eNeurologicalSci 20 (2020) 100257

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Prescription pattern of anti-Parkinson's disease drugs in Japan based on a nationwide medical claims database

Masahiko Suzuki[a], Masaki Arai[b], Ayako Hayashi[b], Mieko Ogino[c,*]

[a] Department of Neurology, The Jikei University Katsushika Medical Center, Tokyo, Japan
[b] Japan Medical Affairs, Takeda Pharmaceutical Company Limited, Tokyo, Japan
[c] International University of Health and Welfare, School of Medicine, Center for Medical Education, Narita, Japan

ARTICLE INFO

Keywords:
Parkinson's disease
Anti-Parkinson's disease drug
Cross-sectional study
Health insurance claims data
Prescription pattern
Japan

ABSTRACT

Introduction: Parkinson's disease (PD) treatment should follow guidelines and be tailored to each patient. Large database analyses can provide insights into prescribing patterns.
Methods: Retrospective, cross-sectional study of patients (≥30 years) with PD diagnosis (ICD-10; schizophrenia/cerebrovascular disease excluded) using health insurance claims data (April 2008–December 2016) from the Japan Medical Data Vision database. Prescription patterns of anti-PD drugs were analysed by patient age and sex, calendar year, and overall.
Results: The analysis comprised 155,493 PD patient-years (56.1% women, mean 73.4 years). Patient number increased each year, mainly because of database expansion. L-dopa as monotherapy was the most common prescription (22.7% of patient-years); non-ergot dopamine agonists (DAs) were also common (7.6% as monotherapy, 6.8% with L-dopa). Monotherapy was prescribed for ~50% of patient-years, two drugs for 14.1%, and at least three drugs for 18.4%. Consistent with Japanese guidelines, L-dopa was mostly prescribed to older patients (≥60 years), whereas non-ergot DAs were mostly prescribed to middle-aged patients (peak at 50–69 years). Between 2008 and 2011, L-dopa prescription decreased while that of non-ergot DAs increased; this pattern reversed between 2012 and 2016.
Conclusion: These results indicate that Japanese clinicians are adhering to Japanese guidelines and tailoring anti-PD treatment to individual patients.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterised by motor dysfunction, including tremor, rigidity, bradykinesia, and gait disturbances [1]. The prevalence of PD increases markedly with age, which has contributed to the recent increase in PD prevalence worldwide [2]. In Japan, between around 127,000 and 256,000 people had PD in 2016 [2–4], with the reported crude prevalence rate of PD in different regions of Japan ranging from 80.6 to 180.3 per 100,000 population [3–5]. Moreover, with the rapid ageing of the Japanese population, the prevalence of PD has increased in recent decades [3]. However, it is difficult to directly compare older estimates of prevalence with more recent estimates because of changes in diagnostic criteria and survey methods [6].

Although current treatments for PD can only ameliorate symptoms, the broad range of available pharmacotherapies allows for individualisation of treatment (Table 1). Most anti-PD drugs act to replace or enhance dopaminergic signalling in the brain [7]. The mainstay of PD treatment is L-dopa (levodopa), a precursor of dopamine. Other major drug classes that target dopaminergic systems are the ergot and non-ergot dopamine agonists (DAs), which directly activate dopamine receptors, and inhibitors of monoamine oxidase-B (MAO-B) and catechol-*O*-methyltransferase (COMT) inhibitors, which slow the metabolism of dopamine. Additional anti-PD drugs target other, often multiple, neurotransmitter systems, including acetylcholine, norepinephrine, glutamate, and adenosine systems [8]. The 2006 National Institute for Health Care Excellence (NICE) guidelines [9] and the 2011 Japanese guidelines [10] generally recommended L-dopa or DAs (particularly non-ergot DAs) as first-line therapy. Although there have

Abbreviations: COMT, catechol-*O*-methyltransferase; DA, dopamine agonist; DPC/PDPS, Japanese Diagnosis Procedure Combination/Per-Diem Payment System; GPP3, Good Publication Practice 3; *ICD-10*, *International Classification of Disease, Tenth Revision*; L-dopa, levodopa; MAO-B, monoamine oxidase-B; MDV, Medical Data Vision; PD, Parkinson's disease

* Corresponding author at: International University of Health and Welfare, School of Medicine, Center for Medical Education, 4-2 Kozunomori, Narita, Chiba 286-8686, Japan.
E-mail addresses: suzukimd@jikei.ac.jp (M. Suzuki), masaki.arai@takeda.com (M. Arai), ayako.hayashi1@takeda.com (A. Hayashi), ogino@iuhw.ac.jp (M. Ogino).

https://doi.org/10.1016/j.ensci.2020.100257
Received 25 October 2019; Received in revised form 9 July 2020; Accepted 13 July 2020
Available online 16 July 2020

Table 1
Classification of anti-Parkinson's disease drugs included in the MDV database (2008–2016).

