Comparison of zonisamide with non-levodopa, anti-Parkinson's disease drugs in the incidence of Parkinson's disease-relevant symptoms

Hirotaka Iwaki[a,*], Masaaki Tagawa[b], Kosuke Iwasaki[c], Koji Kawakami[d], Masahiro Nomoto[a]

[a] Department of Neurology and Clinical Pharmacology, Ehime University Graduate School of Medicine, 454 Shitsukawa, Toon, Ehime 791-0295, Japan
[b] Medical Affairs, Sumitomo Dainippon Pharma Co., Ltd., 13-1 Kyobashi 1-Chome, Chuo-ku, Tokyo 104-8356, Japan
[c] Milliman Inc., 1-6-2 Kojimachi, Chiyoda-ku, Tokyo 102-0083, Japan
[d] Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshida Konoecho, Sakyo-ku, Kyoto 606-8501, Japan

ARTICLE INFO

ABSTRACT

Introduction: Patients with Parkinson's disease (PD) experience various symptoms, both from the disease progression itself and the medication. Few large-scale studies have investigated the associations between zonisamide and these symptoms. This study compared zonisamide and other anti-PD drugs by analyzing their associations with the incidence of PD-relevant symptoms.

Methods: This was a cohort study based on claims data from Diagnosis Procedure Combination hospitals between 2008 and 2014 in Japan. Patients were included in the cohort if they were diagnosed with PD, aged ≥ 40 years, and were prescribed anti-PD drugs from the same single class without switching to/combination use with other classes excepting levodopa. The outcomes were the incidence of PD-relevant symptoms from the following categories; mental/psychiatric, autonomic nervous system, motor-related, and gastric symptoms. The associations between the incidence of these symptoms and the prescriptions of 8 different classes of anti-PD drugs were explored by the survival analysis.

Results: In the final cohort, 9157 patients were included. The zonisamide use was significantly associated with a lower risk of dementia, insomnia, and gastric ulcers than 3 of 7 other classes without levodopa ($p < .05$).

Conclusion: There may be a potential clinical impact of zonisamide on some of the PD-relevant symptoms.

1. Introduction

Parkinson's disease (PD), a progressive and neurodegenerative disease, is pathologically characterized by loss of neural cells including dopaminergic neurons in different regions of the nervous system. The main clinical feature of PD is bradykinesia in combination with resting tremor, muscle rigidity, or both [1]. In addition, the patients suffer from nonmotor symptoms such as depression, hallucinations, cognitive disorder, and autonomic dysfunctions [2–5]. Those symptoms appear and/or worsen as PD progresses or by medication, and decrease a patient's quality of life (QoL). One important objective of pharmacological treatment is to improve those symptoms and patient's QoL. Anti-PD drugs are selected according to the clinical condition of each patient and the characteristics of each agent. The anti-PD drugs available in Japan can be categorized into 10 classes: levodopa, catechol-O-methyltransferase (COMT) inhibitor, non-ergot- and ergot-derived dopamine agonists (non-eDAs and eDAs), monoamine oxidase-B (MAO-B) inhibitors, anticholinergics, droxidopa, zonisamide, amantadine, and istradefylline [6]. In the present study, however, istradefylline was excluded from the analysis because its launch date in Japan (May 2013) was too close to the end date of the available data (December 2014).

Zonisamide was originally discovered as an antiepileptic agent in the early 1980s in Japan and subsequently was reported to ameliorate parkinsonism in PD patients in 2001 [7]. After several randomized controlled trials [8,9], zonisamide, an adjunct to levodopa, was approved as an anti-PD drug in 2009 in Japan. Although the mechanism of action of zonisamide for parkinsonism has not yet been completely clarified, zonisamide was reported not only to inhibit MAO-B [10] and T-type calcium channels [11] while enhancing tyrosine-hydroxylase activity and dopamine release [12], but also to have neuroprotective

effects [13–15]. In some clinical trials, significant effects of zonisamide on both motor and nonmotor symptoms in PD patients were reported [16,17]. However, partly because zonisamide is off-label for PD except for in Japan, situations in which it is more suitable than other drugs have not been sufficiently elucidated. In this study, we analyzed a Japanese large claims database and assessed whether zonisamide use in PD patients was associated with the incidence of PD-relevant symptoms in comparison with other non-levodopa anti-PD drugs which are typically used as the second line therapy after levodopa. Because most patients prescribed zonisamide or other PD drugs used as second line drugs were also taking levodopa, we did not include levodopa as the comparison drug.

2. Methods

2.1. Study design

This study was an observational study using the claims data provided from the Medical Data Vision (MDV) Co., Ltd. (Tokyo, Japan). The claims data included those of patients treated in any of the Diagnosis Procedure Combination (DPC) hospitals in Japan from April 2008 to December 2014 (defined as a study period). The database includes hospitalization data, outpatient data, and prescription data. The detailed dataset in the database are as follows: diagnosis codes according to the International Classification of Diseases 10th revision (ICD-10) coding scheme by World Health Organization, disease names coded with Japanese Disease Name Codes, medical procedures coded with Japanese Procedure Codes, and prescription information containing generic drug names. It should be noted that when a patient is transferred to another hospital or clinic, his/her claims data could no longer be collected continuously.

This study was carried out in accordance with ethical standard as set out in the Declaration of Helsinki and approved by Ehime University's Institutional Review Board of Clinical Research Ethics (Study ID: 1609013). The study was registered in UMIN-CTR (UMIN000026890).

