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Use of Antipsychotic Medications and Cholinesterase Inhibitors and the Risk of Falls and Fractures: self-controlled case series

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ABSTRACT

Objective

To evaluate the association between the use of antipsychotic medications and cholinesterase inhibitors, and the risk of falls and fractures in elderly patients with major neurocognitive disorders.

Design

Self-controlled case series

Setting

Taiwan's National Health Insurance Database

Participants

15,278 patients who were aged 65 or older, were newly prescribed antipsychotic medications and cholinesterase inhibitors, and suffered an incident fall or fracture between 2006 and 2017. Prescription records of cholinesterase inhibitors were used to confirm the diagnosis of major neurocognitive disorders since all use of cholinesterase inhibitors was subject to review by experts based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition and patients' scores of Mini-Mental State Examination. We excluded those with schizophrenia and bipolar disorder before the first prescription of cholinesterase inhibitors to ensure that antipsychotic medications were used for neuropsychiatric symptoms of major neurocognitive disorders.

Main outcome measures

We used conditional Poisson regression to derive the incidence rate ratio and the 95% confidence interval for evaluating the association between the risk of falls and fractures and different exposure periods, including cholinesterase inhibitors alone, antipsychotic medications alone, and combination, as compared with the non-exposure period for the same individual. Moreover, we defined a 14-day pre-exposure period before study drug initiation over concerns about confounding by indication.

Results

Compared with the non-exposure period (incidence rate per 100 person-years; 95% confidence interval: 8.30; 8.14 to 8.46), the highest risk of falls and fractures occurred during the pre-exposure period (52.35; 48.46 to 56.47), followed by combination (10.55; 9.98 to 11.14), antipsychotic medications alone (10.34; 9.80 to 10.89), and cholinesterase inhibitors alone (9.41; 8.98 to 9.86).

Conclusions

The incidence of falls and fractures was especially high in the pre-exposure period, suggesting that factors other than the study medications, such as underlying diseases, should be taken into consideration when evaluating the association between the risk of falls and fractures, and the use of cholinesterase inhibitors and antipsychotic medications. The exposure periods were also associated with a higher risk of falls and fractures, compared with the non-exposure period, although the magnitude was much lower than during the pre-exposure period. Prevention strategies and close monitoring of the risk of falls are still necessary until there is evidence that patients have regained a steady status.

INTRODUCTION

Older adults with major neurocognitive disorders are often considered vulnerable and prone to falls and related fractures (1), which are the most common causes for hospitalization in older adults and are associated with substantial morbidity and mortality (2). Cholinesterase inhibitors are common cognitive enhancers and may be linked to the risk of falls and fractures due to syncope caused by parasympathomimetic effects (3-5). Antipsychotic medications are commonly prescribed for patients with major neurocognitive disorders to treat their neuropsychiatric symptoms (6), and recently there has been increased concern over falls and fractures (7). Due to potential adverse effects of antipsychotic medications, including orthostatic hypotension, sedation, blurred vision, and extrapyramidal symptoms, the U.S. Food and Drug Administration has suggested that a complete assessment of the risk of falls should be undertaken before initiating treatment (8). The Beers Criteria (9) and other studies (10-22) have also suggested that the use of antipsychotic medications may be associated with the risk of falls and fractures.

Although several studies and guidelines have suggested that the use of cholinesterase inhibitors and antipsychotic medications may be associated with the risk of falls and fractures, some previous studies reached diverging conclusions. Jin B et al. and Kim DH et al. found no association between the use of cholinesterase inhibitors and the incidence of falls and fractures in patients with major neurocognitive disorders (23, 24). Two systematic reviews with meta-analyses and an observational study also found that antipsychotic medications were not associated with the risk of falls and fractures (24-26). Confounding by indication may partly explain the conflicting results from these studies. For example, patients with neuropsychiatric symptoms of major neurocognitive disorders may manifest depression, irritability, agitation, and hallucinations that could lead to the prescription of antipsychotic medications, and both the symptoms and the treatments could increase the risk of subsequent falls and fractures. This confounding effect is especially likely when the events are observed within a short period right before patients initiate treatments in response to the neuropsychiatric symptoms of major neurocognitive disorders. However, only a few studies evaluating the association between cholinesterase inhibitors, antipsychotic medications, and the risk of falls and fractures have addressed this issue (18, 27).

