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Antiparkinsonism anticholinergics increase dementia risk in patients with Parkinson's disease

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ABSTRACT

Introduction: Treatment with antiparkinsonism anticholinergics (AAs) has been well-established for patients with Parkinson's disease (PD), especially for tremor. However, concerns regarding the association between anticholinergics and dementia risk are increasing. This retrospective cohort study investigated whether AAs increase the risk of dementia in patients with early-stage PD.

Methods: Data were obtained from the National Health Insurance Research Database of Taiwan. In total, 30,740 patients with newly diagnosed PD were selected and matched based on the propensity score. Patients who were prescribed AAs within the first year of PD diagnosis were further categorized into two groups based on the exposure time, namely ≥6-month and < 6-month exposure groups. Conditional Cox proportional regression analysis was used to examine dementia risk.

Results: Exposure to AAs for ≥6 months conferred a significant increase in dementia risk (adjusted hazard ratio = 1.23, 95% confidence interval: 1.10–1.37). Subgroup analyses indicated that exposure to AAs for ≥6 months positively interacted with the conventional risk factors for dementia, such as age, hypertension, diabetes, and hyperlipidemia, resulting in greater risk of dementia in patients with early-stage PD. A class effect of AAs with other potent anticholinergics was demonstrated on dementia risk; co-exposure did not lead to a further increase in dementia risk.

Conclusions: Greater exposure to AAs increased dementia risk in patients with early-stage PD, which was speculated to result from the class effect of anticholinergics. Although AAs have a therapeutic effect on patients with PD, it should be cautiously prescribed.

1. Introduction

The pathological hallmark of Parkinson's disease (PD) is the loss of dopaminergic neurons, especially in the substantia nigra pars compacta. Resting tremor, rigidity, bradykinesia, and postural instability are the cardinal motor symptoms of PD. Currently, PD management heavily relies on the dopamine replacement strategy for motor symptom attenuation [1]. In addition to dopamine supplements, antiparkinsonism anticholinergics (AAs) are effective in relieving the motor symptoms of PD [2]. Since the 19th century, AAs were prescribed to patients with PD until levodopa was launched [3]. At present, AAs are still recommended for the management of the resting tremor of PD [4].

Apparently, AAs have some side effects. Systemically, they result in dry eye, dry mouth, constipation, and urinary retention; and in the central nervous system, adverse effects include drowsiness, confusion, and hallucination [5]. Furthermore, anticholinergics may worsen cognitive function [6]. Exposure to potent anticholinergics, even at 15–20 years ago was found to be associated with dementia risk [7]. Moreover, cholinesterase inhibitors, which are functionally opposite of anticholinergics, are beneficial in delaying the cognitive decline in patients with dementia [8].

Compared with motor symptoms, patients with PD had numerous non-motor symptoms (NMSs), which greatly affected the quality of life of the patients and their caregivers [9]. Dementia is a prevalent NMS in patients with moderate and advanced PD, which results in more dependency and the requirement of nursing home care [10]. Considering that AAs are one of the mainstream pharmacological treatments of PD, which raise the concern of dementia risk, this study investigated the

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potential risk of dementia by using population-based claims of patients who were prescribed AAs in the early stage of PD.

2. Methods

2.1. Institutional review board

This study was approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB No. 201807044) and the waiver of informed consent was agreed due to study characteristics.

2.2. Data source and study design

This retrospective cohort study was conducted using data from the National Health Insurance Research Database (NHIRD) maintained by the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, Taiwan. The NHIRD is a claims-based database that collects the reimbursement information of beneficiaries under the legislation of Taiwan's National Health Insurance (NHI). NHI covers 99% of residents of Taiwan. NHIRD includes data regarding inpatient, outpatient, and pharmaceutical claims and disease diagnoses coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and tenth version (ICD-10) after 2016. In addition, the enrollment files of beneficiaries and providers were included. Furthermore, NHIRD can be linked to the National Death Registry to obtain death records. The two data sets can be linked according to HWDC regulations.