2.2. Patients

Patients who satisfied all of the inclusion criteria and who did not meet any of the exclusion criteria were eligible for this study. The inclusion criteria included a diagnosis of PD (ICD-10 code G20) during the observation period (period from the initial date of the database entry to the end of the study period or the loss of follow-up within the study period. The observation period may vary patient-by-patient), age of 40 years or older at the initial diagnosis of PD during the observation period, and prescription record of anti-PD drugs from the same single class without switching to/combination use with other drug classes excepting levodopa. All anti-PD drugs were identified by generic names and classified into 9 classes: levodopa, COMT inhibitor, non-eDAs, eDAs, MAO-B inhibitor, anticholinergics, droxidopa, zonisamide, and amantadine (Table 1).

Patients who had only a diagnosis of Parkinson's syndrome (because the ICD code of G20 also includes several types of Parkinson's syndrome), and patients who had any diagnosis with the ICD codes of G21 (secondary parkinsonism), G22 (parkinsonism diseases classified elsewhere), and G23 (other degenerative diseases of basal ganglia), which are frequently misdiagnosed as PD, were excluded from this study.

Among patients selected according to the aforementioned criteria, those who had no diagnosis of a specified PD-relevant symptom before the index date (initial prescription date of any anti-PD drug class during the observation period) were eligible for the survival analysis of that symptom.

2.3. Variables

The patients eligible for the survival analysis of each symptom were

Table 1
Definition of anti-PD drug classes.

Drug classes	Drugs
Levodopa	Carbidopa hydrate/levodopa
	Benserazide hydrochloride/levodopa
	Levodopa
COMT inhibitor	Entacapone
	Entacapone/levodopa/carbidopa hydrate
Non-eDAs	Pramipexole hydrochloride hydrate
	Ropinirole hydrochloride
	Rotigotine
	Apomorphine hydrochloride hydrate
	Talipexole hydrochloride
eDAs	Cabergoline
	Bromocriptine mesilate
	Pergolide mesilate
MAO-B inhibitor	Selegiline hydrochloride
Anticholinergics	Trihexyphenidyl hydrochloride
	Biperiden hydrochloride
	Biperiden
	Profenamine hydrochloride
	Piroheptine hydrochloride
	Mazaticol hydrochloride hydrate
	Profenamine hibenzate
	Metixene hydrochloride
Droxidopa	Droxidopa
Zonisamide	Zonisamide
Amantadine	Amantadine hydrochloride

COMT; catechol-*O*-methyltransferase, eDA; ergot-derived dopamine agonist, MAO-B; monoamine oxidase-B, PD; Parkinson's disease.

divided into different groups based on the anti-PD drug classes they used, and the persistence periods of anti-PD drug therapies (period from the index date to the discontinuation date) among them were identified. Discontinuation was defined as no prescription for 90 days or more since the end of the last prescription. The persistence period was ended on the last day of the observation period if no discontinuation occurred.

In this study, the exposure was the use of one of 8 different classes of anti-PD drugs excepting levodopa, and the outcome was the incidence of PD-relevant symptoms (defined as event) during the persistence period. Total of 15 PD-relevant symptoms commonly developed by disease progression or medication in PD patients were selected and identified by ICD-10 codes in the analysis (Symptom names and corresponding ICD-10 codes are detailed in Table 2).

2.4. Statistical analysis

The time from the index date to each event during the persistence period of each anti-PD drug class was analyzed using a Cox proportional hazards model.

When no event occurred during the persistence period, it was censored at the end of the persistence period. Any event that occurred beyond the end of the persistence period was not included in the analysis. A Cox proportional hazards model included the independent variables of age, sex, and dummy variables of anti-PD drug classes excepting zonisamide (zonisamide was set as a baseline comparator). The significance of each variable in the model was tested using a 2-sided χ^2 test at a level of 0.05. The hazard ratio of using each anti-PD drug class compared with zonisamide was calculated.

The statistical analysis was conducted using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Selection of patients

Fig. 1 shows the patient selection flowchart. Among 146,441 patients from the database, 31,365 PD patients were identified after

Table 2
PD-relevant symptoms and ICD-10 codes used for identification.

Classifications	Disease	ICD-10 code	ICD-10 terms
Mental and psychiatric symptoms	Dementia	F00	Dementia in Alzheimer's disease
		F01	Vascular dementia
		F02	Dementia in other diseases classified elsewhere
		F03	Unspecified dementia
	Depression	F32	Depressive episode
		F33	Recurrent depressive disorder
	Hallucination	F06.0	Organic hallucinosis
		R44	Other symptoms and signs involving general sensations and perceptions
	Delusion	F06.2	Organic delusional [schizophrenia-like] disorder
		F20.0	Paranoid schizophrenia
		F22	Persistent delusional disorders
		F23.3	Other acute predominantly delusional psychotic disorders
		F24	Induced delusional disorder
		F60.0	Paranoid personality disorder
		F61	Mixed and other personality and behavior
	Delirium	F05	Delirium, not induced by alcohol and other psychoactive substances
	Anxiety neurosis/anxiety/neurosis	F40-F48	Neurotic, stress-related and somatoform disorders
	Psychosomatic disease	F50	Eating disorders
		F51	Nonorganic sleep disorders
		F52	Sexual dysfunction, not caused by organic disorder or disease
		F54	Psychological and behavioral factors associated with disorders or diseases classified elsewhere
		F59	Unspecified behavioral syndromes associated with physiological disturbances and physical factors
	Insomnia	F51.0	Nonorganic insomnia
		G47.0	Disorders of initiating and maintaining sleep [insomnias]
Autonomic nervous system symptoms	Orthostatic hypotension (orthostatic dysregulation)	I95.1	Disorders of autonomic nervous system
	Constipation	K59.0	Constipation
	Nausea/vomiting	R11	Nausea and vomiting
Motor-related symptoms	Limb fracture	S42	Fracture of shoulder and upper arm
		S52	Fracture of forearm
		S62	Fracture at wrist and hand level
		S72	Fracture of femur
		S82	Fracture of lower leg, including ankle
		S92	Fracture of foot, except ankle
		T10	Fracture of upper limb, level unspecified
		T12	Fracture of lower limb, level unspecified
	Aspiration pneumonia	J69.0	Pneumonitis due to food and vomit
Gastric symptoms	Gastric ulcer	K25	Gastric ulcer
	Gastritis	K29	Gastritis and docents
		K31.8	Other specified diseases of stomach and duodenum
		K52.8	Other specified noninfective gastroenteritis and colitis
		K93.8	Disorders of other specified digestive organs in diseases classified elsewhere