Class	Generic name	Brand name in Japan	Maximum dose of active drug	Year launched in Japan
L-dopa	Levodopa	Dopaston® capsules, powder	3.5 g/day	1972
	Carbidopa hydrate, levodopa	Menesit® tablets	L-dopa: 1500 mg/day	1980
	Benserazide hydrochloride, levodopa	MADOPAR®, EC-DOPARL®	L-dopa: 600 mg/day	1980
Ergot dopamine agonists	Bromocriptine mesilate	Parlodel® tablets	22.5 mg/day	1979
	Pergolide mesilate	Permax®	1250 μg/day	1994
	Cabergoline	CABASER® tablets	3 mg/day[a]	1999
Non-ergot dopamine agonists	Talipexole hydrochloride	Domin® tablets	3.6 mg/day	1996
	Pramipexole hydrochloride hydrate	BI-Sifrol® tablets	4.5 mg/day	2004
		Mirapex®-LA		2011
	Ropinirole hydrochloride	ReQuip® tablets	IR: 15 mg/day	2006
		ReQuip® CR tablets	CR: 16 mg/day	2012
	Apomorphine hydrochloride hydrate	Apokyn® single use subcutaneous injection	30 mg/day (6 mg/dose)	2012
	Rotigotine	Neupro® patch	36 mg/day	2013
MAO-B inhibitor[b]	Selegiline hydrochloride	FP tablets[c]	10 mg/day	1998
		FP-OD[d]		2007
COMT inhibitors	Entacapone	Comtan® tablets	1600 mg/day (always given with L-dopa/carbidopa or L-dopa/benserazide)	2007
	Entacapone, carbidopa hydrate, levodopa	Stalevo® combination tablets	Entacapone: 1600 mg/day Carbidopa: 150 mg/day L-dopa: 1500 mg/day	2014
Anticholinergic drugs	Trihexyphenidyl hydrochloride	ARTANE® tablets, powder	10 mg/day	1954 (tablets) 1965 (powder; "ARTANE® 100-bai San," renamed "ARTANE® San 1%" in 2001)
	Profenamine hydrochloride	PARKIN® sugar-coated tablets[e]	–	1962
	Biperiden hydrochloride	AKINETON®	6 mg/day	1964 (tablets) 1981 (powder)
	Biperiden lactate	AKINETON® injection	IM: 10 mg/dose[f]	1964
	Profenamine hibenzate	PARKIN® powder[e]	–	1973
	Pyroheptin hydrochloride	TRIMOL® tablets, fine granules	12 mg/day	1974
	Mazaticol hydrochloride hydrate	PENTONA® tablets, powder	12 mg/day	1978
Droxidopa	Droxidopa	DOPS®	900 mg/day	1989
Zonisamide	Zonisamide	EXCEGRAN®[g]	25–50 mg/day[h]	1989
		Trerief®		2009
Amantadine	Amantadine hydrochloride	Symmetrel®	300 mg/day	1975
Istradefylline	Istradefylline	NOURIAST® tablets	40 mg/day	2013

Only anti-Parkinson's disease drugs that were available in Japan during the study period (2008–2016) are shown.
COMT, catechol-*O*-methyltransferase; CR, controlled release; IM, intramuscular; IR, immediate release; MAO-B, monoamine oxidase-B; MDV, Medical Data Vision.
[a] Maximum dose of cabergoline was reduced from 4 mg/day to 3 mg/day in 2008 due to reported heart valve disease.
[b] Rasagiline was not available during the study period as its launch was delayed in Japan.
[c] FP tablets were discontinued in 2011, with the launch of FP-OD.
[d] Monotherapy of FP-OD tablets was approved in Japan in 2015.
[e] PARKIN® sugar-coated tablets and powder were discontinued in 2019.
[f] Maximum dose of AKINETON® injection is shown in dose of biperiden lactate.
[g] EXCEGRAN® (approved for epilepsy in Japan) was included because this brand of zonisamide may have been prescribed for Parkinson's disease before the launch of Trerief®.
[h] 50 mg once-daily dose was approved for "wearing off" effects in Japan in 2013.

not been major changes to the treatment strategy since 2011, newer treatments such as sustained-release DAs, DA patches, apomorphine subcutaneous injection, istradefylline tablets, and continuous L-dopa enteral infusion have been used more frequently [6]. The recent 2018 Japanese guidelines and 2017 NICE guidelines also include MAO-B inhibitors as an alternative to L-dopa [6,11]. The Japanese guidelines further specify that non–L-dopa drugs (DAs and MAO-B inhibitors) may be more suitable for younger patients because of the lower frequency of motor complications and anticholinergic drugs may be less suitable for older patients [6,10]. Because of the progressive nature of PD, most patients will eventually require addition of other drugs and/or dose adjustment to balance symptom control with the occurrence of complications [7].

Given the large number of anti-PD drugs available, and the possibility of various treatment combinations, analyses of hospital or medical insurance databases can provide useful insights into real-world prescribing patterns. Previous database studies from the United States (US) [12–15], Taiwan [16], and Japan [17] have examined prescribing patterns for PD. However, these studies were often limited by small or selective (e.g., only elderly patients) samples that did not reflect nationwide prescribing practice comprehensively. For example, the

previous Japanese study used a database of up to 1 million members of 20 corporate health insurance societies (employees and their families), which included approximately 2000 patients with PD over a 5-year period [17]. In contrast, the Japan Medical Data Vision (MDV) database comprises more than 17 million patient-years from acute-care hospitals, and includes more than 150,000 PD patient-years. The availability of such a large database is due, in part, to the unique Japanese public health insurance system. Medical expenses are subsidised by public health insurance for all residents of Japan. Although there are co-payments, additional subsidies are provided for intractable diseases, including PD (with Hoehn & Yahr scale ≥3). Prescriptions for newly available medications are limited to 14 days for 1 year following their launch, in order to increase the frequency of safety monitoring. This forces patients to visit their doctors every 2 weeks, which may cause inconvenience in patients with chronic diseases such as PD, who generally make hospital visits every 2–3 months. The size and scope of the MDV database allows for an in-depth analysis of the broad range of pharmacotherapy regimens prescribed to patients with PD and provides sufficient data to examine prescription patterns in subgroups of patients, such as older patients.

The aim of this analysis was to use the MDV database to conduct a comprehensive and nationwide analysis of the prescription of anti-PD drugs in Japan between 2008 and 2016. Through this analysis, we aimed to gain insights into the type and number of anti-PD drugs used in Japan, changes in prescriptions over the 8-year period, and differences in prescriptions based on patient age and sex.

2. Materials and methods

2.1. Study design and data source

This was a retrospective, cross-sectional observational study of the pattern of anti-PD drug prescription in Japan using data derived from the MDV database (Medical Data Vision Co., Ltd., Tokyo, Japan). The MDV database includes health insurance claims generated at acute-care hospitals that use the Japanese Diagnosis Procedure Combination/Per-Diem Payment System (DPC/PDPS) fixed-payment reimbursement system. As of May 2015, the DPC/PDPS hospitals (primarily large hospitals) represented approximately 21% of all hospitals and nearly 55% of all hospital beds in Japan. At the time of data collection, the database contained standardised health insurance claims data corresponding to more than 17 million patient-years. The MDV database includes diagnosis codes according to *International Classification of Disease, Tenth Revision (ICD-10)*, Japanese Disease Name Codes, Japanese Procedure Codes, and prescriptions containing generic drug names submitted for health insurance claims. The MDV database includes data obtained during hospitalisation, as well as outpatient data after a hospital visit, except when patients change hospitals. The study analysed claims data from 1 April 2008 to 31 December 2016. Because data from the MDV database are anonymous, informed consent and ethics approval were not required, in line with the Ethical Guidelines for Epidemiological Research from the Japanese Ministry of Health, Labour and Welfare.