2.3. Participants

Patients (age ≥ 45 years) with newly diagnosed PD who had at least two diagnostic claims (ICD-9-CM: 332.0) and had prescription claims for dopaminergic agents between 2002 and 2011 were selected. We used a washout window of at least 2 years to ensure that these patients had newly developed PD. The index date of PD was defined as the date of the first PD diagnosis, hereafter referred to as the PD index date. Patients were excluded from the study, if their sex information was missing, they were not citizens of Taiwan, or had a history of hospitalization for stroke or cancer during the study period. Additionally, patients diagnosed with dementia or who had received any antipsychotic drug before the PD index date were excluded. We also excluded patients who died, or developed dementia or mental disorders, which were categorized into Lewy body dementia, within a year after the PD index date. Patients with newly diagnosed PD were further divided into exposure and non-exposure groups based on their AA prescription claims (Anatomical Therapeutic Chemical code, ATC code: N04AA) within a year after the PD index date. Finally, each patient exposed to AAs was matched with 1 non-exposed patient based on the propensity score using a caliper of width equal to 0.2; consequently, both cohorts had similar baseline characteristics, but differed in AA use. In this study, the propensity score was measured on the basis of sex, age, year of PD diagnosis, comorbidities, such as diabetes mellitus (DM), hypertension (HTN), hyperlipidemia (HL), and hospitalization due to PD, which might represent PD severity at initial diagnosis. The selection of these factors was based on the association with dementia and mental disorders. Patients who were prescribed AAs within the first year of PD diagnosis were further categorized into two groups, namely ≥6-month and < 6-month groups, based on prescription duration. The selection process is presented in Fig. 1.

2.4. Study outcome

Patients exposed to AAs as well as those not exposed to AAs were followed up to determine their risk of dementia or mental disorders. Patients with dementia were included if they had a dementia diagnosis. To ensure the validity of diagnoses, they were selected only if they had received any one of the mental function examinations, such as through the Clinical Dementia Rating, Cognitive Abilities Screening Instrument, or Mini-Mental State Examination, within the same visit to confirm the disease diagnosis. A mental problem was defined as a patient having a discharge diagnosis of a mental illness during the follow-up period, from the completion of a 1-year washout period after the PD index to (1) the date of diagnosis of dementia or mental disorders; (2) the date of death; or (3) December 31, 2016 for the patients who did not develop study outcomes.

2.5. Statistical analysis

Baseline characteristics were analyzed using the standardized mean difference (SMD). An SMD of ≥0.1 indicated non-negligible differences between the two groups. Conditional Cox proportional hazard regression was used to evaluate the risk of dementia or mental disorders associated with AAs. We also considered death as a competing risk while examining the risk of dementia or mental problems; however, no significant difference was observed in the risk of death between the two cohorts. Thus, estimation based on the adjusted hazard ratio (aHR) was only reported. Subgroup analyses were also performed to examine the effect of AA on dementia and mental disorders in several specific groups. All analyses were performed using SAS/STAT version 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA 14 (Stata Corp LP, College Station, TX, USA). A p value of < 0.05 was considered statistically significant.

3. Results

Overall, 33,798 patients with newly diagnosed PD were identified in the study cohort; however, 3058 were excluded because of the occurrence of death, dementia or mental disorder within 1 year of PD diagnosis. Among the remaining 30,740 enrollees, 12,477 were exposed to AAs within 1 year after PD diagnosis. Propensity score matching was conducted based on the following demographic data: gender; age; comorbidities, such as DM, diabetic medications, HTN, and HL; and PD-related hospitalization. Finally, 10,967 participants exposed to AAs and an identical number of non-exposed individuals were selected. In the exposure cohort, 4220 (38.5%) were exposed to AAs for ≥6 months within 1 year after PD diagnosis (Table 1).

