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ORIGINAL COMMUNICATION

Real-world pharmacological treatment patterns of patients with young-onset Parkinson's disease in Japan: a medical claims database analysis

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Abstract

Introduction Young-onset Parkinson's disease is reported to comprise 5–10% of all Parkinson's disease cases; however, as physicians encounter a limited number of these patients, their treatment patterns are still unclear.

Methods We performed a descriptive study using the large Japanese medical claims database to describe the epidemiology and real-world pharmacological treatment patterns of newly diagnosed patients with young-onset Parkinson's disease. Patients aged 21–50 years in whom Parkinson's disease was newly diagnosed between January 1, 2005 and March 31, 2016 were included. We excluded individuals with Parkinson's-related diseases and those using antipsychotics to eliminate the possibility of drug-induced parkinsonism. The patients' demographics, comorbidities, prescribing patterns, and changes in levodopa equivalent daily dose were analyzed.

Results We identified 131 newly diagnosed young-onset Parkinson's disease patients (median age, 44.2 years). The most common comorbidities were depression (23.7%), hypertension (23.7%), and insomnia (22.9%). Of these patients, 122 were prescribed antiparkinson drugs. During the study period, the proportion of patients who were prescribed dopamine agonists, levodopa, and anticholinergics were 77.1%, 44.3%, and 27.5%, respectively. Dopamine agonists (49.2%) were most commonly prescribed initially, followed by anticholinergics (23.8%), levodopa (19.7%), and others (4.1%). The levodopa equivalent daily dose increased steadily with longer disease duration.

Conclusions Dopamine agonists were most frequently prescribed during the study period and were the initial treatment of choice. We also observed a change in levodopa equivalent daily dose over the disease course. This study provides a descriptive overview of real-world prescribing patterns in young-onset Parkinson's disease patients.

Keywords Young-onset Parkinson's disease · Pharmacological treatments · Levodopa equivalent daily dose · Comorbidities · Medical claims database

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Introduction

Parkinson's disease (PD) is an incurable and progressive neurodegenerative disease for which definitive treatment has not yet been established [1]. PD can be classified into juvenile, young, and old based on the age at onset, but no definite consensus has been reached regarding the classification of patients according to age at onset [2]. Across studies, young-onset Parkinson's disease (YOPD) is defined as the age at onset from 21, to 40–50 years [2–4]. It has been reported that 5–10% of PD cases are YOPD [2–4]. In Japan, approximately 2.7% of PD patients with Hoehn–Yahr stage ≥ 3 were under 40 years of age [5]. Hence, as the majority of the PD patients belong to the

old-onset group, the number of YOPD patients encountered by physicians is very limited.

Generally, compared with old-onset PD, the progression of YOPD is slower, but is more likely to involve potentially disabling conditions in the long term [6, 7]. YOPD patients are often the sole earning members of their families; hence, losing the ability to work has a large effect on the quality of life of both the patients themselves and their family members. YOPD is associated with a higher incidence of levodopa-induced dyskinesia [3]. Furthermore, a higher incidence of dystonia at onset and during treatment is reported in YOPD [3]. The characteristics of PD in young patients differ from those in older patients; however, no specific guidelines are available for the treatment of younger patients. Currently, no randomized controlled study focused solely on treatments for YOPD has been conducted [7]. Moreover, only small-scale clinical studies focusing on the age at onset with less than 100 patients, clinicopathological study [4], or clinical record reviews at a single center [2] have been conducted. Therefore, YOPD patients are treated with reference to the clinical guidelines for general PD, although the clinical characteristics of YOPD differ. Because few studies have focused primarily on YOPD, both in Japan and internationally, we aimed to conduct a large-scale study describing the epidemiology and real-world pharmacological treatment patterns of new-onset YOPD patients, using the Japanese medical claims database.

