Risk of Pneumonia is associated with Antipsychotic Drug Use among older patients with Parkinson’s Disease: A Case-control Study

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Abstract

**Objective:** To investigate the risk of pneumonia associated with the use of antipsychotic drugs in older-adult patients with Parkinson’s disease (PD) in Taiwan.

**Methods:** This case-control study was based on data from the longitudinal health insurance database in Taiwan. We analyzed the data of 51,158 older patients with PD for the period between 2001 and 2016. To reduce the potential confounding caused by unbalanced covariates in nonexperimental settings, we used propensity score matching to include older patients without pneumonia to serve as the control group.

**Results:** Compared with patients who had never taken antipsychotics, current (adjusted odds ratios [aOR] = 1.63, 95% confidence interval [CI] = 1.51-1.75), recent (aOR = 1.63, 95% CI = 1.52-1.74), and past (aOR = 1.89, 95% CI = 1.80-2.00) users of antipsychotics had a higher risk of incident pneumonia. Among typical and atypical antipsychotics, haloperidol and clozapine were associated with higher risks of incident pneumonia, respectively. By contrast, aripiprazole was not associated with a higher risk of pneumonia.

**Conclusion:** Older patients with PD receiving typical antipsychotics or atypical antipsychotics had a higher risk of pneumonia. Among these antipsychotics, clozapine had the highest risk of pneumonia. Clinicians should pay attention to the risk of pneumonia in older patients with PD who receive typical antipsychotics and atypical antipsychotics.

Key words: pneumonia, antipsychotics, Parkinson’s disease, pharmacoepidemiology

Introduction

Parkinson’s disease (PD) is the second most common age-related motor neurodegenerative disorder first described in the early 1800s by James Parkinson [1]. As PD progresses, the bulbar muscles are affected, leading to dysphagia. Dysphagia is a common symptom in patients with PD and may occur at any stage in the disease course. Most patients with PD develop oropharyngeal dysphagia in the early stage [2]. Oropharyngeal dysphagia is the sensation of difficulty or an abnormal delay in the movement of a food bolus from the oropharynx to the stomach. Those with PD often report difficulty swallowing, which is also associated with a high risk of aspiration pneumonia [3]. A 10-fold higher incidence of aspiration pneumonia was observed in patients with PD compared with patients without PD [4]. A meta-analysis revealed that the risk of oropharyngeal dysphagia in individuals with PD was approximately three times greater than that in healthy older adults [5]. Aspiration pneumonia is the leading cause of death in patients with PD, and it is estimated to account for 70% of the mortality in this group [6].
More than half of all patients with PD eventually develop PD psychosis, typically after 10 or more years of treatment [7]. The prevalence of various psychiatric disorders is high among those with PD. Antipsychotic drugs are often used for the treatment of behavioral and psychological symptoms in patients with PD [8]. Several observational studies have explored the relationship between the use of antipsychotic drugs and the risk of community-acquired pneumonia, mainly in older patients [9-11]. A systematic review and meta-analysis suggested that exposure to typical and atypical antipsychotic drugs is associated with a significantly increased risk of pneumonia in all age groups [12]. Only one study indicated that the risk of pneumonia was significantly higher for patients with PD who used unsuitable second-generation antipsychotic drugs compared with those taking the appropriate drugs, according to the American Geriatrics Society (AGS) 2015 Beers criteria in older patients [13].

However, few studies have examined the risk of pneumonia associated with the use of antipsychotic medications among patients with PD. Because antipsychotic agents are associated with an increased risk of pneumonia, we hypothesized that patients with PD have a higher risk of all-cause pneumonia. Understanding the risk of pneumonia in patients with PD is critical for clinicians. Therefore, we examined the risk of pneumonia associated with the use of antipsychotic drugs in older patients with PD and investigated the related risk factors for pneumonia by using nationwide data from Taiwan’s longitudinal health insurance database (LHID).

Methods

Database

This study was a case-control study, in which secondary data analysis was conducted. Data were obtained from the LHID released by the Health and Welfare Data Science Center, Ministry of Health and Welfare Taiwan (HWDC, MOHW). The LHID comprises the information of two million beneficiaries randomly selected from the Taiwan National Health Insurance (NHI) program. The NHI program is a nationwide social insurance program that has covered up to 99% of citizens since 1995. Hence, the database is nationally representative of Taiwan. Owing to the anonymity of the database, the requirement for informed consent was waived, and this study was approved as an ethical review by the Institutional Review Board of China Medical University Hospital, Taiwan (No. CMUH107-REC2-004).

