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Adherence to istradefylline in patients with Parkinson's disease: A group-based trajectory analysis

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ABSTRACT

Background: Understanding the different patterns of adherence to istradefylline treatment is essential to identifying Parkinson's disease (PD) patients who might benefit from targeted interventions.
Objectives: This descriptive study aimed to identify longitudinal istradefylline adherence patterns and to characterize factors associated with them.
Methods: We identified PD patients aged 21–99 years who initiated istradefylline treatment in a Japanese hospital administrative database. Group-based trajectory modeling was used to model the monthly proportion of days covered over time to identify distinct 360-day adherence patterns. Factors associated with each adherence pattern were assessed using univariable multinomial logistic regression models.
Results: Of 2088 eligible PD patients, 4 distinct adherence groups were identified: consistently high adherence (56.8%); rapidly declining adherence (25.8%); gradually declining adherence (8.5%); and gradually declining and then recovering adherence (9.0%). Compared to the consistently high adherence group, the other groups had the following characteristics associated with a likelihood of lower adherence: the rapidly declining adherence group received fewer dopamine agonists (63.8% vs. 69.4%), monoamine oxidase B (MAO-B) inhibitors (26.8% vs. 31.6%), and catechol-*O*-methyl transferase inhibitors (31.6% vs. 37.0%) and had a higher prevalence of anxiety/mood disorders (29.9% vs. 24.6%); the gradually declining adherence group received fewer MAO-B inhibitors (22.5% vs. 31.6%) and amantadine (8.4% vs. 16.1%) and had a higher prevalence of mild cognitive impairment/dementia (27.0% vs. 18.8%); and the declining and then recovering adherence group had a higher prevalence of anxiety/mood disorders (34.2% vs. 24.6%).
Conclusions: Clinicians should be aware of the heterogeneous patterns of adherence to istradefylline.

1. Introduction

Istradefylline is a first-in-class, nondopaminergic adenosine A_{2A} receptor antagonist indicated as an adjunctive treatment to levodopa-containing medications in patients with Parkinson's disease (PD) experiencing OFF episodes [1]. The drug was first approved in Japan in 2013 and subsequently in the US in 2019 [1,2]. Istradefylline may offer patients a different treatment option than dopaminergic agents. Recent clinical studies have demonstrated that istradefylline is also effective in the treatment of gait disorders [3], postural abnormalities [4], mood disorders [5], and daytime sleepiness [6], and reduces levodopa dose escalation [7].

Maintenance of high adherence is essential to producing the benefits of istradefylline. Of note, adherence is not a static concept, but rather a dynamic behavior which changes over time [8], as defined by three phases: initiation, implementation, and discontinuation [9]. Classifying

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patient groups based on longitudinal adherence patterns can help understand heterogeneity in the timing of adherence decrease [10]. To date, however, no study has identified specific adherence patterns for istradefylline treatment.

Group-based trajectory modeling (GBTM), which identifies groups with similar longitudinal outcome patterns [11,12], is ideal for analyzing dynamic medication adherence [10]. By characterizing patient profiles in each adherence group, clinicians may be able to identify patients who could be at higher risk of poor adherence to treatment [13].

Here, we first performed GBTM to classify longitudinal adherence patterns of istradefylline treatment into distinct groups. Next, we identified factors associated with membership in each adherence group to characterize patient profiles. Finally, as an adherence-related performance metric, we estimated the probability of continuing istradefylline treatment for 3 years, both in the overall population and in subpopulations stratified by several factors.

2. Methods

2.1. Study design and data source

This longitudinal descriptive study was conducted using a Japanese hospital administrative database maintained by Medical Data Vision Co., Ltd. for the period April 1, 2008, to May 31, 2019 [14–16]. The database covered approximately 28.4 million patients treated at 385 acute care hospitals throughout Japan as of 2019 and contained information on demographic characteristics, inpatient and outpatient diagnoses, procedures, and prescriptions [17]. Patients in the database can be tracked within the same hospital. This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval number: R4023). The requirement for informed consent was waived in accordance with the Japanese ethical guidelines due to the anonymous nature of the data.

2.2. Study population

We identified PD patients aged between 21 and 99 years who initiated istradefylline at a dose of either 20 mg or 40 mg once daily. The date of first istradefylline prescription was defined as the cohort entry date, and was required to be between June 1, 2014, and 450 days before the end of data collection at each hospital. The reason for setting the inclusion period after June 1, 2014, was that from May 30, 2013, when istradefylline was launched, to May 31, 2014, the Japanese Ministry of Health, Labour and Welfare allowed prescriptions of the drug for only up to 14 days at a time, which would likely affect adherence. All patients were required to have had at least one consultation for PD at or within 30 days before cohort entry, as well as concomitant use of levodopa-containing medications at cohort entry. Additionally, they were required to have been continuously enrolled in the database for at least 180 days leading up to cohort entry and to have had two outpatient visits within the previous 180 days [18]. Patients were excluded if they had been diagnosed with schizophrenia or severe liver disease at or before cohort entry. Details of the inclusion and exclusion criteria can be found in Fig. S1 and Table S1 [19,20].