Methods

Data source

Study data were obtained from Japan Medical Data Center Co., Ltd (JMDC, Tokyo, Japan). This database includes the largest population-based longitudinal dataset of medical claims data provided by corporate health insurance societies in Japan [8]. Currently, it covers over three million insured salaried workers and their family members [9]. The database utilizes the International Classification of Disease, tenth revision (ICD-10) and the Japanese standardized disease code for disease names. The JMDC database began registration of data in 2005 and was based on the 2003 update of the ICD-10 [8]. The master table of the standardized disease code is maintained by the Medical Information System Development Center (MEDIS-DC), which is under the entrustment of the Ministry of Health, Labour and Welfare in Japan [8]. The prescribing data are coded based on the Anatomical Therapeutic Chemical Classification System (ATC).

Ethics considerations

This study protocol was approved by the Ethics Committee of Kyoto University Graduate School of Medicine, Japan (R0919-1). Informed consent was waived due to the untraceable and de-identified nature of the data.

Selection of the study population and data collection

Patients aged 21–50 years in whom PD was diagnosed between January 1, 2005 and March 31, 2016, among all of the registrants in the database, were included in the study, by extracting data for patients who had medical claims for PD (ICD-10:G20). This code does not have subclasses and includes PD-related conditions, such as familial PD, parkinsonian syndromes, and dementia in PD. Therefore, the extraction of data for PD or YOPD cases was achieved through further identification using the Japanese standardized disease code. We excluded patients who were co-coded with secondary parkinsonism (ICD-10:G21) and those who were prescribed antipsychotics (ATC-N05A) to exclude possible drug-induced parkinsonism cases. We included patients regardless of their PD stages, as Hoehn & Yahr staging is not mandatory and is not recorded in many claims.

The "first PD diagnosis date" was designated as the index date. The onset of PD can be defined as the date at which PD was first diagnosed by the physician or the date at which PD symptoms were first observed by the patients. In this database, a "first consultation date" indicates the first date when the diagnosis was made; this date is issued for each diagnosis at every medical facility that a particular patient visits. Patients who visit multiple medical facilities are issued multiple "first consultation dates" for a single condition. Hence, we used the oldest "first consultation date" to determine the "first PD diagnosis date" and to calculate the age at onset. To obtain an adequate patient history, we selected patients who underwent follow-ups for at least 12 months after the index date. Additionally, to ensure that they were all newly diagnosed, we included only patients with an index date that followed the observation start date during the study period.

Comorbidities were identified using the Japanese standardized disease code, up to 3 months prior to the first PD diagnosis. Conditions that were observed in more than 5% of the final cohort were recorded. For prescribing patterns, we extracted information on the antiparkinson drugs (APDs) listed in ATC-N04 from the patients' prescribing data. The levodopa equivalent daily dose (LED) was also calculated using the published converting factors [10,

11]: L-dopa (mg) × 1, L-dopa with decarboxylase inhibitor (mg) × 1, L-dopa with decarboxylase inhibitor and entacapone (mg) × 1.33, amantadine (mg) × 1, apomorphine (mg) × 10, bromocriptine (mg) × 10, cabergoline (mg) × 67, pergolide (mg) × 100, pramipexole (mg) × 100, ropinirole (mg) × 20, rotigotine (mg) × 30, selegiline (mg) × 10, and talipexole (mg) × 67.

Statistical analysis

Descriptive analyses of demographic characteristics, comorbidities, and prescribing patterns of APDs are summarized by frequency, percentage, and median with range or interquartile range (Q1–Q3), where appropriate. LEDs are presented as the median with interquartile range (Q1–Q3). Statistical analyses were conducted using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

A scatter plot of LED against disease duration with a smooth spline curve with 95% confidence intervals was computed using R software version 3.42 (The R Foundation for Statistical Computing), using the generalized additive model (GAM) [12] function from the mcgv package 1.8–22. This model was selected to account for variations in the prescribing frequencies as well as the intervals between prescriptions among the patients. The smoothing parameter was estimated using generalized cross validation. The outcome variable was the LED and the adjustment factors were sex, age at first diagnosis, and disease duration.

Results

The total number of registrants during our study period was 2,350,673 individuals. Among them, 4271 patients were diagnosed with PD or PD-related conditions (ICD-10:G20), and were also aged 21–50 years. Figure 1 shows the flowchart of further patient selection. Of these 4271 patients, 623 specifically received a diagnosis of PD, YOPD, or both. In total, 254 patients were newly diagnosed with PD and underwent at least 12 months of follow-up. Finally, the exclusion of 121 patients who were treated with antipsychotics and two patients with missing prescription records resulted in a final study cohort of 131 patients.