Study participants

All study participants were older patients (aged 265 years) with PD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]: 332; International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]: G20) at any period from 2001 to 2016. Older patients who received a principal diagnosis of pneumonia (ICD-9-CM: 480-486, ICD-10-CM: J12-J18) comprised the case group. To reduce the potential confounding caused by unbalanced covariates in nonexperimental settings, we used 1:4 propensity score matching to include older patients without pneumonia to serve as the control group. The propensity score of the study was the probability of patients incident pneumonia, calculated by sex, age, income level, urbanization, and Charlson comorbidity index (CCI).

Study design

In this case-control study, we investigated the risk of pneumonia associated with incident antipsychotic use among older patients with PD. We defined antipsychotic use by the following Anatomic Therapeutic Chemical classification system codes: typical antipsychotics-haloperidol (N05AD01) and chlorpromazine (N05AA01)-and atypical antipsychotics-clozapine (N05AH02), olanzapine (N05AH03), quetiapine (N05AH04), aripiprazole (N05AX12), and risperidone (N05AX08). The observation period for assessing the antipsychotic use of each patient was the full year before the pneumonia diagnosis. The study calculated the duration of receiving antipsychotic drugs for each study subject. The definition of "current use" was the medication duration covered the date of incident pneumonia or ended at most 30 days before pneumonia; Antipsychotic use was categorized as "recent use" if the medication duration ended 31-90 days before pneumonia; If the medication duration ended more than 90 days was defined as "past use". Patients who had never been prescribed an antipsychotic before their pneumonia diagnosis served as the reference group.

Statistical analysis

We investigated the association between antipsychotic drugs and pneumonia through a conditional logistic regression. Each antipsychotic drug was seen as an independent variable. The study subjects may receive two or more kinds of antipsychotic drugs in the observation period. The conditional logistic regression analysis would estimate the odds ratio of each antipsychotic by adjusted all independent variables. The control variables were sex, age, income level, urbanization, CCI score, and comorbidities related to pneumonia. The following comorbidities were considered: diabetes mellitus (ICD-9-CM: 250; ICD-10-CM: E08-
Institute Inc., Cary, NC, USA) was used for statistical analysis. In the case group, 34.59% of patients had pneumonia, 57.99% had COPD, 2.51% had periodontitis, 17.96% had heart failure, 21.96% had diabetes, 57.99% had COPD, 2.51% had periodontitis,

Table 1. Baseline characteristics of older patients with Parkinson’s disease

| Variables                  | Pneumonia Without | Pneumonia With | p-value |
|----------------------------|-------------------|----------------|---------|
| Total                      | 40,948            | 100.00        | 100.00  |
| Gender                     |                   |                |         |
| Female                     | 21,750            | 53.12          | 53.14   | 0.078 |
| Male                       | 19,198            | 46.88          | 46.86   |        |
| Age (year) (mean ± SD)     |                   |                |         |
| 65-70                      | 4,771             | 11.65          | 11.47   | 0.626 |
| 75-85                      | 8,396             | 20.50          | 20.60   |        |
| 80-85                      | 11,921            | 29.11          | 29.67   |        |
| ≥85                        | 2,323             | 5.67           | 5.36    |        |
| Income level               |                   |                |         |
| Low income (<21,000)       | 21,784            | 53.20          | 53.47   | 0.267 |
| Middle income (21,000-33,000) | 11,528         | 28.15          | 28.54   |        |
| High income (>33,000)      | 7,636             | 18.65          | 17.96   |        |
| Urbanization               |                   |                |         |
| Urban                     | 27,298            | 66.67          | 66.52   | 0.622 |
| Suburban                  | 9,042             | 22.08          | 22.46   |        |
| Rural                     | 4,608             | 11.25          | 11.02   |        |
| CCI score                  |                   |                |         |
| 0                         | 6,977             | 17.04          | 17.14   | 0.827 |
| 1                         | 9,701             | 23.69          | 24.00   |        |
| 2                         | 9,762             | 23.84          | 23.99   |        |
| ≥3                        | 14,508            | 35.43          | 35.26   |        |
| Diabetes mellitus          |                   |                |         |
| No                        | 25,104            | 61.31          | 61.31   | <0.001 |
| Yes                       | 15,844            | 38.69          | 38.69   |        |
| Hypertension               |                   |                |         |
| No                        | 11,091            | 27.09          | 27.09   | <0.001 |
| Yes                       | 29,857            | 72.91          | 72.91   |        |
| Cerebrovascular disease    |                   |                |         |
| No                        | 19,668            | 48.03          | 48.12   | <0.001 |
| Yes                       | 21,280            | 51.97          | 51.88   |        |
| Arrhythmia                 |                   |                |         |
| No                        | 33,605            | 82.07          | 81.36   | 0.134 |
| Yes                       | 7,343             | 17.93          | 18.64   |        |
| Upper respiratory tract infection | 19,948        | 48.72          | 48.78   | 0.944 |
| Yes                       | 21,000            | 51.28          | 51.22   |        |

