, the rapid-increment cluster exhibited stable on-time motor symptoms, whereas the efficacy of antiparkinsonian medications declined over time. The risk of disability related to walking and balance milestones and motor complications was twice as high in the initial-increment and rapid-increment clusters than in the slow-increment cluster.

Conclusion Heterogeneity is noted in the increase in the use of antiparkinsonian medications, which is driven by changes in motor phenotype, medication efficacy, and the occurrence of PD-relevant milestones. Subtyping patients on the basis of LEDD trajectories may provide insight into clinical heterogeneity for future research on individualized treatment strategies for patients with PD.

Keywords Parkinson's disease; Levodopa equivalent daily dose; Heterogeneity; Motor phenotype.

INTRODUCTION

Parkinson's disease (PD) is characterized by cardinal parkinsonian motor features such as resting tremors, rigidity, bradykinesia, and postural instability, which result from the loss of nigral dopaminergic neurons.¹ The primary symptomatic treat-

ment for PD is the substitution of endogenous striatal dopamine through the administration of levodopa, which is subsequently metabolized into dopamine in the brain, and other dopaminergic therapies. There have been concerns regarding levodopa-sparing strategies²; however, recent evidence supports the early use of levodopa to improve quality of life.³⁻⁵ Despite this, there are no es-

Received: April 15, 2025 Revised: June 3, 2025 Accepted: July 18, 2025

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tablished guidelines or consensus on when and how to escalate antiparkinsonian medications as the disease progresses.

The levodopa equivalent daily dose (LEDD) was introduced to compare the efficacy of various antiparkinsonian medication regimens and is calculated by converting the actual dose of each antiparkinsonian medication into the equivalent dose of levodopa and summing them to produce a single number.^{6,7} Along with motor progression, LEDD is expected to increase, but the rate and amount of LEDD change vary among individual patients. Clinical situations to explain the distinct rates of increase in LEDD could include faster exacerbation of motor symptoms,⁸⁻¹¹ the development of motor phenotypes that are unresponsive to medications or require higher dosages,¹² changes in pharmacokinetics,¹³ and the development of motor complications, including dyskinesia or motor fluctuations.

Although the longitudinal trajectory of LEDD exhibits considerable heterogeneity, the clinical factors and reasons for the increase in LEDD have not been thoroughly examined. Some clinical studies have used LEDD as a surrogate marker for measuring the effects of drugs without considering heritable variability. Furthermore, previous clinical subtyping studies of PD have compared only cross-sectional LEDD, not longitudinal changes in LEDD.⁸⁻¹¹ Therefore, we performed clustering of longitudinal LEDD trajectories in drug-naïve PD patients without prior data and then evaluated the clinical features and progression associated with longitudinal changes in LEDD. These data suggest the potential value of LEDD trajectory-based subtyping as a framework for exploring individualized treatment strategies in patients with PD.

MATERIALS & METHODS

Study participants

The data analyzed in this study were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data), a multicenter observational study designed to identify biomarkers associated with PD progression using clinical, imaging, and biological assessments. The inclusion criteria for PD patients in the PPMI cohort were as follows: 1) age ≥ 30 years; 2) absence of prior dopamine replacement therapy; 3) within 2 years of diagnosis; 4) Hoehn and Yahr scale (H&Y) stage <3 at baseline; and 5) imaging evidence of a dopaminergic deficit consistent with PD, confirmed by dopamine transporter (DAT) scans using 123I-FP-CIT single-photon emission computed tomography.¹⁴ For this current analysis, a total of 301 drug-naïve PD patients were enrolled, all of whom were followed for a minimum of 3 years after the initiation of antiparkinsonian medications, with detailed medication logs available. All study

procedures complied with the ethical standards committee of the respective institutional review boards, and written informed consent was obtained from all participants. The study was registered at clinicaltrials.gov (NCT01141023), with enrollment commencing on June 1, 2010.

Clustering of the longitudinal trajectories of LEDD

The participants were evaluated at 3-month intervals during the first year, followed by 6-month intervals thereafter. Medication prescriptions were reviewed at each visit to confirm whether participants had initiated new medications, discontinued prior medications, or maintained their current regimen. The dosages of antiparkinsonian medications, including levodopa, dopamine agonists, monoamine oxidase-B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, and any combination of drugs, were converted using a previously proposed LEDD conversion formula.⁶ The cumulative LEDD was calculated at each visit. LEDD data were analyzed up to 60 months after medication initiation.

We employed a simplified version of the two-step clustering strategy, combining linear mixed-effects models (LMMs), with LEDD as the outcome variable and time as the predictor, adjusting for site of enrollment as a covariate (Supplementary Table 1 in the online-only Data Supplement), with k-means clustering. Random intercepts and slopes were included in the models to account for the subject-specific changes. After model estimation, k-means clustering was applied to the estimated random effects to classify participants into clusters with similar longitudinal patterns.^{15,16} Euclidean distance was used as the dissimilarity metric in the clustering process. The optimal number of clusters was determined using the elbow and silhouette method (Supplementary Figure 1 in the online-only Data Supplement).