2.3. Medication adherence

For each patient, the monthly proportion of days covered (PDC) [21], a measure of adherence, was calculated at 30-day intervals during the assessment period of up to 360 days from the cohort entry date. This 360-day assessment period was chosen based on the following three considerations: (1) it is one of the most commonly used periods for GBTM [22–24]; (2) the finding that persistence for many chronic medications [25], including anti-PD medications [26], most strongly declines in the first year of treatment; and (3) the need to have a sufficient number of patients for analysis (the longer the assessment period, the fewer the patients included in the analysis). Patients were included in the PDC calculation until death, loss to follow-up, or the end of the 360-day assessment period, whichever occurred first [27]. When a subsequent prescription was issued before the supply from the previous prescription had run out, the overlap was added to the end date of the subsequent prescription.

2.4. Patient characteristics

Baseline patient characteristics included demographics (age, sex), PD treatment duration, calendar year of cohort entry, medication use (istradefylline dose, levodopa dose, levodopa equivalent dose [28,29], anti-PD medications, antipsychotics), and comorbidities (mild cognitive impairment [MCI]/dementia, anxiety/mood disorders, orthostatic hypotension). We used PD treatment duration as a proxy measure for PD duration since the exact PD duration data were not available; however, we noted that only the treatment duration recorded within the same hospital after April 2008 was available. A full list of patient characteristics, their definitions, and the time window for their assessment is shown in Table S2.

2.5. Statistical analysis

We used GBTM, a specialized application of finite mixture modeling, to identify differential longitudinal adherence patterns of istradefylline treatment in a two-step process [10–12]. In the first step, we selected the optimal number of groups to include in the model [11,30]. We used a censored normal distribution for monthly PDCs and estimated models with 2 to 7 groups of trajectories [30,31], one of which was specified to follow a zero-order trajectory, and the remaining groups were specified to follow a third-order trajectory [11]. The zero-order trajectory was specified to accommodate the group whose monthly PDCs remained approximately 1.0 throughout the assessment period, based on domain knowledge [11,30]. The monthly PDCs of patients who died or were lost to follow-up during the 360-day assessment period were treated as missing after their occurrence and were included in the dropout modeling [27,32]. We used the Bayesian information criterion (BIC) to select the optimal number of groups [11]. If BIC continued to improve with the addition of more groups, the number of groups was determined based on clinical interpretability [11]; for example, if adding another group (the 5th group) resulted in 2 groups with similar trajectory patterns, the former model (4 groups) was selected [30]. In the second step, we determined the order of the polynomial that specifies the shape of each trajectory [11]. Models were fitted with all possible combinations of trajectory in the order 0 to 3. We selected the final model based on (1) the BIC, with the largest value indicating the best-fitting model and (2) 4 criteria recommended by Nagin (Table S3) [11,12]. Adherence groups from the final model were labeled according to the appearance of the trajectory.

We performed three additional analyses. First, to characterize patient profiles, we identified factors associated with membership in each GBTM-defined adherence group using univariable multinomial logistic regression models. Analyzed variables included baseline patient characteristics, except PD treatment duration, calendar year of cohort entry, and levodopa equivalent dose. We did not adjust for covariates because, for descriptive studies, covariate adjustment can lead to the misinterpretation of results [33,34]. Second, we estimated the probability of continuing istradefylline treatment at 1, 2, and 3 years after cohort entry, both in the overall population and in subpopulations stratified by the same factors used in multinomial logistic regression models. The probability was estimated as 1 minus the cumulative incidence function accounting for the competing risk of death. Patients were followed from cohort entry until istradefylline discontinuation, death, loss to follow-up (including end of data collection at each hospital), or end of the 3-year follow-up, whichever occurred first. Istradefylline discontinuation was

defined as no subsequent prescription within 60 days after the last day of supply for an existing prescription (discontinuation date). Further, we calculated the differences in probability of continuing istradefylline treatment between the aforementioned subpopulations. The 95% confidence intervals (CIs) for the differences were computed using the percentile bootstrap method with replacement with 10,000 replicates [35]. Third, as a post-hoc analysis, we described the 3-year trend in median levodopa dose for each GBTM-defined adherence group to quantify the impact of each adherence trajectory on this exploratory effectiveness outcome.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.) with the SAS PROC TRAJ macro [36], and R version 4.3.1 (R Foundation for Statistical Computing).

3. Results

3.1. Characteristics of the study population

A total of 2088 PD patients were eligible for this study (Fig. 1). Median age was 74.0 years (interquartile range [IQR], 67.0 to 79.0) and 53.8% were female (Table 1). The median levodopa dose was 400.0 mg/day (IQR, 300.0 to 500.0) and the median levodopa equivalent dose was 574.3 mg/day (IQR, 400.0 to 771.4). Dopamine agonists (DAs) were the most common concomitant anti-PD medications (68.3%), followed by catechol-*O*-methyltransferase (COMT) inhibitors (35.0%) and monoamine oxidase B (MAO-B) inhibitors (29.2%). The median number of anti-PD medications used was 4 (IQR, 3 to 4). Among patients, 27.4% had anxiety/mood disorders, 20.5% had MCI/dementia, and 6.8% had orthostatic hypotension. Median follow-up duration was 360 days (IQR, 360 to 360) for GBTM and 410 days (IQR, 80 to 848) for analysis of the probability of continuing istradefylline treatment (Table S4).