2.2. Study population

Patients with a diagnosis of PD were identified using an algorithm based on diagnosis codes. Within each calendar year, patients were included in the analysis for that year if they had a clinically established diagnosis of PD based on both the *ICD-10* code G20 and a Japanese Disease Code for PD, were at least 30 years of age, and did not have a diagnosis of schizophrenia (*ICD-10* code F20), excluded to avoid patients with drug-induced parkinsonism, or cerebrovascular disease (*ICD-10* codes I60 − I69), excluded to avoid patients with vascular parkinsonism. Because tracking of individual patients was not possible, patients who changed hospitals may have met the inclusion criteria in more than 1 year. Therefore, patients who changed hospitals may have been counted more than once. The age and sex of patients were analysed for each year and for the overall period.

2.3. Prescription pattern of anti-PD drugs

Anti-PD drugs were categorised according to drug class or individual drug and included L-dopa, non-ergot DA, ergot DA, MAO-B inhibitors, COMT inhibitors, anticholinergic drugs, droxidopa, zonisamide, amantadine, and istradefylline (Table 1). Analysis of the prescription pattern of anti-PD drugs included the percentage of patients prescribed each type of anti-PD drug overall, by calendar year, and by age and sex, as well as the number of concomitant anti-PD drugs.

2.4. Statistical analysis

Data were collected and analysed by Milliman, Inc. (Tokyo, Japan). All data are presented as descriptive statistics only (no inferential statistics).

3. Results

3.1. Characteristics of patients with PD

The analysis included 155,493 PD patient-years from the MDV database, which comprised more than 17 million patient-years (Fig. 1). The number of patients with PD identified increased with each calendar year (Table 2), primarily because of the increasing size of the MDV database. The mean age of patients increased steadily from 71.8 years in 2008 to 73.8 years in 2016 (Table 2). The age distribution of patients with PD peaked between 70 and 85 years (Fig. 2), and 56.1% of patients were women (Table 2). Patients with PD who were middle-aged (30–60 years) comprised 13,322 patient-years, with approximately equal numbers of men and women (Fig. 2). In contrast, there were more women than men among the older age groups (60 years and older) (Fig. 2).

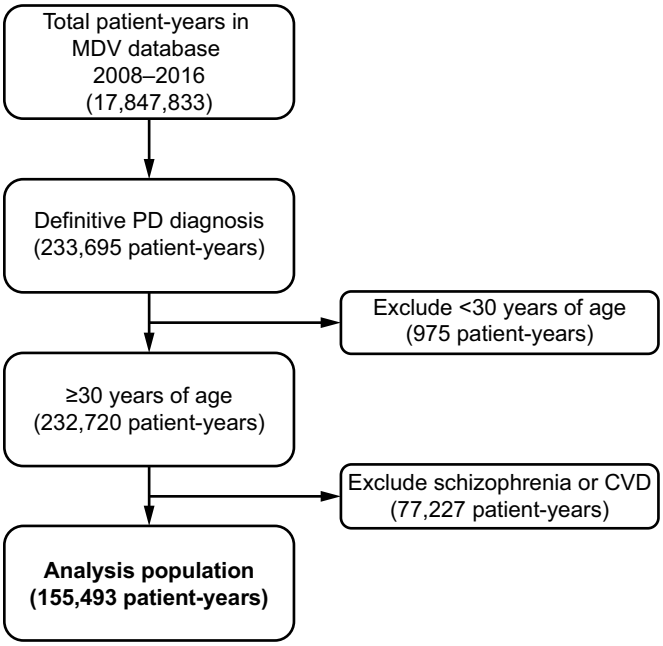


Fig. 1. Identification of patients with PD in the MDV database from 2008 to 2016. The analysis population includes patients who are identified in more than one calendar year (i.e., patients may be counted more than once). CVD, cerebrovascular disease; MDV, Medical Data Vision; PD, Parkinson's disease.

Table 2
Profile of registered Parkinson's disease patients in the MDV database from 2008 to 2016 by calendar year.

Year	Total MDV database		Patients with PD		
	Hospitals, *n*	Patients, *n*	Patients, *n*	Mean age, years	Female, %
2008	7	147,384	536	71.8	55.8
2009	17	461,003	1464	71.7	57.8
2010	57	1,497,102	4794	72.4	56.7
2011	81	2,793,384	7960	72.8	56.5
2012	119	4,501,317	11,839	73.1	56.8
2013	169	7,304,009	20,012	73.2	56.5
2014	252	11,241,465	31,105	73.4	56.4
2015	291	14,969,275	37,271	73.6	55.8
2016	342	19,083,925	40,512	73.8	55.6
Total patient-years		–	155,493[a]	73.4	56.1

MDV, Medical Data Vision.
[a] Includes patients who are identified in more than one calendar year (i.e., patients may be counted more than once).

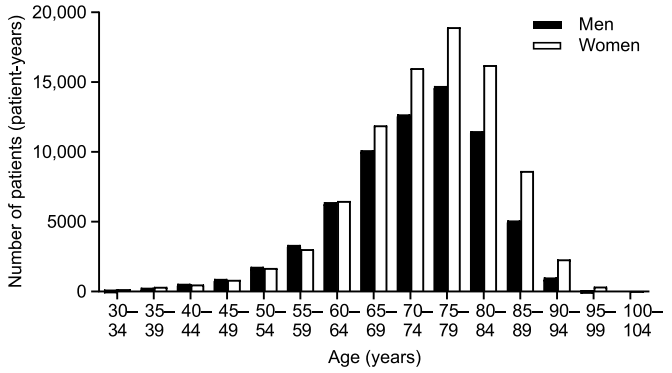


Fig. 2. Age distribution of male (black bars) and female (white bars) patients (patient-years) with Parkinson's disease identified in the database.

3.2. Prescription pattern of anti-PD drugs

3.2.1. Overall pattern

More than 600 different prescription patterns representing different drugs used as monotherapy or in combination were identified in the MDV database, as expected given the complexity and variability of symptoms in individual patients. L-dopa as monotherapy was the most common prescription pattern (22.7% of patient-years; Fig. 3). There was no prescription for any year in the database for approximately 20% of the patient-years. Non-ergot DA drugs were commonly prescribed as monotherapy (7.6% of patient-years) or with L-dopa (6.8% of patient-years). Monotherapy was prescribed for approximately 50% of the patient-years (Fig. 4), two drugs were prescribed for 14.1%, and three or more drugs were prescribed for 18.4%.