ICD-10; International Classification of Disease 10th revision, PD; Parkinson's disease.

excluding those who had not been diagnosed with the ICD-10 code G20, those who had been diagnosed with any of the ICD-10 codes G21 to G23, and those who only had a diagnosis of Parkinson's syndrome.

To identify the persistence period of anti-PD drug, 9157 patients aged 40 years or older and who had been prescribed anti-PD drugs from the same single class without switching to/combination with other classes excepting levodopa were selected. The mean ± SD age of the selected patients was 72.9 ± 10.3 years and 46.3% were male.

The number of patients treated with each anti-PD drug class in the analysis of each PD-relevant symptom is shown in Table 3.

3.2. Association between anti-PD drugs and incidence of PD-relevant symptoms

The hazard ratios for anti-PD drugs in different classes compared with those for zonisamide in PD-relevant symptoms adjusted by age and sex are shown in Table 3.

3.2.1. Mental and psychiatric symptoms

The hazard ratio of dementia was significantly lower in patients treated with zonisamide than COMT inhibitor, anticholinergics, and amantadine (hazard ratios of 4.800, 2.850, and 2.974, respectively, all

$P < .05$) (Fig. 2A). Compared with other classes, zonisamide also tended to show a generally lower hazard ratio of dementia.

The hazard ratio of depression was significantly higher in patients treated with zonisamide than MAO-B inhibitor (hazard ratio: 0.302, $P < .05$). The hazard ratio of insomnia was significantly lower in patients treated with zonisamide than eDAs, anticholinergics, and droxidopa (hazard ratios of 1.619, 2.035, and 1.561, respectively, all $P < .05$) (Fig. 2B).

3.2.2. Other than mental and psychiatric symptoms

Compared with droxidopa, zonisamide had a significantly lower hazard ratio of orthostatic hypotension and constipation, with hazard ratios of 9.854 and 1.501, respectively (both $P < .05$).

The hazard ratio of limb fracture was significantly lower for zonisamide than for anticholinergics (hazard ratio: 2.639, $P < .05$). Compared with other drug classes, zonisamide tended to show a generally lower hazard ratio of limb fracture.

The hazard ratio of aspiration pneumonia was significantly higher for zonisamide than for non-eDAs and MAO-B inhibitor (hazard ratios of 0.350 and 0.388, respectively, both $P < .05$).

The hazard ratio of gastric ulcer significantly lower in patients treated with zonisamide than eDAs, droxidopa, and amantadine
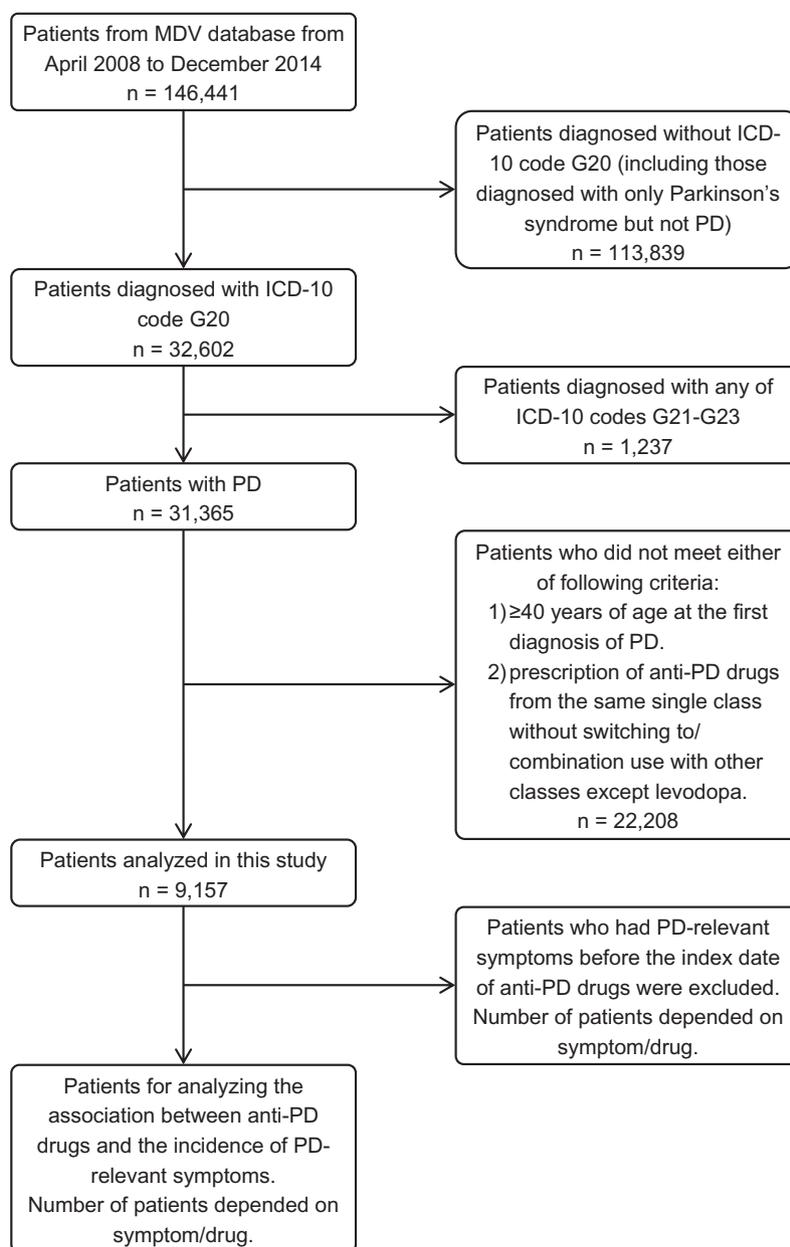
Fig. 1. Flowchart of patient selection.
ICD-10; International Classification of Diseases 10th revision, MDV; Medical Data Vision Co., Ltd., PD; Parkinson's disease.