3.2. Istradefylline adherence patterns

The 4-group model was selected because it had a better BIC than models with fewer groups (Table S5), while models with 5 or more groups were sometimes unstable and did not identify additional adherence groups that were clinically meaningful (Fig. S2). Among 256 combinations of trajectories, the final 4-group model (Fig. 2) had the largest BIC and met the 4 criteria recommended by Nagin (Table S3). The 4 groups consisted of (1) consistently high adherence (56.8%); (2) rapidly declining adherence (25.8%); (3) gradually declining adherence (8.5%); and (4) gradually declining and then recovering adherence (9.0%). The mean monthly PDC over time in each adherence group is shown in Table S6.

3.3. Associations between patient characteristics and istradefylline adherence patterns

Compared to the consistently high adherence group, the other groups had the following characteristics associated with a likelihood of lower adherence (Tables 1 and 2): the rapidly declining adherence group received fewer concomitant anti-PD medications, with fewer DAs (63.8% vs. 69.4%), MAO-B inhibitors (26.8% vs. 31.6%), and COMT inhibitors (31.6% vs. 37.0%) and had a higher prevalence of anxiety/mood disorders (29.9% vs. 24.6%); the gradually declining adherence group received fewer MAO-B inhibitors (22.5% vs. 31.6%) and amantadine (8.4% vs. 16.1%) and had a higher prevalence of MCI/dementia (27.0% vs. 18.8%); and the gradually declining and then recovering adherence group had a higher prevalence of anxiety/mood disorders (34.2% vs. 24.6%).

The following patient characteristics were not associated with a likelihood of lower adherence: age, sex, levodopa dose, zonisamide, anticholinergics, antipsychotics, or orthostatic hypotension.

3.4. Probability of continuing istradefylline treatment

Probabilities of continuing istradefylline treatment in the overall population and in subpopulations stratified by baseline patient characteristics are shown in Fig. 3, Fig. S3, and Table S7. In the overall population, probability was 57.0% (95% CI, 54.9% to 59.2%) at 1 year, 44.9% (95% CI, 42.7% to 47.2%) at 2 years, and 37.7% (95% CI, 35.4% to 40.1%) at 3 years. The 3-year probability was lower in females (difference, −3.9%; 95% CI, −7.5% to −0.3%), patients with a levodopa dose ≥400 mg/day (difference, −5.7%; 95% CI, −9.2% to −2.1%), those with MCI/dementia (difference, −9.1%; 95% CI, −13.4% to −4.8%), those with anxiety/mood disorders (difference, −8.2%; 95% CI, −12.0% to −4.2%), and those with orthostatic hypotension (difference, −13.4%; 95% CI, −19.9% to −6.8%). The 3-year probability was higher for patients using more anti-PD medications (e.g., those using 6 to 8

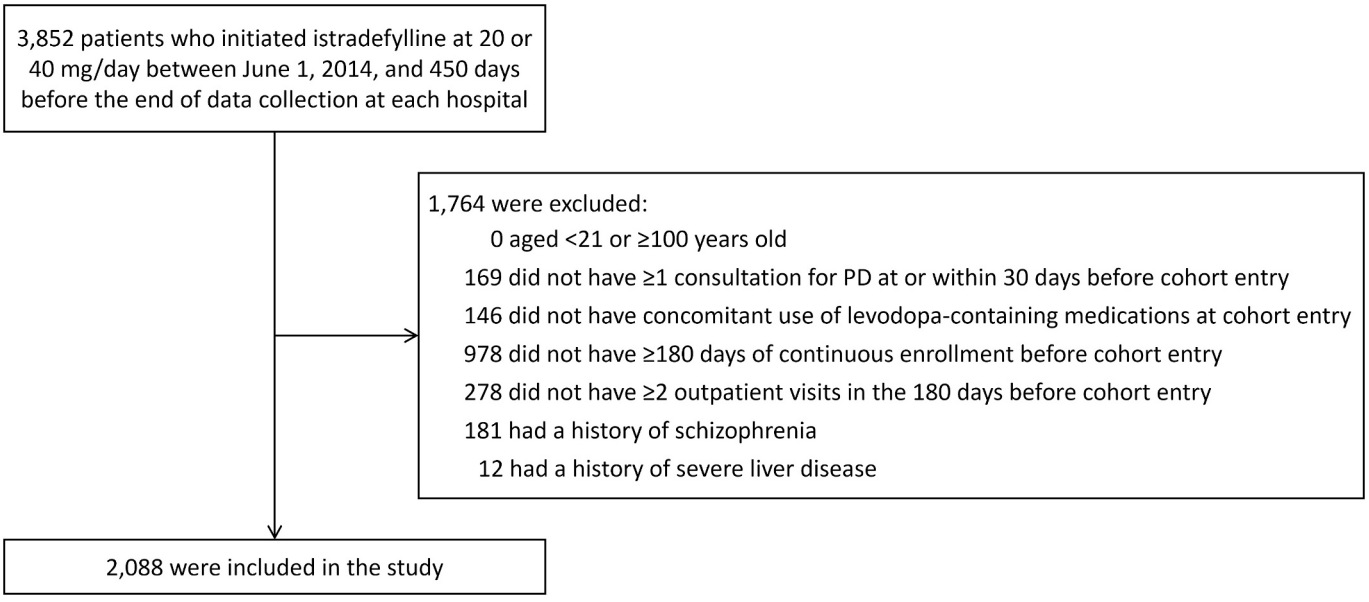

Fig. 1. Flow diagram for this longitudinal descriptive study.
Abbreviation: PD, Parkinson's disease.

