Article

Pneumonia Risk Associated with the Use of Individual Benzodiazepines and Benzodiazepine Related Drugs among the Elderly with Parkinson’s Disease

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Abstract: Most patients with Parkinson’s disease (PD) gradually develop oropharyngeal dysphagia which is often associated with pneumonia risk. The possible association of benzodiazepine (BZD) and benzodiazepine related drugs (BZRD) use with pneumonia risk has received increasing attention but remains controversial. We investigated pneumonia risk associated with the use of BZDs and BZRDs in older adult patients with PD. This case-control study analyzed data of 551,975 older adult patients with PD between 2001 and 2018 in Taiwan. To minimize potential confounding, we used 1:4 propensity score matching to include older adult patients without pneumonia as controls. Incident pneumonia risk was significantly higher in current (adjusted odds ratio (aOR) = 1.25, 95% CI = 1.23–1.27) and past (aOR = 1.13, 95% CI = 1.11–1.15) users of BZDs. Regarding BZRDs, recent (aOR = 1.08, 95% CI = 1.06–1.11) and past (aOR = 0.89, 95% CI = 0.88–0.91) users had higher and lower risks of incident pneumonia, respectively. Pneumonia risk varied based on their use of BZDs and BZRDs. In these individuals, incident pneumonia risk was high in users of BZDs, such as midazolam, lorazepam, flunitrazepam, estazolam, and clonazepam. Regarding the use of BZRDs, zopiclone increased incident pneumonia risk.

Keywords: benzodiazepines; benzodiazepine related drugs; pneumonia; Parkinson’s disease

1. Introduction

With Parkinson’s disease (PD) progression, the bulbar muscles get affected, leading to dysphagia. Dysphagia is a common symptom in patients with PD and may occur at any stage of the disease. Most patients with PD gradually develop oropharyngeal dysphagia [1]. Patients with oropharyngeal dysphagia have difficulty swallowing and are associated with increased aspiration pneumonia risk [2].

Sleep disturbance is a common nonmotor symptom among patients with PD, which may affect their quality of life. Sleep disorders can affect 38% to 98% of patients with PD [3]. These patients with sleep disturbance are commonly prescribed hypnotics [4]. Benzodiazepine receptor agonists (BZRAs), including benzodiazepines (BZDs) and benzodiazepine related drugs (BZRDs), act on the gamma-aminobutyric acid (GABA) type A receptor and are the mainstay treatments for insomnia [5]. PD is characterized by the progressive loss...
of dopaminergic neurons and neuronal degeneration of the substantia nigra [6]. Animal studies have shown that GABA agonists decrease extracellular striatal dopamine concentrations [7]. Therefore, BZDs may worsen PD symptoms [8]. Furthermore, animal studies have shown that BZDs could be a risk factor for pneumonia probably through the direct suppression of innate immunity [9]. Several studies have reported increased susceptibility to spontaneous bacterial infection and mortality in relation to the use of BZDs and BZRDs in an infection setting [9,10]. Most studies have shown that BZDs use is associated with an increased pneumonia risk [11,12]. Conversely, a population-based case-control study involving older adult people did not find a statistically significant association between BZDs and pneumonia [13]. The precise mechanism through which BZDs and BZRDs increase pneumonia risk are unknown.

However, few studies have examined how pneumonia risk is associated with the use of BZDs and BZRDs in older adult patients with PD. However, whether BZDs and BZRDs are associated with an increased pneumonia risk is still debatable. Our study hypothesized that the risk of pneumonia increases with the use of BZDs and BZRDs among patients with PD. The action mechanism underlying the development of pneumonia may differ between BZDs and BZRDs, and a drug-by-drug evaluation of such a mechanism is necessary. Therefore, in this study, we investigated pneumonia risk associated with the use of individual BZD and BZRD in patients with PD. Furthermore, we investigated the related risk factors for pneumonia by using nationwide data from Taiwan’s National Health Insurance (NHI) Research Database.

2. Materials and Methods

2.1. Database

This study conducted a secondary data analysis on the Longitudinal Health Insurance Database (LHID), which covers the period of 2001 to 2018 and is published by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW). The LHID includes details of beneficiaries enrolled in Taiwan’s NHI program that covers up to 99% of its citizens. Hence, the LHID is a nationally representative health database for Taiwan. Information provided in the LHID, including detailed clinical records on outpatient visits, hospitalizations, diagnostic codes, and prescriptions, is highly concordant between NHI claims records and patients’ self-reports. Therefore, the LHID is frequently used to determine drug safety, including that relating to drug-induced pneumonia. The LHID is anonymous, and the HWDC deidentifies insured patients to protect their privacy. The requirement for informed consent was waived. This study protocol was approved by the Central Regional Research Ethics Committee of China Medical University, Taiwan (No. CRREC-109-011).

2.2. Study Participants

From the LHID, we identified patients aged ≥ 65 years with a diagnosis of PD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 332 and International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] G20) at any time between 2002 and 2018. Older adult patients with a principal diagnosis of pneumonia (ICD-9-CM 480-486 and ICD-10-CM J12-J18) were included in the case group. To minimize potential confounding caused by unbalanced covariates in nonexperimental settings, we performed propensity score matching at a 1:4 ratio and included older adult patients without pneumonia as controls. The propensity score of the study was the probability that a patient received BZDs or BZRDs, calculated based on sex, age, income level, urbanization, and Charlson comorbidity index (CCI). After matching, a total of 551,975 older adult patients with PD were enrolled in the study between 2001 and 2018 in Taiwan.
2.3. Study Design

This was a case–control study designed to investigate pneumonia risk associated with the use of BZDs and BZRDs drugs in older adult patients with PD. The dependent variable was the incident pneumonia and the independent variable was the use of individual BZD and BZRD. A patient was defined as using BZDs or BZRDs if they used any of the following, according to the Anatomic Therapeutic Chemical (ATC) classification system: BZDs, namely midazolam (N05CD08), triazolam (N05CD05), alprazolam (N05BA12), lorazepam (N05BA06), flunitrazepam (N05CD03), estazolam (N05CD04), oxazepam (N05BA04), diazepam (N05BA01), clonazepam (N03AE01), chlordiazepoxide (N05BA02), and flurazepam (N05CD01), and BZRDs, namely zolpidem (N05CF02) and zopiclone (N05CF01).

