PHARMACOTHERAPY

ORIGINAL RESEARCH ARTICLES

Association between Anticholinergic Medication Use and Risk of Dementia among Patients with Parkinson's Disease

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Study Objectives To evaluate the association between anticholinergic medication use, categorized by anticholinergic cognitive burden (primary objective) and cumulative dose (secondary objective), and the risk of developing dementia among patients with Parkinson's disease.

Design Retrospective cohort study with an active comparator design.

Data Source National Health Insurance Research Database in Taiwan (2001–2011).

Patients A total of 1232 adults with Parkinson's disease who were diagnosed between 2002 and 2004 and taking at least one antiparkinson medication during this period were included. Of these patients, 694 were exposed to anticholinergic medications categorized as mild (reference group), and 538 were exposed to anticholinergic medications categorized as moderate or severe (exposure group).

Measurements and Main Results Exposure to different types of anticholinergic medications was categorized by using the Anticholinergic Cognitive Burden (ACB) scale, and cumulative doses of anticholinergic medications were measured by using the cumulative minimum doses (cMD) method. Associations between anticholinergic medication use and risk of dementia were assessed by multivariable Cox proportional hazards models. The type of anticholinergics used (moderate or severe vs mild ACB) was not significantly associated with an increased risk of developing dementia (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.72–1.27). After adjusting for confounders, a high cumulative dose of anticholinergic drug (> 1095 cumulative minimum doses [cMDs]) was found to be significantly associated with an increased risk of developing dementia when compared with a low cumulative dose of anticholinergic drug (≤ 90 cMDs) (HR 3.06, 95% CI 1.35–6.97).

Conclusion Among patients with Parkinson's disease in Taiwan, those with a high cumulative dose of anticholinergics had an increased risk of being diagnosed with dementia. Physicians should consider

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prescribing the lowest therapeutic dose of anticholinergic medication when making treatment decisions for patients with Parkinson's disease.

KEY WORDS Parkinson's disease, anticholinergic drugs, dementia, dose, National Health Insurance Research Database.

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Dementia is a debilitating condition that greatly impairs physical and mental function among the aging population.[1, 2] Patients with Parkinson's disease are more likely to develop dementia when compared to healthy individuals.[3, 4] Previous studies have reported that cognitive decline is common among patients with Parkinson's disease.[5, 6] In the early stage of Parkinson's disease, the prevalence of mild cognitive decline can reach 25%.[3, 4] About 40% of patients in the late stage of Parkinson's disease will eventually develop dementia.[3]

In addition to levodopa, patients with Parkinson's disease are often prescribed anticholinergic medication for the treatment of motor symptoms.[7, 8] Despite commonly reported adverse effects, anticholinergics, which act on postsynaptic receptors for neurotransmitters in the striatum that affect motor activity, are usually considered first-line treatment for patients with severe tremor when compared to other drug classes such as dopamine agonists, amantadine, monoamine oxidase type B inhibitors, and catechol-*O*-methyltransferase inhibitors.[7] In addition, anticholinergics are commonly prescribed to treat symptoms of urinary dysfunction such as overactive bladder, which often occurs in the late stage of the disease.[9, 10] As a result of exposure to anticholinergics, patients often experience discomfort from adverse effects such as drowsiness, sedation, or a decline in cognitive function.[7, 8]

Previous studies have shown a link between anticholinergic medication use and an increased risk of cognitive impairment.[11–13] Although cognitive decline induced by anticholinergics was often considered to be short term and reversible, recent studies have raised the concern about the potential link between anticholinergic medication use and an increased risk of a long-term cognitive decline such as dementia.[13–15] For example, a recent case-control study conducted in the United Kingdom found an association between anticholinergic use and the risk of dementia among older adults.[15]

Whether taking anticholinergic drug use is associated with long-term and irreversible cognitive impairment such as dementia among patients with Parkinson's disease remains unknown. Previous studies have shown that older people taking high cumulative doses of anticholinergics have an increased risk of dementia.[13, 16, 17] However, the association between the dosage prescribed and development of dementia in patients with Parkinson's disease remains unclear. The fact that dementia is prevalent among patients with Parkinson's disease and the use of anticholinergics is common, further investigation to evaluate the association between anticholinergic medication use and the risk of dementia is necessary.