During the follow-up period, the incidence of mortality was 4.57, 4.33, and 4.59 per 100 person-years for the non-exposed patients, patients with < 6 months of AA exposure, and patients with ≥6 months of AA exposure, respectively. Compared with the non-exposure cohort, the < 6-month exposure group had a significantly lower risk of mortality (aHR = 0.93, 95% confidence interval [CI]: 0.87–0.98). Nevertheless, the ≥6-month exposure group did not have the same benefit (aHR = 1.01, 95% CI: 0.94–1.08). The < 6-month exposure group did not have an increased dementia risk; however, the ≥6-month exposure group was associated with significantly higher dementia risk than their non-exposed counterparts (aHR = 1.23, 95% CI: 1.10–1.32, $p < 0.001$). To prevent the misclassification of dementia with mental disorders, such as depression, anxiety, confusion, or delirium, we also analyzed the association between AA prescription and mental disorder-related disease claims. Compared with the non-exposure group, patients with < 6 months or ≥6 months of AA exposure did not have lower risk of being diagnosed with mental disorders (Table 2).

Subgroup analyses revealed that both men and women from the ≥6-month AA exposure group had significantly higher dementia risk than other groups, namely non-exposure and < 6-month exposure groups. The well-known risk factors for dementia, such as age, HTN, DM, and HL, significantly interacted with the ≥6-month AA exposure to the increased risk of dementia in a positive manner (Fig. 2).

To confirm the effect of AA on the increased dementia risk was a class effect of the anticholinergics, we analyzed the interaction between AA with other well-known medicines with strong anticholinergic

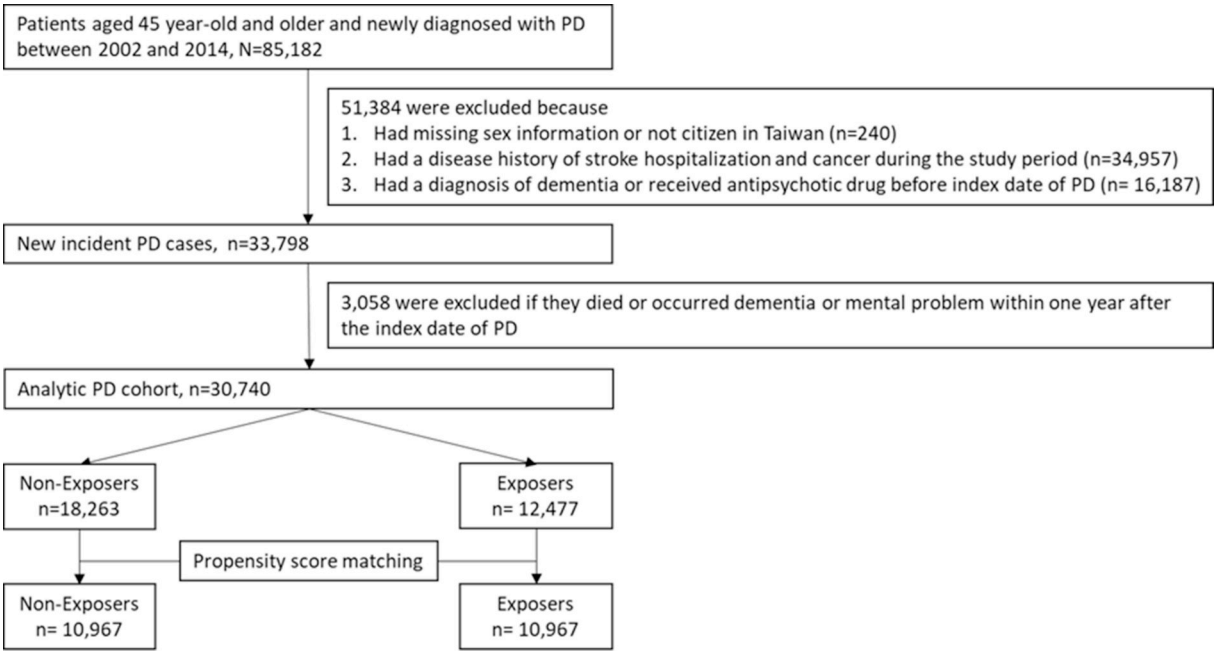

Fig. 1. Selection process of patients with Parkinson's disease (PD).