With the coming of an aging society, the incidence of major neurocognitive disorders and associated neuropsychiatric symptoms continues to increase. Though the use of antipsychotic medications may be associated with falls and fractures, as reported by the U.S. Food and Drug Administration and the Beers Criteria, antipsychotic medications may still be prescribed to control neuropsychiatric symptoms in patients with major neurocognitive disorders. Therefore, it has become increasingly important to understand the risk profiles of patients receiving cholinesterase inhibitors and antipsychotic medications, in order to prevent the occurrence of falls and fractures. This study aimed to evaluate the associated risk of falls and fractures in patients receiving both cholinesterase inhibitors and antipsychotic medications. Specifically, we assessed the risk of falls and fractures during the period before treatments to understand whether the risk arose predominantly from the exposure to the drugs, or from the underlying diseases that necessitated the treatment.

METHODS

Data Sources

This study utilized data from the National Health Insurance Database from 2003 to 2017, provided by the Health and Welfare Data Science Centre in Taiwan. Details of The National Health Insurance Database have been described elsewhere (28). Briefly, the National Health Insurance Database is derived from the National Health Insurance program of Taiwan, and it contains records of approximately 23 million individuals (nearly 99.9% of the total population of Taiwan). The National Health Insurance Database includes records of diagnoses, medications, and procedures from outpatient- and inpatient settings, emergency rooms, and contracted pharmacies. Many major disease diagnoses in the National Health Insurance Database have been validated by previous studies, including ischemic stroke (29), epilepsy (30), hypertension (31), diabetes (31), hyperlipidemia (31), coronary artery disease (31), atrial fibrillation (31), heart failure (32), Parkinson's disease (33), major neurocognitive disorders (33), schizophrenia (34), bipolar disorder (34), and depression (34). The diagnosis codes for osteoarthritis (35), osteoporosis (35), cataract (35), falls (36), and fractures (35) have not been validated, but they were selected based on previous studies and expert opinions from a psychiatrist and a geriatrician. The study drugs - cholinesterase inhibitors and antipsychotic medications - are mostly reimbursed by the National Health Insurance program in Taiwan, meaning that the majority of prescription records have been captured. Additionally, we linked the National Health Insurance Database to the "Cause of Death" registry data in order to precisely identify patients who died within the study period. The study protocol has been approved by the Institutional Review Board of National Cheng Kung University Hospital (B-ER-107-012).

Study Population

The study period was from 2006 to 2017. We selected older adults aged 65 years or above on 1st Jan 2006 who had received at least one prescription of both antipsychotic medications and cholinesterase inhibitors for neuropsychiatric symptoms of major neurocognitive disorders, and who had experienced at least one episode of fall or fracture during the study period. The prescription records of cholinesterase inhibitors were used to confirm the diagnosis of major neurocognitive disorders since all use of cholinesterase inhibitors was subject to review by experts from the National Health Insurance Administration, based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition and patients' scores of Mini-Mental State Examination. We did not consider low-dose sulpiride (50mg/day) as an antipsychotic medication because it is frequently used for gastroduodenal ulcers; similarly, prochlorperazine was excluded as an antipsychotic medication because it is more widely used as an antiemetic in Taiwan. We excluded patients with a record of antipsychotic medication or cholinesterase inhibitor, or an episode of fall or fracture from 2003 to 2005 (washout period) to ensure that the whole study population consisted of new users of the study medications with no history of falls or fractures. We also excluded patients with underlying schizophrenia or bipolar disorder to ensure that antipsychotic medications were used to treat the neuropsychiatric symptoms of major neurocognitive disorders. The study selection flowchart is presented in **Figure 1**.