Therefore, the purpose of this study was to evaluate the association between anticholinergic medication use and the risk of dementia among patients with Parkinson's disease. The primary aim was to evaluate the association between the type of anticholinergics prescribed and the risk of dementia. The type of anticholinergics prescribed was categorized by the burden of the anticholinergic effect of each drug. We hypothesized that among patients with Parkinson's disease, taking a drug with a high burden of the anticholinergic effect would be associated with an increased risk of dementia compared to taking a drug with a low burden of the anticholinergic effect. The secondary aim was to evaluate the association between the cumulative dose effect of anticholinergics and the risk of dementia. We hypothesized that a high cumulative dose of anticholinergic drug use would be associated with an increased risk of dementia compared to a low cumulative dose of anticholinergic drug use.

Methods

Data Source

This study was conducted using the National Health Insurance Research Database (NHIRD), which is maintained by the Bureau of National Health Insurance of Taiwan and managed by the National Health Research Institute (NHRI).[18] Since 1995, a single-payer National Health

Insurance (NHI) program has been implemented in Taiwan, and up to 99.9% of 23 million Taiwanese residents are enrolled.[19] In the NHI program, health records of all beneficiaries are recorded in the NHIRD, which is a de-identified, administrative claims database that contains beneficiaries' demographics, diagnosis, inpatient and outpatient procedures, ambulatory care records, prescription drugs, and enrollment information.[18]

This study was conducted using three cohorts (2000, 2005, 2010) of the Longitudinal Health Insurance Database (LHID), providing an 11-year observation period from January 1, 2001, to December 31, 2011. Each cohort consists of 1 million Taiwanese beneficiaries randomly selected from the NHIRD.[19] For example, all of the claims data of the 1 million beneficiaries drawn in 2010 were extracted and obtained from NHIRD from 2001 to 2011. In the end, all claims data of the 3 million beneficiaries were obtained for up to 11 years.

Study Design and Patient Population

This is a retrospective cohort study. The study population consisted of patients with Parkinson's disease. Patients were eligible to be included in the study if they were aged 18 years or older between January 1, 2002, and December 31, 2004 (the enrollment period), and had at least two outpatient visits or one inpatient visit during which they were diagnosed with Parkinson's disease. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code was used to identify the study population. Patients were included if the first three digits of the ICD-9-CM code was 332 (Parkinson's disease). The disease was required to be diagnosed by a neurologist to increase validity. To further ensure the validity of the diagnosis, all patients with Parkinson's disease were required to be taking at least one antiparkinson medication during the enrollment period.

The Anticholinergic Cognitive Burden (ACB) scale[20, 21] was used to identify all anticholinergic medications assessed in this study. The name of each drug on the ACB scale is provided in Table 1. The ACB Scale categorizes each drug into one of three groups: mild, moderate, or severe based on the anticholinergic activity associated with negative cognitive effects including delirium, mild cognitive impairment, dementia, or cognitive decline.[20, 21] For example, drugs with possible anticholinergic effects but without clinically relevant negative cognitive effects are labeled as mild. In contrast, drugs with clinically relevant cognitive anticholinergic effects, with development of delirium, and could pass the blood-brain barrier are labeled as moderate or severe.[20] We chose to use the ACB scale because it is the most frequently used, validated, expert-based anticholinergic scale for assessing negative cognitive effects.[22]

The new drug user design for the use of anticholinergics was implemented in this study. The date of the first anticholinergic medication observed during the enrollment period was defined as the index date. To identify patients who were new users of anticholinergic medication treatment, we excluded patients receiving any anticholinergic medication treatment within

Table 1. Anticholinergic Cognitive Burden Scale Scoring of Drugs

Score 1 (Mild)	Score 2 (Moderate)	Score 3 (Severe)
Alprazolam	Amantadine	Amitriptyline
Atenolol	Belladonna alkaloids	Amoxapine
Brompheniramine maleate	Carbamazepine	Benztropine
Bupropion hydrochloride	Cyclobenzaprine	Carbinoxamine
Captopril	Cyproheptadine	Chlorpheniramine
Chlorthalidone	Loxapine	Clemastine
Cimetidine hydrochloride	Meperidine	Clomipramine
Clorazepate	Methotrimeprazine	Clozapine
Codeine	Molindone	Darifenacin
Colchicine	Oxcarbazepine	Desipramine
Diazepam	Pimozide	Dicyclomine
Digoxin		Dimenhydrinate
Dipyridamole		Diphenhydramine
Disopyramide phosphate		Doxepin
Fentanyl		Flavoxate
Isosorbide		Hydroxyzine
Loperamide		Imipramine
Metoprolol		Meclizine
Morphine		Nortriptyline
Nifedipine		Olanzapine
Prednisone		Orphenadrine
Quinidine		Oxybutynin
Risperidone		Paroxetine
Theophylline		Perphenazine
Trazodone		Procyclidine
Triamterene		Promethazine
		Quetiapine
		Scopolamine
		Thioridazine
		Tolterodine
		Trifluoperazine
		Trihexyphenidyl
		Trimipramine