burdens and greater risk of dementia (such as antidepressants and urological and respiratory medicines identified by Richardson et al. [7]) on the risk of dementia in our study participants. The ≥6-months AA exposure group that was not co-exposed to other potent anticholinergic medicines was associated with a higher dementia risk (aHR = 1.23, 95% CI: 1.05–1.46, p = 0.013). The effect of ≥6-month AA exposure on the increased dementia risk remained for patients who were exposed to those anticholinergics for a short term (< 6 months). However, in patients with PD who were exposed to the defined potent anticholinergics for longer (≥6 months), AAs for ≥6 months were not significantly associated with an increased dementia risk (Table 3). Similarly, the increased dementia risk in patients prescribed with the defined potent anticholinergics for ≥6 months was non-significant once the study participants were co-exposed to AA for ≥6 months (Supplementary Table 1).

Table 1
Basic characteristics of patients who received (exposers) and did not receive AA (non-exposers) before and after PSM.

	Before PSM					After PSM				
	Non-exposers		Exposers			Non-exposers		Exposers		
	n	(%)	n	(%)	SMD	n	(%)	n	(%)	SMD
Sample size, N	18,263		12,477			10,967		10,967		
Days of drug prescription within a year										
≥6 months	–	–	4842	(38.8)		–	–	4220	(38.5)	
< 6 months	–	–	7635	(61.2)		–	–	6747	(61.5)	
Male	9291	(50.9)	5952	(47.7)	0.063	5297	(48.3)	5297	(48.3)	< 0.001
Age (y), [mean, SD]	[70.9, 10.2]		[69.0, 9.8]			[69.4, 9.6]		[69.4, 9.0]		0.001
45–64	4841	(26.5)	4010	(32.1)	0.124	3295	(30.0)	3298	(30.1)	0.001
65–74	5941	(32.5)	4480	(35.9)	0.071	4010	(36.6)	3993	(36.4)	0.003
75 or older	7481	(41.0)	3987	(32.0)	0.188	3662	(33.4)	3676	(33.5)	0.003
Diagnostic year										
2002–2006	4535	(24.8)	4228	(33.9)	0.124	3327	(30.3)	3327	(30.3)	< 0.001
2007–2010	5775	(31.6)	3866	(31.0)	0.071	3495	(31.9)	3495	(31.9)	< 0.001
2011–2014	7953	(43.5)	4383	(35.1)	0.188	4145	(37.8)	4145	(37.8)	< 0.001
Comorbidity, yes										
Diabetes	3761	(20.6)	2360	(18.9)	0.042	1777	(16.2)	1882	(17.2)	0.026
Hypertension	7676	(42.0)	4706	(37.7)	0.088	4175	(38.1)	4153	(37.9)	0.004
Hyperlipidemia	3842	(21.0)	2333	(18.7)	0.059	1884	(17.2)	1879	(17.1)	0.001
Hospitalization due to PD	1368	(7.5)	862	(6.9)	0.023	506	(4.6)	558	(5.1)	0.022
Diabetic medications										
Insulin	518	(2.8)	272	(6.9)	0.042	123	(1.1)	122	(1.1)	0.001
Number of oral drugs										
1	1174	(6.4)	750	(6.0)	0.017	520	(4.7)	575	(5.2)	0.023
2	1340	(7.3)	800	(6.4)	0.037	701	(6.4)	684	(6.2)	0.006
3+	565	(3.1)	380	(3.0)	0.001	278	(2.5)	322	(2.9)	0.026
Follow-up period (y), [mean, SD]	[5.1, 3.2]	[5.9, 3.5]	[5.7, 3.4]	[5.7, 3.4]		[5.1, 3.2]	[5.9, 3.4]	[5.7, 3.4]	[5.7, 3.4]	

Abbreviations: AA, antiparkinsonism anticholinergics; PD, Parkinson disease; PSM, propensity score matching; SMD, standardized mean difference.
SMD > 0.1 indicates the presence of non-negligible differences between the two groups.