Study Design

We applied the self-controlled case series design in this study (37). Self-controlled case series includes individuals who have both the outcome and the exposure of interest during a pre-specified study period. These participants act

as their own control, and thus all time-constant covariates varying between individuals are controlled. Self-controlled case series enables risk estimates by comparing the incidence rates of the outcome between the non-exposure and exposure periods, based on the conditional Poisson regression model.

Outcome Events and Exposure Periods

The primary outcome of interest was a composite of falls (International Classification of Disease-9 code: E880-E888; International Classification of Disease-10 code: W00-W19) and traumatic fractures (International Classification of Disease-9 code: 800-829; International Classification of Disease-10 code: S02, S12, S22, S32, S42, S52, S62, S72, S82, S92), whereby we also analyzed falls and fractures separately in secondary analyses. We only considered the first occurrence of an outcome in the analysis because recurrences of falls and fractures were not independent. In addition, we included falls and fractures leading to hospitalization as a more severe outcome for a secondary analysis, which was defined by the primary diagnosis from the inpatient claims. We classified the study time into five discrete periods: 1) 14-day pre-exposure period prior to the exposure to drugs, 2) exposure to cholinesterase inhibitors alone, 3) exposure to antipsychotic medications alone, 4) exposure to a combination of cholinesterase inhibitors and antipsychotic medications, and 5) non-exposure when neither cholinesterase inhibitors nor antipsychotic medications were given. The 14-day pre-exposure period was designed to evaluate the increased incidence of falls and fractures due to neuropsychiatric symptoms of major neurocognitive disorders before the initiation of medications, and to benchmark the risk magnitude during the exposure periods. **Figure 2** presents the exposure periods as defined above. Continuous use of drugs was defined as patients refilling their prescriptions within 14 days after the end date of the last prescription (i.e., 14-day grace period).

Statistical Analysis and Covariates

For continuous variables, we present the mean with standard deviation or the median with interquartile range, and we present the number with proportion for categorical variables. Assessment of patient baseline characteristics was based on the covariates extracted from within one year before 1st Jan 2006, including age, sex, subtype of major neurocognitive disorders, comorbidities, and co-medications (**Table 1**). Subtypes of major neurocognitive disorders included Alzheimer's disease, Parkinson's dementia, vascular dementia, mixed type (i.e., those who had been diagnosed with more than one subtype of major neurocognitive disorders), others or unspecified (38, 39). The subtypes of major neurocognitive disorders and comorbidities were defined using International Classification of Disease codes listed in **Supplementary Table 1.** We also evaluated patients' characteristics at the time of outcome events, including their age on the event date, settings of the event being diagnosed, mortality after the event, type of exposure, anticholinergic burden measured by the anticholinergic drug scale, and the ratio of prescribed daily dose to defined daily dose for cholinesterase inhibitors and antipsychotic medications (**Table 1**). Anticholinergic drug scale is a widely used measure developed through the expert opinion process and consisting of a four-point scale ranging from 0 for no known activity to 3 for high anticholinergic activity (40). Prescribed daily dose is calculated as the sum of actual doses of each medication, while defined daily dose is a standard unit widely applied for the crosswalk of drugs with different strengths, developed by the World Health Organization (41). It is an assumed average maintenance dose per day for each medication.

We used the conditional Poisson regression model to calculate the incidence rates of falls and fractures in different study periods, and we generated the incidence rate ratios with 95% confidence intervals using the non-exposure period as the reference group. Self-controlled case series eliminates time-constant confounders, but it is sensitive

to time-varying factors such as the progression of major neurocognitive disorders. Therefore, we adopted a one-year boundary to split the study period in order to take into account possible age-related effects. That is, we partitioned the observation period not only by the exposure status but also by one-year intervals (e.g., the first, second, and third years, etc.) This time-varying method to adjust for age effects has been described in detail elsewhere (37). Because some potentially important confounders such as patients' bodyweight, daily life activities, and the use of walking aids were not available in the database, we adopted a quantitative bias assessment tool, the E-value approach, to evaluate the minimum effect from an unmeasured confounder that would suffice to obviate the association found between the exposure and the outcome (42). For example, an E-value of 5 indicates that the unmeasured confounder would need to be associated with both exposure and outcome by a factor of more than five times in order to render the observed association irrelevant. Computation of the E-value was based on the work of Mathur et al (43).