From Reference.[20]

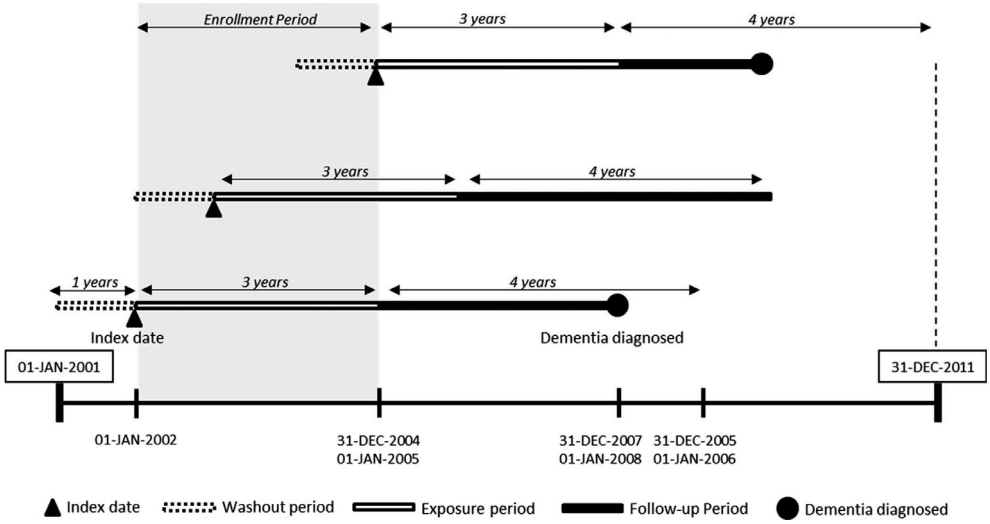

Figure 1. The design of the study. Overall study period: 2001/1/1–2011/12/31; Enrollment period: 2002/1/1–2004/12/31; Index date: the first date of the anticholinergic medication use; Washout period: pre-index date (1-year). Exposure: 3-years after each index date, calculating cMD, the latest one: 2005/1/1–2007/12/31; Follow up periods: 4-years, the latest one: 2008/1/1–2011/12/31.

1 year (i.e., the pre-index period) before the index date. Figure 1 shows the definitions of each phase during the study period.

We excluded patients if they had ever used cholinesterase inhibitors or *N*-methyl-D-aspartate (NMDA) receptor antagonists (donepezil, rivastigmine, galantamine, and memantine) during the 1-year pre-index period. Cholinesterase inhibitors or NMDA receptor antagonists are often used to manage dementia-related symptoms or slow the development of symptoms.[23] Patients were also excluded if they received multiple anticholinergic medications on the index date. In addition, patients were excluded if they were diagnosed with dementia (ICD-9-CM codes 290.0–290.4, 294.1, 331.0–331.2) and other cerebral degeneration conditions (ICD-9-CM codes 331.8–331.9), Huntington's disease (ICD-9-CM code 333.4), or Creutzfeldt–Jakob disease (ICD-9-CM codes 046.11, 046.19) during the 1-year pre-index period. These diseases are believed to have a link with dementia.[23] Finally, patients who received treatment for all types of dementia on the index date were also excluded. Appendix shows the inclusion and exclusion criteria for the study.

Anticholinergic Exposure

An active comparator pharmacoepidemiology design was conducted in this study.[24] Patients in both the exposure group (defined later) and the reference group (defined below) were anticholinergic medication users. Patients not taking anticholinergics were excluded for two reasons. First, a nonuser comparison group may introduce bias from confounding by indication.[25, 26] An active comparator design increases the similarity in patient characteristics and treatment indications between the exposure and reference groups.[25, 26] Second, most patients with Parkinson's disease are likely to be prescribed anticholinergics. Given that non-anticholinergic medication users would have constituted only 0.3% of the population in our study, we decided to exclude anticholinergic nonusers and adopted the active comparator design to better evaluate the association between anticholinergics and dementia.