Results

Baseline characteristics of the sample

Table 1 presents the baseline characteristics of the sample. After matching was conducted, the data of 51,158 older patients with PD were included for analysis, including 10,237 and 40,948 patients with and without incident pneumonia, respectively. The mean age of the patients with pneumonia was 77.10 ± 5.84 years. As expected, the distributions of sex, age, income level, urbanization, and CCI did not significantly differ between the case and control groups after matching. In the case group, 34.59% of patients had diabetes mellitus, 68.67% had hypertension, 59.83% had cerebrovascular disease, 18.57% had arrhythmia, 51.32% had upper respiratory tract infection, 17.96% had heart failure, 21.96% had diabetes, 57.99% had COPD, 2.51% had periodontitis,
2.51% had chronic kidney disease, 10.71% had chronic liver disease, 18.36% had Alzheimer disease, 2.51% had rheumatoid arthritis, 17.93% had cancer, 11.70% had epilepsy, and 6.96% had major depressive disorder.

**Incidence of pneumonia with antipsychotic use**

Table 2 lists the incidence rate of pneumonia with antipsychotic use. The incidence rate of pneumonia was 19.06% in patients who had never received any antipsychotics, 30.49% in current users, 29.85% in recent users, and 31.39% in past users (p < 0.001). As for typical antipsychotic use, incident pneumonia was diagnosed in 19.84% of patients who had never taken any antipsychotics, in 35.23% of current users, in 31.71% of recent users, and in 32.28% of past users (p < 0.001).

The distribution of incident pneumonia among the usage groups differed significantly for individual typical antipsychotics (p < 0.001). Incident pneumonia also differed significantly between each atypical antipsychotic, except for aripiprazole.

**Association of incident pneumonia and antipsychotic use**

Table 3 reveals the adjusted odds ratios (aORs) for antipsychotics after sex, age, income level, urbanization, and related comorbidities were controlled for. Compared with patients who had never taken antipsychotics, those currently taking antipsychotics had a higher risk of incident pneumonia (aOR = 1.63, 95% confidence interval [CI] =1.51–1.75), recent users (aOR = 1.63, 95% CI = 1.52–1.74), and past users (aOR = 1.89, 95% CI = 1.80–2.00). As for typical antipsychotics, compared with patients who had never taken typical antipsychotics, incident pneumonia risk was higher in current users (aOR = 1.76, 95% CI = 1.46–2.13), recent users (aOR = 1.46, 95% CI = 1.23–1.73), and past users (aOR = 1.10, 95% CI = 1.00–1.21). As for atypical antipsychotics, compared with patients who had never taken atypical antipsychotics, incident pneumonia risk was higher in current users (aOR = 1.57, 95% CI = 1.45-1.70), recent users (aOR = 1.61, 95% CI = 1.50-1.73), and past users (aOR = 1.94, 95% CI = 1.83-2.05). Among typical antipsychotics, haloperidol had a higher risk of incident pneumonia for both current users (aOR = 1.72, 95% CI = 1.41-2.11) and recent users (aOR = 1.41, 95% CI = 1.17-1.69). For chlorpromazine, only current users had a higher risk (aOR = 1.84, 95% CI = 1.13-2.98).