Table 1
Baseline characteristics of the study population.

Characteristic	Overall (n = 2088; 100%)	Consistently high adherence (n = 1185; 56.8%)	Rapidly declining adherence (n = 538; 25.8%)	Gradually declining adherence (n = 178; 8.5%)	Gradually declining and then recovering adherence (n = 187; 9.0%)
Age, median (IQR), years	74.0 (67.0 to 79.0)	74.0 (67.0 to 79.0)	74.0 (67.0 to 79.0)	74.0 (67.0 to 79.0)	74.0 (68.0 to 78.0)
21 to 74 years	1130 (54.1)	646 (54.5)	294 (54.6)	95 (53.4)	95 (50.8)
75 to 99 years	958 (45.9)	539 (45.5)	244 (45.4)	83 (46.6)	92 (49.2)
Sex					
Male	964 (46.2)	564 (47.6)	231 (42.9)	82 (46.1)	87 (46.5)
Female	1124 (53.8)	621 (52.4)	307 (57.1)	96 (53.9)	100 (53.5)
PD treatment duration, median (IQR), years	2.20 (1.17 to 3.55)	2.21 (1.17 to 3.61)	2.00 (1.04 to 3.36)	2.47 (1.32 to 3.51)	2.48 (1.44 to 3.87)
Calendar year of cohort entry					
2014	501 (24.0)	287 (24.2)	119 (22.1)	44 (24.7)	51 (27.3)
2015	575 (27.5)	343 (28.9)	143 (26.6)	41 (23.0)	48 (25.7)
2016	468 (22.4)	249 (21.0)	133 (24.7)	46 (25.8)	40 (21.4)
2017	483 (23.1)	272 (23.0)	131 (24.3)	40 (22.5)	40 (21.4)
2018	61 (2.9)	34 (2.9)	12 (2.2)	7 (3.9)	8 (4.3)
Istradefylline dose					
20 mg/day	1922 (92.0)	1116 (94.2)	479 (89.0)	159 (89.3)	168 (89.8)
40 mg/day	166 (8.0)	69 (5.8)	59 (11.0)	19 (10.7)	19 (10.2)
Levodopa dose, median (IQR), mg/day	400.0 (300.0 to 500.0)	400.0 (300.0 to 500.0)	400.0 (300.0 to 500.0)	400.0 (300.0 to 500.0)	400.0 (300.0 to 500.0)
0 to <400 mg/day	994 (47.6)	568 (47.9)	259 (48.1)	75 (42.1)	92 (49.2)
≥400 mg/day	1094 (52.4)	617 (52.1)	279 (51.9)	103 (57.9)	95 (50.8)
Levodopa equivalent dose, median (IQR), mg/day	574.3 (400.0 to 771.4)	579.6 (400.0 to 779.6)	553.5 (400.0 to 755.0)	585.8 (450.0 to 748.5)	550.0 (419.7 to 798.0)
Concomitant anti-PD medications					
Dopamine agonists	1427 (68.3)	822 (69.4)	343 (63.8)	126 (70.8)	136 (72.7)
MAO-B inhibitors	610 (29.2)	374 (31.6)	144 (26.8)	40 (22.5)	52 (27.8)
COMT inhibitors	730 (35.0)	439 (37.0)	170 (31.6)	55 (30.9)	66 (35.3)
Zonisamide	384 (18.4)	228 (19.2)	88 (16.4)	31 (17.4)	37 (19.8)
Amantadine	296 (14.2)	191 (16.1)	70 (13.0)	15 (8.4)	20 (10.7)
Anticholinergics	133 (6.4)	69 (5.8)	39 (7.2)	15 (8.4)	10 (5.3)
No. anti-PD medications used, median (IQR)	4.0 (3.0 to 4.0)	4.0 (3.0 to 5.0)	4.0 (3.0 to 4.0)	3.0 (3.0 to 4.0)	4.0 (3.0 to 4.0)
2*	281 (13.5)	144 (12.2)	94 (17.5)	24 (13.5)	19 (10.2)
3	669 (32.0)	361 (30.5)	171 (31.8)	69 (38.8)	68 (36.4)
4	655 (31.4)	372 (31.4)	167 (31.0)	51 (28.7)	65 (34.8)
5	354 (17.0)	227 (19.2)	80 (14.9)	26 (14.6)	21 (11.2)
6 to 8	129 (6.2)	81 (6.8)	26 (4.8)	8 (4.5)	14 (7.5)
Antipsychotics	78 (3.7)	43 (3.6)	21 (3.9)	6 (3.4)	8 (4.3)
Comorbidities					
MCI/dementia	427 (20.5)	223 (18.8)	110 (20.4)	48 (27.0)	46 (24.6)
Anxiety/mood disorders	572 (27.4)	292 (24.6)	161 (29.9)	55 (30.9)	64 (34.2)
Orthostatic hypotension	141 (6.8)	75 (6.3)	34 (6.3)	15 (8.4)	17 (9.1)

Abbreviations: COMT, catechol-*O*-methyltransferase; IQR, interquartile range; MAO-B, monoamine oxidase B; MCI, mild cognitive impairment; PD, Parkinson's disease.