Table 2
Incidence (per 100 PY) and adjusted HR of death, dementia, and mental disorders in patients with PD who were exposed to AAs for different periods.

Events	Exposure to AAs	PY	No. of events	Incidence	(95% CI)	Adjusted*HR	(95% CI)	*P* value	*P* for trend
Death									
	Non-exposers	61,992	2831	4.57	(4.60–4.98)	1.00	(Ref.)		0.319
	Exposers < 6 months	37,354	1619	4.33	(4.23–4.70)	0.93	(0.87–0.98)	0.013	
	Exposers ≥6 months	25,451	1167	4.59	(4.35–4.93)	1.01	(0.94–1.08)	0.751	
Dementia									
	Non-exposers	55,612	1967	3.54	(3.50–3.85)	1.00	(Ref.)		0.002
	Exposers < 6 months	33,355	1238	3.71	(3.64–4.10)	1.00	(0.91–1.10)	0.981	
	Exposers ≥6 months	22,165	942	4.25	(4.07–4.67)	1.23	(1.10–1.37)	< 0.001	
Mental disorders									
	Non-exposers	59,476	897	1.51	(1.45–1.68)	1.00	(Ref.)		0.305
	Exposers < 6 months	35,881	533	1.49	(1.38–1.66)	0.99	(0.86–1.13)	0.861	
	Exposers ≥6 months	24,098	420	1.74	(1.59–1.96)	1.11	(0.95–1.30)	0.200	

*Adjusted the variables list in Table 1.
Abbreviation: AA, antiparkinsonism anticholinergics; CI, confidence interval; HR, hazard ratio; PD, Parkinson disease; PY, person-years; No., number.

4. Discussion

The present study demonstrated that greater exposure to AAs within the first year after PD diagnosis was associated with higher dementia risk afterwards. This increased risk positively interacted with other conventional risk factors for dementia. A class effect of anticholinergics on the risk of dementia in patients with PD was also demonstrated, which may indicate a deleterious effect of AA from the anticholinergic capability. This study presents a population-based real-world data of the cholinergic burden on cognitive function in patients with early-stage PD, who are prescribed with AAs for the management of their motor symptoms.

In the basal ganglia neuronal circuit, the cholinergic neuron serves as the interneuron. Cholinergic projection modulates neuronal activity in the substantia nigra and subthalamic nucleus [11]. AAs have been prescribed to patients with PD for hundreds of years. In the 19th century, Ordenstein had mentioned in his medical thesis regarding treatment of PD tremor with belladonna alkaloids, which are centrally acting AAs [3]. Although AAs have certain adverse effects, they are genuine effective drugs for alleviating the resting tremor in patients with PD. In recent treatment guidelines for PD, administration of AAs has been retained in the recommended treatments, with some warnings for elderly patients [12,13].

In the era of superior management of PD motor symptoms with levodopa, dementia poses a new threat to patients with moderate and advanced disease stages. PD-related dementia results from either the progression of Lewy body pathology to the cortex or the mixture of Alzheimer's disease (AD) pathology, such as amyloid plaque or neurofibrillary tangle, which leads to the loss of not only dopaminergic but also serotonergic and cholinergic neurons. Cholinergic activity enhances attentional processes and cerebral perfusion [6], and anticholinergics impair various cognitive domains such as memory [14] and language [15]. Moreover, anticholinergics have been associated with a reduction in glucose metabolism and increased brain atrophy [16]. Dysfunctional limbic–paralimbic and salience cholinergic networks have been associated with PD dementia [17], and one of the AAs, trihexyphenidyl was found to cause reduction of cortical and striatal cerebral blood flow and the oxygen metabolic rate that mimicked PD dementia [18]. Currently, PD-related dementia is managed with rivastigmine, a cholinesterase inhibitor. All the aforementioned evidence further raise concerns regarding the possibility of administration of AA for motor symptoms, which may increase the risk of PD-related dementia afterwards. Studies have reported that patients with PD who were prescribed antimuscarinic medication for a long term had a 2.5-fold increased risk of having AD pathology [19]. Medications with a high cholinergic burden, such as those for urinary diseases, depression, and PD, increase dementia risk [7]. The present study focused on patients with PD who were prescribed AAs and had revealed a similar finding. AA prescription for PD management in the first year after diagnosis, especially for a longer duration (≥6 months), conferred an increased dementia risk in patients during the follow-up period. The deleterious effect was non-significant only if there was co-exposure to other potent anticholinergics at a considerable concentration for a longer duration (≥6 months). Small number of study participants for this dual long duration (≥6 months) co-exposure analysis may account for loss of statistical significance. However, this finding may support a