Patients’ medication using a year before pneumonia diagnosis was assessed. Exposure to BZDs and BZRDs was classified as “current” when the most recent prescription was within 30 days before pneumonia diagnosis. Furthermore, exposure to BZDs and BZRDs was classified as “recent” and “past” when prescriptions were 31 to 90 days and ≥90 days before pneumonia diagnosis, respectively. In addition, patients who were never prescribed BZDs and BZRDs before pneumonia diagnosis were included in the reference group.

The control variables in this study included sex, age, income level, urbanization, CCI score, and comorbidities related to pneumonia. The comorbidities were diabetes mellitus (ICD-9-CM 250 and ICD-10-CM E08-E13), hypertension (ICD-9-CM 401-405 and ICD-10-CM I10-I11 and I15), cerebrovascular disease (ICD-9 CM 430-438 and ICD-10-CM I60-I69), arrhythmia (ICD-9-CM 427 and ICD-10-CM I47-I49), upper respiratory tract infection (ICD-9-CM 465.9 and ICD-10-CM J00-J06 and J30-39), heart failure (ICD-9-CM 428.0 and ICD-10-CM I50), asthma (ICD-9-CM 493 and ICD-10-CM J45), chronic obstructive pulmonary disease (COPD; ICD-9-CM 490-492 and 494-496 and ICD-10-CM J40-J44 and J47), periodontitis (ICD-9-CM 523 and ICD-10-CM K05.4), chronic kidney disease (ICD-9-CM 585 and ICD-10-CM N18), chronic liver disease (ICD-9-CM 571 and ICD-10-CM K70-K76), alcoholism (ICD-9-CM 305 and ICD-10-CM F10.2), Alzheimer disease (ICD-9-CM 331.0 and 290.1 and ICD-10-CM G30 and F00), rheumatoid arthritis (ICD-9-CM 714 and ICD-10-CM M05-M06 and M45), cancer (ICD-9-CM 140-239 and ICD-10-CM C00-C97), epilepsy (ICD-9-CM 345 and ICD-10-CM G40-G41), schizophrenia (ICD-9-CM 295-295.65 and 295.8-295.95 and ICD-10-CM F20-F20.9), bipolar disorder (ICD-9-CM 296.7 and ICD-10-CM F31.9), major depressive disorder (MDD; ICD-9-CM 296.3 and ICD-10-CM F32.9), and anxiety (ICD-9-CM 300.0 and ICD-10-CM F40 and F41).

2.4. Statistical Analysis

Descriptive statistics were first used to show distributions of participants’ characteristics, including sex, age, income level, urbanization, CCI score, and comorbidities related to pneumonia. We used the Chi-square test to examine the variables’ proportion because all variables were categorical data. We investigated the association between BZDs or BZRDs and pneumonia through a conditional logistic regression after adjusting all control variables. Statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was indicated if p-value < 0.05.

3. Results
3.1. Baseline Characteristics

Table 1 presents the baseline characteristics of the study participants. After matching, 551,975 older adult patients with PD were included in the study. Among them, 110,395 and 441,580 patients received and did not receive a diagnosis of pneumonia, respectively. The age of patients with pneumonia was 80.14 ± 5.85 years. As expected, the distribution of sex, age, income level, urbanization, and CCI between the case and control groups were not significantly different after matching. The case group had patients with diabetes mellitus (31.06%), hypertension (61.42%), cerebrovascular disease (45.11%), arrhythmia (14.83%), upper respiratory tract infection (37.98%), congestive heart failure (14.44%), asthma (13.37%), COPD (38.75%), periodontitis (1.23%), chronic kidney disease (2.41%),
chronic liver disease (8.28%), alcoholism (0.09%), Alzheimer’s disease (11.13%), rheumatoid arthritis (1.43%), cancer (14.40%), epilepsy (5.42%), schizophrenia (1.58%), bipolar disorder (1.42%), MDD (4.61%), or anxiety (13.61%).