To address the primary objective, we evaluated the association between type of anticholinergic, categorized by the burden of the anticholinergic effect (ACB scale), and risk of dementia. The exposure group consisted of patients who were prescribed anticholinergic medications categorized as moderate or severe on the ACB scale on the index date. In contrast, the reference group consisted of patients those who were prescribed anticholinergic medications categorized as mild on the ACB scale. We designed the analysis plan for this objective similar to the strategy of an intention-to-treat analysis in a randomized controlled trial and did not further identify patients who discontinued

anticholinergic use or switched to different anticholinergic drugs.

To address the secondary objective, we evaluated the association between the cumulative dose effect of anticholinergics and the risk of dementia. Cumulative minimum dose (cMD) was used to define exposure. We measured the minimum dose (MD) during the 3-year exposure period based on the recommended MD of each anticholinergic drug listed on the ACB scale.[20, 21] We adopted the defined daily dose (DDD) recommended by World Health Organization to calculate the cMD of each drug.[27] The use of DDD, which measures the average drug consumption per day to maintain effectiveness, allowed us to sum the total MDs for all anticholinergics that each patient used during the 3-year exposure period after the index date. Finally, we calculated cMDs for each user and categorized the cMDs into five groups: ≤ 90 (reference group), 91–365, 366–730, 731–1095 and > 1095.

Study Outcomes

The outcome was occurrence of dementia, which was defined as the time to the first diagnosis of dementia (ICD-9-CM codes 290.0–290.4, 294.1, 331.0–331.2). The occurrence of dementia was measured from the end of the 1-year induction period in the primary objective and was measured from the end of the 3-year exposure period in the secondary objective, respectively, to the date of the dementia diagnosis or to the date of censoring. The induction period was required to avoid bias from reverse causation[28] and ensure that the occurrence of dementia was after exposure to anticholinergics because dementia is a disease with a gradual decline in cognitive function. Patients were censored at the earliest date of insurance withdrawal, death, or the end of the 4-year follow-up period.

Covariates

Covariates—including patient characteristics, condition-related factors, and medication-related factors—were considered to be potential confounders in the study, and they were measured in the 1-year pre-index period. Covariates were selected based on clinical knowledge from prior studies.[13, 21, 29–31] Patient characteristics included age and sex. Condition-related factors included duration of Parkinson's disease before the index date, hypertension, stroke, hypercholesterolemia, diabetes mellitus, depression, anxiety, psychotic-related disorder, alcohol-related disorder, sleep disorder, and head injury. Concomitant medication-related factors included drug classes of antihypertensive drugs, antidiabetic drugs, anticoagulants, antihyperlipidemic drugs, antidepressants, benzodiazepines, and antipsychotics. Patients were identified whether they had ever used the above medications during the pre-index period.

Statistical Analysis

For both study objectives, χ^2 tests were used to compare patient characteristics between groups. Adjusted multivariable logistic regression models were used to evaluate the association between anticholinergic medication use and the risk of dementia. Multivariable Cox proportional hazards models were used to estimate the relative hazards of developing dementia, comparing patients with each cMD to the reference group. SAS proprietary software, release 9.4 (SAS institute Inc., Cary, NC) was used for all analyses in this study. A two-sided p value ($p<0.05$) was used to determine statistical significance. This study was reviewed and obtained an exemption from the Taipei Medical University Joint Institutional Review Board.

Results

Table 2 shows the baseline characteristics of the study population. Of the three million beneficiaries who were initially examined, 1232 individuals with Parkinson's disease who met the inclusion/exclusion criteria were identified. The 1232 patients were all new anticholinergic medication users, of whom 538 (43.7%) were in the exposure group (those who used anticholinergics that were categorized as moderate or severe on the ACB scale). Compared to patients in the reference group (those who used anticholinergics categorized as mild on the ACB scale), patients in the exposure group were less likely to have hypertension (15.1% vs 23.5%, $p<0.01$), stroke (6.7% vs 11.7%, $p<0.01$), and hypercholesterolemia (7.1% vs 10.5%, $p<0.05$).