Note: Data are presented as number (percentage) of patients unless otherwise indicated.

* All patients used at least 2 anti-PD medications (istradefylline and levodopa-containing medications).

medications compared to those using 2 medications; difference, 9.7%; 95% CI, 0.5% to 19.0%), those using MAO-B inhibitors (difference, 5.1%; 95% CI, 1.1% to 9.0%), those on zonisamide (difference, 5.0%; 95% CI, 0.4% to 9.7%), and those on amantadine (difference, 6.8%; 95% CI, 1.6% to 11.9%). Probability was also higher at 1 year for those on DAs (difference, 5.1%; 95% CI, 1.5% to 8.6%) and at 1 to 2 years for those on COMT inhibitors (difference, 4.3%; 95% CI, 0.6% to 7.8%), but no significant differences were noted thereafter. No differences in probability were observed in subpopulations stratified by age (21 to 74 years vs. 75 to 99 years), anticholinergic use, or antipsychotic use.

3.5. Levodopa dosage over time among adherence groups

In the consistently high adherence group, median levodopa dose was maintained at 400 mg/day until day 600, after which it increased to 450 mg/day (Fig. S4). In the rapidly declining adherence group, median levodopa dose was maintained at 400 mg/day until day 420 and then generally increased to 450 mg/day, with some fluctuation. In the gradually declining adherence group, median levodopa dose was maintained at 400 mg/day until day 450 and then generally increased to 450 mg/day, with some fluctuation. In the gradually declining and then recovering adherence group, median levodopa dose remained at 400 mg/day until day 600, increased to 450 mg/day, and then eventually reached 500 mg/day by day 900.

4. Discussion

In this longitudinal descriptive study of PD patients who initiated istradefylline, we used GBTM to identify the following 4 distinct adherence groups: consistently high adherence; rapidly declining adherence; gradually declining adherence; and gradually declining and then recovering adherence. Membership in the lower adherence groups was associated with fewer concomitant anti-PD medications, anxiety/mood disorders, and MCI/dementia, and these appeared to have influenced the probability of continuing istradefylline treatment. Clinicians need to understand the heterogeneity of istradefylline adherence and consider different intervention strategies based on patient characteristics to address non-adherence issues.

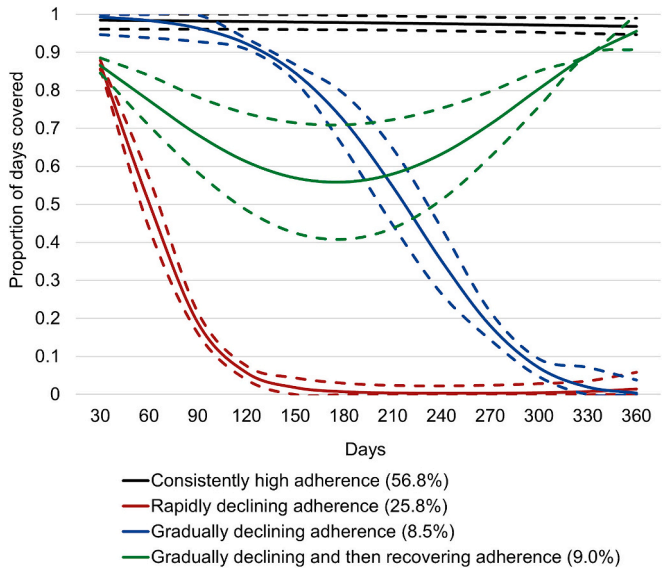

Fig. 2. Trajectories of 360-day adherence to istradefylline.
The consistently high adherence group was specified to follow a zero-order trajectory; the rapidly declining adherence group was specified to follow a third-order trajectory; and the remaining groups were specified to follow a second-order trajectory.

We observed that the consistently high adherence group accounted for 56.8% of the total, and found that when combined with the gradually declining and then recovering adherence group, the total was 65.8%. This result is generally consistent with the results of a post-marketing surveillance study of istradefylline in Japan, which showed a persistence of 70.2% during the first year of treatment [37]. The gradually declining and then recovering adherence group had more anxiety/mood disorders than the consistently high adherence group. Conversely, this contrast may suggest that istradefylline is effective in the treatment of anxiety/mood disorders in PD patients. An open-label study examining the efficacy of istradefylline for mood disorders in PD patients reported improvements in apathy, anhedonia, and depression, independent of improvement in parkinsonian motor symptoms [5].