3.2.2. Prescription rate by year

L-dopa was the most commonly prescribed anti-PD drug in each year (Fig. 5). Between 2008 and 2011, the rate of L-dopa prescription fell from 61% of patients to 49% of patients; however, after 2011, the rate increased again to 56% in 2016. The observed change after 2011 coincides with the publication of updated Japanese guidelines recommending L-dopa [10]. The second most common anti-PD drug was the non-ergot DA class. The rate of non-ergot DA prescription increased from 25% in 2008 to 33% in 2012, and then decreased to 27% in 2016. As with the change in L-dopa prescriptions, the decrease in non-ergot DA prescription occurred after publication of the 2011 guidelines [10]. All other anti-PD drugs were prescribed to less than 20% of patients in each year. During the observation period, the prescription of ergot DA drugs decreased markedly (from 18% to 3% of patients). Conversely,

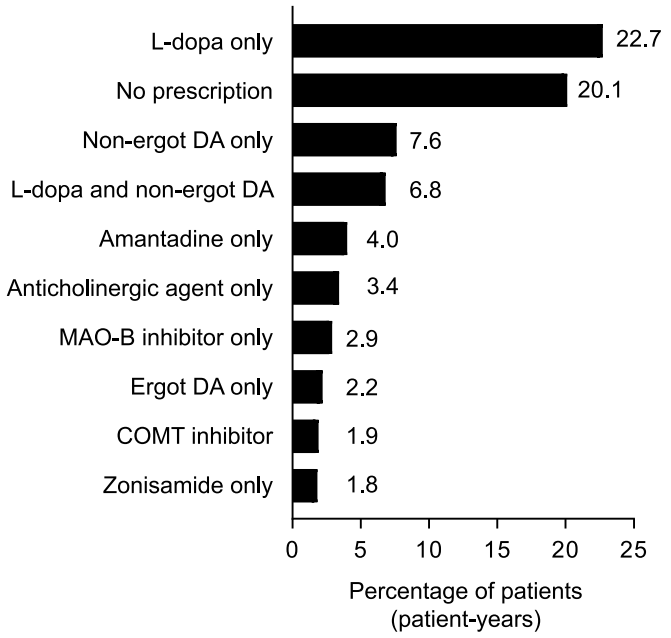


Fig. 3. Ten most common anti-Parkinson's disease prescription patterns during the 2008–2016 period. COMT, catechol-*O*-methyltransferase; DA, dopamine agonist; MAO-B, monoamine oxidase-B. COMT inhibitor includes both Comtan® and Stalevo® (Table 1).

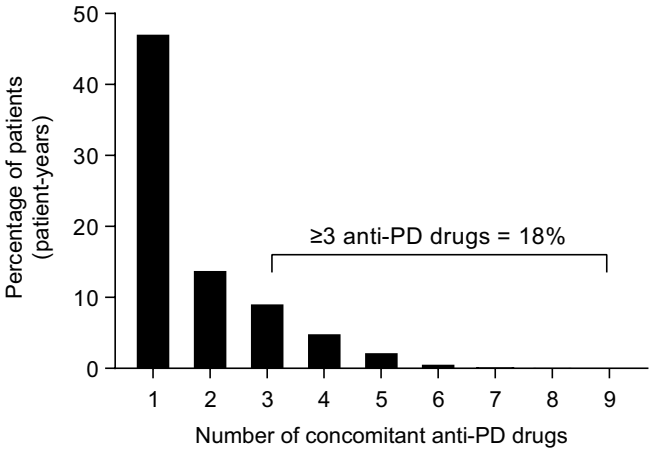


Fig. 4. Number of concomitant anti-Parkinson's disease (anti-PD) drugs prescribed.

the prescription of the new drugs zonisamide (approved for PD in 2009, but previously available for epilepsy) and istradefylline (first available in 2013) increased during this period. Prescription of MAO-B inhibitors and COMT inhibitors also increased.

3.2.3. Prescription rate by age and sex

The prescription rate (per patient-years) of L-dopa was highest in older patients and peaked at nearly 60% for patients aged 80 to 89 years (Fig. 6). In contrast, non-ergot DAs were mostly prescribed to middle-aged patients and peaked at approximately 35% for patients aged 50 to 69 years. Prescription of MAO-B inhibitors and COMT inhibitors was highest for patients aged 50 to 79 years. Anticholinergic drugs were prescribed primarily to middle-aged patients younger than 60 years of age. The number of prescribed anti-PD drugs, indicated by cumulative percentages greater than 100% in Fig. 6, was highest among patients 50–69 years and decreased markedly in older patients. Prescription patterns were generally similar in men and women.