Clinical assessment

Motor and nonmotor symptoms were evaluated using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts II and III. The scores used for baseline characterization were taken from the most recent visit within 1 year prior to medication initiation, and follow-up assessments were collected at each subsequent visit. Higher scores indicate greater symptom severity. Motor phenotype classifications were determined using established methods. Specifically, tremor scores were calculated as the mean tremor subscores, whereas postural instability and gait difficulty (PIGD) scores were derived from gait and postural instability subscores.¹⁷ Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA). Rapid eye movement sleep behavior disorder (RBD) was screened using the RBD screening questionnaire (RBDSQ), and depressive symptoms were evaluated using the

Geriatric Depression Scale (GDS). Motor symptom-associated progression milestones of PD, including walking and balance and motor complications, were computed as previously described.¹⁸ In brief, walking and balance milestones are defined as any disability of walking and balance (MDS-UPDRS Item 2.12 ≥ 3), freezing (Item 2.13 ≥ 3), gait (Item 3.10 ≥ 3), freezing of gait (Item 3.11=4), postural instability (Item 3.12 ≥ 3), or H&Y stage ≥ 4 . Motor complication milestones were defined as any event of dyskinesia (Items 4.1 ≥ 3 and 4.2 ≥ 3), functionally impactful fluctuations (Items 4.4 ≥ 3), or complex fluctuations (Items 4.5 ≥ 3). The latency to milestones was defined as the time from medication initiation to the first documented occurrence within 5 years of follow-up.

Statistical analysis

Statistical analyses of the clinical data were performed using R statistical software (version 4.3.1; R Foundation for Statistical Computing). Analysis of variance and chi-square tests were used to compare demographic variables between the clusters classified by the longitudinal trajectories of LEDD. The initial response to LEDD was computed as the MDS-UPDRS part III score change between the visit immediately preceding medication initiation and after medication initiation within 1 year to account for the titration period. The efficacy of LEDD was computed as the change in off-time and on-time MDS-UPDRS part III scores divided by LEDD. To evaluate whether clinical trajectories differed between clusters, we applied LMMs using the nlme package (version 3.1-165). These models included random intercepts and slopes for each participant, with a first-order autoregressive residual covariance structure. This structure accounts for the correlation between repeated measurements over time, assuming that observations closer together are more highly correlated. The number of years of follow-up from the initiation of the medications was used as a time predictor in the model. Interaction terms between cluster and time (year) were used as predictors to measure the difference in the rate. The risks of developing PD-relevant milestones were further computed using Cox proportional hazard models to estimate hazard ratios (HRs) according to the clusters using the survival package (version 3.7-0). The models were adjusted for age, sex, and disease duration.

RESULTS

Baseline characteristics

A total of 301 participants were included in the study and were divided into three clusters on the basis of the clustering of longitudinal LEDD trajectories: slow-increment ($n=167$, 55.5%), initial-increment ($n=90$, 29.9%), and rapid-increment ($n=44$,

14.6%) clusters (Figure 1). The demographic and clinical characteristics at the visit immediately preceding medication initiation within 1 year are presented in Table 1. The mean age was comparable across the clusters (62.6 ± 9.5 , 64.3 ± 10.0 , and 63.1 ± 9.0 years for the slow-, initial-, and rapid-increment clusters, respectively; $p=0.402$). The duration of symptoms was also similar (2.1 ± 1.1 , 2.2 ± 1.4 , and 2.0 ± 1.1 years; $p=0.574$). A significant difference was observed in the proportion of male participants (63.5%, 64.4%, and 86.4%; $p=0.013$). Post hoc analysis indicated that the rapid-increment cluster had a significantly greater proportion of males compared to other clusters. With respect to body mass index (BMI), the rapid-increment cluster had a significantly greater BMI (28.1 ± 4.6 kg/m²) compared with the slow-increment cluster (26.1 ± 4.2 kg/m², $p=0.021$). The MDS-UPDRS part II score was significantly higher in the initial-increment cluster (7.9 ± 5.0) than in the slow-increment cluster (6.2 ± 4.1 , $p<0.001$). Although there was no significant difference in the MDS-UPDRS part III scores among the clusters (23.3 ± 9.6 , 25.4 ± 10.5 , and 21.6 ± 8.6 ; $p=0.085$), the tremor score was higher in the initial-increment cluster (0.6 ± 0.4) than in the rapid-increment cluster (0.5 ± 0.3 , $p=0.032$), whereas the PIGD score was higher in the initial-increment cluster (0.3 ± 0.3) compared to the slow-increment cluster (0.2 ± 0.2 , $p=0.017$). There were no significant differences in the distributions of motor phenotypes, including tremor dominant and PIGD types, across the clusters ($p=0.595$). The RBDSQ score was significantly higher in the