Table 3 shows the results of the multivariable logistic regression model and Cox proportional hazards model. About 17.7% of patients taking anticholinergics with moderate or severe anticholinergic effects developed dementia. After adjustment for confounders, the type of anticholinergics used was not significantly associated with a higher likelihood or risk of developing

Table 2. Baseline Characteristics of the Study Population

	Anticholinergic Medication Use						
	Overall		ACB Scale Class: Mild (Reference Group)		ACB Scale Class: Moderate Or Severe (Exposure Group)		
	(n=1232)		(n=694 [56.3%])		(n=538 [43.7%])		
Variables	No.	%	No.	%	No.	%	p Value
Characteristics							
Age (yrs)							
< 40	134	10.9	73	10.5	61	11.3	0.18
40–49	88	7.1	40	5.8	48	8.9	
50–59	157	12.7	86	12.4	71	13.2	
60–69	264	21.4	148	21.3	116	21.6	
70–79	424	33.4	243	35.0	181	33.6	
≥ 80	165	13.4	104	15.0	61	11.3	
Sex							
Male	688	55.8	397	57.2	291	54.1	0.26
Female	544	44.2	297	42.8	247	45.9	
Duration of Parkinson's disease (yrs)							
0 to < 1	1084	88.0	602	86.7	484	90.0	0.08
1–4	148	12.0	92	13.3	54	10.0	
Conditions							
Hypertension	244	19.8	163	23.5	81	15.1	< 0.01
Stroke	117	9.5	81	11.7	36	6.7	< 0.01
Hypercholesterolemia	111	9.0	73	10.5	38	7.1	< 0.05
Diabetes mellitus	161	13.1	83	12.0	78	14.5	0.19
Depression	38	3.1	21	3.0	17	3.2	0.89
Anxiety	128	10.4	81	11.7	47	8.7	0.09
Psychotic-related disorder	43	3.5	19	2.7	24	4.5	0.11
Alcohol-related disorder	7	0.6	5	0.7	2	0.4	0.40
Sleep disorder	109	8.6	52	7.5	57	10.6	0.06
Head injury	25	2.0	17	2.4	8	1.5	0.22
Medications							
Antihypertensives	120	9.7	74	10.7	46	8.6	0.21
Antidiabetics	44	3.6	23	3.3	21	3.9	0.58
Anticoagulants	45	3.7	30	4.3	15	2.8	0.14
Antihyperlipidemic drugs	17	1.4	10	1.4	7	1.3	0.83
Antidepressants	9	0.7	5	0.7	4	0.7	0.96
Benzodiazepines	92	7.5	61	8.8	31	5.8	< 0.05
Antipsychotics	43	3.5	24	3.5	19	3.5	0.94

ACB = Anticholinergic Cognitive Burden.

dementia (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.71–1.31; hazard ratio [HR] 0.97, 95% CI 0.72–1.27).

Table 4 shows the association between the risk of developing dementia and the cumulative dose effect of anticholinergic drugs among patients with Parkinson's disease. A significant association with an increased occurrence of dementia was identified in both the logistic regression model and Cox proportional hazards model. Among patients with Parkinson's disease, use of a high cumulative dose of anticholinergic drug was significantly associated with a higher risk of developing dementia when compared to use of a low cumulative dose of anticholinergic drug (731–1095 cMD group: OR 2.75 [95% CI 1.02–7.41], HR 2.50 [95% CI 1.01–6.22]; > 1095 cMD group: OR 3.33 [95% CI 1.38–8.05], HR 3.06 [95% CI 1.35–6.97]).

Discussion

To our knowledge, this is the first large population-based study to investigate the association between anticholinergic drug use and risk of developing dementia among patients with Parkinson's disease. In this retrospective cohort study of Taiwanese adults with Parkinson's diseases, although the type of the anticholinergics, which were classified by the burden of the anticholinergic effect, was not consistently associated with the risk of developing dementia, the cumulative dose effect of anticholinergic drugs was significantly associated with an increased

Table 3. Association between Risk of Developing Dementia and Anticholinergic Medication Use: Results of the Adjusted Multivariable Logistic Regression Model and Cox Proportional Hazards Model[a]