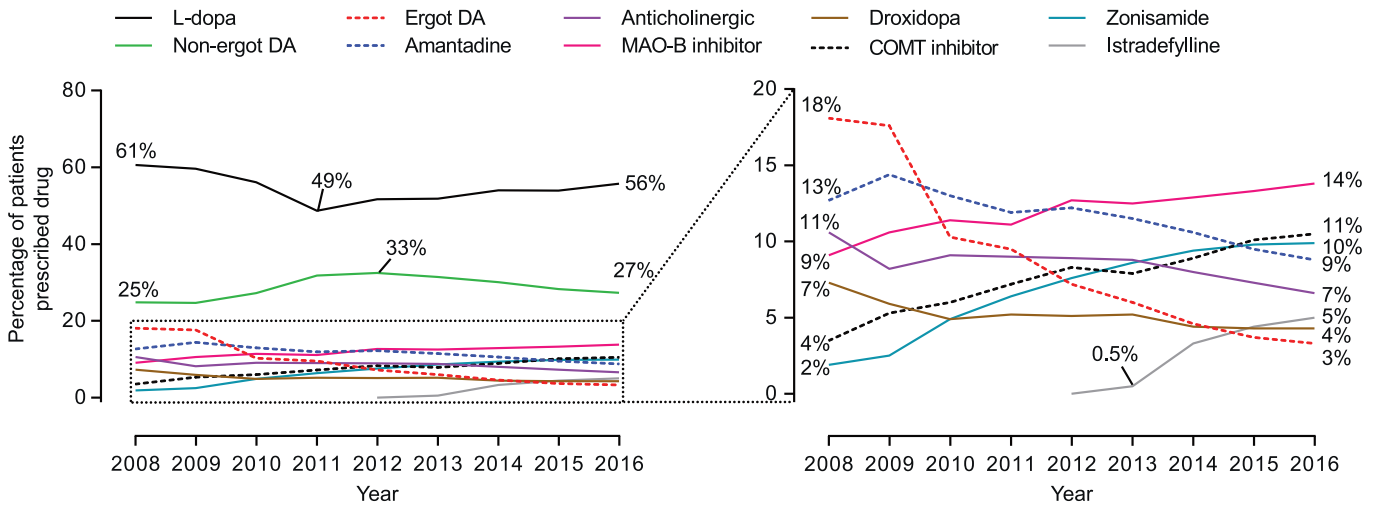
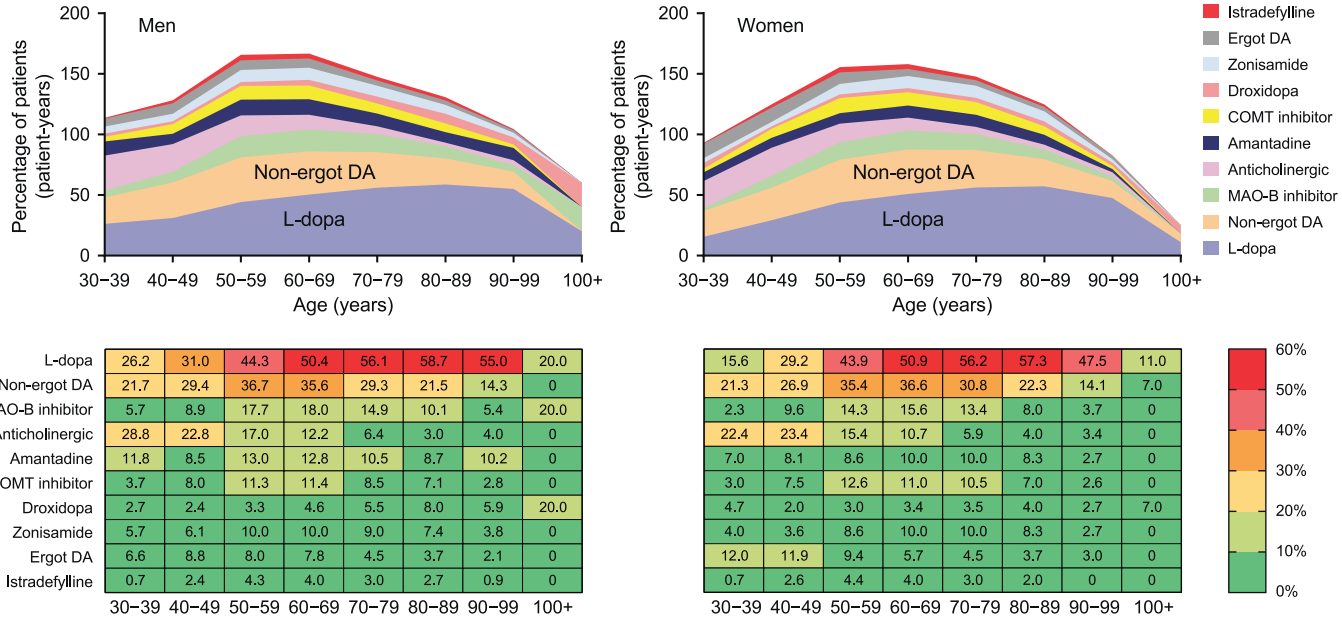


Fig. 5. Percentage of patients prescribed each type of anti-Parkinson's disease drug by calendar year. Note that istradefylline did not become available until 2013; therefore, the prescription rate is graphed starting from 2012 (zero prescriptions). COMT, catechol-*O*-methyltransferase (includes Comtan® and Stalevo®); DA, dopamine agonist; MAO-B, monoamine oxidase-B.

4. Discussion

This is the first analysis to use data derived from a large, nationwide medical claims database to determine the patterns of anti-PD drug prescriptions for more than 150,000 PD patient-years over an 8-year period in Japan. In 2016, we identified 40,512 patients with PD, which corresponds to approximately 16% of the prevalence count (256,455) reported by the Global Burden of Disease study [2]. Most of the patients were 70 to 84 years old, in line with the actual age of most patients with PD in Japan [3], and women outnumbered men, particularly among the older patients. Our analysis has shown that L-dopa continues to be the most commonly prescribed anti-PD drug, followed by non-ergot DAs, confirming the results of a previous Japanese study of PD prescriptions between 2005 and 2010 [17]. The previous study focussed on the decrease in ergot DA prescriptions and corresponding increase in non-ergot DA prescriptions among middle-aged patients that occurred following regulatory changes in 2007 [17]. In the current study, the high proportions of patients in both the 15–64 and ≥ 65-year age ranges (i.e., 52.4% and 34.1%) in the MDV database allowed us to examine age-specific differences in prescriptions [18]. L-dopa was primarily prescribed to older patients, whereas non-ergot DAs were prescribed to relatively younger, middle-aged patients, consistent with Japanese guidelines [10]. The identification of more than 600 unique prescription patterns suggests that clinicians in Japan might be tailoring treatment of individual patients to optimise control of symptoms that vary markedly between patients and to minimise side effects. Furthermore, the longitudinal nature of our study allowed us to examine changes in PD prescription patterns for individual anti-PD drugs between 2008 and 2016, as discussed in detail below.