Among groups, the rapidly declining and gradually declining adherence groups had fewer concomitant anti-PD medications than the consistently high adherence group: the rapidly declining adherence group had fewer DAs, MAO-B inhibitors, and COMT inhibitors; and the gradually declining adherence group had fewer MAO-B inhibitors and amantadine. The protective effect of concomitant medications on adherence is not simply determined by the number of medications, but rather by the complexity of the concomitant medication regimen [38,39]. Those who took more medications and were able to manage more complex regimens may have had stronger medication-taking habits and greater access to resources to maintain adherence [23,40], and may therefore have been more adherent to simple once-daily istradefylline. Other characteristics included more anxiety/mood disorders in the rapidly declining adherence group and more MCI/dementia in the gradually declining adherence group than in the consistently high adherence group. The influence of these factors on poor adherence has been well documented in several studies [41,42].

Baseline characteristics that differed in the probability of istradefylline treatment continuation were identical to those associated with membership in the low adherence groups as defined by GBTM, except for sex, levodopa dose, and orthostatic hypotension. The difference between the two results is not surprising given that the probability of treatment continuation reflects only the first treatment discontinuation, whereas GBTM reflects a more flexible pattern of treatment discontinuation, including timing and treatment reinitiation after discontinuation. The lower probability of treatment adherence among females compared to males might have been due to differences in the proportion of spouses. A previous study suggested that treatment adherence for PD is lower among those without a spouse than among those with a spouse [43], and as of 2015, the proportion of Japanese elderly persons ≥65 years with a spouse was lower among females than among males (51.4% vs. 80.1%) [44]; however, this is speculative since marital status data were not available. The rapidly declining adherence group defined by GBTM tended to be more female than the consistently high adherence group, although this was not significant (OR, 1.21; 95% CI, 0.98 to 1.48). Regarding levodopa dosage, we observed a lower probability of continuing istradefylline treatment in this study for doses of ≥400 mg/

Table 2
Associations between patient characteristics and istradefylline adherence pattern.

Characteristic	Odds ratio (95% CI)		
	Rapidly declining adherence (vs. consistently high adherence)	Gradually declining adherence (vs. consistently high adherence)	Gradually declining and then recovering adherence (vs. consistently high adherence)
Age			
21 to 74 years	1 [Reference]	1 [Reference]	1 [Reference]
75 to 99 years	1.00 (0.81 to 1.22)	1.05 (0.76 to 1.44)	1.16 (0.85 to 1.58)
Sex			
Male	1 [Reference]	1 [Reference]	1 [Reference]
Female	1.21 (0.98 to 1.48)	1.06 (0.78 to 1.46)	1.04 (0.77 to 1.42)
Levodopa dose			
0 to <400 mg/day	1 [Reference]	1 [Reference]	1 [Reference]
≥400 mg/day	0.99 (0.81 to 1.22)	1.26 (0.92 to 1.74)	0.95 (0.70 to 1.29)
Concomitant anti-PD medications			
Dopamine agonists	0.78 (0.63 to 0.96)	1.07 (0.76 to 1.51)	1.18 (0.83 to 1.66)
MAO-B inhibitors	0.79 (0.63 to 0.99)	0.63 (0.43 to 0.91)	0.84 (0.59 to 1.18)
COMT inhibitors	0.79 (0.63 to 0.98)	0.76 (0.54 to 1.07)	0.93 (0.67 to 1.28)
Zonisamide	0.82 (0.63 to 1.08)	0.89 (0.59 to 1.34)	1.04 (0.70 to 1.53)
Amantadine	0.78 (0.58 to 1.05)	0.48 (0.28 to 0.83)	0.62 (0.38 to 1.02)
Anticholinergics	1.26 (0.84 to 1.90)	1.49 (0.83 to 2.67)	0.91 (0.46 to 1.81)
No. anti-PD medications used			
2*	1 [Reference]	1 [Reference]	1 [Reference]
3	0.73 (0.53 to 1.00)	1.15 (0.69 to 1.90)	1.43 (0.83 to 2.46)
4	0.69 (0.50 to 0.95)	0.82 (0.49 to 1.39)	1.32 (0.77 to 2.29)
5	0.54 (0.38 to 0.78)	0.69 (0.38 to 1.24)	0.70 (0.36 to 1.35)
6 to 8	0.49 (0.30 to 0.82)	0.59 (0.26 to 1.38)	1.31 (0.62 to 2.75)
Antipsychotics	1.08 (0.63 to 1.84)	0.93 (0.39 to 2.21)	1.19 (0.55 to 2.57)
Comorbidities			
MCI/dementia	1.11 (0.86 to 1.43)	1.59 (1.11 to 2.29)	1.41 (0.98 to 2.02)
Anxiety/mood disorders	1.31 (1.04 to 1.64)	1.37 (0.97 to 1.93)	1.59 (1.15 to 2.21)
Orthostatic hypotension	1.00 (0.66 to 1.52)	1.36 (0.76 to 2.43)	1.48 (0.85 to 2.57)

Abbreviations: CI, confidence interval; COMT, catechol-*O*-methyltransferase; MAO-B, monoamine oxidase B; MCI, mild cognitive impairment; PD, Parkinson's disease.
* All patients used at least 2 anti-PD medications (istradefylline and levodopa-containing medications).