Variables	Patients Who Developed Dementia		Logistic Regression Model Odds Ratio (95% CI)	Cox Proportional Hazards Model Hazard Ratio (95% CI)
	No.	%		
Anticholinergic medication use: ACB scale class				
Moderate or severe	95	17.7	0.96 (0.71–1.31)	0.97 (0.72–1.27)
Mild	135	19.5	Reference	Reference

CI = confidence interval; ACB = Anticholinergic Cognitive Burden.
[a]Adjusted variables including age, sex, duration of Parkinson's disease before index date, conditions (hypertension, stroke, hypercholesterolemia, diabetes mellitus, depression, anxiety, psychotic-related disorder, alcohol-related disorder, sleep disorder, and head injury), and medications (antihypertensives, antidiabetics, anticoagulants, antihyperlipidemic drugs, antidepressants, benzodiazepines, and antipsychotics).

Table 4. Association between Risk of Developing Dementia and Cumulative Dose Effect of Anticholinergic Drugs among Patients with Parkinson's Disease: Results of the Adjusted Multivariable Logistic Regression Model and Cox Proportional Hazards Model[a]

Variable	Patients Who Developed Dementia		Logistic Regression Model		Cox Proportional Hazards Model	
	No.	%	Odds Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Cumulative minimum doses						
≤ 90	26	13.5	Reference		Reference	
91–365	60	16.7	1.35 (0.48–3.78)	0.57	1.34 (0.51–3.49)	0.55
366–730	55	24.1	2.37 (0.91–6.19)	0.08	2.28 (0.94–5.54)	0.07
731–1095	33	23.6	2.75 (1.02–7.41)	< 0.05	2.50 (1.01–6.22)	< 0.05
> 1095	56	18.0	3.33 (1.38–8.05)	< 0.01	3.06 (1.35–6.97)	< 0.01

CI = confidence interval.
[a]Adjusted variables including age, sex, duration of Parkinson's disease before index date, conditions (hypertension, stroke, hypercholesterolemia, diabetes mellitus, depression, anxiety, psychotic-related disorder, alcohol-related disorder, sleep disorder, and head injury), and medications (antihypertensives, antidiabetics, anticoagulants, antihyperlipidemic drugs, antidepressants, benzodiazepines, and antipsychotics).

risk of developing dementia. These findings support the notion that use of anticholinergic medication is associated with increased risk of developing dementia among patients with Parkinson's disease. This potential risk effect, however, appears to be derived from a high cumulative dose of anticholinergics.

Previous studies found an association between anticholinergic medication use and the risk of cognitive impairment, cognitive decline, or even dementia among the general older population.[11–13] Our findings further extend these reports to focus on a more specific population, patients with Parkinson's disease. In addition, our study found the impact of the cumulative dose effect on dementia. This finding is consistent with the results of a study[13] that found that the risk of developing dementia was associated with higher cumulative anticholinergic exposure in a United States–based study. In combination with our findings and findings of previous studies,[11–13] our study further confirms the association between anticholinergic medication use and the increased risk of developing dementia.

For our primary study objective, we did not find an association between type of anticholinergics prescribed, categorized by the cognitive burden of the anticholinergic effect of the drug, and increased risk of developing dementia among patients with Parkinson's disease. Although the patients in the exposure group took anticholinergics with a higher cognitive burden effect, the effect was not significant enough to result in an increased risk of developing dementia when compared to patients in the reference group taking anticholinergics with a lower cognitive burden effect. Two reasons can potentially explain this nonsignificant finding. First, we used an active comparator design so that patients in both the exposure and reference groups took anticholinergics. The cognitive negative effects from different anticholinergics may not be significant enough to make a statistically significant difference. Second, the nonsignificant finding could be the result of the fact that the exposure was measured only on the index date without defining exposure period.[11, 14] One study found that the risk of dementia increased with greater

exposure to and longer duration of anticholinergics.[15] After considering the exposure period and measuring the cumulative dose in the secondary study objective, the results became significant and consistent with the results reported in the prospective cohort study among older adults.[13]

The actual mechanisms contributing to the association between anticholinergic medication use and development of dementia among patients with Parkinson's disease are not fully understood. Patients with Parkinson's disease may be vulnerable to the central anticholinergic effects because of age-related decline in hepatic and renal drug function.[32] Patients with Parkinson's disease may also have cortical cholinergic deficits caused by the degeneration of projection fibers from the basal forebrain cholinergic system.[33] Previous research[34] suggested that anticholinergics may be associated with functional and structural changes in the brain. The research team found that patients who took anticholinergics had reduced brain glucose metabolism and increased brain atrophy, which was detrimental to cognition.[34] In addition, a neuropathologic study[35] found that long-term anticholinergic medication use could be associated with increased Alzheimer-type pathology such as the amyloid plaque and neurofibrillary tangles, which could also contribute to the development of dementia.