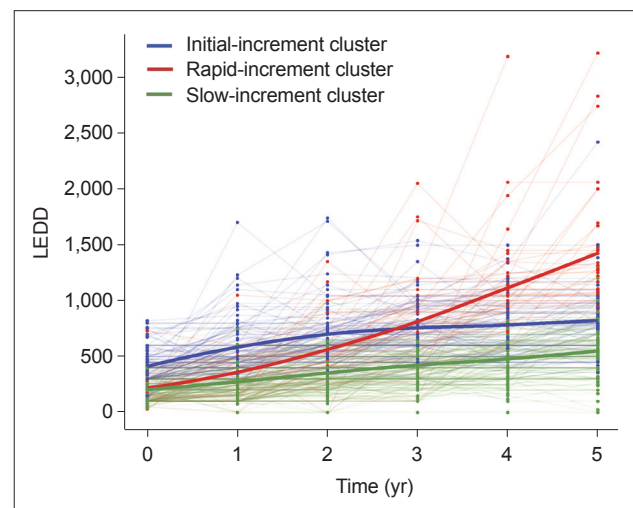


Figure 1. Clustering of longitudinal trajectories of LEDD in drug-naïve Parkinson's disease patients. k-means clustering was applied to the estimated random effects from linear mixed-effects models, with LEDD as the outcome variable and time as the predictor, adjusting for the site of enrollment as a covariate. Smoothed trajectories within each cluster were visualized using locally estimated scatterplot smoothing to capture average trends. Three distinct longitudinal LEDD trajectory clusters were identified: slow-increment (green), rapid-increment (red), and initial-increment (blue) clusters. LEDD, levodopa equivalent daily dose.

Table 1. Baseline demographics and clinical characteristics

Cluster	Slow-increment	Initial-increment	Rapid-increment	p value
Number	167 (55.5)	90 (29.9)	44 (14.6)	
Age at baseline (yr)	62.6±9.5	64.3±10.0	63.1±9.0	0.402
Symptom duration (yr)	2.1±1.1	2.2±1.4	2.0±1.1	0.574
Male	106 (63.5) [‡]	58 (64.4) [§]	38 (86.4) [§]	0.013*
Education (yr)	15.7±2.6	15.4±3.0	16.2±2.4	0.338
Body mass index (kg/m ²)	26.1±4.2 [‡]	26.9±4.2	28.1±4.6 [‡]	0.025*
MDS-UPDRS part I	5.6±4.1	6.4±4.1	6.3±4.2	0.246
MDS-UPDRS part II	6.2±4.1 [†]	7.9±5.0 [†]	6.8±4.8	0.012*
MDS-UPDRS part III	23.3±9.6	25.4±10.5	21.6±8.6	0.085
Tremor score	0.5±0.4	0.6±0.4 [§]	0.5±0.3 [§]	0.038*
PIGD score	0.2±0.2 [†]	0.3±0.3 [†]	0.2±0.2	0.015*
Motor phenotype				0.595
Tremor dominant	111 (69.4)	60 (71.4)	30 (71.4)	
Indeterminate	16 (10.0)	9 (10.7)	7 (16.7)	
PIGD	33 (20.6)	15 (17.9)	5 (11.9)	
Modified Hoehn & Yahr stage				0.219
0 or 1	63 (37.7)	29 (32.2)	21 (47.7)	
2 or 3	104 (62.3)	61 (67.8)	23 (52.3)	
MoCA	27.1±2.5	26.5±2.5	27.0±2.2	0.139
Geriatric Depression Scale	2.5±2.5	2.2±2.0	2.2±2.5	0.543
RBDSQ	3.9±2.7	3.6±2.4 [§]	4.9±2.9 [§]	0.038*
Caudate DAT uptake	1.9±0.5	1.9±0.6	1.8±0.6	0.235
Putamen DAT uptake	0.8±0.3	0.7±0.2	0.7±0.2	0.149

Data are presented as mean±standard deviation or number (%). Results from the analysis of variance or chi-square test were used as appropriate.

*significant *p* values are <0.05; [†]significantly different between slow-increment and initial-increment cluster; [‡]significantly different between slow-increment and rapid-increment cluster; [§]significantly different between initial-increment and rapid-increment cluster.

MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PIgd, postural instability and gait difficulty; MoCA, Montreal Cognitive Assessment; RBDSQ, rapid eye movement sleep behavior disorder screening questionnaire; DAT, dopamine transporter.

rapid-increment cluster (4.9±2.9) than in the initial-increment cluster (3.6±2.4, *p*=0.030). No significant differences were observed in years of education, modified H&Y stage, MoCA scores, GDS scores, or caudate and putamen DAT uptake values.

Initial response to antiparkinsonian medications across the clusters

The improvements in motor symptoms were compared before and within one year after the initiation of antiparkinsonian medications (Figure 2A). The initial-increment cluster showed greater improvements (6.0±9.1) compared to other clusters (3.5±8.7 and 1.8±9.8 for slow- and rapid-increment clusters, respectively; analysis of variance [ANOVA], *p*=0.028) (Supplementary Table 2 in the online-only Data Supplement). The LEDD was highest in the initial-increment cluster (604.4±243.8), fol-

lowed by the rapid-increment cluster (366.0±218.8) and slow-increment cluster (282.2±146.0; ANOVA *p*<0.001) (Figure 2B, Supplementary Table 2 in the online-only Data Supplement). However, when the efficacy of LEDD, measured as the change in the off-time and on-time MDS-UPDRS part III scores per unit of LEDD, was evaluated, the three clusters showed comparable efficacy (ANOVA, *p*=0.061) (Figure 2C).