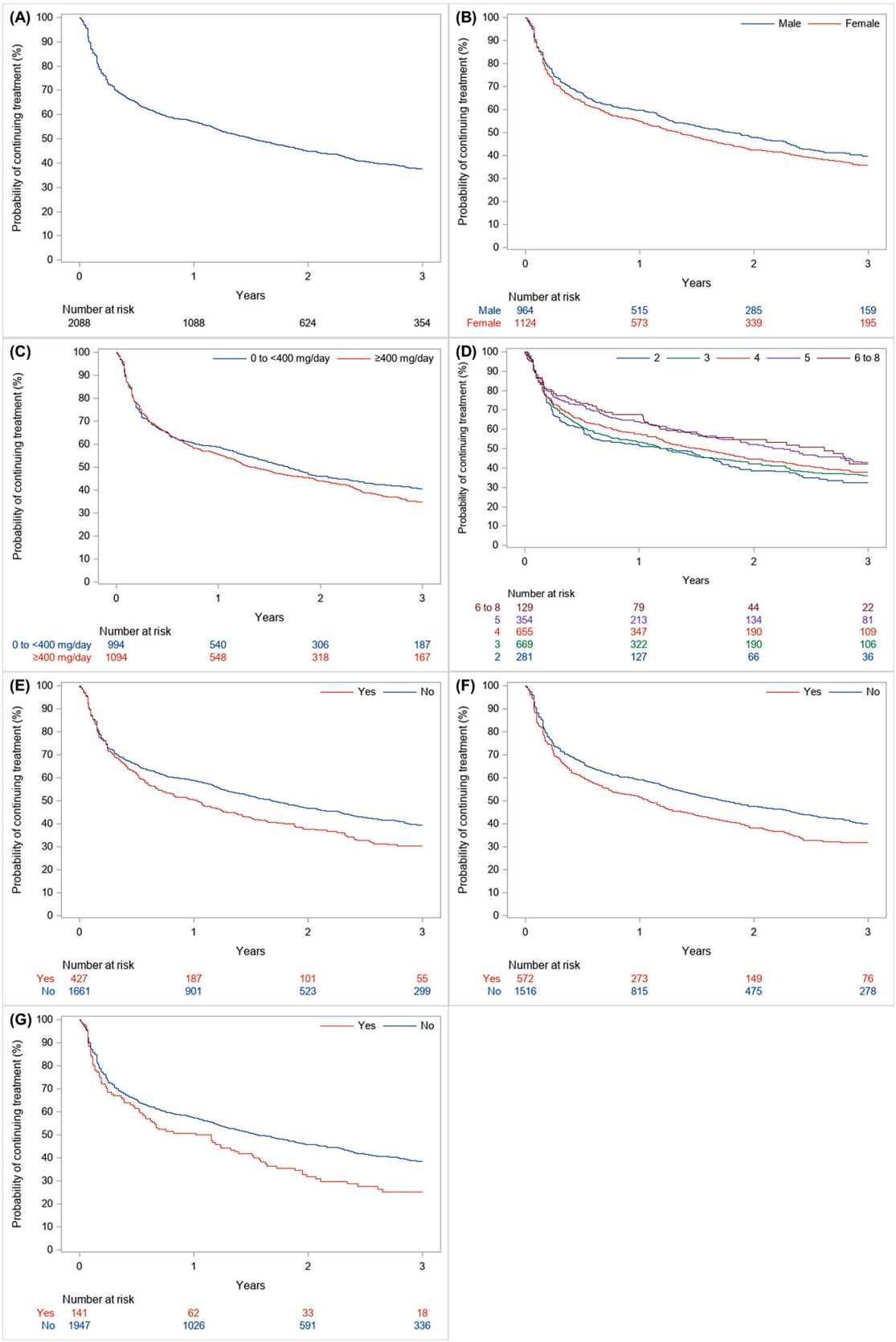

Fig. 3. Probability of continuing istradefylline treatment in the (A) overall population and in subpopulations stratified by (B) sex; (C) levodopa dose; (D) number of anti-Parkinson's disease medications used; and the presence of (E) mild cognitive impairment/dementia, (F) anxiety/mood disorders, and (G) orthostatic hypotension.

day compared to 0 to <400 mg/day, but the difference was relatively small. Also, this does not suggest a causal relationship, as the present study was a descriptive analysis only [33,34]. For orthostatic hypotension, the probability of continuing istradefylline treatment was lower in patients with orthostatic hypotension than in those without. Indeed, orthostatic hypotension was slightly, albeit not significantly more common in the group with gradually declining adherence than in the group with consistently high adherence; thus, a larger study might have identified orthostatic hypotension as one of the factors characterizing the gradually declining adherence pattern.