Data on patient demographics and comorbidities are shown in Table 1. The median age of YOPD patients was 44.2 years, and 61.1% were males. The number of patients increased steadily with age: 15 (11.5%) were aged 21–30 years, 31 (23.7%) were 31–40 years, and 85 (64.9%) were 41–50 years. The proportion of male patients was higher than that of female patients in all age groups. The median follow-up period was 2.7 years. The comorbidities observed in at least 5% of patients in our study cohort are also shown in Table 1. A total of 26 comorbidities were

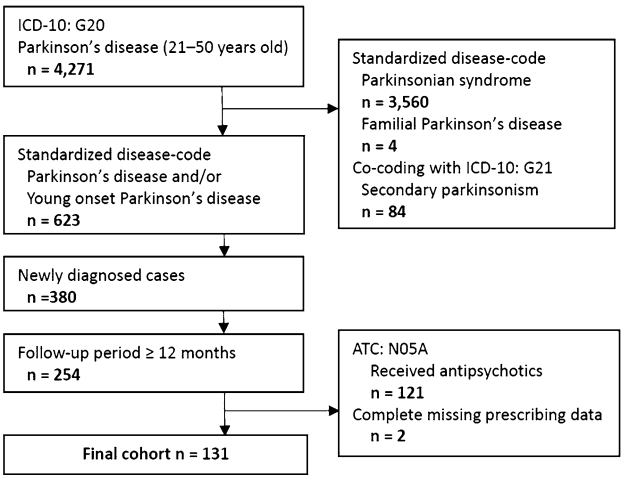

Fig. 1 Flowchart showing the number of patients who met the inclusion criteria. *ATC* anatomical therapeutic chemical classification system, *ICD-10* international classification of disease, tenth revision

identified and were classified into nine major disease conditions. Depression ($n = 31$), hypertension ($n = 31$), insomnia ($n = 30$), and allergic rhinitis ($n = 24$) were the most frequent comorbidities.

The median number of days from when a particular patient's data began to be recorded in the JMDC database to the first PD diagnosis (Q1–Q3) was 557 (217–1504). Excluding nine patients who did not receive APDs during the study period, the median number of days from the first PD diagnosis to the first prescription of APDs (Q1–Q3) was 0 (0–7).

With respect to all prescriptions observed during the study period, the proportions of patients who ever received those medications are indicated in the left column of Table 2. Dopamine agonists (DAs) were the most frequently prescribed medications during the study period (77.1%), followed by L-dopa (44.3%), anticholinergics (27.5%), monoamine oxidase B (MAO-B) inhibitors (13.0%), and other classes of drugs (19.8%). In total, 6.9% of patients ($n = 9$) did not receive APDs during the study period. Pramipexole (38.9%), trihexyphenidyl (26.7%), and L-dopa with carbidopa (21.4%) were the most frequently prescribed medications.

The right column of Table 2 shows the initial pharmacotherapy received by the patients. Upon initiation of treatment with APDs, most patients were on monotherapy (96.7%). DAs (49.2%) were the most commonly prescribed drugs, followed by anticholinergics (23.8%), L-dopa (19.7%), and others (4.1%). Four patients (3.3%) were prescribed combinations of APDs ranging from two to five drugs. Pramipexole (30.3%) was the most regularly prescribed monotherapy, followed by trihexyphenidyl (23.0%), and L-dopa with carbidopa (15.6%).