Longitudinal changes in motor symptoms and BMI across the clusters

The LMM for the off-time MDS-UPDRS part III score showed a continuous deterioration of motor symptoms over time across all clusters (β estimate of time=1.79, standard error [SE]=0.13, *p*<0.001) (Figure 3A). In the LMM for the on-time UPDRS part III score, the initial increment cluster exhibited a more rapid deterioration of motor symptoms during on-time compared to the rapid increment cluster [β estimate of time×(rapid-increment–initial-increment cluster)=−0.86, SE=0.36, *p*=0.017] and slow increment cluster [β estimate of time×(initial-increment–slow-increment cluster)=0.57, SE=0.26, *p*=0.031] (Figure 3B, Supplementary Table 3 in the online-only Data Supplement). When the LMMs for off-time tremor and PIgd scores were compared across the clusters, the off-time PIgd score increased more rapidly in the initial-increment cluster than in the slow-increment cluster [β estimate of time×(initial increment–slow increment cluster)=0.03, SE=0.01, *p*<0.001] (Figure 4A, Supplementary Table 3 in the online-only Data Supplement), whereas the off-time tremor score decreased more rapidly in the initial-increment cluster than in the slow-increment cluster [β estimate of time×(initial-increment–slow-increment cluster)=−0.02, SE=0.01, *p*=0.021] (Figure 4B, Supplementary Table 3 in the online-only Data Supplement). When the longitudinal changes in the off-time and on-time MDS-UPDRS part III scores per unit of LEDD were compared, the rapid-increment cluster experienced the fastest decline in LEDD efficacy compared with the slow-increment cluster [β estimate of time×(rapid-increment–slow-increment cluster)=−0.002, SE=0.001, *p*=0.005] (Figure 4C, Supplementary Table 3 in the online-only Data Supplement). In the LMM for BMI, the rapid-increment cluster showed a continuous decline in BMI compared with the slow-increment cluster [β estimate of time×(rapid-increment–slow-increment cluster)=−0.22, SE=0.05, *p*<0.001] and the initial-increment cluster [β estimate of time×(rapid-increment–initial-increment cluster)=0.19, SE=0.07, *p*=0.004] (Figure 4D, Supplementary Table 3 in the online-only Data Supplement).

Risk of motor complications and PD-relevant milestones according to LEDD cluster

For up to 5 years of follow-up, subgroups of participants ex-

perienced either walking and balance milestones ($n=52$, 17.3%) or motor fluctuation milestones ($n=52$, 17.3%). Compared with the slow-increment cluster, both the rapid-increment cluster

and the initial-increment cluster presented twofold greater risks of reaching the walking and balance milestones (HR=2.00 [95% confidence interval, CI=1.03–3.90]; HR=2.06 [95% CI=1.18–