(hazard ratios of 2.129, 1.881, and 1.691, respectively, all *P* < .05) (Fig. 2C).

4. Discussion

In this study, we performed survival analyses to compare the incidence of PD-relevant symptoms with zonisamide use to other anti-PD drug classes, which are typically used as the second line therapy after levodopa, based on real-world data in Japan. The hazard ratios of dementia, insomnia, and gastric ulcer in PD patients treated with zonisamide were significantly lower than with 3 of 7 other anti-PD drug classes. Zonisamide also showed significant lower risk in the incidence of orthostatic hypotension, constipation, and limb fracture; and higher risk in the incidence of depression and aspiration pneumonia than at least one of the other drug classes. Although we cannot infer causality, we provide some literature reviews of each association in the following discussion.

4.1. Association between anti-PD drugs and incidence of dementia

The hazard ratio of dementia was lower for zonisamide than for other drug classes. Incidence of dementia developed in PD patients was reported 60% to 80% within 12 to 20 years after the first diagnosis of PD [18,19]. Moreover, it preceded death by 3.3 years on average despite of PD duration [20]. Therefore, dementia is considered as a crucial complication in PD.

In the rat medial prefrontal cortex, zonisamide moderately increased dopamine release [21] and the moderate increase of catecholamine such as dopamine and norepinephrine there is likely to be associated with improved cognitive functions [22], suggesting that zonisamide might have a potential for improving cognitive functions. Additionally, several preclinical studies reported that zonisamide might inhibit neurodegeneration [13,14], and a clinical observational study reported that zonisamide could delay presynaptic denervation of the nigrostriatal pathway in patients with relatively early-stage PD [15],

Table 3
Hazard ratios of age, sex, and anti-PD drugs in different classes compared with zonisamide for PD-relevant symptoms.

Hazard ratio (Number of patients in the analysis)

Mental and psychiatric symptoms

	Dementia (n = 8982)		Depression (n = 8698)		Hallucination (n = 9146)		Delusion (n = 9139)		Delirium (n = 9113)		Anxiety neurosis/anxiety/neurosis (n = 8607)		Psychosomatic disease (n = 9099)		Insomnia (n = 8122)	
Age	1.058*		1.003		1.035		0.993		1.062*		0.991*		1.005		1.005	
Female	0.918		1.220*		2.577		1.379		0.637*		1.263*		0.564*		1.038	
Versus zonisamide																
Zonisamide	-	(335)	-	(322)	-	(342)	-	(343)	-	(341)	-	(319)	-	(340)	-	(294)
COMT inhibitor	4.800*	(210)	0.906	(204)	0.000	(211)	0.000	(211)	0.696	(210)	0.969	(204)	1.087	(213)	1.095	(189)
Non-eDAs	1.334	(3671)	0.919	(3509)	0.250	(3716)	0.253	(3716)	0.617	(3704)	0.829	(3465)	0.346	(3699)	1.352	(3261)
eDAs	1.929	(349)	1.281	(340)	0.465	(353)	0.000	(353)	1.200	(351)	0.904	(339)	0.951	(352)	1.619*	(329)
MAO-B inhibitor	2.146	(652)	0.302*	(647)	0.542	(660)	0.000	(660)	0.609	(659)	0.732	(624)	0.310	(658)	0.942	(600)
Anticholinergics	2.850*	(1351)	1.593	(1298)	0.625	(1374)	0.996	(1370)	1.639	(1367)	1.308	(1290)	1.057	(1366)	2.035*	(1220)
Droxidopa	2.204	(720)	1.125	(708)	0.000	(747)	0.000	(746)	0.484	(745)	0.808	(705)	1.487	(740)	1.561*	(654)
Amantadine	2.974*	(1694)	1.092	(1670)	0.000	(1743)	0.314	(1740)	0.531	(1736)	0.835	(1661)	1.637	(1731)	1.347	(1575)

Autonomic nervous system symptoms — **Motor-related symptoms** — **Gastric symptoms**