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

| Variables                  | Pneumonia       | p-Value |
|----------------------------|-----------------|---------|
|                            | Without         | With    |         |
|                            | N  | %   | N  | %   |
| Total                      | 441,580 | 100.00 | 110,395 | 100.00 |
| Gender                     |     |      |     |      |
| Female                     | 220,311 | 49.89 | 54,554 | 49.42 |
| Male                       | 221,269 | 50.11 | 55,841 | 50.58 |
| Age (year)                 |     |      |     |      |
| 65–70                      | 16,185 | 3.67  | 4064  | 3.68  |
| 70–75                      | 64,198 | 14.54 | 16,039 | 14.53 |
| 75–80                      | 119,984 | 27.17 | 30,080 | 27.25 |
| 80–85                      | 136,585 | 30.93 | 34,545 | 31.29 |
| ≥85                        | 104,628 | 23.69 | 25,667 | 23.25 |
| Mean ± SD                  | 79.94 ± 5.74   | 80.14 ± 5.85 |
| Income level               |     |      |     |      |
| Low income                 | 235,250 | 53.27 | 58,886 | 53.34 |
| Middle income              | 95,549  | 21.64 | 23,860 | 21.61 |
| High income                | 110,781 | 25.09 | 27,649 | 25.04 |
| Urbanization               |     |      |     |      |
| Level 1                    | 100,034 | 22.65 | 25,063 | 22.70 |
| Level 2                    | 126,121 | 28.56 | 31,408 | 28.45 |
| Level 3                    | 64,910  | 14.70 | 16,344 | 14.81 |
| Level 4                    | 80,281  | 18.18 | 19,887 | 18.01 |
| Level 5                    | 17,518  | 3.97  | 4321  | 3.91  |
| Level 6                    | 29,281  | 6.63  | 7462  | 6.76  |
| Level 7                    | 23,435  | 5.31  | 5910  | 5.35  |
| CCI score                  |     |      |     |      |
| 0                          | 10,504  | 2.38  | 2629  | 2.38  |
| 1                          | 45,358  | 10.27 | 11,340 | 10.27 |
| 2                          | 85,852  | 19.38 | 21,350 | 19.34 |
| ≥3                         | 300,136 | 67.97 | 75,076 | 68.01 |
| Diabetes mellitus          |     |      |     |      |
| No                         | 291,857 | 66.09 | 76,109 | 68.94 |
| Yes                        | 149,723 | 33.91 | 34,286 | 31.06 |
| Hypertension               |     |      |     |      |
| No                         | 167,083 | 37.84 | 42,593 | 38.58 |
| Yes                        | 274,497 | 62.16 | 67,802 | 61.42 |
| Cerebrovascular disease    |     |      |     |      |
| No                         | 266,852 | 60.43 | 60,600 | 54.89 |
| Yes                        | 174,728 | 39.57 | 49,795 | 45.11 |
| Arrhythmia                 |     |      |     |      |
| No                         | 381,796 | 86.46 | 94,022 | 85.17 |
| Yes                        | 59,784  | 13.54 | 16,373 | 14.83 |
| Upper respiratory tract infection |     |      |     |      |
| No                         | 269,133 | 60.95 | 68,469 | 62.02 |
| Yes                        | 172,447 | 39.05 | 41,926 | 37.98 |
| Congestive heart failure   |     |      |     |      |
| No                         | 388,929 | 88.08 | 94,455 | 85.56 |
| Yes                        | 52,651  | 11.92 | 15,940 | 14.44 |
| Asthma                     |     |      |     |      |
| No                         | 401,943 | 91.02 | 95,638 | 86.63 |
| Yes                        | 39,637  | 8.98  | 14,757 | 13.37 |
### Table 1. Cont.

| Variables                  | Without | With       | p-Value |
|----------------------------|---------|------------|---------|
|                            | N       | %          | N       | %       |
| COPD                       |         |            |         |         |
| No                         | 335,009 | 75.87      | 67,621  | 61.25   | <0.001  |
| Yes                        | 106,571 | 24.13      | 42,774  | 38.75   |
| Periodontitis              |         |            |         |         |
| No                         | 434,730 | 98.45      | 109,035 | 98.77   | <0.001  |
| Yes                        | 6850    | 1.55       | 1360    | 1.23    |
| Chronic kidney disease     |         |            |         |         |
| No                         | 430,789 | 97.56      | 107,732 | 97.59   | 0.544   |
| Yes                        | 10,791  | 2.44       | 2663    | 2.41    |
| Chronic liver disease      |         |            |         |         |
| No                         | 396,726 | 89.84      | 101,256 | 91.72   | <0.001  |
| Yes                        | 44,854  | 10.16      | 9139    | 8.28    |
| Alcoholism                 |         |            |         |         |
| No                         | 441,204 | 99.91      | 110,297 | 99.91   | 0.713   |
| Yes                        | 376     | 0.09       | 98      | 0.09    |
| Alzheimer disease          |         |            |         |         |
| No                         | 408,047 | 92.41      | 98,103  | 88.87   | <0.001  |
| Yes                        | 33,533  | 7.59       | 12,292  | 11.13   |
| Rheumatoid arthritis       |         |            |         |         |
| No                         | 433,895 | 98.26      | 108,813 | 98.57   | <0.001  |
| Yes                        | 7685    | 1.74       | 1582    | 1.43    |
| Cancer                     |         |            |         |         |
| No                         | 369,884 | 83.76      | 94,499  | 85.60   | <0.001  |
| Yes                        | 71,696  | 16.24      | 15,896  | 14.40   |
| Epilepsy                   |         |            |         |         |
| No                         | 431,457 | 97.71      | 104,411 | 94.58   | <0.001  |
| Yes                        | 10,123  | 2.29       | 5984    | 5.42    |
| Schizophrenia              |         |            |         |         |
| No                         | 438,195 | 99.23      | 108,656 | 98.42   | <0.001  |
| Yes                        | 3385    | 0.77       | 1739    | 1.58    |
| Bipolar disorder           |         |            |         |         |
| No                         | 436,522 | 98.85      | 108,831 | 98.58   | <0.001  |
| Yes                        | 5058    | 1.15       | 1564    | 1.42    |
| Major depressive disorder  |         |            |         |         |
| No                         | 420,971 | 95.33      | 105,309 | 95.39   | <0.001  |
| Yes                        | 20,609  | 4.67       | 5086    | 4.61    |
| Anxiety                    |         |            |         |         |
| No                         | 363,846 | 82.40      | 95,365  | 86.39   | <0.001  |
| Yes                        | 77,734  | 17.60      | 15,030  | 13.61   |

### 3.2. Incidence Rate of Pneumonia with BZD Use

Table 2 presents the incidence rate of pneumonia with BZD use. Incident pneumonia was noted in 20.00%, 22.21%, 19.66%, and 20.44% of nonusers, current users, recent users, and past users of BZDs, respectively (\( p < 0.001 \)). Compared with patients not receiving BZDs, current (adjusted odds ratio (aOR) = 1.25, 95% CI = 1.23 to 1.27) and past (aOR = 1.13, 95% CI = 1.11 to 1.15) users had a significantly higher incident pneumonia risk, whereas recent users had a non-significantly higher incident pneumonia risk (aOR = 1.01, 95% CI = 1.00 to 1.03).
Table 2. Pneumonia risk associated with benzodiazepines use.