To quantify the impact of each adherence trajectory on treatment effectiveness, we conducted a post-hoc analysis describing the trend in median levodopa dose for each adherence group. The consistently high adherence group showed a delay in the median increase of 50 mg/day in levodopa dose by 150–180 days compared to both the rapidly declining and gradually declining adherence groups. These results are consistent with a randomized controlled study which demonstrated that istradefylline may have a similar impact on preventing levodopa dose escalation as an additional 50 mg/day of levodopa [7]. A Japanese database study also showed that istradefylline moderates increases in levodopa dosage over the long term [45]. These findings suggest that istradefylline potentially reduces the incidence of side effects of dopaminergic drugs due to levodopa dose escalation [46]. Of note, our results are descriptive in nature and should be interpreted with caution, as patient drop-out or other anti-PD medications may have changed over the follow-up period. Although clinical studies have indicated that istradefylline improves off-time, gait disorders [3], postural abnormalities [4], mood disorders [5], and daytime sleepiness [6], we could not assess these outcomes due to the limitations of the database we used. However, since "Drugs don't work in patients who don't take them [47]," it is evident that if adherence to istradefylline is poor, especially in the rapidly declining or gradually declining adherence groups, patients will not be able to obtain its benefits, even if our study does not necessarily assess therapeutic effectiveness.

The main strength of this study is its use of GBTM to identify istradefylline adherence patterns over time. Many conventional adherence studies have reported adherence at a single point in time with a binary classification (i.e., adherent vs. non-adherent) [48–50], which oversimplifies this complex behavior, overlooks important long-term variation, and obscures opportunities to improve adherence [51]. Our present study provides important insights regarding the heterogeneity of istradefylline adherence patterns. Knowledge of the characteristics associated with each adherence group may help predict the pattern of non-adherence that individual patients follow, and help clinicians customize the content, timing, duration, and intensity of interventions to maintain adherence. Since istradefylline is known to have a slower onset of effect than levodopa [1], intervention in the rapidly declining adherence group would be particularly meaningful, as patients in this group may have prematurely assumed the treatment was ineffective and discontinued it before obtaining sufficient clinical benefit. Better resource allocation to patients at risk of non-adherence may ultimately improve disease management and outcomes [52]. Additionally, to our knowledge, this study is the first to implement GBTM in the assessment of medication adherence in PD patients, and should prompt the reevaluation of adherence to other PD medications that have been more simply assessed in the past [50,53].

Six limitations should be noted. First, in calculating the PDC, we assumed that istradefylline was consumed as prescribed, which is not always true. Second, we were unable to distinguish whether treatment discontinuation was clinician-guided or patient self-directed. Third, factors that we did not analyze may have been associated with adherence group membership. While demographic and clinical characteristics are readily available in electronic healthcare databases, our study, in line with other research, found that these characteristics did not differ greatly between groups and did not effectively discriminate between different patient adherence trajectories [51,54]. PD duration, PD severity, dyskinesia, and hallucination can affect decreased adherence [37], but these were not available or were difficult to reasonably identify from the database. Socioeconomic status also has the potential to influence adherence; any such impact on the results in Japan is thought to be small, however, because of the low economic burden that treatment places on patients due to the universal health insurance system and the designated intractable disease system. Medication beliefs – a psychographic factor – may be a stronger predictor of medication adherence than clinical or sociodemographic factors [55], but was also lacking in the database. Using GBTM to inform adherence patterns is the first step to understanding the complex underlying dynamics [54]. The next approach should focus more on patient psychographic factors, using qualitative methods. Fourth, if a patient was also receiving treatment at a different medical institution to the one where he or she was receiving istradefylline treatment, or if the patient transferred to another institution, the patient data were not available. However, unless the patient does transfer, PD-related treatments are typically performed at a single institution, making it likely that these treatments were in fact captured in the database. In addition, only 10.2% of patients were lost to follow-up within one year, and the associated nonrandom population attrition was considered in the GBTM. Fifth, the generalizability of the present findings is limited because the subjects of this study were PD patients attending acute care hospitals in Japan [56]. Specifically, the results may change in studies of patients in clinics or chronic care hospitals. Sixth, the transportability of our findings to other regions may be limited by differences in healthcare environment, particularly in insurance systems, between Japan and the US. However, Japan's universal health insurance system significantly reduces the financial burden of istradefylline treatment for patients, likely minimizing its impact on treatment adherence. Thus, our findings are expected to predominantly reflect medical factors such as the effectiveness and tolerability of istradefylline, and thereby provide clinically meaningful insights.

5. Conclusions

We identified four longitudinal adherence patterns to istradefylline treatment in PD patients and found that more than half of the patients belonged to a pattern of consistently high adherence during the first year of treatment. For the other three patterns, in which adherence was suboptimal, targeted interventions to improve adherence may be helpful, based on an understanding of the patient characteristics associated with those patterns.

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CRediT authorship contribution statement

Toshiki Fukasawa: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Etsuro Nakanishi:** Writing – review & editing, Methodology, Conceptualization. **Hiroo Shimoda:** Writing – review & editing, Project administration, Conceptualization. **Katsumi Shinoda:** Writing – review & editing, Project administration, Conceptualization. **Satoru Ito:** Writing – review & editing, Conceptualization. **Shinji Asada:** Writing – review & editing, Conceptualization. **Satomi Yoshida:** Writing – review & editing, Conceptualization. **Sachiko Tanaka-Mizuno:** Writing – review & editing, Conceptualization. **Kayoko Mizuno:** Writing – review & editing, Conceptualization. **Ryosuke Takahashi:** Writing – review & editing, Conceptualization. **Koji Kawakami:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary data

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