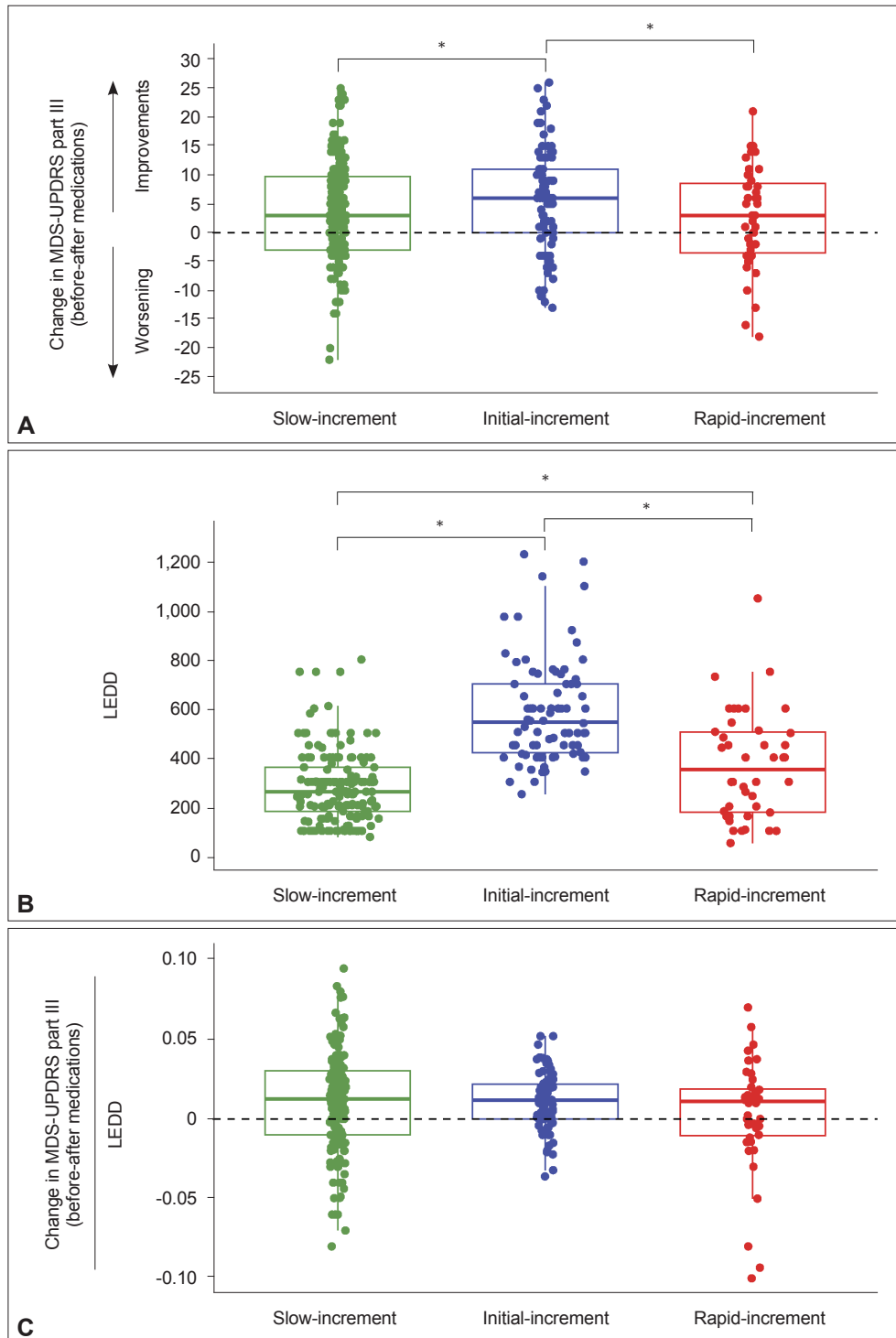


Figure 2. Initial response to anti-parkinsonian medications across LEDD clusters. Change of motor symptoms by anti-parkinsonian medications was measured as the change of MDS-UPDRS part III before and after the initiation of medications within 1 year (A). The amount of LEDD (B) and change of motor symptoms per unit of LEDD (C) was compared across the clusters. *significant p values (<0.05) are indicated. MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose.

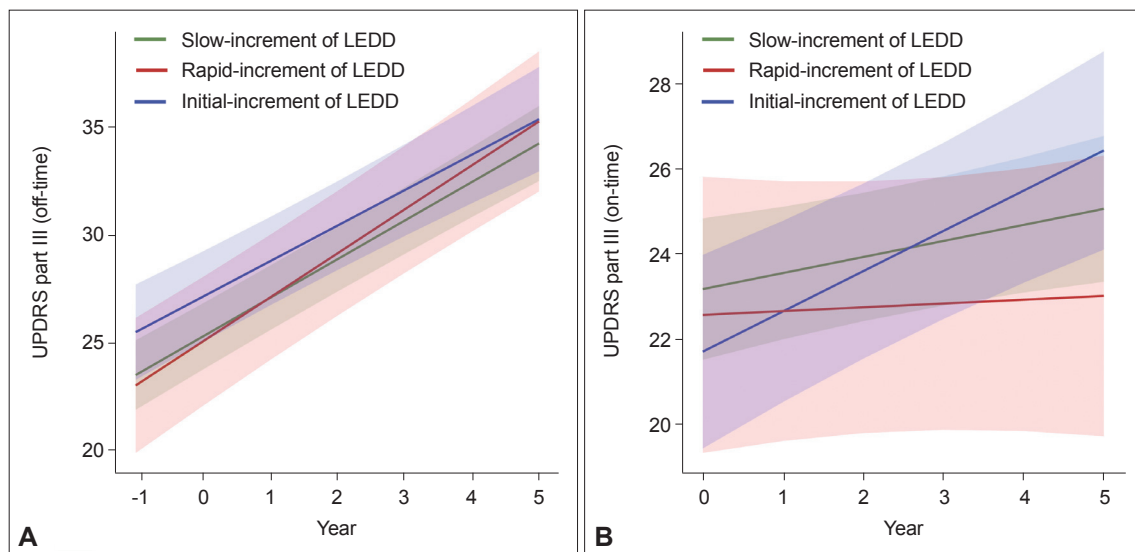


Figure 3. Longitudinal changes in off-time and on-time motor symptoms across LEDD clusters. Linear mixed models for off-time (A) and on-time (B) MDS-UPDRS part III scores were conducted to compare across the clusters. The time point labeled as -1 year represents the assessment conducted prior to the initiation of symptomatic treatment. Shaded areas represent 95% confidence intervals around the model-estimated means. LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

3.60]) for the rapid-increment and initial-increment clusters, respectively) (Figure 5A). The likelihood of reaching any motor complication milestone was 134% greater in the initial-increment cluster than in the slow-increment cluster (HR=2.34, 95% CI=1.34–4.12) (Figure 5B).

DISCUSSION

In this longitudinal observational study, 55.5% of patients experienced a slow increase in LEDD, 29.9% of patients experienced an initial increase, and 14.6% of patients experienced a rapid increase in LEDD. At baseline, the initial-increment cluster showed the highest degree of response at the highest LEDD compared with the other clusters, but the efficacy of LEDD was comparable across the clusters. Longitudinally, the initial-increment cluster showed a rapid increase in the PIGD score but a rapid decrease in the tremor score with stable low-efficacy LEDD. Although the LEDD increased exponentially in the rapid-increment cluster, the on-time motor scores did not improve accordingly, indicating a continuous decline in the efficacy of the LEDD over time. Compared with the slow-increment cluster, both the rapid- and initial-increment clusters presented increased risks of walking and balance milestones, and the initial-increment cluster presented an increased risk of motor complications. Subtyping PD based on longitudinal trajectories of LEDD revealed clinical heterogeneity in the progression of tremor and PIGD symptom severity, the efficacy of LEDD, and the development of PD-relevant milestones.