Sensitivity Analyses

To examine the robustness of our findings, we conducted sensitivity analyses using different definitions of the study population, exposures, outcomes, and lengths of the pre-exposure period. We stratified the patients by sex (male or female) and age group (65 to 74 years, 75 to 84 years, and 85 years or above) to examine any differential effects within age and sex strata **(Supplementary Table 3-1 and 3-2)**. Anticholinergic burden (i.e., the cumulative effect of taking multiple medications with anticholinergic activities) is a critical issue that may also be associated with falls and fractures in the elderly (44). A high anticholinergic burden has been reported to adversely affect cognitive and physical functions, and may also increase the risk of falls, hospitalization, and death (45-48). To account for the potential impact, we included the anticholinergic drug scale to classify patients by their anticholinergic burden for the sensitivity analyses **(Supplementary Table 3-3)**. To examine the dosage effect, we stratified the study population based on their cumulative doses of antipsychotic medications (above or below the median) using the ratio of prescribed daily dose to defined daily dose **(Supplementary Table 3-4)**.

Furthermore, patients in different care settings may have different baseline risks of falls and fractures. To understand the impact of care settings, we conducted an additional analysis whereby we restricted outcomes to only those recorded at outpatient settings in an effort to better reflect the risk in the community, where interventions to prevent falls and fractures might be insufficient **(Supplementary Table 3-5)**. To examine the effect of excluding schizophrenia and bipolar disorder, we conducted sensitivity analyses without exclusion of these mental conditions. We then further stratified this population by schizophrenia, bipolar disorder, and depression to examine the individual effects from these conditions **(Supplementary Table 3-6)**. Since patients who died from an outcome event would not have a subsequent exposure, potentially violating the assumption of self-controlled case series, we performed two sensitivity analyses after removing patients who died during the study period and patients who died within three months after the events, respectively **(Supplementary Table 3-7)**. Moreover, we carried out a sensitivity analysis and selected specific diagnostic codes for falls and fractures (i.e., falls from a different level [International Classification of Disease-9: E880-E884; International Classification of Disease-10: W00.1, W00.2, W05-W17], falls from the same level [International Classification of Disease-9: E885-E886; International Classification of Disease-10: W00.0, W01-W04, W18], and hip fractures [International Classification of Disease-9: 820; International Classification of Disease-10: S72]) to examine the validity of the outcomes**.** The reason for selecting hip fractures was that more than 95% of hip fractures were found to be related to falls (49) **(Supplementary Table 3-8)**. In the main analysis, we only included the first incidence of falls or fractures since

subsequent events might not be independent of previous falls or fractures. However, we performed a sensitivity analysis including all episodes of falls and fractures in order to evaluate whether the exclusion of subsequent outcomes had significantly impacted the results **(Supplementary Table 3-9)**. We further redefined the pre-exposure period to include various lengths of 7, 21, and 28 days to test the adequacy of a 14-day pre-exposure period in the main analysis (**Supplementary Table 3-10**)**.**

Each antipsychotic medication has different affinities to alpha-adrenergic receptors, histamine receptors, and dopamine receptors, which can lead to varying degrees of effects that possibly provoke falls and fractures, such as heart rate reduction, vasodilation, orthostatic hypotension, blurred vision, sedation, and extrapyramidal symptoms (8). Therefore, we conducted subgroup analyses to evaluate individual antipsychotic medications separately. We selected haloperidol, risperidone, olanzapine, and quetiapine for the subgroup analyses because they were the most commonly used antipsychotic medications for elderly patients in Taiwan (**Supplementary Table 3-11**). Some studies have found strong associations between antipsychotic medications and falls and fractures immediately after treatment initiation or shortly after discontinuation of treatment (17, 50). We therefore defined two more study periods of 14 days: one after treatment initiation and the other following treatment discontinuation (**Supplementary Table 3-12**)**.** We used SAS version 9.4 for all analyses.