| Variables | Without | With | p-Value | Adjusted Model | p-Value |
|-----------|---------|------|---------|----------------|---------|
| Any one of BZD | | | | | |
| No | 339,345 80.69 | 81,203 19.31 | 1 | | |
| Current users | 102,235 77.79 | 29,192 22.21 | <0.001 | 1.25 | 1.23 | 1.27 | <0.001 |
| Recent users | 145,250 80.34 | 35,553 19.66 | <0.001 | 1.01 | 1.00 | 1.03 | 0.093 |
| Past users | 324,647 79.56 | 83,397 20.44 | <0.001 | 1.13 | 1.11 | 1.1 | <0.001 |
| Short-acting | | | | | |
| Midazolam | | | | | |
| No | 438,869 80.30 | 107,694 19.70 | 1 | | |
| Current users | 2711 50.09 | 2701 49.91 | <0.001 | 3.93 | 3.71 | 4.15 | <0.001 |
| Recent users | 4033 75.54 | 1306 24.46 | <0.001 | 1.26 | 1.18 | 1.35 | <0.001 |
| Past users | 28,624 74.02 | 10,048 25.98 | <0.001 | 1.29 | 1.26 | 1.32 | <0.001 |
| Triazolam | No | 439,377 80.00 | 109,828 20.00 | 1 | | |
| Current users | 2203 79.53 | 567 20.47 | 0.536 | 1.05 | 0.95 | 1.15 | 0.324 |
| Recent users | 3074 81.82 | 683 18.18 | 0.005 | 0.93 | 0.86 | 1.01 | 0.101 |
| Past users | 15,204 78.87 | 4073 21.13 | <0.001 | 1.00 | 0.96 | 1.04 | 0.952 |
| Intermediate-acting | | | | | |
| Alprazolam | No | 412,901 79.88 | 104,009 20.12 | 1 | | |
| Current users | 28,679 81.79 | 6386 18.21 | <0.001 | 0.94 | 0.91 | 0.96 | <0.001 |
| Recent users | 42,468 82.90 | 8758 17.10 | <0.001 | 0.88 | 0.86 | 0.90 | <0.001 |
| Past users | 161,774 80.48 | 39,232 19.52 | <0.001 | 0.94 | 0.93 | 0.95 | <0.001 |
| Lorazepam | No | 417,686 80.23 | 102,900 19.77 | 1 | | |
| Current users | 23,894 76.12 | 7495 23.88 | <0.001 | 1.27 | 1.24 | 1.31 | <0.001 |
| Recent users | 35,122 79.26 | 9189 20.74 | <0.001 | 1.08 | 1.05 | 1.11 | <0.001 |
| Past users | 162,821 78.44 | 44,867 21.60 | <0.001 | 1.16 | 1.14 | 1.18 | <0.001 |
| Flunitrazepam | No | 437,602 80.03 | 109,214 19.97 | 1 | | |
| Current users | 3978 77.11 | 1181 22.89 | <0.001 | 1.15 | 1.08 | 1.23 | <0.001 |
| Recent users | 5355 79.53 | 1477 20.47 | <0.001 | 1.11 | 1.05 | 1.18 | <0.001 |
| Past users | 19,118 76.64 | 5827 23.36 | <0.001 | 1.12 | 1.08 | 1.15 | <0.001 |
| Estazolam | No | 423,084 80.18 | 104,590 19.82 | 1 | | |
| Current users | 18,496 76.11 | 5805 23.89 | <0.001 | 1.28 | 1.24 | 1.32 | <0.001 |
| Recent users | 27,496 78.44 | 7558 21.56 | <0.001 | 1.14 | 1.11 | 1.18 | <0.001 |
| Past users | 98,439 78.22 | 27,416 21.78 | <0.001 | 1.11 | 1.10 | 1.13 | <0.001 |
| Oxazepam | No | 440,855 79.99 | 110,269 20.01 | 1 | | |
| Current users | 725 85.19 | 126 14.81 | <0.001 | 0.68 | 0.56 | 0.83 | <0.001 |
| Recent users | 1009 83.80 | 195 16.20 | <0.001 | 0.80 | 0.68 | 0.93 | 0.005 |
| Past users | 7257 80.17 | 1,795 19.83 | 0.683 | 0.96 | 0.91 | 1.01 | 0.106 |
| Long-acting | | | | | |
| Diazepam | No | 431,029 80.02 | 107,603 19.98 | 1 | | |
| Current users | 10,551 79.08 | 2792 20.92 | 0.007 | 1.08 | 1.03 | 1.13 | 0.001 |
| Recent users | 16,796 83.65 | 3284 16.35 | <0.001 | 0.82 | 0.79 | 0.85 | <0.001 |
| Past users | 136,677 80.76 | 32,570 19.24 | <0.001 | 0.90 | 0.88 | 0.91 | <0.001 |
| Clonazepam | No | 409,759 80.14 | 101,522 19.86 | 1 | | |
| Current users | 31,821 78.20 | 8873 21.80 | <0.001 | 1.10 | 1.07 | 1.13 | <0.001 |
| Recent users | 47,504 79.45 | 12,286 20.55 | <0.001 | 1.05 | 1.03 | 1.07 | <0.001 |
| Past users | 146,600 79.23 | 38,436 20.77 | <0.001 | 1.05 | 1.03 | 1.06 | <0.001 |
Table 2. Cont.