The clinical heterogeneity of PD is well recognized, with considerable interindividual variability in the rates of motor symptom progression, the response to pharmacological treatment, and the development of motor complications.^{8-11,19} Along with this variability, no standardized guidelines or consensus exist regarding dose escalation following the initiation of antiparkinsonian medication. In clinical practice, adjustments to the medication dosage are primarily based on the patient's response to treatment and the observed progression of symptoms.² Previous studies have categorized PD subtypes on the basis of early motor and nonmotor symptoms, demonstrating differences in initial medication dosages and treatment responses according to these subtypes.⁸⁻¹⁰ However, a cross-sectional comparison of the LEDD does not inform the heterogeneity in terms of dosage escalation over time. To address this gap, the present study classified PD patients on the basis of LEDD trajectories, analyzing a cohort that had been followed for a minimum of 3 years after the initiation of medications. Given that LEDD adjustments in routine clinical practice take into account factors such as the degree of motor symptom worsening, the effectiveness of previous prescriptions, and the emergence of motor complications, our LEDD-based clustering approach provides insights into how pharmacological treatment is adjusted in clinical settings. Furthermore, this analysis allows for a comprehensive evaluation of interindividual differences in medication titration and disease progression.

When initiating antiparkinsonian medications, patients with more severe baseline symptoms require higher doses, whereas those with milder symptoms experience improvements with

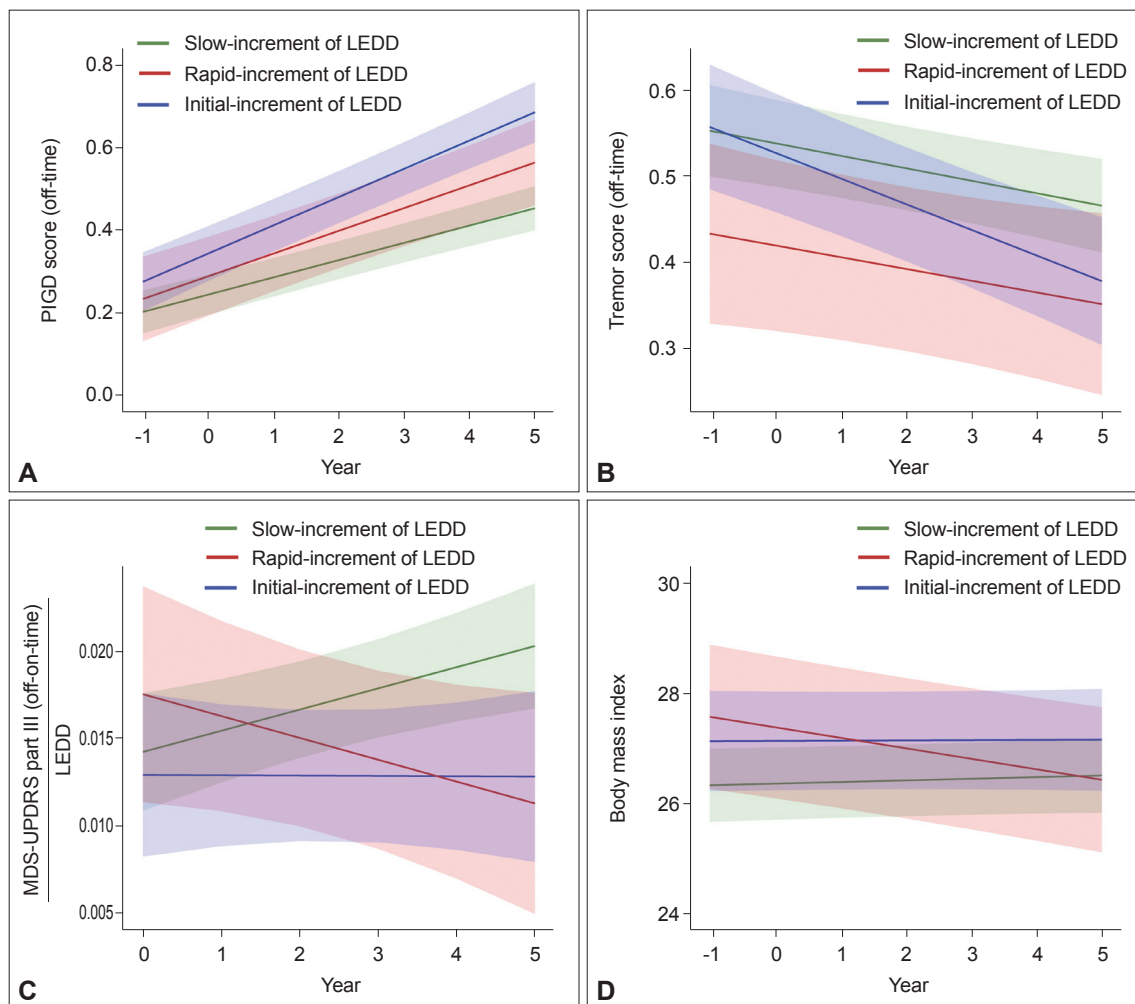


Figure 4. Longitudinal changes in motor symptoms and body mass index across LEDD clusters. Linear mixed models for off-time PIGD score (A), off-time tremor score (B), change of off-time and on-time MDS-UPDRS part III score per unit of LEDD (C), and body mass index (D) were conducted across the clusters. The time point labeled as -1 year represents the assessment conducted prior to the initiation of symptomatic treatment. Shaded areas represent 95% confidence intervals around the model-estimated means. LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PIGD, postural instability and gait disturbance.

lower doses. Previous studies have shown that subtypes with mild symptoms exhibit a good response to levodopa and require a lower LEDD.^{10,11} However, these findings were based on measurements taken during the disease course rather than at the initiation of treatment. In our study, we compared motor symptoms observed within the first year after starting treatment, considering the initial titration process. Both the changes in motor scores before and after medication initiation and the LEDD were greater in the initial-increment cluster, likely due to the higher baseline scores for tremor and PIGD scores at treatment initiation. However, the degree of motor symptom improvement per unit of LEDD was comparable across the clusters. This finding suggests that the initial response within the first year of treatment follows a dose-response pattern, with comparable efficacy of LEDD, regardless of the long-term LEDD increment trajectory.