Patient and Public Involvement

Patients and the public were not involved in this study due to the constrained situation during the COVID-19 pandemic in Taiwan, as well as funding restrictions.

RESULTS

Patient Characteristics at Baseline

We identified 15,278 patients eligible for the self-controlled case series (**Figure 1**), with a mean age at baseline of 74.5 (standard deviation: 5.5) years, of whom 66.7% were female. Although all diagnoses of major neurocognitive disorders had been reviewed by licensed neurologists or psychiatrists, most of the study populations were recorded as unspecified major neurocognitive disorders (69.2%). The most common comorbidities were hypertension (50.9%), osteoarthritis (30.8%), and cataract (27.9%). Non-steroidal anti-inflammatory drugs were the most commonly prescribed co-medications (74.8%), followed by antihistamines (63.7%) and anxiolytics (51.7%).

Patient Characteristics at Event Occurrence

The mean age on the event date was 79.7 (standard deviation: 6.1) years old. We found that about 48.6% experienced falls or fractures that required hospitalization or emergency room visit, and 1.7% died within three months after the events. The median anticholinergic drug scale was 1.0 (interquartile range: 3.0), and the median ratio of prescribed daily dose to defined daily dose representing the cumulative antipsychotic dose was 12.3 (interquartile range: 49.0). Of the entire study population, 12.8% were using cholinesterase inhibitors and 9.0% were using antipsychotic medications when the event occurred. The median dose of cholinesterase inhibitors ranged from 0.7 to 1.0 ratio of prescribed daily dose to defined daily dose, and the median dose of antipsychotic medications ranged from 0.1 to 0.5 ratio of prescribed daily dose to defined daily dose, which was similar to previous studies (51-53). Detailed patient characteristics are presented in **Table 1**.

Evaluation of the Risk of Falls and Fractures

Compared with the non-exposure period, the risk of falls and fractures was higher under exposure to cholinesterase inhibitors alone (adjusted incidence rate ratio; 95% confidence interval: 1.17; 1.10 to 1.24; E-value: 1.62), antipsychotic medications alone (1.33; 1.24 to 1.43; E-value: 1.99), and combination (1.35; 1.26 to 1.45; E-value: 2.04). The risk was even higher during the pre-exposure period (6.17; 5.69 to 6.69; E-value: 11.82) compared with the non-exposure period. In the analysis of falls, the adjusted incidence rate ratios were 0.91 (0.71, 1.18), 1.36 (1.02, 1.93), 1.55 (1.17, 2.05), and 10.39 (8.08, 13.37) for the exposure to cholinesterase inhibitors alone, antipsychotic medications alone, combination, and the pre-exposure period, respectively. In the analysis of fractures, the adjusted incidence rate ratios were 1.18 (1.11, 1.26), 1.34 (1.24, 1.43), 1.35 (1.25, 1.45), and 6.11 (5.62, 6.63) for the exposure to cholinesterase inhibitors alone, antipsychotic medications alone, combination, and the pre-exposure period, respectively. We included 7,364 cases with hospitalized falls or fractures, and the results were also consistent with the main analysis (**Table 2**).

Sensitivity Analyses

The results from the sensitivity analyses were generally consistent with the main analysis. The exposure periods to cholinesterase inhibitors and antipsychotic medications carried higher risks of falls and fractures compared with the non-exposure period, and the pre-exposure period had a much higher risk of falls and fractures than any other period **(Table 3**). Specifically, compared with the non-exposure period, we found the adjusted incidence rate ratios of the pre-exposure period were 2.81 (2.03, 3.90), 6.11 (5.49, 6.80), and 8.07 (7.03, 9.26) among patients aged 65 to 74 years, 75 to 84 years, and 85 years or above, respectively; 7.63 (6.73, 8.65) and 5.35 (4.80, 5.95) among male and female patients, respectively. The adjusted incidence rate ratios of the pre-exposure period were 5.30 (4.74,