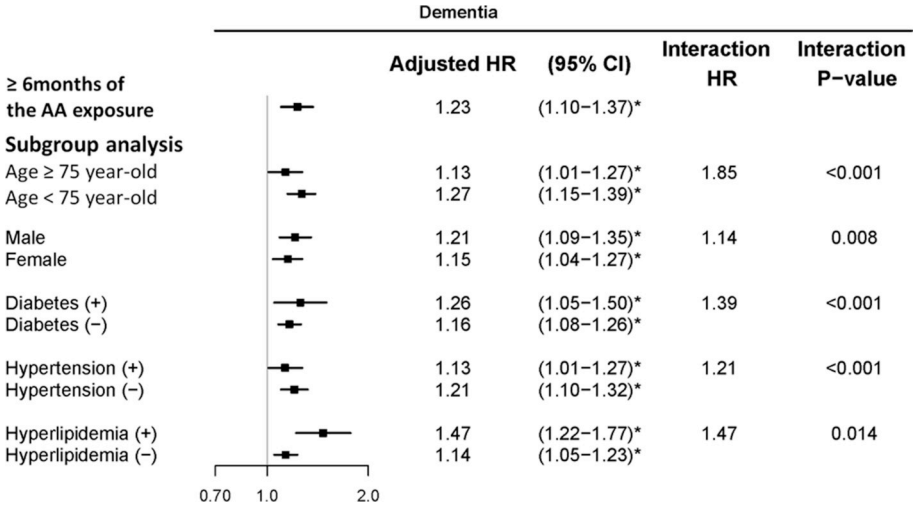

Fig. 2. Comparison of subgroup and interaction analyses of the hazard ratio (HR) of dementia of the ≥6-month antiparkinsonism anticholinergic (AA) exposure group with other groups (non-exposure and < 6-months of exposure). Abbreviation: AA = antiparkinsonism anticholinergic, HR = hazard ratio, PD = Parkinson's disease.

Table 3
Incidence (per 100 PY) and adjusted HR of dementia in people with PD who were not exposed and exposed to AA and other potent anticholinergics.

Exposure to potent anticholinergics	Exposure to AAs	No. of patients	PY	No. of events	Incidence	(95% CI)	Adjusted*HR	(95% CI)	*P* value	*P* for trend
Non-exposers	**Non-exposers**	7137	36,548	1228	3.36	(3.17–3.55)	1.00	(Ref.)		0.164
	Exposers < 6 months	4305	21,397	759	3.55	(3.30–3.81)	0.89	(0.77–1.03)	0.119	
	Exposers ≥6 months	2930	15,633	636	4.07	(3.76–4.40)	1.23	(1.05–1.46)	0.013	
Exposers < 6 months	**Non-exposers**	3389	16,955	638	3.76	(3.48–4.07)	1.00	(Ref.)		0.031
	Exposers < 6 months	2185	10,754	423	3.93	(3.57–4.33)	1.10	(0.84–1.45)	0.486	
	Exposers ≥6 months	1133	5814	267	4.59	(4.06–5.18)	1.50	(1.03–2.18)	0.033	
Exposers ≥6 months	**Non-exposers**	441	2109	101	4.79	(3.90–5.82)	1.00	(Ref.)		0.764
	Exposers < 6 months	257	1204	56	4.65	(3.51–6.04)	0.97	(0.70–1.35)	0.864	
	Exposers ≥6 months	157	718	39	5.43	(3.86–7.43)	1.25	(0.86–1.82)	0.250	