| Variables          | Without | With                  | p-Value 1 | Adjusted Model 2 | p-Value |
|--------------------|---------|-----------------------|-----------|------------------|---------|
|                    | N       | %                     | N         | %                | OR      | 95% CI |         |        |
| Chlordiazepoxide   |         |                       |           |                  |         |        |         |        |
| No                 | 440,728 | 79.99                 | 110,244   | 20.01            | 1       |        |         |        |
| Current users      | 852     | 84.95                 | 151       | 15.05            | <0.001  | 0.75   | 0.63    | 0.89   | 0.001  |
| Recent users       | 1311    | 86.48                 | 205       | 13.52            | <0.001  | 0.70   | 0.60    | 0.81   | <0.001 |
| Past users         | 14,166  | 81.76                 | 3161      | 18.24            | <0.001  | 0.90   | 0.87    | 0.94   | <0.001 |
| Flurazepam         |         |                       |           |                  |         |        |         |        |
| No                 | 440,857 | 80.01                 | 110,164   | 19.99            | 1       |        |         |        |
| Current users      | 723     | 75.79                 | 231       | 24.21            | 0.001   | 1.19   | 1.02    | 1.39   | 0.024  |
| Recent users       | 1057    | 78.47                 | 290       | 21.53            | 0.160   | 1.10   | 0.97    | 1.26   | 0.146  |
| Past users         | 7826    | 79.77                 | 1985      | 20.23            | 0.562   | 0.93   | 0.89    | 0.98   | 0.008  |

1 Chi-square test. 2 All models were analyzed via the conditional logistic regression. Extraneous factors adjusted in the model contained all comorbidities.

With regard to individual BZDs, high incident pneumonia risk was observed in current, recent, and past users of midazolam (aOR = 3.93, 95% CI = 3.71 to 4.15; aOR = 1.26, 95% CI = 1.18 to 1.35; and aOR = 1.29, 95% CI = 1.26 to 1.32, respectively), lorazepam (aOR = 1.27, 95% CI = 1.24 to 1.31; aOR = 1.08, 95% CI = 1.05 to 1.11; and aOR = 1.16, 95% CI = 1.14 to 1.18, respectively), flunitrazepam (aOR = 1.15, 95% CI = 1.08 to 1.23; aOR = 1.11, 95% CI = 1.05 to 1.18; and aOR = 1.12, 95% CI = 1.08 to 1.15, respectively), estazolam (aOR = 1.28, 95% CI = 1.24 to 1.32; aOR = 1.14, 95% CI = 1.11 to 1.18; and aOR = 1.11, 95% CI = 1.10 to 1.13, respectively), and clonazepam (aOR = 1.10, 95% CI = 1.07 to 1.13; aOR = 1.05, 95% CI = 1.03 to 1.07; and aOR = 1.05, 95% CI = 1.03 to 1.06, respectively). Diazepam current users had a high incident pneumonia risk (aOR = 1.08, 95% CI = 1.06 to 1.11), whereas recent (aOR = 0.82, 95% CI = 0.79 to 0.85) and past (aOR = 0.90, 95% CI = 0.88 to 0.91) users had a low incident pneumonia risk. Low incident pneumonia risk was observed in current, recent, and past users of alprazolam (aOR = 0.94, 95% CI = 0.91 to 0.96; aOR = 0.88, 95% CI = 0.86 to 0.90; and aOR = 0.94, 95% CI = 0.93–0.95, respectively) and clordiazepoxide (aOR = 0.75, 95% CI = 0.63 to 0.89; aOR = 0.70, 95% CI = 0.60 to 0.81; and aOR = 0.90, 95% CI = 0.87 to 0.94, respectively). Furthermore, incident pneumonia risk was low in current (aOR = 0.68, 95% CI = 0.56 to 0.83) and recent (aOR = 0.80, 95% CI = 0.68 to 0.93) users of oxazepam.

3.3. Incidence Rate of Pneumonia with BZRD Use

Table 3 presents the incidence rate of pneumonia with BZRD use. Incident pneumonia was noted in 20.05%, 19.44%, 18.58%, and 21.28% of nonusers, current users, recent users, and past users of BZRDs, respectively (p < 0.001). Compared with patients who did not receive BZRDs, recent users had a high incident pneumonia risk (aOR = 1.08, 95% CI = 1.06 to 1.11), whereas past users had a low incident pneumonia risk (aOR = 0.89, 95% CI = 0.88 to 0.91).

Among BZRDs, current (aOR = 0.94, 95% CI = 0.91 to 0.97) and recent (aOR = 0.86, 95% CI = 0.86 to 0.91) users of zolpidem had a low risk of incident pneumonia, whereas past users of the drug had a high risk of incident pneumonia (aOR = 1.07, 95% CI = 1.06 to 1.09). Furthermore, current (aOR = 1.14, 95% CI = 1.08 to 1.20), recent (aOR = 1.07, 95% CI = 1.02 to 1.11), and past (aOR = 1.11, 95% CI = 1.08 to 1.13) users of zopiclone had a high risk of incident pneumonia.
Table 3. Pneumonia risk associated with benzodiazepine related drugs use.

| Variables            | Pneumonia Without | Pneumonia With | p-Value 1 | Adjusted Model 2 |
|----------------------|-------------------|----------------|-----------|------------------|
|                      | N     | %     | N     | %     | OR | 95% CI | p-Value |
| Any one of BZRD      |       |       |       |       |    |       |         |
| No                   | 407,779 | 79.95 | 102,238 | 20.05 | 1   |       |         |
| Current users        | 33,801 | 80.56 | 8157  | 19.44 | 0.003 | 1.02 | 0.99–1.04 | 0.239 |
| Recent users         | 47,714 | 81.42 | 10,891 | 18.58 | <0.001 | 1.08 | 1.06–1.11 | <0.001 |
| Past users           | 158,308 | 78.72 | 42,787 | 21.28 | <0.001 | 0.89 | 0.88–0.91 | <0.001 |
| Zolpidem             |       |       |       |       |    |       |         |
| No                   | 414,818 | 79.91 | 104,319 | 20.09 | 1   |       |         |
| Current users        | 26,762 | 81.50 | 6076  | 18.50 | <0.001 | 0.94 | 0.91–0.97 | <0.001 |
| Recent users         | 38,005 | 82.28 | 8187  | 17.72 | <0.001 | 0.88 | 0.86–0.91 | <0.001 |
| Past users           | 140,526 | 78.99 | 37,379 | 21.01 | <0.001 | 1.07 | 1.06–1.09 | <0.001 |
| Zopiclone            |       |       |       |       |    |       |         |
| No                   | 433,958 | 80.05 | 108,153 | 19.95 | 1   |       |         |
| Current users        | 7622  | 77.27 | 2242  | 22.73 | <0.001 | 1.14 | 1.08–1.20 | <0.001 |
| Recent users         | 11,014 | 78.50 | 3017  | 21.50 | <0.001 | 1.07 | 1.02–1.11 | 0.003 |
| Past users           | 50,767 | 77.49 | 14,744 | 22.51 | <0.001 | 1.11 | 1.08–1.13 | <0.001 |

1 Chi-square test. 2 All models were analyzed via the conditional logistic regression. Extraneous factors adjusted in the model contained all comorbidities.