**Table 2. Incidence of pneumonia in older patients with Parkinson’s disease**

| Variables | Pneumonia | p-value |
|-----------|-----------|---------|
|           | Without | With |         |
| N | % | N | % |
| Any one of Antipsychotic | | | |
| No | 38,030 | 80.94 | 8,957 | 19.06 | <0.001 |
| Current users | 2,918 | 69.51 | 1,280 | 30.49 | <0.001 |
| Recent users | 3,813 | 70.12 | 1,625 | 29.88 | <0.001 |
| Past users | 6,695 | 68.61 | 3,184 | 31.39 | <0.001 |
| Typical antipsychotics | | | |
| No | 40,595 | 80.16 | 10,045 | 19.84 | <0.001 |
| Current users | 353 | 64.77 | 192 | 35.23 | <0.001 |
| Recent users | 488 | 68.83 | 221 | 31.17 | <0.001 |
| Past users | 1,904 | 71.36 | 766 | 28.64 | <0.001 |
| Haloperidol | No | 40,649 | 80.14 | 10,074 | 19.86 | <0.001 |
| Current users | 299 | 64.72 | 163 | 35.28 | <0.001 |
| Recent users | 429 | 69.08 | 192 | 30.92 | <0.001 |
| Past users | 1,658 | 70.67 | 688 | 29.33 | <0.001 |
| Chlorpromazine | No | 40,891 | 80.02 | 10,208 | 19.98 | <0.001 |
| Current users | 57 | 66.28 | 29 | 33.72 | 0.002 |
| Recent users | 66 | 68.75 | 30 | 31.25 | 0.006 |
| Past users | 299 | 70.85 | 123 | 29.15 | <0.001 |
| Atypical antipsychotics | No | 38,328 | 80.78 | 9,122 | 19.22 | <0.001 |
| Current users | 2,620 | 70.15 | 1,115 | 29.85 | <0.001 |
| Recent users | 3,407 | 70.29 | 1,440 | 29.71 | <0.001 |
| Past users | 5,917 | 67.72 | 2,821 | 32.28 | <0.001 |
| Clozapine | No | 40,851 | 80.04 | 10,185 | 19.96 | <0.001 |
| Current users | 97 | 65.10 | 52 | 34.90 | <0.001 |
| Recent users | 122 | 58.37 | 87 | 41.63 | <0.001 |
| Past users | 245 | 58.06 | 177 | 41.94 | <0.001 |
| Olanzapine | No | 40,771 | 80.05 | 10,160 | 19.95 | <0.001 |
| Current users | 177 | 69.69 | 77 | 30.31 | <0.001 |
| Recent users | 236 | 75.88 | 75 | 24.12 | 0.009 |
| Past users | 611 | 66.41 | 309 | 33.59 | <0.001 |
| Quetiapine | No | 39,128 | 80.45 | 9,509 | 19.55 | <0.001 |
| Current users | 1,820 | 71.43 | 728 | 28.57 | <0.001 |
| Recent users | 2,391 | 70.89 | 982 | 29.11 | <0.001 |
| Past users | 4,227 | 67.48 | 2,037 | 32.52 | <0.001 |
| Aripiprazole | No | 40,878 | 80.01 | 10,212 | 19.99 | <0.001 |
| Current users | 70 | 73.68 | 25 | 26.32 | 0.124 |
| Recent users | 87 | 75.00 | 29 | 25.00 | 0.178 |
| Past users | 255 | 75.44 | 83 | 24.56 | 0.036 |
| Risperidone | No | 40,425 | 80.23 | 9,960 | 19.77 | <0.001 |
| Current users | 523 | 65.38 | 277 | 34.63 | <0.001 |
| Recent users | 708 | 67.11 | 347 | 32.89 | <0.001 |
| Past users | 1,990 | 65.57 | 1,045 | 34.43 | <0.001 |

Among atypical antipsychotics, clozapine had a higher risk of incident pneumonia regardless of whether its use was current (aOR = 1.77, 95% CI = 1.24–2.51), recent (aOR = 2.60, 95% CI = 1.95–3.46), or in the past (aOR = 1.81, 95% CI = 1.46–2.23). Patients with current (aOR = 1.60, 95% CI = 1.21–2.51) or past (aOR = 1.20, 95% CI = 1.03–1.40) olanzapine use had a higher risk of incident pneumonia, compared with those who had never taken atypical antipsychotics. Finally, compared with those who had never taken atypical antipsychotics, both quetiapine users (current: aOR = 1.44, 95% CI = 1.31–1.58; recent user: aOR = 1.53, 95% CI = 1.41–1.66; past users: aOR = 1.71,
95% CI = 1.60–1.82), and risperidone users (current user: aOR = 1.81, 95% CI = 1.55–2.11; recent user: aOR = 1.62, 95% CI = 1.41–1.86; past users: aOR = 1.52, 95% CI = 1.39–1.66) had a higher risk of incident pneumonia.