*Adjusted the variables list in Table 1.
Abbreviation: AA, antiparkinsonism anticholinergics; CI, confidence interval; HR, hazard ratio; PD, Parkinson disease; PY, person-years; No., number.

class effect of anticholinergics on dementia risk, where simultaneous long-term prescription of more than one medication with an anticholinergic effect may cause saturation of cholinergic antagonization in the brain. Therefore, to preserve the cognition of patients with PD, neurologists should prescribe AAs more cautiously as well as review the exposure of other possible detrimental medications with a strong anticholinergic effect.

The strength of this study is that it presents a large-scale real-world evidence of the association between AA prescription and dementia risk in patients with early-stage PD. A previous small-scale case-controlled study claimed that AAs were associated with PD dementia [20]; however, the strength of the evidence provided was not sufficient to alter the prescription pattern of neurologists. Moreover, the present study focused on investigation of dementia risk in patients early-stage PD who were prescribed AAs, which is more relevant in the management of patients with PD, rather than the elderly patients or patients with PD who were prescribed AAs for other health conditions. In addition, the separation of < 6-month- and ≥6-month exposure groups in the present study provided a possible cause–consequence relationship in a dose-dependent manner; only significant exposure was associated with an increased dementia risk in patients with PD. Finally, the increase in risk was moderate; however, a 20% higher risk of dementia is still crucial and remarkable. For example, it is expected that elimination of apolipoprotein E (ε4 allele), which is the most widely acknowledged genetic risk factor for dementia, could decrease the incidence of dementia by 7% [21]. Lastly, alternatives for managing the resting tremor in patients with PD exist, including zonisamide [22], deep brain stimulation [23], and magnetic resonance-guided focused ultrasound surgery [24], which can replace AAs and further avoid dementia risk.

This study has some limitations due to the type of health care research databases and the lack of information regarding the motor phenotype of PD, which is associated with treatment choice and prognosis. AAs are mainly prescribed for patients with tremor-dominant (TD) PD, which is characterized by late onset, slow progression, and a benign disease course [25]. The present study identified a lower mortality rate during the follow-up period for patients who were prescribed AAs, which indicated that those exposed to AA were likely to be of the TD subtype. Considering that TD is the most benign form of PD, increased risk of dementia is more likely to stem from the prescription of AAs. Regarding dementia, the present study utilized the propensity score to match the age, gender, and comorbidities of both patient groups, which were the crucial risk factors present in the database. However, some of the essential factors, such as obesity, life style, genetic profile, and details of the cognitive examinations, which could further identify the patients with mild cognitive impairment, were missing. However, all participants were followed from the first PD diagnosis, which lessened the discrepancy in disease severity. The other shortcoming was the lack of chronological medical histories. Patients with PD may discontinue or resume treatment with AAs during the disease course. Therefore, analyzing the accumulative dosage of AAs to address this concern may be possible in a case–control study; however, this was a cohort study. Finally, the disease-claim healthcare database cannot provide a direct causal relationship between PD and dementia. Nevertheless, the present study excluded patients with any events of stroke or malignancy during the entire study period, which only eliminated most of the secondary causes of dementia (vascular or systemic illness-related dementia).

In conclusion, the present study revealed that patients with newly diagnosed PD have an increased risk of dementia at a later stage in life due to the administration of higher quantities of AAs. Therefore, AAs should be prescribed more cautiously and alternative treatments for PD tremor management should be considered.

Conflicts of interest

The authors have no conflicts of interest.

Disclosure

None to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.06.022.

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