4. Discussion

Different drugs have different pharmaceutical properties that can substantially affect biological properties. These individual BZD or BZRD drugs may have different action mechanisms that drive the development of pneumonia. This case–control study analyzed data of 551,975 older adult patients with PD between 2001 and 2018 in Taiwan. Our study revealed that for individual BZDs, midazolam, lorazepam, flunitrazepam, estazolam, and clonazepam were associated with increased incident pneumonia risk in current, recent, and past users in elderly patients with PD. However, several individual BZDs such as alprazolam and clordiazepoxide were associated with decreased incident pneumonia risk in current, recent, and past users. Among BZRDs, zolpidem current and recent users had a low incident pneumonia risk, whereas past users had a high incident pneumonia risk. Furthermore, zopiclone current, recent, and past users had a high incident pneumonia risk.

For treating sleep disturbance among patients with PD, several sedative-hypnotics are prescribed, including BZDs and BZRDs, which are mainstay treatments for insomnia [5]. BZDs, as GABA modulators, are commonly used for the treatment of sleep disorders, anxiety, and some forms of depression [14]. PD is the second most common age-related motoric neurodegenerative disorder, which is likely to lead to oropharyngeal dysphagia and may increase aspiration pneumonia risk [2]. Several studies have indicated that BZDs and BZRDs are associated with an increased pneumonia risk in older adult patients [11,12]. However, a study in older adult patients did not find a statistically significant association between BZDs and pneumonia (OR = 1.08, 95% CI = 0.84 to 1.47), which may partly be due to low numbers of patients exposed to BZDs in this study [13]. By contrast, another study showed that BZDs may be associated with a decreased pneumonia risk. However, this study used questionnaires to determine drug exposure and thus has potential recall and reporting bias [15]. Previous studies have not specifically examined the association between BZRAs and pneumonia, and the small sample size may have decreased the power of the study [15]. The association of the use of BZDs and BZRDs with pneumonia risk has received increasing attention but is still controversial. However, no study has explored whether patients with PD who use BZDs and BZRDs have increased pneumonia risk. Therefore, our study was conducted to investigate pneumonia risk associated with the use of BZDs and BZRDs among older adult patients with PD in the Taiwan population. The large sample size used was representative of the population and allowed for robust findings.
in our analysis. To the authors’ knowledge, this is the first study to directly evaluate the association of BZDs and BZRDs with pneumonia risk among older adult patients with PD.

Pneumonia risk among older adult patients with PD varies depending on the use of BZDs or BZRDs. As for individual BZDs, midazolam, lorazepam, flunitrazepam, estazolam, and clonazepam were associated with increased incident pneumonia risk in current, recent, and past users. However, several BZDs such as alprazolam and chlordiazepoxide were associated with decreased incident pneumonia risk in current, recent, and past users. Among BZRDs, zolpidem current and recent users had a low incident pneumonia risk, whereas past users had a high incident pneumonia risk. Furthermore, current, recent, and past users of zopiclone had a high incident pneumonia risk.

In our study, compared with patients not receiving BZDs, current and past users of BZDs had a significantly increased incident pneumonia risk. Several mechanisms have been proposed in animal and physiological studies to explain the possible association of BZD or BZRD use with pneumonia risk. First, BZDs can sedate, may prolong hypoventilation duration [16], and may lead to pneumonia with increased aspiration risk. The clearing of oral salivary secretions may be impaired during deep sedation, particularly during peak drug concentrations. The swallowing of saliva is strongly inhibited during deep sleep [17]. Second, animal studies have indicated that GABA agonists can decrease extracellular striatal dopamine concentrations, and, therefore, BZDs may worsen PD symptoms [8]. Third, according to the anticholinergic burden score for drugs in Germany, BZDs and BZRDs have weak anticholinergic effects [18]. Medications exerting an anticholinergic effect may lead to oropharyngeal swallowing impairment, which results in aspiration pneumonia [19]. Anticholinergic drugs are one of the risk factors for pneumonia in older adult patients. As BZDs and BZRDs have weak anticholinergic effects, they may be associated with pneumonia risk among older adult patients with PD. Fourth, BZDs relax the lower esophageal sphincter and increase reflux events during sleep [20], which could increase pneumonia risk. BZDs decrease lower esophageal sphincter pressure, perhaps through the activation of peripherally situated GABA receptors [21]. Fifth, BZDs may directly influence the pulmonary system by activating GABA receptors located in the peripheral nervous system or peripheral tissue [21]. Importantly, mouse and human immune cells, (including alveolar macrophage) express GABA receptors [9], thus serving as translational evidence that humans may be at risk. BZDs depress central respiratory drive and decrease inspiratory and expiratory respiratory muscle strength in a dose-dependent manner, thus reducing respiration [22]. Similarly, BZRs may cause respiratory depression by decreasing respiratory muscle strength, suppressing central respiratory drive, and increasing upper airway resistance [23]. Finally, BZRAs also suppress peripheral immunity through the activation of GABA receptors [9] or peripheral BZD receptors (PBRs) [24]. Several studies have indicated that the activation of GABA receptors may weaken the immune system [9]. An in vivo study showed that PBR ligands inhibit both inflammatory cytokine production in acute inflammation [25] and macrophage production of several key immune response cytokines [26].