	Orthostatic hypotension (n = 8916)		Constipation (n = 7600)		Nausea/vomiting (n = 8799)		Limb fracture (n = 8859)		Aspiration pneumonia (n = 8914)		Gastric ulcer (n = 8296)		Gastritis (n = 8086)	
Age	0.997		1.016*		0.973*		1.043*		1.053*		1.010*		1.005	
Female	0.809		0.936		1.512*		2.246*		0.447*		0.906		1.091	
Versus zonisamide														
Zonisamide	-	(336)	-	(263)	-	(328)	-	(333)	-	(326)	-	(306)	-	(285)
COMT inhibitor	1.865	(211)	0.995	(178)	0.477	(200)	1.344	(209)	1.102	(208)	1.575	(193)	0.610	(197)
Non-eDAs	0.895	(3623)	1.110	(3067)	0.814	(3536)	1.217	(3623)	0.350*	(3656)	1.333	(3367)	0.944	(3253)
eDAs	1.851	(353)	1.308	(302)	0.763	(346)	1.491	(345)	0.941	(346)	2.129*	(327)	0.996	(326)
MAO-B inhibitor	1.106	(643)	1.137	(548)	0.716	(626)	1.156	(640)	0.388*	(652)	1.217	(608)	0.881	(598)
Anticholinergics	0.970	(1351)	1.124	(1170)	0.578	(1331)	2.639*	(1320)	0.820	(1349)	1.531	(1257)	0.891	(1229)
Droxidopa	9.854*	(695)	1.501*	(584)	0.891	(726)	1.537	(714)	0.826	(707)	1.881*	(671)	1.031	(633)
Amantadine	1.422	(1704)	1.162	(1488)	0.764	(1706)	1.789	(1675)	1.043	(1670)	1.691	(1567)	0.911	(1565)

COMT; catechol-O-methyltransferase, eDA; ergot-derived dopamine agonist, MAO-B; monoamine oxidase-B, PD; Parkinson's disease.
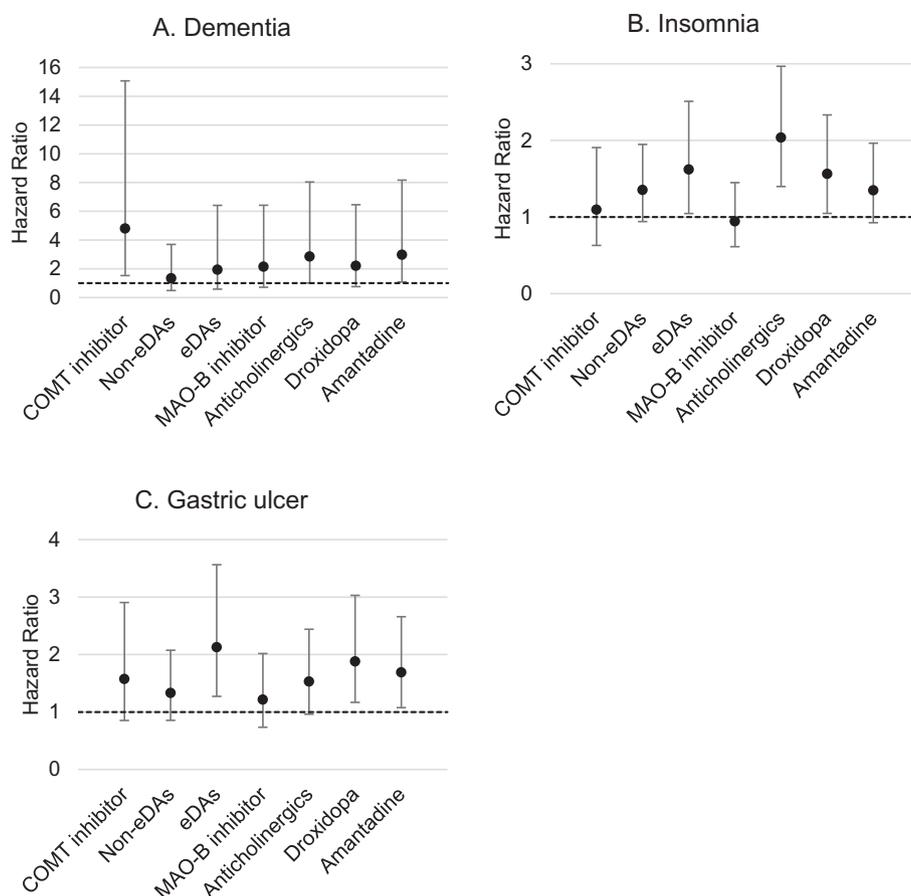* Statistically significant hazard ratios (significance level: 0.05).

Fig. 2. Hazard ratios with 95% confidence intervals of anti-PD drugs in different classes compared with zonisamide for A. dementia, B. insomnia, and C. gastric ulcer. COMT; catechol-*O*-methyltransferase, eDA; ergot-derived dopamine agonist, MAO-B; monoamine oxidase-B, PD; Parkinson's disease.

possibly leading to a delay in progression of cognitive dysfunction. However, there has been no report that zonisamide symptomatically ameliorates or delay cognitive dysfunction in PD patients. On the other hand, cognitive impairment can also develop as a side effect of drugs. Zonisamide did not significantly increase the development of cognitive impairment compared with placebo in clinical trials [8,9], thereby indicating that zonisamide may be related to a reduction in the development of such symptoms more notably than other anti-PD drugs. Also, the observed associations may be explained by the feature of each comparative drug. Anticholinergics are thought to impair cognitive function [23]. COMT inhibitor and amantadine are reported to be beneficial for cognitive function [24–27]; consequently, physicians may tend to prescribe COMT inhibitor and amantadine for patients with a risk of dementia, resulting in a higher hazard ratio.

4.2. Association between anti-PD drugs and incidence of insomnia or gastric ulcer

Zonisamide use was implicated to result in a lower risk of developing insomnia or gastric ulcer than 3 of 7 other anti-PD drug classes.