5.94) and 7.41 (6.60, 8.33) among patients with an anticholinergic drug scale of 0 to 1 and 2 or above points, respectively. The adjusted incidence rate ratios of the pre-exposure period were 5.73 (4.54, 7.24) and 5.45 (4.54, 6.53) among patients who had higher and lower cumulative doses of antipsychotic medications, respectively. Only 513 patients were excluded from the main analysis due to schizophrenia or bipolar disorder, and when we re-selected the study population without excluding schizophrenia and bipolar disorder, the adjusted incidence rate ratio of the pre-exposure period was 6.07 (5.60, 6.57). The adjusted incidence rate ratios of the pre-exposure period were 2.94 (0.70, 12.37) for those with schizophrenia, 3.24 (1.76, 5.99) for those with bipolar disorder, and 4.13 (3.49, 4.90) for those with depression. Of note is the large confidence interval of the schizophrenia group, which is due to its limited sample size (n=98). When we redefined the outcome by specific diagnosis codes, the adjusted incidence rate ratio of the pre-exposure period was 10.16 (9.10, 11.35). When we redefined multiple lengths of the pre-exposure period as 7, 21, and 28 days, the adjusted incidence rate ratios of these pre-exposure periods were 9.49 (8.64, 10.43), 4.91 (4.56, 5.30), and 4.43 (4.14, 4.75), respectively. In the analyses focusing on individual antipsychotic medications, we found that the adjusted incidence rate ratios were 3.75 (3.15, 4.47), 1.15 (0.99, 1.35), 1.35 (1.00, 1.82), and 1.16 (1.07, 1.26) under exposure to haloperidol, risperidone, olanzapine, and quetiapine, respectively. Finally, the adjusted incidence rate ratios were 3.31 (2.96, 3.70) within 14 days after treatment initiation and 1.24 (1.05, 1.47) within 14 days after discontinuation of treatment. **Table 3** presents a summary of results for adjusted incidence rate ratios only. Detailed results are presented in **Supplementary Tables 3-1 to 3-12**.

DISCUSSION

Principal Findings

From this population-based self-controlled case series, we found that exposures to cholinesterase inhibitors and antipsychotic medications were both associated with a higher risk of falls and fractures compared with the non-exposure period. However, the results should be interpreted carefully. The 14-day pre-exposure period revealed an exceptionally high incidence rate of falls and fractures, indicating that patients may have already been at high risk of outcome events before receiving the medications. The observed higher risks during the exposure periods, as compared with the non-exposure period, may result from neuropsychiatric symptoms in addition to the medication use. This implied that the patients might not have fully regained a steady condition, despite receiving treatment. This conclusion remained robust throughout a series of subgroup and sensitivity analyses.

Previous studies have reported that both cholinesterase inhibitors and antipsychotic medications were associated with falls and fractures, with the magnitude of risk increasing up to 18% (5) to 63% (3) among patients receiving cholinesterase inhibitors, and up to 21% (14) to 54% (22) among patients receiving antipsychotic medications. Consistent with previous studies, our findings suggest that compared with the non-exposure period, exposures to cholinesterase inhibitors and antipsychotic medications led to a 17% and 33% increase, respectively, in the risk of falls and fractures. However, this result showing that the exposure periods were associated with an elevated risk of falls and fractures should be interpreted carefully. Our results showed that patients may have already been at high risk before receiving the treatment, implying that the interconnection among patients' underlying conditions, drug effects on relieving neuropsychiatric symptoms, and side effects of cholinesterase inhibitors and antipsychotic medications has increased the difficulty of delineating the exact contributing factors and quantifying the magnitude of the risk of falls and fractures that each factor poses. Similar findings have been reported in previous studies. For example, Brännström et al. (27) reported that the highest risk of hip fractures occurred before the initiation of antipsychotic medications (odds ratio: 9.09; 95% confidence interval: 7.00 to 11.81 within -16 to -30 days and odds ratio: 5.84; 95% confidence interval: 4.42 to 7.71 within -1 to -15 days), rather than after receiving treatment (odds ratio: 4.31; 95% confidence interval: 3.05 to 6.10 within 1 to 15 days). Pratt et al. (18) also found that the risk of hospitalization for hip fractures was the highest within one week before antipsychotic medications initiation (incidence rate ratio 10.99; 95% confidence interval: 7.94 to 15.21), and the risk reduced within one week after antipsychotic medications initiation (incidence rate ratio 1.04; 95% confidence interval: 0.40 to 2.70). These findings suggested that the observed higher risk of outcomes during the exposure periods might not be attributable to the medications alone.