Table 1 Demographic characteristics and comorbidities of young-onset Parkinson's disease patients ($n=131$)

Characteristics		
Male	80	(61.1)
Age, median, [IQR]	44.2	[37.8–48.2]
Male	44.1	[39.2–47.6]
Female	44.5	[37.2–48.4]
Age group [male/female]		
21–30 years	15	[9/6]
31–40 years	31	[19/12]
41–50 years	85	[52/33]
Follow-up years [range]	2.74	[1.02–10.4]
Comorbidities[a]		
Mental and behavioral disorders		
Depression	31	(23.7)
Neurosis	15	(11.5)
Dissociative disorder	9	(6.9)
Generalized anxiety disorders	8	(6.1)
Nervous system diseases		
Insomnia	30	(22.9)
Epilepsy	13	(9.9)
Neuropathy	12	(9.2)
Restless leg syndrome	11	(8.4)
Migraine	8	(6.1)
Sleep apnea syndrome	7	(5.3)
Respiratory diseases		
Allergic rhinitis	24	(18.3)
Asthma	9	(6.9)
Chronic sinusitis	7	(5.3)
Cardiovascular diseases		
Hypertension	31	(23.7)
Metabolic diseases		
Diabetes mellitus	18	(13.7)
Hyperlipidemia	12	(9.2)
Musculoskeletal diseases		
Spondylosis	14	(10.7)
Low back pain	13	(9.9)
Ophthalmological diseases		
Astigmatism	16	(12.2)
Allergic conjunctivitis	10	(7.6)
Digestive diseases		
Chronic gastritis	15	(11.5)
Constipation	12	(9.2)
Gastric ulcer	11	(8.4)
Miscellaneous		
Menopausal disorders	8	(6.1)
Headache	7	(5.3)
Nausea and vomiting	7	(5.3)

Unless noted otherwise, data are shown as the number of patients with percentages given in parentheses

IQR Interquartile range Q1–Q3

[a]Only those with prevalence ≥ 5% are listed in comorbidities

Figure 2 illustrates the relationship between the LED and disease duration. Of the 3241 APDs prescribed for 122 patients (excluding 373 APDs that were flagged as pro re nata), the LEDs for 2014 APDs were calculated. APDs prescribed on the same day were added; in total, 1641 LEDs for 92 patients were plotted against the disease duration. The median (Q1–Q3) of the LED at 2.5-year intervals was as follows: 137.5 (25.0–300.0) mg/day at < 2.5 years; 282.9 (67.5–450.0) mg/day at 2.5–5 years; 500.0 (400.0–750.0) mg/day at 5–7.5 years; and 1098 (897–1098) mg/day at 7.5–10 years. The number of plotted LEDs and the number of patients observed in each interval were 1247 ($n=92$), 298 ($n=27$), 89 ($n=9$), and 7 ($n=1$), respectively. Thus, the LED increased steadily with disease duration.

Discussion

To the best of our knowledge, this is the first large-scale study to elucidate the real-world prescribing patterns for YOPD patients using the Japanese medical claims database. In the majority of previous studies on PD, younger populations were not thoroughly analyzed [13–16]. Therefore, our aim was to focus on patients who were newly diagnosed with YOPD by applying various strict inclusion and exclusion criteria to eliminate other PD-related diseases that could affect the analysis.

The period prevalence of YOPD in this studied population is 5.57/100,000 persons. Based on the reported prevalence of PD in Japan as 109–167/100,000 persons [17, 18], YOPD can be calculated as 3.3–5.1% of all PD cases. An increasing number of patients with YOPD was observed with increasing age (Table 1), which is consistent with the findings of a previous report from Japan [5]. Another study in Japan [16] reported a higher incidence of PD in women (male:female ratio; 1:1.24); in contrast, we found a higher incidence of YOPD in men (61.1%), which is similar to the results of a Rotterdam study (male:female; 1.5:1) in the general population [19]. However, it is possible that these results are due to the male-dominant nature of the working population in this corporate-derived database.

Depression (23.7%) and hypertension (23.7%) were the most common comorbidities found in this study cohort (Table 1). Previous studies have indicated that symptoms of depression may develop, even in the pre-motor stage of PD [20]. However, a large prospective study found that a history of hypertension is not associated with PD risk [21]. The second most frequent comorbidity was insomnia (22.9%). A previous prescribing pattern study targeting PD patients aged 38–87 years reported a similar rate of sleep disturbances (19.2%) [13]. Notably, in the present study, nearly 20% of the patients had allergic rhinitis. A previous case–control study reported that PD patients were more