The clinical preference for L-dopa versus DAs as initial PD therapy has fluctuated over the past 20 years as evidence for and against both drug classes has emerged [19–22]. In the current study, L-dopa and



	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100+
L-dopa	26.2	31.0	44.3	50.4	56.1	58.7	55.0	20.0
Non-ergot DA	21.7	29.4	36.7	35.6	29.3	21.5	14.3	0
MAO-B inhibitor	5.7	8.9	17.7	18.0	14.9	10.1	5.4	20.0
Anticholinergic	28.8	22.8	17.0	12.2	6.4	3.0	4.0	0
Amantadine	11.8	8.5	13.0	12.8	10.5	8.7	10.2	0
COMT inhibitor	3.7	8.0	11.3	11.4	8.5	7.1	2.8	0
Droxidopa	2.7	2.4	3.3	4.6	5.5	8.0	5.9	20.0
Zonisamide	5.7	6.1	10.0	10.0	9.0	7.4	3.8	0
Ergot DA	6.6	8.8	8.0	7.8	4.5	3.7	2.1	0
Istradefylline	0.7	2.4	4.3	4.0	3.0	2.7	0.9	0

	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100+
L-dopa	15.6	29.2	43.9	50.9	56.2	57.3	47.5	11.0
Non-ergot DA	21.3	26.9	35.4	36.6	30.8	22.3	14.1	7.0
MAO-B inhibitor	2.3	9.6	14.3	15.6	13.4	8.0	3.7	0
Anticholinergic	22.4	23.4	15.4	10.7	5.9	4.0	3.4	0
Amantadine	7.0	8.1	8.6	10.0	10.0	8.3	2.7	0
COMT inhibitor	3.0	7.5	12.6	11.0	10.5	7.0	2.6	0
Droxidopa	4.7	2.0	3.0	3.4	3.5	4.0	2.7	7.0
Zonisamide	4.0	3.6	8.6	10.0	10.0	8.3	2.7	0
Ergot DA	12.0	11.9	9.4	5.7	4.5	3.7	3.0	0
Istradefylline	0.7	2.6	4.4	4.0	3.0	2.0	0	0

Fig. 6. Percentage of patients (patient-years) prescribed each type of anti-Parkinson's disease drug by patient age and sex. Upper panels display cumulative percentages, which may exceed 100% because of multiple drug prescriptions. Lower panels display "heat maps" with percentage of patients colour-coded from green (≤10%) through to red (≥50%). COMT, catechol-*O*-methyltransferase; DA, dopamine agonist; MAO-B, monoamine oxidase-B.

non-ergot DAs, alone and in combination, were the most commonly prescribed anti-PD drugs between 2008 and 2016. More than half of patients were prescribed L-dopa, which reflects its well-established efficacy, acceptable tolerability, low cost, and ability to be combined with adjunct therapies at later stages [7,23]. This practice is consistent with previous studies [12–15,17] and with treatment guidelines [10,11,24]. Between 2008 and 2011, the prescription of L-dopa decreased while that of non-ergot DAs increased; this pattern reversed during the later years of the study, after publication of the 2011 Japanese guidelines [10]. The initial decrease in L-dopa prescription may have reflected concerns about whether the drug accelerated neurodegeneration and PD progression [25]. Although the ELLDOPA study, published in 2005, suggested that L-dopa is not neurotoxic and actually either slows PD progression or has long-lasting effects on disease symptoms, it did not resolve concerns with L-dopa–induced dyskinesia that can occur with long-term use [26]. Around the same time, sustained-release tablets of DA became available, and expectations for the effectiveness of DAs rose. Several studies demonstrated that initial treatment for 3–5 years with DAs delays the onset of motor complications, dyskinesia, and "wearing off" compared with L-dopa [19,20]. These results were confirmed in a 2008 meta-analysis; however, the meta-analysis also concluded that DAs are associated with poorer symptom control and a higher incidence of non-motor side effects (e.g., oedema, somnolence) than L-dopa [27]. Furthermore, in a 14-year follow-up study published in 2008, Katzenschlager et al. concluded that initial DA treatment possesses neither long-term benefits nor a clinically relevant disease-modifying effect [21]. Since then, clinicians have gradually begun reviewing L-dopa use based on these studies and daily clinical practice [10,22]. Finally, although the Great East Japan earthquake occurred in 2011, it is unlikely that this had a significant effect on the prescription of PD medications during the study period.

Among the other anti-PD drugs, the prescription rates of ergot DAs, amantadine, anticholinergic agents, and droxidopa decreased, whereas rates of MAO-B inhibitors, COMT inhibitors, and the newer drugs zonisamide and istradefylline increased. Greater recognition of treatment-related adverse effects may have contributed to the decreased use of amantadine and anticholinergic agents, especially in elderly patients. Increased availability of MAO-B inhibitors, COMT inhibitors, zonisamide, and istradefylline, and greater familiarity with their use, may have led to increased prescription of these anti-PD drugs. Multiple anti-PD drug combination options were also provided in order to control symptoms in line with the patient's status/needs.

Almost half of patients were prescribed a single anti-PD drug, 14% were prescribed two drugs, and 18% were prescribed three or more anti-PD drugs, consistent with a study of Medicare patients in the US [13]. This pattern reflects the common need for adjunct therapies as PD progresses. About 20% of patients did not have any anti-PD drug prescriptions, again consistent with the US study [13]. These instances with no prescription may represent first consultations, second opinion consultations, or consultations where medication was reassessed.

The prescription of anti-PD drugs differed between younger and older patients, indicating that age was a factor in clinical decisions, as recommended in the 2011 Japanese PD guidelines [10]. Unlike most international guidelines [11,24], the 2011 Japanese PD guidelines made specific recommendations for the treatment of younger and older patients [10]. In our study, the mean age of patients increased steadily during the study period, in line with the ageing of the general population of Japan [18]. Consistent with the guidelines, older patients were primarily treated with L-dopa because of its effectiveness at controlling motor symptoms and tolerability. Non-ergot DAs were prescribed mainly for younger patients, presumably because these drugs have fewer motor complications than L-dopa for long-term use [27]. Anticholinergic agents were prescribed mainly to patients younger than 60 years of age, in keeping with recommendations to avoid this class in older patients because of the potential effects on memory and cognitive function [10] and an increased risk of falls [6]. Patients aged 50–70 years were often prescribed multiple anti-PD drugs to actively provide greater symptom control and improved quality of life. As patients with PD age, their ability to tolerate and adhere to complex medication regimens decreases, especially in the case of patients with comorbidities [28]. Consequently, we observed a progressive decrease in the number of concomitant anti-PD drugs in patients older than 70 years of age.

Sex-related differences in initial presenting signs, symptom severity, and dyskinesia development may influence the choice of anti-PD drugs in men and women [12,29]. In our study, the overall anti-PD drug prescription trends were generally similar regardless of sex, consistent with the findings of a large multicentre study demonstrating that there were no sex differences in the type and dose of dopaminergic medication use in early PD [30]. Nevertheless, different prescription trends between male and female patients of middle age are possible given that men represent a larger proportion of the labour force than women in Japan (68.4% vs. 46.9%) [31].