Human epidemiological data have revealed that BZD use is a risk factor for complicated community-acquired lower respiratory tract infection [27]. BZDs are associated with increased pneumonia risk because BZDs have a relatively high affinity for both intracellular and cell surface receptors, whereas the GABAergic mechanism is probably responsible for BZRD-induced pneumonia owing to the lower affinity of BZRD for PBRs [28]. Different drugs have different pharmaceutical properties that can substantially affect biological properties. These individual BZD or BZRD drugs may have different action mechanisms that drive the development of pneumonia. To investigate the immune response among older adult patients with PD for each BZD or BZRD is necessary.

Our study revealed that several BZDs increase incident pneumonia risk, including midazolam, lorazepam, clonazepam, flunitrazepam, and estazolam. Midazolam use was likely to result in the development of pneumonia among older PD patients receiving BZDs, and midazolam users had a high incident pneumonia risk. Some possible mechanisms
have been suggested that support the relationship between midazolam use and pneumonia risk. Midazolam probably acts on PBR, impairing the response to infection in mice, mainly through the inhibition of macrophage spread, phagocytosis function, and oxidative bursts of neutrophils and macrophages [11]. Another possible mechanism is that midazolam significantly increases the incidence of pharyngeal dysfunction from 16% to approximately 48% [29]. A study showed that at 2 h after midazolam administration, the swallowing reflex was depressed, thus increasing the latency time to initiate a swallowing action even after recovery to normal consciousness [30]. Our study found that lorazepam users had a high incident pneumonia risk. We found that clonazepam users had a high incident pneumonia risk. A study indicated that compared with other BZDs, clonazepam has a strong binding capacity to PBRs in rat aortic smooth muscles [31] and can thus impair the response to infection.

In theory, BZDs can normalize these brain areas in patients with hypoactive GABA [32]. In general, anxiogenic BZDs suppress the immune response, whereas anxiolytic BZDs may protect the individual from stress-induced immunosuppression [33]. Our study revealed that several BZDs decreased incident pneumonia risk, including alprazolam, oxazepam, and chlordiazepoxide. Alprazolam users had a low risk of incident pneumonia. An in vitro study demonstrated that triazolo-BZDs (alprazolam and triazolam) do not modify the phagocytosis and killing by human polymorphonuclear cells and monocytes. Alprazolam was found to be efficacious in controlling PD symptoms [34]. Our study revealed that chlordiazepoxide users had a low incident pneumonia risk. This may be because chlordiazepoxide is a BZD with anxiolytic and sedative-hypnotic properties [32]. However, the mechanism remains unclear, and further investigation is necessary. Furthermore, our study revealed that diazepam current users had a high incident pneumonia risk, whereas recent and past users had a low incident pneumonia risk. Another study reported that the dose-dependent effect of diazepine (ranging from stimulation to inhibition) may be caused by different BZD receptors involved in the process [35]. Previous studies have suggested that the long-term use of BZDs may weaken the immune system, although no conclusive evidence is available to support this claim [36].

BZRDs exhibit greater selectivity than BZDs do for GABA receptors containing alpha1 subunits, which exert considerable hypnotic effects [37]. BZD-induced pneumonia has a relatively high affinity for PBRs, whereas BZRD-induced pneumonia has a low affinity for PBRs [28]. Our study revealed that the risk of BZRD-induced pneumonia is lower than that of BZD-induced pneumonia among patients with PD. Furthermore, we found that compared with patients not receiving BZRDs (zolpidem and zopiclone), recent BZRD users had an increased incident pneumonia risk, whereas past users had a decreased incident pneumonia risk.

We observed that current and recent users of Zolpidem had a low incident pneumonia risk, whereas past users had a high incident pneumonia risk. Some possible mechanisms underlie the relationship between zolpidem use and pneumonia risk. Zolpidem may increase sleep apnea incidence and suppress the respiratory drive [38]. A study observed that zolpidem use increased infection risk in patients with sleep disturbance [39]. Several studies have shown that zolpidem can improve neuropsychiatric symptoms and motor dysfunction in patients with PD [40–42]. We found that zopiclone users had a high risk of incident pneumonia. Zopiclone may adversely affect the immune system, increasing the risk of infections. Obiora et al. found an approximately two-fold increase in pneumonia risk with BZD or zopiclone use within 30 days of therapy [43]. However, this study was limited by the effects of BZD and BZRD use not being distinguished. Furthermore, the effect of zopiclone on the immune system in patients with PD is unknown.

This study has several strengths. First, we used a large sample size that was representative of the entire Taiwanese population, which allowed for robust findings. This is a nationwide population-based case–control study with nearly complete follow-up information with regard to health care institutes among the whole study population, and the data set is routinely monitored for diagnostic accuracy by the NHI Bureau of Taiwan. Second,
the follow-up period of this study was divided into current use (<30 days), recent use (31–90 days), and past use (>90 days) to investigate the relationship between drug use and pneumonia risk. Thus, the relationship between the drug and pneumonia risk at different stages of its use could be studied.

This study has several limitations that must be addressed. First, some factors related to pneumonia cannot be obtained from the LHID, such as alcohol consumption and smoking status, chest X-ray results, pneumonia etiology, and laboratory parameters. The LHID only can present information that are part of a health insurance declaration, and medical information in uninsured treatments cannot be obtained. Thus, the use of BZDs or BZRDs may be underestimated. Third, inclusion of prevalent BZD and BZRD users could potentially result in an underestimation of the overall risks because they might have developed a tolerance for pneumonia. Fourth, the study used only the ICD code to define diseases and did not consider medical procedure codes. Hence, pneumonia may be overrepresented. Fifth, this study was an observational study, which precluded any inference that BZD or BZRD use causes pneumonia. In future studies, information from other relational databases or questionnaires must be obtained to infer causality.