Table 2 Distribution of all antiparkinson drugs (APDs) prescribed and the first APDs prescribed during the study period

All prescriptions (131 patients)	Patients		Initial prescriptions (122 patients)[a]	Patients	
	n	(%)		*n*	(%)
Dopamine agonists	101	(77.1)	Dopamine agonist monotherapy	60	(49.2)
Pramipexole	51	(38.9)	Pramipexole	37	(30.3)
Ropinirole	18	(13.7)	Ropinirole	8	(6.6)
Rotigotine	14	(10.7)	Bromocriptine	5	(4.1)
Bromocriptine	7	(5.3)	Cabergoline	4	(3.3)
Cabergoline	6	(4.6)	Rotigotine	4	(3.3)
Pergolide	4	(3.1)	Pergolide	1	(0.8)
Talipexole	1	(0.8)	Talipexole	1	(0.8)
L-dopa	58	(44.3)	Anticholinergic monotherapy	29	(23.8)
L-dopa + carbidopa	28	(21.4)	Trihexyphenidyl	28	(23.0)
L-dopa + carbidopa + entacapone	14	(10.7)	Biperiden	1	(0.8)
L-dopa + benserazide	12	(9.2)	L-dopa monotherapy	24	(19.7)
L-dopa + benserazide + entacapone	4	(3.1)	L-dopa + carbidopa	19	(15.6)
Anticholinergics	36	(27.5)	L-dopa + benserazide	5	(4.1)
Trihexyphenidyl	35	(26.7)	Other monotherapy	5	(4.1)
Biperiden	1	(0.8)	Amantadine	2	(1.6)
Monoamine oxidase B inhibitors	17	(13.0)	Droxidopa	2	(1.6)
Selegiline	17	(13.0)	Selegiline	1	(0.8)
Others	26	(19.8)	Combinations	4	(3.3)
Amantadine	8	(6.1)	Two drugs		
Zonisamide	7	(5.3)	Amantadine, L-dopa + carbidopa		
Istradefylline	6	(4.6)	Pramipexole, Rotigotine		
Droxidopa	5	(3.8)	Four drugs		
No APD medications	9	(6.9)	Pramipexole, Droxidopa, L-dopa + benserazide, Zonisamide		
			Five drugs		
			Amantadine, Trihexyphenidyl, Selegiline, Zonisamide, L-dopa + carbidopa + entacapone		

[a]Nine patients are excluded as they were non-APD users

likely to experience immediate-type hypersensitivity including allergic rhinitis (OR 2.9; 95% CI 1.3–6.4), suggesting a role of inflammation in PD [22]. Interestingly, our results showed that spondylosis and low back pain were present in approximately 10% of the patients. A study by Leoni et al. suggested that rigidity and abnormal postural tone in PD could contribute to those musculoskeletal symptoms [13].

PD is known to be associated with a wide spectrum of non-motor symptoms (NMSs) that include autonomic and sensory symptoms, cognitive and neuropsychiatric disorders, and sleep disturbances [20, 23]. Additionally, NMSs can precede the appearance of motor symptoms and are considered as potential clinical markers of the premotor phase in PD [24]. Many of the comorbidities shown in Table 1 can be regarded as NMSs: depression, generalized anxiety disorders, insomnia, restless leg syndrome, constipations, etc. Though differing methodologies and cohorts were examined, previous studies showed that NMSs are consistently present not only at advanced stage but also at the early and untreated stage of PD [25]. There is a possibility that these NMSs were underrepresented in the present study, as we excluded patients who were prescribed antipsychotics to eliminate possible drug-induced parkinsonism cases for the purpose of extracting more authentic YOPD cases from the database.