In clinical practice, health care providers need to be aware that the use of anticholinergic drugs poses a potential risk factor for developing dementia among patients with Parkinson's disease, especially for users with a high cumulative dose. It is important to check all medications administered to patients with Parkinson's disease for anticholinergic effects and to use a lower dose or shorten the treatment period to prevent an increased risk of dementia. In addition, physicians should regularly screen patients with Parkinson's disease for dementia if patients routinely take medications with anticholinergic effects and adjust treatment regimens if there is evidence of cognitive decline.

Our study has several strengths. A new drug user design and an active comparator design in pharmacoepidemiology were used in our study to evaluate the medication exposure and dementia outcome.[24, 36] The two designs significantly reduced the immortal time bias and bias due to confounding by indication that often happens in observational studies.[24, 36] In addition, the exposure period after an anticholinergic was started allowed for the measurement of the cumulative dose effect of anticholinergics before the onset of dementia in the follow-up period. This design reduced bias from reverse causation.[24, 36] Finally, our study measured the dose and duration of anticholinergic use, which significantly improved the clinical implications of the study findings.

Despite the strengths, there are limitations to the study. Our data did not include information regarding sociodemographic or socioeconomic variables such as education or family income, which were plausible confounders. Other factors such as the smoking, dietary habits, and physical activity were not included. The residual confounding effect from these factors could still exist. Therefore, only association but not the causality can be implied. As our study used health administrative claims data, we did not have a definitive measure of the disease severity. Findings from a systematic review and community-based studies have shown a link between the progression of Parkinson's disease and increased risk of dementia.[37–40] The longer that patients had Parkinson's disease, the more likely they were to develop dementia.[37–40] The residual confounding effect derived from Parkinson's disease severity could not be fully eliminated even though we adjusted for disease duration, which may potentially serve as a proxy of the disease severity in the regression model. When comparing the baseline characteristics of the study population, we found significant differences between the reference and exposure groups in the prevalence of hypercholesterolemia, stroke, and hypertension that was associated with the risk of dementia. Recent literature has shown that hypercholesterolemia, stroke, and hypertension are strong risk factors associated with cognitive decline or dementia.[41, 42] We addressed this issue by controlling for hyperlipidemia, stroke, and hypertension in our multivariable regression model. Several scales other than the ACB scale have been used to measure anticholinergic burden.[43–45] Our results could have been different if a different scale had been used.[43–45] In addition, misclassification of dementia was possible because we were unable to obtain neurologic examinations, cognitive assessment, and laboratory data such as brain images and biomarker information used to diagnose dementia.[46] Finally, the study was limited to the population of Taiwan; thus, results may not necessarily be generalized to populations other than Taiwanese.

Conclusion

A higher cumulative dose of anticholinergic drug use was found to be significantly associated with an increased risk of developing dementia in this population-based cohort with Parkinson's disease. Physicians may consider prescribing medications that do not exhibit anticholinergic effects, or, if required, prescribe an anticholinergic starting at the lowest therapeutic dose. Regular cognitive screening assessments are necessary for patients with Parkinson's disease who are exposed to long-term anticholinergic therapy to prevent dementia. Future studies investigating the underlying mechanisms between the use of anticholinergics and the risk of developing dementia are warranted.

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Author's Contributions

A significant role in the contribution of each author is listed below. Dr. Sheu contributed to the design of the study, interpretation of the data, and drafting the article. Ms. Tsai contributed to data analysis, data management, interpretation of the data, and revising the article. Dr. Erickson contributed to the design of the study, interpretation of the data, and revising the article. Dr. Wu contributed to the design of the study, acquisition of data, analysis and interpretation of the data, and drafting the article. All authors approved the version of the article.

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Appendix. Study inclusion and exclusion criteria. ID = identification; LHIH = Longitudinal Health Insurance Database; NMDA = *N*-methyl-D-aspartate.