5. Conclusions

Older patients with PD receiving BZDs and BZRDs had associated with the risk of pneumonia. Among these medications, BZDs, such as midazolam, lorazepam, flunitrazepam, estazolam, and clonazepam, had the highest risk of pneumonia. Regarding the use of BZRDs, zopiclone also increased incident pneumonia risk. Clinicians should pay attention to the risk of pneumonia in older patients with PD who receive BZDs and BZRDs.

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Institutional Review Board Statement: This study protocol was approved as a completely ethical review by the Central Regional Research Ethics Committee of China Medical University, Taiwan (No. CRREC-109-011). Due to the database being anonymous, the requirement for informed consent was waived.

Informed Consent Statement: Data were obtained from the Health and Welfare Data Science Center, Ministry of Health and Welfare Taiwan provides scrambled random identification numbers for insured patients to protect the privacy of beneficiaries. The data is anonymous, and the HWDC deidentifies insured patients to protect their privacy. The requirement for informed consent was waived. This study protocol was approved from a completely ethical review by the Central Regional Research Ethics Committee of China Medical University, Taiwan (No. CRREC-109-011).

Data Availability Statement: The National Health Insurance Database used to support the findings of this study were provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW) under license and so cannot be made freely available. Requests for access to these data should be made to HWDC (https://dep.mohw.gov.tw/dos/np-2497-113.html, accessed on 12 July 2021).

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29. Hardemark Cedborg, A.I.; Sundman, E.; Boden, K.; Hedstrom, H.W.; Kuylenstierna, R.; Ekberg, O.; Eriksson, L.I. Effects of morphine and midazolam on pharyngeal function, airway protection, and coordination of breathing and swallowing in healthy adults. *Anesthesiology* 2015, 122, 1253–1267. [CrossRef]

30. D’Honneur, G.; Rimaniol, J.M.; El Sayed, A.; Lambert, Y.; Duvaldestin, P. Midazolam/propofol but not propofol alone reversibly depress the swallowing reflex. *Acta Anaesthesiol. Scand.* 1994, 38, 244–247. [CrossRef]

31. Cox, D.A.; Ellinor, P.; Kirley, T.; Matlib, M.A. Identification of a 17-kDa protein associated with the peripheral-type benzodiazepine receptor in vascular and other smooth muscle types. *J. Pharmacol. Exp. Ther.* 1991, 258, 702–709. [PubMed]

32. Guina, J.; Merrill, B. Benzodiazepines I: Upping the care on downers: The evidence of risks, benefits and alternatives. *J. Clin. Med.* 2018, 7, 17. [CrossRef]

33. Zavala, F. Benzodiazepines, anxiety and immunity. *Pharmacol. Ther.* 1997, 75, 199–216. [CrossRef]

34. Moylan, S.; Giorlando, F.; Nordfjærn, T.; Berk, M. The role of alprazolam for the treatment of panic disorder in Australia. *Aust. N. Z. J. Psychiatry* 2012, 46, 212–224. [CrossRef]

35. Devoino, L.V.; Beletskaya, I.O. Action of benzodiazepines on the immune response. *Bull. Exp. Biol. Med.* 1988, 105, 440. [CrossRef]

36. Elmesallamy, G.E.; Abass, M.A.; Ahmed Refat, N.A.; Atta, A.H. Differential effects of alprazolam and clonazepam on the immune system and blood vessels of non-stressed and stressed adult male albino rats. *Interdiscip. Toxicol.* 2011, 4, 132–143. [CrossRef]

37. Sys, J.; Van Cleynenbreugel, S.; Deschodt, M.; Van der Linden, L.; Tournoy, J. Efficacy and safety of non-benzodiazepine and non-Z-drug hypnotic medication for insomnia in older people: A systematic literature review. *Eur. J. Clin. Pharmacol.* 2019, 76, 363–381. [CrossRef]

38. Cirignotta, F.; Mondini, S.; Zucconi, M.; Gerardi, R.; Farolfi, A.; Lugaresi, E. Zolpidem-polysomnographic study of the effect of a new hypnotic drug in sleep apnea syndrome. *Pharmacol. Biochem. Behav.* 1988, 29, 807–809. [CrossRef]

39. Huang, C.-Y.; Chou, F.H.-C.; Huang, Y.-S.; Yang, C.-J.; Su, Y.-C.; Juang, S.-Y.; Chen, P.-F.; Chou, P.; Lee, C.-A. The association between zolpidem and infection in patients with sleep disturbance. *J. Psychiatr. Res.* 2014, 54, 116–120. [CrossRef]

40. Chen, Y.-Y.; Sy, H.-N.; Wu, S.-L. Zolpidem improves akinesia, dystonia and dyskinesia in advanced Parkinson’s disease. *J. Clin. Neurosci.* 2008, 15, 955–956. [CrossRef]

41. Daniele, A.; Albanese, A.; Gainotti, G.; Gregori, B.; Bartolomeo, P. Zolpidem in Parkinson’s disease. *Lancet* 1997, 349, 1222–1223. [CrossRef]

42. Huang, H.Y.; Hsu, Y.T.; Wu, Y.C.; Chiou, S.M.; Kao, C.H.; Tsai, M.C.; Tsai, C.H. Zolpidem improves neuropsychiatric symptoms and motor dysfunction in a patient with Parkinson’s disease after deep brain stimulation. *Acta Neurol. Taiwan* 2012, 21, 84–86.

43. Obiora, E.; Hubbard, R.; Sanders, R.D.; Myles, P.R. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: A nested case-control and survival analysis in a population-based cohort. *Thorax* 2013, 68, 163–170. Available online: [http://thorax.bmj.com/](http://thorax.bmj.com/) (accessed on 8 September 2020). [CrossRef] [PubMed]