Our study found that DAs were the most commonly prescribed medication for YOPD (77.1%), followed by L-dopa (44.3%) (Table 2). The studies targeting general or old-onset PD in Japan reported the opposite trend, in which L-dopa (96.4%) was the most frequently prescribed type of medication, followed by DAs (44.8%) [26]. A similar trend involving the L-dopa dominant prescribing pattern in general or old-onset PD has been reported in two cross-sectional studies [13, 14]. Anticholinergics were prescribed in 27.5% of patients (Table 2). Other Japanese studies that included all age groups reported prescription rates of 25% [15] to 45% [26], whereas other countries reported lower prescription rates of anticholinergics [2, 13]. Anticholinergics were the first drugs available for the symptomatic treatment of

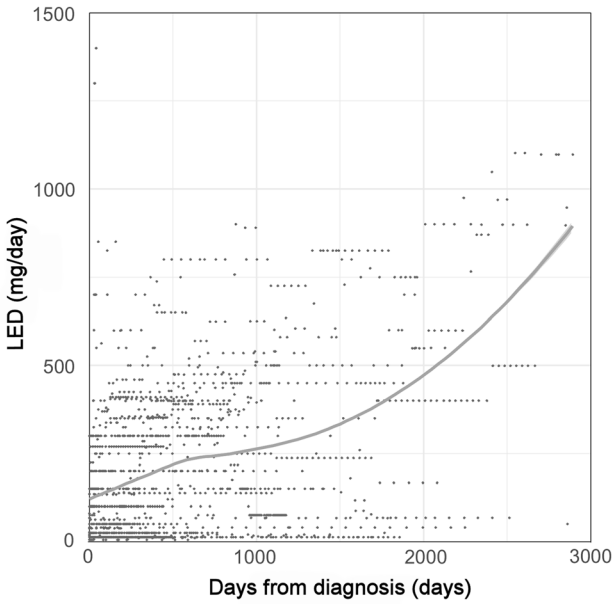

Fig. 2 Scatter plot with an added spline curve illustrating the relationship between levodopa equivalent daily dose (LED; mg/day) and disease duration. Shaded area: 95% confidence interval which cannot be recognized because of the narrow interval

PD [27]. The long historic use of this medication prior to the appearance of L-dopa treatment [27] and the classical hypothesis of an imbalance between dopamine and acetylcholine [28] may be the underlying reason for this higher prescribing rate in Japan. Although anticholinergics are not considered routine in the treatment of old-onset PD because of both peripheral and central adverse effects, they have been regarded as a classical treatment for younger patients with severe predominant tremor [29] and provide relief for YOPD patients in whom resting tremor is the predominant symptom [30]. Selegiline was prescribed in 13.0% of patients overall. MAO-B inhibitors may be prescribed more readily due to the new recommendation in the most recent guideline in Japan [31].

DAs were also most commonly prescribed in nearly half of the YOPD patients (49.2%) as the initial monotherapy, followed by anticholinergics (23.8%) and L-dopa (19.7%) (Table 2). Although there are currently no specific guidelines for YOPD, the guidelines of the Japanese Society of Neurology [32], as well as those in the UK [33], recommended DAs as the first choice of drug therapy for PD. Compared with L-dopa, DAs in general are thought to cause fewer voluntary motor complications [34, 35]. In addition, DAs are used as an L-dopa-sparing therapy to delay the onset of dyskinesia associated with L-dopa [2, 13, 14]. We observed two cases that included prescriptions for four or five drug combinations as initial therapy. Although we set strict inclusion criteria, it is possible that the patients may have been already diagnosed; however, the time point at which this diagnosis was made was not recorded as the first consultation date.

Two recent studies that included age groups similar to those of our cohort evaluated the first pharmacological therapy prescribed for newly diagnosed patients with PD. A retrospective single-center chart review in the USA reported that the most frequent initial choice of medication in patients under 49 years of age is L-dopa with carbidopa (51.7%), followed by DAs (25%), MAO-B inhibitors (16.7%), and amantadine (11.7%) [2]. A study using the National Health Insurance Research Database in Taiwan reported that 90.6% of patients below the age of 40 were prescribed MAO-B inhibitors, amantadine, or anticholinergics as initial medications, rather than L-dopa or DAs. The rest were prescribed L-dopa (7.1%) or DAs (2.4%), either alone or combined with other APDs (MAO-B inhibitors, amantadine or anticholinergics) [36]. These studies show that the initial choice of medication varies among countries. Several factors have been reported regarding the possible influence of ethnicity on the presentation and treatment of PD. The prevalence of genetic mutations that may underlie the different clinical presentations of PD appears to be dependent on ethnicity [37]. In this regard, LRRK2 G2019s mutation carriers are associated with more frequent lower extremity involvement at onset and postural instability and gait difficulty [38]. The glucocerebrosidase (GBA) mutation is associated with an earlier age at onset and a higher prevalence of NMSs [39]. In addition, genetic polymorphisms in the catechol-*O*-methyltransferase enzyme that influences the rate of L-dopa metabolism, have been reported in varying populations [40]. In view of clinical practice settings, other factors, such as cultural differences related to ethnicity, access to specialists, and non-availability of certain drugs [41], may influence the prescribing decisions in each country and may also contribute to this discrepancy.