Longitudinally, the efficacy of LEDD diverges as the disease progresses. In clinical practice, the primary reasons for dose escalation include a reduction in the duration of on-time, worsening of on-time motor symptoms, and the emergence of drug-resistant symptoms.¹² Conversely, clinicians and patients may refrain from further dose increases when symptoms become unresponsive to medication adjustments, when higher doses fail to yield further clinical improvement, or when adverse effects emerge with dose escalation. In our analysis, the initial-increment cluster exhibited a rapid increase in LEDD over the first 2 years, followed by a relatively slow phase of dose escalation. Several explanations are possible for this phenomenon. First, the worsening of symptoms that do not respond to LEDD increment, such as PIGD, freezing, and falls, may contribute to this slow phase.¹² Notably, the initial-increment cluster demonstrated

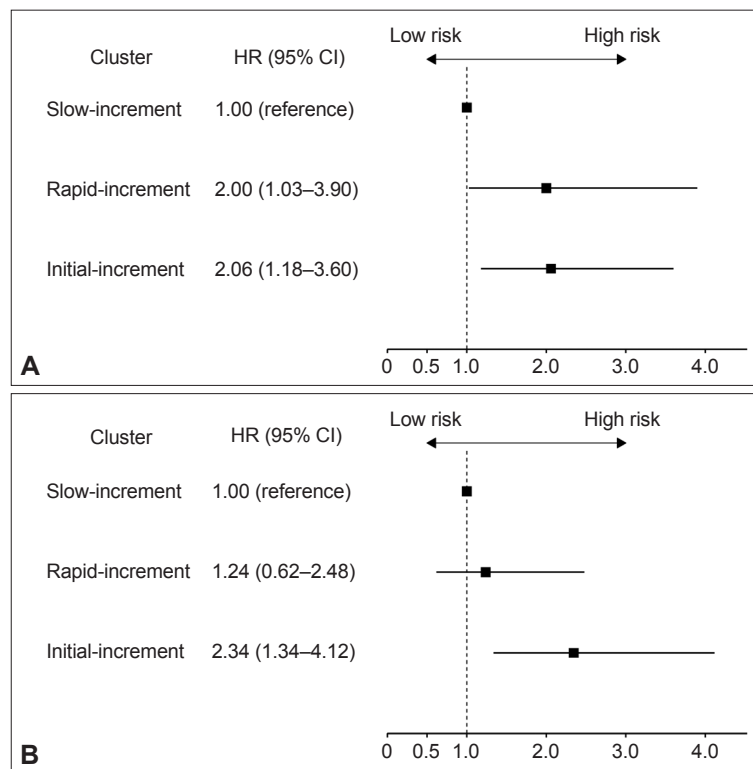


Figure 5. Risk of Parkinson's disease-relevant milestones according to levodopa equivalent daily dose clusters. Risk of (A) walking and balance milestone and (B) any motor fluctuation milestone were estimated based on Cox proportional hazard models adjusted for age, sex, and disease duration. HR, hazard ratio; CI, confidence interval.

a more rapid increase in PIGD scores compared to other clusters, whereas tremor score declined more rapidly. Additionally, the risk of reaching walking and balance milestones was greater in the initial-increment cluster than in the slow-increment cluster. Second, a ceiling effect in medication efficacy may limit the benefits of further dose increases. Patients in the initial-increment cluster exhibited more rapid aggravation of on-time motor symptoms compared with those in other clusters; however, the motor symptom improvement per unit of LEDD remained consistently low. This suggests that although some benefit is maintained, further dose escalation does not enhance clinical outcomes, reflecting a pharmacological limit to the effectiveness of LEDD. Third, the development of motor complications may restrict further dose escalation.

Compared with the slow-increment cluster, the initial-increment cluster demonstrated an increased risk of motor complications, including both dyskinesia and motor fluctuations. Although previous longitudinal studies have reported no significant difference in disease progression or the prevalence of levodopa-induced dyskinesia (LID) between early and delayed initiation of levodopa,^{3,5} several factors—such as cumulative levodopa exposure, age, sex, and BMI—have been shown to influence the development of LID.²⁰ A previous study using the PPMI dataset

also demonstrated an association between cumulative LEDD and dyskinesia onset.²¹ Importantly, our findings suggest that not only the cumulative amount of LEDD but also the rate of dose escalation may contribute to the risk of motor complications. This aligns with previous studies reporting that a faster rate of levodopa titration is associated with a greater risk of motor complications.²²