Our study is unique in its use of data derived from a very large, Japan-wide medical claims database that included patients of all ages. However, this study also has several limitations. Firstly, although the data allowed a nationwide analysis, data from small-scale or chronic-phase hospitals and clinics are not included in the MDV database. Moreover, the rapid increase in the number of patients in or around 2011 might have led to bias. In the future, this analysis will become more accurate as the database matures. Secondly, owing to the nature of administrative databases, which require patient anonymisation and lack of patient treatment history, the MDV database does not allow us to: (1) examine more detailed clinical information in order to evaluate the accuracy of the diagnosis or understand the factors that influence treatment choice; (2) retrieve the patient's medical history from their original paper-based or electronic medical records; or (3) track hospital transfers of patients, meaning that patients who changed hospitals were not tracked and may have been counted more than once, and thus the analysis was based on the apparent total number of patients. Thirdly, this analysis includes patients who were prescribed any anti-PD agent at least once per year; therefore, the same patients may have been counted several times over the course of 8 years. Consequently, the total number of patients is likely to have been overestimated, because it was impossible to accurately identify individuals in the MDV database. Fourthly, because the analysis focussed on pharmacological treatments, device-aided treatments, such as deep brain stimulation, were not assessed. Fifthly, the combination tablet Stalevo® was counted only as a COMT inhibitor, which would underestimate the number of patients receiving L-dopa and the number of concomitant medications in patients prescribed Stalevo®. Finally, because this study identified PD patients using the *ICD-10* code, it is possible that a small number of patients with non-PD parkinsonism were included in the analysis.

5. Conclusion

In conclusion, using a large, nationwide medical claims database, we have documented prescription patterns of anti-PD drugs in Japanese patients with PD over an 8-year period. L-dopa and non-ergot DAs were the most commonly prescribed anti-PD drugs, and were targeted appropriately to older and younger patients, respectively, in line with Japanese guidelines [10]. Other than L-dopa, older drugs, some of which have unacceptable side effects, were used less frequently over time, and were replaced by newer drugs. Overall, these results indicate that Japanese clinicians are adhering to local guidelines and are tailoring anti-PD treatment to individual patient needs.

Role of the sponsor

Takeda Pharmaceutical Company Limited was involved in the study design, data collection, data analysis, and preparation of the manuscript.

Role of contributors

All authors participated in the study design, interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript.

Data statement

The data used for this study are available from Medical Data Vision Co., Ltd. but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Medical Data Vision Co., Ltd.

Other contributors/acknowledgments

The authors would like to thank Mr. Kosuke Iwasaki at Milliman, Inc. for data collection and analysis; Ms. Yayoi Kawata at Takeda Pharmaceutical Company Limited for her support in this study; Mr. Kentaro Yamato at Takeda Pharmaceutical Company Limited for his support in the publication process; and Ms. Manami Yoshida, Dr. Shu Okamoto, and Dr. Shinzo Hiroi for their contribution to the study design and launch.

Medical writing assistance was provided by Rebecca Lew, PhD, CMPP, and Serina Stretton, PhD, CMPP, of ProScribe – Envision Pharma Group, and was funded by Takeda Pharmaceutical Company Limited. ProScribe's services complied with international guidelines for Good Publication Practice 3 (GPP3).

Declaration of Competing Interest

MS is a speaker for Eisai Co., Ltd., Janssen Pharmaceutica, Kyowa Hakko Kirin Co., Ltd., Nihon Medi-Physics Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., and Takeda Pharmaceutical Company Limited. MA and AH are employees of Takeda Pharmaceutical Company Limited. MO has received lecture fees from Kyowa Hakko Kirin Co., Ltd., Otsuka Pharmaceutical Co., Ltd., GlaxoSmithKline plc., Novartis Pharma K.K., and Takeda Pharmaceutical Company Limited.

Acknowledgments

This study was sponsored by Takeda Pharmaceutical Company Limited, manufacturer/licensee of rasagiline in Japan.