The most recent guidelines in Japan [31] and UK [42]recommend L-dopa, DAs, or MAO-B inhibitors as initial medication for early PD, based on potential benefits and risks. The effectiveness and safety of rasagiline monotherapy for Japanese patients with early stage PD was recently reported [43]. In the future, MAO-B inhibitors may be more preferable as initial therapy for YOPD in Japan, although only one case (0.8%) was observed in the present study (Table 2). This small number was possibly due to the fact that in Japan, selegiline was the only MAO-B inhibitor available as an adjunctive therapy in Japan since 2007 and was not approved as a monotherapy until 2015. Rasagiline was only approved very recently in 2018. Moreover, unique regulation surrounding selegiline in Japan makes it a less preferred choice for patients. Despite its use for medical purposes, it is regulated under the Japanese Stimulants Control Act [44] which prevents patients from carrying it with them when

traveling overseas, and switching to other PD medications for this reason is a great burden for patients.

In our study cohort, patients were initially prescribed APDs as soon as they were diagnosed with PD, as the median number of days from first diagnosis to first APD prescription was 0. This suggests that specialists may advocate for early pharmacological therapy to maximize clinical benefits for patients when their symptoms begin interfering with daily tasks. These observations are in line with a recent review [1], as well as guidelines in Japan [31, 32] and the UK [33].

With respect to DAs, ergot derivatives, such as pergolide (0.8%) and cabergoline (3.3%), were not commonly prescribed as initial treatment (Table 2). The decline in the use of ergot derivatives is well documented elsewhere, due to increased concerns regarding long-term adverse effects [15], specifically cardiac fibrosis [45]. Hence, non-ergot derivatives are the initial choice of DAs, regardless of the patient's age. Interestingly, pramipexole was most frequently prescribed both during the study period and as an initial medication. This may be related to the fact that 23.7% of patients in this study had depression, and that pramipexole is reportedly associated with successful outcomes for depression in PD patients [46].

In our study, zonisamide (1.6%) and droxidopa (2.4%) were initially prescribed for some patients and accounted for 5.3% and 3.8% respectively, of all APD prescriptions during the study period. These are specific therapeutic options first approved and mostly used in Japan. The anti-epileptic drug zonisamide was discovered to reduce rigidity and akinesia in patients with PD during clinical observation and is currently used as an add-on therapy to L-dopa or DAs to treat motor symptoms [31, 47]. It has multiple mechanisms of action, including increased dopamine synthesis, inhibition of MAO-B, and T-type calcium channel blockade [48]. Droxidopa (L-threo-dihydroxyphenylserine) is an orally activated prodrug of norepinephrine converted by dopa-decarboxylase; the same enzyme that converts L-dopa into dopamine. It was initially approved for use in Japan for the treatment of freezing of gait [49] and is also currently used for orthostatic dizziness associated with PD. In the USA, it has been approved for neurogenic orthostatic hypotension since 2014 [50].