Insomnia is known as a sleep disturbance in PD patients as well as a side effect of medication [28]. Brunner et al. reported that dopaminergic medication including levodopa and cabergoline increased the number of awakening and duration of stage 1 sleep, by comparing between pre-medication and post-medication in the de novo PD patients [29]. Anticholinergics such as trihexyphenidyl and biperiden decreased REM sleep and/or increase wakefulness in rats [30]. In contrast, zonisamide has both dopaminergic and non-dopaminergic activities [10–14]. Thereby its multi-mechanism of action may result in a lower risk of developing insomnia compared with other drug classes.

With respect to gastric ulcer as well as duodenal ulcer, there was a controversy over their associations with dopamine agonists. Desai et al. reported the opposite ulcerogenic effects by dopamine receptor subtype [31]. Although gastrointestinal ulcer is listed as an adverse effect in labeling information of some dopaminergic medications including levodopa and bromocriptine, no prospective or systematic studies has not been reported about the base frequency and its associations with PD medications. Therefore, this study could provide a new insight on this topic.

4.3. Association between anti-PD drugs and incidence of depression or aspiration pneumonia

In our study, zonisamide use was implicated to result in a higher risk of depression than MAO-B inhibitor use; however, the hazard ratios of depression did not vary much between zonisamide and other anti-PD drug classes excepting the MAO-B inhibitor. Selegiline hydrochloride was the only MAO-B inhibitor approved for PD in Japan during the study period, and has been reported to be associated with clinical antidepressant effects in patients with major depression in a few clinical trials [32,33]. This may explain the lower hazard ratio of the MAO-B inhibitor than zonisamide as well as the other anti-PD drug classes.

Zonisamide use was also implicated to result in a higher risk of aspiration pneumonia than non-eDA or MAO-B inhibitor use. Generally, the incidence of dysphagia increases as PD progresses, possibly resulting in aspiration pneumonia [6,34]. Non-eDAs are recommended as an option for the first-line therapy of PD in the Japanese practice guideline for PD [6], and MAO-B inhibitor is used as a monotherapy agent, resulting in treatment of relatively mild PD. On the other hand, zonisamide was approved as an adjunct to levodopa, and thus it may be

prescribed more often for the advanced PD than non-eDAs or MAO-B inhibitor, resulting in a higher hazard ratio for aspiration pneumonia.

4.4. Association between anti-PD drugs and incidence of orthostatic hypotension

Droxidopa use was found to result in a much higher risk of orthostatic hypotension than zonisamide use. In Japan, droxidopa is also available for treating vertigo, dizziness, and weakness, which are associated with orthostatic hypotension, in hemodialysis patients. Therefore, clinicians may tend to prescribe droxidopa rather than zonisamide and other anti-PD drugs to patients with those symptoms, possibly leading to the diagnosis of orthostatic hypotension.

4.5. Comparison with previous similar studies

No study has reported the association between the use of zonisamide and the incidence of PD-relevant symptoms in comparison with other anti-PD drugs. Nakaoka et al. analyzed claims data that was collected from January 2005 to November 2010 and reported about zonisamide use [35]. However, they mainly reported the prescribing trends of zonisamide as well as other anti-PD drugs. Our study used more recent data from April 2008 to December 2014, and explored the associations between PD-relevant symptoms and the use of zonisamide compared with other anti-PD drugs. As these associations have not been analyzed before, our exploratory study is unique. Notably, a lower risk of PD-related dementia was found to be associated with the use of zonisamide compared with other anti-PD drug classes. This result from a real-world data analysis might contribute to the research and the improvement of PD treatment in the future.

4.6. Limitations

In this study, patients in each group may have different attributes and clinical histories that might influence prescribing patterns and incidence of symptoms. However, the directions of associations were consistently in favor of zonisamide for dementia, insomnia and gastric ulcer (7/7 for dementia, 6/7 for insomnia and 7/7 for gastric ulcer), indicating the unique potential of zonisamide.

The claims data used in this study was collected from DPC hospitals with the limited number (approximately 10% of all hospitals) including relatively large hospitals. However, most PD patients visit those hospitals, which use DPC system, therefore, we assumed that the study population correctly reflects the general PD population in Japan. On the other hand, because of the exploratory nature of our study, we did not correct for multiple testing of hazard ratios. Thus, the statistical significance of hazard ratios was susceptible to alpha error.

We used the records of diagnoses in this database to define PD patients and those who developed PD-relevant symptoms, but did not confirm the accuracy of diagnoses by other sources such as medical records. Therefore, the diagnosed patients may include those who were not actual patients of the disease. These potential wrong diagnoses could affect the accuracy of the results and may cause biases.

5. Conclusions

This study used real-world data from a claims database to analyze the association between the incidence of PD-relevant symptoms and anti-PD drugs. Zonisamide was associated with a lower risk of dementia, insomnia, and gastric ulcer in PD patients compared with 3 of 7 other non-levodopa anti-PD drugs. For these three symptoms, the direction of the hazard ratio was mostly consistent in the remaining 4 classes, and thus may be interesting for further investigations.

Author contributions

All authors had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: HI, MT, and KI.
Critical revision of the manuscript: All authors.
Statistical analysis: KI.
Supervision: KK and MN.

Conflict of interest disclosures

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

HI received a scholarship from the Japanese Society of Clinical Pharmacology and Therapeutics, and the Michael J Fox Foundation.

MT is an employee of Sumitomo Dainippon Pharma Co., Ltd.

KI is an employee of Milliman Inc.