The rapid-increment cluster starts with a lower LEDD but increases exponentially, surpassing the average LEDD of the initial-increment cluster by the third year. The rate of change in the off-time PIGD and tremor scores in this cluster is comparable to that in the slow-increment cluster, whereas the on-time motor symptoms remain more stable than those in the other clusters. However, the efficacy of LEDD progressively decreases over time. This suggests that although patients in the rapid-increment cluster do not experience worsening of on-time motor symptoms by dose escalation, the LEDD required to maintain the same therapeutic effect gradually increases. A potential hypothesis could be related to pharmacokinetic changes.²³ Notably, patients in the rapid-increment cluster exhibited a rapid decline in BMI. A reduction in BMI could lead to altered drug distribution, potentially decreasing the transfer of medications from the peripheral bloodstream to the central nervous system, thereby

increasing the required LEDD over time. However, given that levodopa-associated weight loss has also been reported,²⁴ caution is needed when interpreting the causal relationship between BMI and increasing LEDD.

The slow-increment cluster comprised approximately half of the patients and was characterized by a gradual and linear increase in LEDD. Although both the PIGD and tremor scores increased and the on-time motor scores worsened over time, the efficacy of LEDD continued to increase, suggesting that even a small increase in LEDD could be beneficial. Overall, the three clusters identified on the basis of LEDD trajectories provide valuable insights into the heterogeneity of medication response in patients with PD and highlight the potential limitations of LEDD escalation in certain patient subgroups.

By integrating our findings, three main clinical scenarios can be anticipated regarding the increase in LEDD: 1) slow-increment cluster: this cluster represents patients with mild symptoms and slow disease progression, in which the efficacy of LEDD does not decrease over time. These patients may benefit more from minimal LEDD adjustments than from high-dose escalation. 2) Initial-increment cluster: this group includes patients with severe baseline symptoms and a more rapid decline in PIGD scores. Although on-time motor symptoms initially improve, these patients have a greater risk of developing motor complications. Given the potential for ceiling effects or drug-related side effects, short-term follow-up and careful medication adjustments are crucial. 3) Rapid-increment cluster: patients in this cluster may experience dynamic changes between off-time and on-time states as the disease progresses, requiring progressively higher doses of antiparkinsonian medications while maintaining a stable response.

Several limitations should be considered when our findings are interpreted. First, a key limitation is the potential influence of clinician-level variability in prescribing practices on LEDD trajectories. In the PPMI study, information on individual treating physicians was not available, preventing direct adjustment for this factor. Although we adjusted for the site of enrollment, differences in how individual physicians escalated dopaminergic therapy—especially without standardized titration protocols—may influence medication patterns independently of disease progression. This makes it difficult to determine to what extent LEDD trajectories reflect true patient-driven changes versus treatment-related variability. Second, the follow-up duration was limited to a maximum of 5 years in the current study. This time period may not be sufficient to determine whether the observed LEDD patterns persist with longer-term follow-up. Additional follow-up data might reveal new clustering patterns or different LEDD trajectories that require further investigation. Third, LEDD trajectories should not be interpreted causally. Because

PD treatment is symptomatic, increases in LEDD generally reflect changes in symptom severity and clinician-driven adjustments rather than representing an independent predictor of disease progression. As such, the LEDD-based clusters identified in this study should be viewed as descriptive groupings, not predictive subtypes. Fourth, LEDD may influence downstream clinical outcomes, such as dyskinesia or other motor complications. In this sense, LEDD could function not only as a response to disease severity but also as a modifier of the clinical course. Although we observed differences in motor symptom progression and medication efficacy between clusters, these findings more likely reflect clinical heterogeneity in therapeutic response rather than direct causality. Fifth, only 7 participants (2.3% of the cohort) were diagnosed with PD before age 40 years. Owing to this small sample size, we were unable to perform meaningful age-stratified analyses. Although these early-onset cases likely had minimal influence on the overall clustering results, their distinct clinical characteristics merit further investigation in future studies. It may be appropriate in similar studies to either analyze early-onset PD separately or exclude it to reduce heterogeneity.

In summary, by analyzing longitudinal LEDD trajectories, we identified three distinct patterns of increasing LEDD: slow-increment, initial-increment, and rapid-increment clusters. Since these clusters exhibit different changes in motor phenotypes, LEDD efficacy, and the risk of reaching disease milestones, it would be beneficial to consider such clinical heterogeneity when adjusting antiparkinsonian medication dosages.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.14802/jmd.25099>.

Conflicts of Interest

The authors have no financial conflicts of interest.

Funding Statement

This work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI22C0977) and by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (grant number: RS-2023-00245506).

Acknowledgments

PPMI—a public-private partnership—is funded by the Michael J. Fox Foundation for Parkinson's Research (MJFF) and funding partners, including Abbvie, Acurex Therapeutics, Allergan, Amathus Therapeutics, Avid Radiopharmaceuticals, BIAL Biotech, Biogen, BioLegend, Bristol Myers Squibb, Celgene, Denali, 4D Pharma PLC, GE Healthcare, Genentech, GlaxoSmith-Kline, Golub Capital, Handl Therapeutics, insitro, Janssen Neuroscience, Lilly, Lundbeck, Merck, Meso Scale Discovery, Neurocrine Biosciences, Pfizer, Piramal, Prevail Therapeutics, Roche, Sanofi Genzyme, Servier, Takeda, Teva, UCB, Verily, and Voyager Therapeutics.

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