### Table 3. Association between antipsychotic drugs and pneumonia

| Variables                    | Model 1 | Model 2 | Model 3 |
|------------------------------|---------|---------|---------|
|                              | OR      | 95% CI  | OR      | 95% CI  | OR      | 95% CI  |
| **Any one of Antipsychotic** |         |         |         |         |         |         |
| No (ref.)                    | 1       | -       | -       | -       | -       | -       |
| Current users                | 1.63    | 1.51–1.75 | -       | -       | -       | -       |
| Recent users                 | 1.63    | 1.52–1.74 | -       | -       | -       | -       |
| Past users                   | 1.89    | 1.80–2.00 | -       | -       | -       | -       |
| **Typical antipsychotics**   |         |         |         |         |         |         |
| No (ref.)                    | 1       | -       | -       | -       | -       | -       |
| Current users                | -       | -       | 1.76    | 1.46–2.13 | -       | -       |
| Recent users                 | -       | -       | 1.46    | 1.23–1.73 | -       | -       |
| Past users                   | -       | -       | 1.10    | 1.00–1.21 | -       | -       |
| **Haloperidol**              |         |         |         |         |         |         |
| No (ref.)                    | 1       | -       | -       | -       | -       | -       |
| Current users                | -       | -       | 1.72    | 1.41–2.11 | -       | -       |
| Recent users                 | -       | -       | 1.41    | 1.17–1.69 | -       | -       |
| Past users                   | -       | -       | 1.08    | 0.97–1.19 | -       | -       |
| **Chlorpromazine**           |         |         |         |         |         |         |
| No (ref.)                    | 1       | -       | -       | -       | -       | -       |
| Current users                | -       | -       | 1.84    | 1.13–2.98 | -       | -       |
| Recent users                 | -       | -       | 1.44    | 0.90–2.30 | -       | -       |
| Past users                   | -       | -       | 1.13    | 0.90–1.43 | -       | -       |
| **Atypical antipsychotics**  |         |         |         |         |         |         |
| No (ref.)                    | 1       | -       | -       | -       | -       | -       |
| Current users                | -       | -       | 1.77    | 1.24–2.51 | -       | -       |
| Recent users                 | -       | -       | 2.60    | 1.95–3.46 | -       | -       |
| Past users                   | -       | -       | 1.81    | 1.46–2.23 | -       | -       |
| **Olanzapine**               |         |         |         |         |         |         |
| No (ref.)                    | 1       | -       | -       | -       | -       | -       |
| Current users                | -       | -       | 1.60    | 1.21–2.13 | -       | -       |
| Recent users                 | -       | -       | 1.15    | 0.87–1.51 | -       | -       |
| Past users                   | -       | -       | 1.20    | 1.03–1.40 | -       | -       |
| **Quetiapine**               |         |         |         |         |         |         |
| No (ref.)                    | 1       | -       | -       | -       | -       | -       |
| Current users                | -       | -       | 1.44    | 1.31–1.58 | -       | -       |
| Recent users                 | -       | -       | 1.53    | 1.41–1.66 | -       | -       |
| Past users                   | -       | -       | 1.71    | 1.60–1.82 | -       | -       |
| **Aripiprazole**             |         |         |         |         |         |         |
| No (ref.)                    | 1       | -       | -       | -       | -       | -       |
| Current users                | -       | -       | 1.56    | 0.97–2.51 | -       | -       |
| Recent users                 | -       | -       | 1.46    | 0.94–2.26 | -       | -       |
| Past users                   | -       | -       | 0.98    | 0.75–1.27 | -       | -       |
| **Risperidone**              |         |         |         |         |         |         |
| No (ref.)                    | 1       | -       | -       | -       | -       | -       |
| Current users                | -       | -       | 1.81    | 1.55–2.11 | -       | -       |
| Recent users                 | -       | -       | 1.62    | 1.41–1.86 | -       | -       |
| Past users                   | -       | -       | 1.52    | 1.39–1.66 | -       | -       |

### Discussion

Oropharyngeal dysphagia is a frequent symptom in neurological disease. In neurodegenerative disorders such as PD and related disorders, as the disease progresses, patients have an increased risk of rapidly developing dysphagia [5]. Patients with PD are at greater risk of aspiration pneumonia than are individuals in the general population [14]. Because no studies have examined whether those with PD who use antipsychotic drugs also have a higher risk of pneumonia, we investigated the risk of pneumonia associated with the use of antipsychotic drugs among older patients with PD.