KK received collaborative research funds from Sumitomo Dainippon Pharm Co., Ltd., Novartis Pharma K.K., Bayer Yakuhin, Ltd., Olympus Corporation, Stella Pharma Corporation, CMIC Co., Ltd., and Amgen Astellas BioPharma K.K.; consulting fees from Kaken Pharmaceutical Co., Ltd., and Kyowa Hakko Kirin Co., Ltd.; honoraria from Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Novartis Pharm K.K., Bayer Yakuhin, Ltd., AbbVie GK, Eisai Co., Ltd., and Shionogi & Co., Ltd. There are no patents, products in development, or marketed products to declare, relevant to the listed companies.

MN received honoraria for consulting and/or lecturing from Hisamitsu Pharma Co. Ltd., Kissei Pharma Co. Ltd., Kyowa Hakko Kirin Co., Ltd., and Sumitomo Dainippon Pharma Co., Ltd.

References

[1] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, J. Obeso, K. Marek, I. Litvan, A.E. Lang, G. Halliday, C.G. Goetz, T. Gasser, B. Dubois, P. Chan, B.R. Bloem, C.H. Adler, G. Deuschl, MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (2015) 1591–1599, https://doi.org/10.1002/mds.26424.
[2] C. Pont-Sunyer, A. Hotter, C. Gaig, K. Seppi, Y. Compta, R. Katzenschlager, N. Mas, D. Hofeneder, T. Brücke, A. Bayés, K. Wenzel, J. Infante, H. Zach, W. Pirker, I.J. Posada, R. Álvarez, L. Ispierto, O. De Fàbregues, A. Callén, A. Palasí, M. Aguilar, M.J. Martí, F. Valldeoriola, M. Salamero, W. Poewe, E. Tolosa, The onset of non-motor symptoms in Parkinson's disease (the ONSET PD study), Mov. Disord. 30 (2015) 229–237, https://doi.org/10.1002/mds.26077.
[3] R.F. Pfeiffer, Non-motor symptoms in Parkinson's disease, Parkinsonism Relat. Disord. 22 (2016) S119–S122, https://doi.org/10.1016/j.parkreldis.2015.09.004.
[4] C. Papagno, L. Trojano, Cognitive and behavioral disorders in Parkinson's disease: an update. I: cognitive impairments, Neurol. Sci. 39 (2018) 215–223, https://doi.org/10.1007/s10072-017-3154-8.
[5] L. Trojano, C. Papagno, Cognitive and behavioral disorders in Parkinson's disease: an update. II: behavioral disorders, Neurol. Sci. 39 (2018) 53–61, https://doi.org/10.1007/s10072-017-3155-7.
[6] Japanese Society of Neurology Task Force on Practice Guidelines for Parkinson's Disease, Practice guidelines for Parkinson's disease, Igaku Shoin, Tokyo, (2018), p. 2018.
[7] M. Murata, E. Horiuchi, I. Kanazawa, Zonisamide has beneficial effects on Parkinson's disease patients, Neurosci. Res. 41 (2001) 397–399, https://doi.org/10.1016/S0168-0102(01)00298-X.

[8] M. Murata, K. Hasegawa, I. Kanazawa, The Japan Zonisamide on PD Study Group, Zonisamide improves motor function in Parkinson disease: a randomized, double-blind study, Neurology 68 (2007) 45–50, https://doi.org/10.1212/01.wnl.0000250236.75053.16.

[9] M. Murata, K. Hasegawa, I. Kanazawa, K. Shirakura, K. Kochi, R. Shimazu, The Zonisamide PD Study Group, Randomized placebo-controlled trial of zonisamide in patients with Parkinson's disease, Neurol. Clin. Neurosci. 4 (2016) 10–15, https://doi.org/10.1111/ncn3.12026.

[10] P.K. Sonsalla, L.Y. Wong, B. Winnik, B. Buckley, The antiepileptic drug zonisamide inhibits MAO-B and attenuates MPTP toxicity in mice: clinical relevance, Exp. Neurol. 221 (2010) 329–334, https://doi.org/10.1016/j.expneurol.2009.11.018.

[11] M. Kito, M. Maehara, K. Watanabe, Mechanisms of T-type calcium channel blockade by zonisamide, Seizure 5 (1996) 115–119, https://doi.org/10.1016/S1059-1311(96)80104-X.

[12] M. Okada, S. Kaneko, T. Hirano, K. Mizuno, T. Kondo, K. Otani, Y. Fukushima, Effects of zonisamide on dopaminergic system, Epilepsy Res. 22 (1995) 193–205, https://doi.org/10.1016/0920-1211(95)00078-X.

[13] M. Asanuma, I. Miyazaki, F.J. Diaz-Corrales, N. Kimoto, Y. Kikkawa, M. Takeshima, K. Miyoshi, M. Murata, Neuroprotective effects of zonisamide target astrocyte, Ann. Neurol. 67 (2010) 239–249, https://doi.org/10.1002/ana.21885.

[14] M.E. Choudhury, T. Moritoyo, M. Kubo, W.T. Kyaw, H. Yabe, N. Nishikawa, M. Nagai, S. Matsuda, M. Nomoto, Zonisamide-induced long-lasting recovery of dopaminergic neurons from MPTP-toxicity, Brain Res. 1384 (2011) 170–178, https://doi.org/10.1016/j.brainres.2011.02.017.

[15] K. Ikeda, M. Yanagihashi, K. Miura, Y. Ishikawa, T. Hirayama, T. Takazawa, O. Kano, K. Kawabe, N. Mizumura, Y. Iwasaki, Zonisamide cotreatment delays striatal dopamine transporter reduction in Parkinson disease: a retrospective, observational cohort study, J. Neurol. Sci. 391 (2018) 5–9, https://doi.org/10.1016/j.jns.2018.05.013.