To understand the trend between LED and disease duration, we plotted a graph using these two parameters (Fig. 2). Such a graph facilitates interpretation of results with a non-linear relationship. Two points were observed to have an extremely high LED of approximately 1400 mg/day at day 0. We are unable to determine the exact reason for this from the database; however, it is possible that all of the drugs were prescribed at once for the patient's convenience, or to allow for dose adjustments. The summary of the median LED at an interval of 2.5 years showed a steady increase from 137.5 mg/day at 2.5 years to 1,098 mg/day at 10 years. A recent observational study, performed at a Japanese outpatient clinic that mainly treated older patients, reported that the levodopa dose (mean ± SD) increased with disease duration from 416 ± 223 mg at 5 years or less to 614 ± 256 mg at 6–10 years [26]. Although a direct comparison between the median and average cannot be established, a similar trend of dose increase was observed for both our YOPD patients and their older PD patients. As the progression of YOPD is generally considered to be slower than that of old-onset PD [6, 7], this similar trend of dose increase may imply that YOPD is treated more rigorously to meet the needs of young patients with PD to control their symptoms, so that their work and daily living activities remain unaffected.

The present database provides a rich source of information for the purpose of identifying prescribing patterns among YOPD patients in Japan. Notably, the database can track treatments across medical facilities and is robust in its ability to investigate chronic conditions. However, the use of the medical claims database has a few inherent limitations. First, our study used existing data collected as part of the health care system from corporate health insurance societies. These data were mainly obtained from the working population. Patients with severe PD who cannot work are potentially excluded from the database; therefore, the results obtained in this study may not be generalizable to the full population. Second, these data were recorded for reimbursement and record-keeping purposes (i.e., not for research purposes). Generally, the records in this database are reliable as false claims are not allowed; however, it is possible that suspected cases or "diagnosis for receipt" were recorded in order to receive reimbursements for medications and tests. Finally, PD is generally considered as a difficult condition to clinically diagnose, especially at the onset of disease [51]. The validity of diagnosis coding in the field of neurology has not yet been conducted for the Japanese claims database.

In conclusion, our results show that DAs are the most frequently prescribed class of APDs and are the most preferred choice of initial medication for the treatment of YOPD. Furthermore, changes in LED over the disease course were observed. Thus, our study provides a descriptive overview of real-world prescribing patterns in YOPD patients to help inform current clinical practice. Further investigation is warranted to understand the differences in outcomes of these prescribing patterns, to improve the management of YOPD.

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Compliance with ethical standards

Conflicts of interest Shiro Tanaka has received consultation or outsourcing fee from the Pharmaceuticals and Medical Devices Agency, DeNA Life Science Inc., Boehringer Ingelheim Co. Ltd, Public Health Research Foundation, Japan Breast Cancer Research Group, and Satt Co. Ltd; grants from the Japan Agency for Medical Research and Development, the Japanese Ministry of Health Labour and Welfare, and the Japanese Ministry of Education, Science, and Technology. Ryosuke Takahashi is an employee of the Japan Agency for Medical Research and Development; has served on advisory boards for Kan Institute Co. Ltd, and Sumitomo Dainippon Pharma Co. Ltd; has performed corporate-sponsored research for Novartis Pharma K.K. Co., Otsuka Pharmaceutical Co. Ltd, Pfizer Japan Inc., Takeda Pharmaceuticals Co. Ltd, Nippon Boehringer Ingelheim Co. Ltd, Sumitomo Dainippon Pharma Co. Ltd, Kyowa Hakko-Kirin Co. Ltd, Nihon Medi-physics Co. Ltd, Mitsubishi Tanabe Pharma Co. and Konica Minolta Inc.; and has received honoraria from Sumitomo Dainippon Pharma Co Ltd, and FP Pharmaceutical Co. Koji Kawakami received collaborative research funds from Sumitomo Dainippon Pharma Co. Ltd., Novartis Pharma K.K., Bayer Yakuhin Ltd, Olympus Co., Stella Pharma Co., Cmic Holdings Co. Ltd., Pfizer Japan Inc., and Astellas Amgen BioPharma K.K.; consulting fees from Kaken Pharmaceutical Co. Ltd, and Kyowa Hakko Kirin Co. Ltd; honoraria from Otsuka Pharmaceutical, Santen Pharmaceutical, Takeda Pharmaceutical Co. Ltd., Novartis Pharm K.K., Bayer Yakuhin Ltd, Abbvie GK, Eisai Co Ltd, and Daiichi-Sankyo Co. Ltd. There are no patents, products in development, or marketed products to declare, relevant to the listed companies.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, the requirement for informed consent was waived by the institutional research committee.

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