Antipsychotics have varying degrees of anticholinergic effects and could lead to aspiration pneumonia because of dry mouth and impaired oropharyngeal bolus transport [15]. Anticholinergic drug use is a risk factor for pneumonia in older patients. A Taiwanese study indicated that older patients receiving anticholinergic drugs have an increased risk of incident pneumonia [16]. One established mechanism for pneumonia is dry mouth, which is frequently caused by the anticholinergic side effects of medications; a dry mouth may lead to oropharyngeal swallowing impairment, which may result in aspiration pneumonia and even lead to death [17]. Anticholinergic burden scores for drugs in Germany indicated that antipsychotics such as aripiprazole and risperidone have weak anticholinergic effects (score = 1); haloperidol, olanzapine, and quetiapine have moderate anticholinergic effects (score = 2); and clozapine has strong anticholinergic effects (score = 3) [18]. Another scale for anticholinergic activity drugs used in Brazil indicated that antipsychotics such as...
atypical antipsychotics, such as clozapine, quetiapine, or risperidone, can modulate the cytokine network [26, 27], and clozapine directly influences the plasma levels of several cytokines that resemble an inflammatory reaction [24]; clozapine might also enhance susceptibility to infections during treatment [28].

The main strength of our study is that it is the first to investigate the relationship between antipsychotic use and pneumonia risk in older patients with PD by dividing the follow-up period into current use, recent use, and past use. Compared with patients who had never taken typical antipsychotics, current users (aOR = 1.76, 95% CI = 1.46-2.13), recent (aOR = 1.46, 95% CI = 1.23-1.73), and past (aOR = 1.10, 95% CI = 1.00-1.21) users of typical antipsychotics had a higher risk of incident pneumonia. Furthermore, compared with patients who had never taken atypical antipsychotics, current (aOR = 1.57, 95% CI = 1.45-1.70), recent (aOR = 1.61, 95% CI = 1.50-1.73), and past (aOR = 1.94, 95% CI = 1.83-2.05) users of atypical antipsychotics had a higher risk of incident pneumonia. Our study revealed that older patients with PD with current, recent, or past use of haloperidol, olanzapine, quetiapine, risperidone, or clozapine had a higher risk of pneumonia, whereas only those currently using chlorpromazine had a higher risk of pneumonia; by contrast, those taking aripiprazole did not have an increased risk of pneumonia.

To the best of our knowledge, ours is the first study to identify the risk factors for pneumonia in those with PD who receive antipsychotic drugs. A univariate Cox proportional hazards analysis indicated that patients with PD with comorbid cerebrovascular disease, congestive heart failure, asthma, COPD, alcoholism, Alzheimer’s disease, or epilepsy had a lower risk of incident pneumonia. Our study also revealed that in patients with PD, combined psychiatric disorder (schizophrenia and bipolar disorder) is an independent predictive factor for the development of pneumonia in patients with PD. The risk of pneumococcal disease in each psychiatric group was significantly higher than that for the general population. Patients with psychiatric disorders (e.g., schizophrenia, bipolar disorder, depression, and anxiety) have an increased risk of pneumonia [29]. Patients with schizophrenia have an increased risk of pneumonia [30], and all-cause mortality is higher in this group than in the general population [31]. This finding is supported by earlier investigations on the in vitro production of cytokines in people with these disorders [24]. Another study indicated that cerebrovascular disease, congestive heart failure, COPD, and epilepsy are associated with
a higher risk of pneumonia in those with PD [32].

Typical antipsychotics act predominantly through dopamine D_{2} receptor antagonism, which also exacerbates parkinsonian motor deficits [33]. According to the AGS 2015 Beers criteria, atypical antipsychotics (except for aripiprazole, clozapine, and quetiapine) are unsuitable for patients with PD because of the risk of worsening parkinsonian symptoms [34]. According to the 2019 Beers criteria, for patients with PD, all antipsychotics have the potential to aggravate parkinsonian symptoms; however, pimavanserin and clozapine appear to be less likely to precipitate worsening of PD. Quetiapine has only been studied in low-quality clinical trials with efficacy reported in five trials and efficacy similar to that of clozapine reported in two others [35]. Those with PD treated with quetiapine exhibit increased mortality, with a higher risk of death compared with those not using an antipsychotic; similar results were also observed for olanzapine and risperidone but not for clozapine [36]. These data indicate that clozapine may be a suitable medication for individuals with PD who experience psychotic symptoms.