[16] M.S. Wilson, R.L. Findling, Zonisamide for bipolar depression, Expert. Opin. Pharmacother. 8 (2007) 111–113, https://doi.org/10.1517/14656566.8.1.111.

[17] P.E. Bermejo, C. Ruiz-Huete, B. Anciones, Zonisamide in managing impulse control disorders in Parkinson's disease, J. Neurol. 257 (2010) 1682–1685, https://doi.org/10.1007/s00415-010-5603-7.

[18] T.C. Buter, A. van den Hout, F.E. Matthews, J.P. Larsen, C. Brayne, D. Aarsland, Dementia and survival in Parkinson disease: a 12-year population study, Neurology 70 (2008) 1017–1022, https://doi.org/10.1212/01.wnl.0000306632.43729.24.

[19] M.A. Hely, W.G.J. Reid, M.A. Adena, G.M. Halliday, J.G.L. Morris, The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years, Mov. Disord. 23 (2008) 837–844, https://doi.org/10.1002/mds.21956.

[20] P.A. Kempster, S.S. O'Sullivan, J.L. Holton, T. Revesz, A.J. Lees, Relationships between age and late progression of Parkinson's disease: a clinico-pathological study, Brain 133 (2010) 1755–1762, https://doi.org/10.1093/brain/awq059.

[21] J. Ichikawa, J. Dai, H.Y. Meltzer, Lithium differs from anticonvulsant mood stabilizers in prefrontal cortical and accumbal dopamine release: role of 5-HT$_{1A}$ receptor agonism, Brain Res. 1049 (2005) 182–190, https://doi.org/10.1016/j.brainres.2005.05.005.

[22] R.C. Spencer, D.M. Devilbiss, C.W. Berridge, The cognition-enhancing effects of psychostimulants involve direct action in the prefrontal cortex, Biol. Psychiatry 77

[23] R. Katzenschlager, C. Sampaio, J. Costa, A. Lees, Anticholinergics for symptomatic management of Parkinson's disease, Cochrane Database Syst. Rev. 2 (2003) CD003735, https://doi.org/10.1002/14651858.CD003735.

[24] J.A. Apud, V. Mattay, J. Chen, B.S. Kolachana, J.H. Callicott, R. Rasetti, G. Alce, J.E. Iudicello, N. Akbar, M.F. Egan, T.E. Goldberg, D.R. Weinberger, Tolcapone improves cognition and cortical information processing in normal human subjects, Neuropsychopharmacology 32 (2007) 1011–1020, https://doi.org/10.1038/sj.npp.1301227.

[25] P. Roussos, S.G. Giakoumaki, P. Bitsios, Tolcapone effects on gating, working memory, and mood interact with the synonymous catechol-O-methyltransferase rs4818c/g polymorphism, Biol. Psychiatry 66 (2009) 997–1004, https://doi.org/10.1016/j.biopsych.2009.07.008.

[26] F. Bandini, M. Pierantozzi, I. Bodis-Wollner, The visuo-cognitive and motor effect of amantadine in non-Caucasian patients with Parkinson's disease. A clinical and electrophysiological study, J. Neural Transm. 109 (2002) 41–51, https://doi.org/10.1007/s702-002-8235-5.

[27] A. Rajput, Can amantadine therapy delay the onset of dementia in Parkinson's disease? Nat. Clin. Pract. Neurol. 2 (2006) 648–649, https://doi.org/10.1038/ncpneuro0322.

[28] D.O. Claassen, S.J. Kutscher, Sleep disturbances in Parkinson's disease patients and management options, Nat. Sci. Sleep 3 (2011) 125–133, https://doi.org/10.2147/NSS.S18897.

[29] H. Brunner, T.C. Wetter, B. Hoegl, A. Yassouridis, C. Trenkwalder, E. Friess, Microstructure of the non-rapid eye movement sleep electroencephalogram in patients with newly diagnosed Parkinson's disease: effects of dopaminergic treatment, Mov. Disord. 17 (2002) 928–933, https://doi.org/10.1002/mds.10242.

[30] R.K. Zoltoski, J. Velazquez-Moctezuma, P.J. Shiromani, J.C. Gillin, The relative effects of selective M1 muscarinic antagonists on rapid eye movement sleep, Brain Res. 608 (1993) 186–190, https://doi.org/10.1016/0006-8993(93)91457-4.

[31] J.K. Desai, R.K. Goyal, N.S. Parmar, Characterization of dopamine receptor subtypes involved in experimentally induced gastric and duodenal ulcers in rats, J. Pharm. Pharmacol. 51 (1999) 187–192, https://doi.org/10.1211/0022357991772123.

[32] J.D. Amsterdam, J.A. Bodkin, Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial, J. Clin. Psychopharmacol. 26 (2006) 579–586, https://doi.org/10.1097/01.jcp.0000239794.37073.70.

[33] K.C. Lee, J.J. Chen, Transdermal selegiline for the treatment of major depressive disorder, Neuropsychiatr. Dis. Treat. 3 (2007) 527–537.

[34] J.H. Lee, K.W. Lee, S.B. Kim, S.J. Lee, S.M. Chun, S.M. Jung, The functional dysphagia scale is a useful tool for predicting aspiration pneumonia in patients with Parkinson disease, Ann. Rehabil. Med. 40 (2016) 440–446, https://doi.org/10.5535/arm.2016.40.3.440.

[35] 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 (2014) e99021, https://doi.org/10.1371/journal.pone.0099021.