References

[1] J. Jankovic, Parkinson's disease: clinical features and diagnosis, J. Neurol. Neurosurg. Psychiatry 79 (4) (2008) 368–376.
[2] GBD 2016 Parkinson's Disease Collaborators, Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet Neurol. 17 (11) (2018) 939–953.
[3] M. Yamawaki, M. Kusumi, H. Kowa, K. Nakashima, Changes in prevalence and incidence of Parkinson's disease in Japan during a quarter of a century, Neuroepidemiology 32 (4) (2009) 263–269.
[4] Y. Osaki, Y. Morita, T. Kuwahara, I. Miyano, Y. Doi, Prevalence of Parkinson's disease and atypical parkinsonian syndromes in a rural Japanese district, Acta Neurol. Scand. 124 (3) (2011) 182–187.
[5] W. Muangpaisan, H. Hori, C. Brayne, Systematic review of the prevalence and incidence of Parkinson's disease in Asia, J. Epidemiol. 19 (6) (2009) 281–293.
[6] Development Committee for Parkinson's Disease Treatment Guideline, Parkinson's Disease Treatment Guideline 2018 [in Japanese], Igaku-Shoin, Tokyo, Japan, (2018).
[7] W. Oertel, J.B. Schulz, Current and experimental treatments of Parkinson disease: a guide for neuroscientists, J. Neurochem. 139 (S1) (2016) 325–337.
[8] M.E. Freitas, S.H. Fox, Nondopaminergic treatments for Parkinson's disease: current and future prospects, Neurodegener. Dis. Manag. 6 (3) (2016) 249–268.
[9] National Institute for Health and Care Excellence, Parkinson"s disease, Diagnosis and Management in Primary and Secondary Care 2006, http://www.ipts.org.il/_Uploads/dbsAttachedFiles/parkinsons.pdf , Accessed date: 14 April 2020.
[10] Development Committee for Parkinson's Disease Treatment Guideline, Parkinson's Disease Treatment Guideline 2011 [in Japanese], Igaku-Shoin, Tokyo, Japan, (2011).
[11] National Institute for Health and Care Excellence, Parkinson's disease in adults, http://nice.org.uk/guidance/ng71, (2017) , Accessed date: 17 December 2018.
[12] J.A. Crispo, Y. Fortin, D.P. Thibault, M. Emons, L.M. Bjerre, D.E. Kohen, S. Perez-Lloret, D. Mattison, A.W. Willis, D. Krewski, Trends in inpatient antiparkinson drug use in the USA, 2001–2012, Eur. J. Clin. Pharmacol. 71 (8) (2015) 1011–1019.
[13] N. Dahodwala, A.W. Willis, P. Li, J.A. Doshi, Prevalence and correlates of anti-Parkinson drug use in a nationally representative sample, Mov. Disord. Clin. Pract. 4 (3) (2016) 335–341.
[14] F.F. Richy, G. Pietri, K.A. Moran, E. Senior, L.E. Makaroff, Compliance with pharmacotherapy and direct healthcare costs in patients with Parkinson's disease: a retrospective claims database analysis, Appl. Health Econ. Health Policy 11 (4) (2013) 395–406.
[15] Y.-J.J. Wei, B. Stuart, I.H. Zuckerman, Use of antiparkinson medications among elderly Medicare beneficiaries with Parkinson's disease, Am. J. Geriatr. Pharmacother. 8 (4) (2010) 384–394.
[16] Y.-J. Guo, Y.-C. Liao, C.-H. Lin, M.-H. Chang, Initial medication in patients of newly diagnosed Parkinson's disease in Taiwan, PLoS One 9 (9) (2014) e107465.
[17] S. Nakaoka, T. Ishizaki, H. Urushihara, T. Satoh, S. Ikeda, M. Yamamoto, T. Nakayama, Prescribing pattern of anti-Parkinson drugs in Japan: a trend analysis from 2005 to 2010, PLoS One 9 (6) (2014) e99021.
[18] S. Saokaew, T. Sugimoto, I. Kamae, C. Pratoomsoot, N. Chaiyakunapruk, Healthcare databases in Thailand and Japan: potential sources for health technology assessment research, PLoS One 10 (11) (2015) e0141993.
[19] R.G. Holloway, I. Shoulson, S. Fahn, K. Kieburtz, A. Lang, K. Marek, M. McDermott, J. Seibyl, W. Weiner, B. Musch, C. Kamp, M. Welsh, A. Shinaman, R. Pahwa, L. Barclay, J. Hubble, P. LeWitt, J. Miyasaki, O. Suchowersky, M. Stacy, D.S. Russell, B. Ford, J. Hammerstad, D. Riley, D. Standaert, F. Wooten, S. Factor, J. Jankovic, F. Atassi, R. Kurlan, M. Panisset, A. Rajput, R. Rodnitzky, C. Shults, G. Petsinger, C. Waters, R. Pfeiffer, K. Biglan, L. Borchert, A. Montgomery, L. Sutherland, C. Weeks, M. DeAngelis, E. Sime, S. Wood, C. Pantella, M. Harrigan, B. Fussell, S. Dillon, B. Alexander-Brown, P. Rainey, M. Tennis, E. Rost-Ruffner, D. Brown, S. Evans, D. Berry, J. Hall, T. Shirley, J. Dobson, D. Fontaine, B. Pfeiffer, A. Brocht, S. Bennett, S. Daigneault, K. Hodgeman, C. O'Connell, T. Ross, K. Richard, A. Watts, P.S. Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial, Arch. Neurol. 61 (7) (2004) 1044–1053.
[20] W.H. Oertel, E. Wolters, C. Sampaio, S. Gimenez-Roldan, B. Bergamasco, M. Dujardin, D.G. Grosset, G. Arnold, K.L. Leenders, H.-P. Hundemer, A. Lledó, A. Wood, P. Frewer, J. Schwarz, Pergolide versus levodopa monotherapy in early Parkinson's disease patients: the PELMOPET study, Mov. Disord. 21 (3) (2006) 343–353.
[21] R. Katzenschlager, J. Head, A. Schrag, Y. Ben-Shlomo, A. Evans, A.J. Lees, Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD, Neurology 71 (7) (2008) 474–480.
[22] Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Pharmaceuticals and Medical Devices Safety Information, No. 245, www.pmda.go.jp/files/000153249.pdf#page=15, (2008) , Accessed date: 12 April 2019.
[23] J.E. Ahlskog, Cheaper, simpler, and better: tips for treating seniors with Parkinson disease, Mayo Clin. Proc. 86 (12) (2011) 1211–1216.
[24] S.H. Fox, R. Katzenschlager, S.-Y. Lim, B. Barton, R.M.A. de Bie, K. Seppi, M. Coelho, C. Sampaio, International Parkinson and Movement Disorder Society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease, Mov. Disord. 33 (8) (2018) 1248–1266.
[25] S. Fahn, Parkinson disease, the effect of levodopa, and the ELLDOPA trial, Arch. Neurol. 56 (5) (1999) 529–535.
[26] S. Fahn, D. Oakes, I. Shoulson, K. Kieburtz, A. Rudolph, A. Lang, C.W. Olanow, C. Tanner, K. Marek, Parkinson Study Group, Levodopa and the progression of Parkinson's disease, N. Engl. J. Med. 351 (2004) 2498–2508.
[27] R.L. Stowe, N.J. Ives, C. Clarke, J. van Hilten, J. Ferreira, R.J. Hawker, L. Shah, K. Wheatley, R. Gray, Dopamine agonist therapy in early Parkinson's disease, Cochrane Database Syst. Rev. (2) (2008) (CD006564).
[28] G. McLean, J.V. Hindle, B. Guthrie, S.W. Mercer, Co-morbidity and polypharmacy in Parkinson's disease: insights from a large Scottish primary care database, BMC Neurol. 17 (1) (2017) 126.
[29] Y. Baba, J.D. Putzke, N.R. Whaley, Z.K. Wszolek, R.J. Uitti, Gender and the Parkinson's disease phenotype, J. Neurol. 252 (10) (2005) 1201–1205.
[30] C.C. Umeh, A. Pérez, E.F. Augustine, R. Dhall, R.B. Dewey Jr., Z. Mari, D.K. Simon, A.M. Wills, C.W. Christine, J.S. Schneider, O. Suchowersky, No sex differences in use of dopaminergic medication in early Parkinson disease in the US and Canada - baseline findings of a multicenter trial, PLoS One 9 (12) (2014) e112287.
[31] Statistics Japan, Statistics Bureau, Ministry of Internal Affairs and Communications, https://www.stat.go.jp/english/data/roudou/lngindex.html , Accessed date: 16 May 2019.