In a study conducted according to the 2015 Beers criteria, Cox regression analyses revealed an increased risk of pneumonia in nursing home residents with PD who were taking inappropriate antipsychotic agents compared with those taking appropriate agents [13]. Older people with PD in long-term care who have therapy-related psychosis and use inappropriate antipsychotic medications may experience a deterioration in parkinsonian symptoms [37]. Inappropriate antipsychotic medications can potentially affect overall voluntary movements and swallowing movements because of their antagonism of the D_{2} receptors in patients with PD [38, 39]. This increased risk of aspiration pneumonia is of particular concern in older patients with PD [40]. Our study revealed that clozapine led to the highest risk of pneumonia in older people with PD. This finding is supported by the fact that clozapine has strong anticholinergic effects [18, 19], in addition to inflammatory effects [27].

The limitations of this study are as follows. First, information on some factors affecting pneumonia are unavailable on the LHID, such as alcohol and tobacco consumption behavior and laboratory measurements. There is also no information about the health status and physical performance, such as self-rated health, activities of daily living (ADL), and instrumental activities of daily living (IADL) disability. Furthermore, the LHID only includes information that is part of the health insurance declaration, and medical information from self-funded medical treatment cannot be obtained. Thus, antipsychotic use may be underestimated. Second, the study only used ICD codes to define the disease without consideration of medical procedure codes; this approach may lead to overdiagnosis. Third, some medications that may potentially increase the risk of incident pneumonia were not enrolled in the study, such as proton pump inhibitors (PPIs). In order to focus on the antipsychotics, the study reduced the medication confounding by adjusting comorbidity disease. Besides, NHI has a strict payment guideline for PPIs that are only paid for severe gastrointestinal diseases. Fourth, all participants in the study were above 65 years old. Since older patients are already at higher risk for pneumonia, future studies can establish a younger PD comparison group to verify the effect of antipsychotics on older patients with PD. In addition, the severity of PD and the disease duration of PD may also affect the study results. This study was a nationwide population-based study. Thus, the study results have the accuracy and representativeness. Besides, its observational research design precluded this study from inferring that antipsychotic use causes pneumonia. Future studies should obtain more information from other databases or through questionnaires to infer causality.

In conclusion, older patients with PD receiving typical antipsychotics or atypical antipsychotics had a higher risk of pneumonia. Among these antipsychotics, clozapine had the highest risk of pneumonia. Clinicians should pay attention to the risk of pneumonia in older patients with PD who receive typical antipsychotics and atypical antipsychotics, especially when prescribing antipsychotics with clozapine, to minimize adverse effects.

**Abbreviations**

PD: Parkinson’s disease; AGS: American Geriatrics Society; LHID: longitudinal health insurance database; HWDC: Health and Welfare Data Science Center Taiwan; MOHW: Ministry of Health and Welfare Taiwan; NHI: National Health Insurance; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification; COPD: chronic obstructive pulmonary disease; aOR: adjusted odds ratios; CI: confidence interval; ADL: activities of daily living; IADL: instrumental activities of daily living; PPIs: proton pump inhibitors.

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Ethics Committee Approval
This study was approved as an ethical review by the Institutional Review Board of China Medical University Hospital, Taiwan (No. CMUH107-REC2-004). Owing to the anonymity of the database, the requirement for informed consent was waived.

Author Contributions
Conceptualization, Kuang-Hua Huang, Wei-Yin Kuo and Chien-Ying Lee; Data curation, Yu-Hsiang Kuan and Yu-Chia Chang; Formal analysis, Yu-Hsiang Kuan, Yu-Chia Chang and Tung-Han Tsai; Methodology, Yu-Hsiang Kuan and Chien-Ying Lee; Validation, Kuang-Hua Huang, Wei-Yin Kuo and Chien-Ying Lee; Writing – original draft, Kuang-Hua Huang, Wei-Yin Kuo and Chien-Ying Lee; Writing – review & editing, Chien-Ying Lee.

Competing Interests
The authors have declared that no competing interest exists.

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