Strengths and Weaknesses

We used a large population-based database to provide sufficient statistical power to evaluate the association between the drugs and potential adverse reactions. The nature of the self-controlled case series design allows controlling for time-constant confounders through within-individual comparisons (37). We also adjusted the incidence rate ratios by a time-varying method using regression models.

However, there are some limitations to our study. First, data on the severity of major neurocognitive disorders and valid diagnosis of neuropsychiatric symptoms were not available from the database, which may have caused confounding by indication. Furthermore, our method of confirming the diagnosis of major neurocognitive disorders by the prescription records of cholinesterase inhibitors has not been validated. Second, we evaluated the risk of

falls and fractures based on prescription records. We used a 14-day grace period in order to address the residual effects of drugs after discontinuation, but the possibility of misclassification bias remains. Third, we selected all diagnosis codes related to falls and fractures to ensure we had captured all possible outcome events from the database. However, some of the codes, such as E888 in International Classification of Disease-9 and W19 in International Classification of Disease-10 (i.e., unspecified falls), might not have been specific enough to reflect the relationship between exposures and outcomes in this study. To evaluate the potential impact of these non-specific outcomes, we conducted a sensitivity analysis selecting only specific codes for falls and fractures. The results were consistent with those in the main analysis. Fourth, some patients might have discontinued the medications due to minor falls or related symptoms. This meant those who continued the treatment might represent a group of patients who tolerated the medications well, which might have affected the evaluation of the outcomes. Therefore, we performed a post-hoc analysis to understand the extent of medication discontinuation after a fall or a fracture. We found that only 7.9% of patients discontinued their medications after events; thus, medication discontinuation and its subsequent impact on outcome evaluation might be limited. Fifth, patients living in different care settings might have different baseline risks and this should be considered in the self-controlled case series. For example, the higher risk of outcomes during the pre-exposure period might be because the patients were living at home, with more trip hazards from rugs, stairs, and walking. Similarly, the lower risks during the medication treatment periods could partially be due to support from healthcare facilities. To assess the possibility of the care setting effect, we conducted an additional analysis by including only outcome events recorded at outpatient settings. The results showed that incidence rate ratios were smaller after limiting outcomes to only those that occurred in the community, but the risk for the pre-exposure period remained higher than for the non-exposure period. Sixth, our study may be subject to unmeasured confounders such as patients' daily life activities. The quantitative bias assessment (i.e., E-value) showed that the potentially unmeasured confounders need to have a very large effect size to refute the observed high risk of falls and fractures during the pre-exposure period. According to the literature (1), potential unmeasured confounders have not been shown to have such a large effect size, and we thus concluded that the results were not affected significantly by these confounders. Seventh, we did not have the exact outcome dates for those who had falls or fractures during hospitalization because the diagnoses were registered on the discharge date, and thus the outcome dates we analyzed may have been later than the dates of actual event occurrences. Therefore, we may have underestimated the risk during the exposure periods for those who had falls or fractures during hospitalization and then discontinued the medications. Lastly, our study did not evaluate the dose-response relationship between the drugs and the risk of falls and fractures. However, we did compare the dosages of antipsychotic medications from our study population with those reported in guidelines and previous studies, and the dosages were within the suggested ranges (51-53). Moreover, the stratification analysis by the ratio of prescribed daily dose to defined daily dose indicated that the dosages of antipsychotic medications did not have a differential impact on the risk of falls and fractures.

Meaning of the Study

Patients with major neurocognitive disorders often suffer from cognitive impairment and neuropsychiatric symptoms that may cause substantial morbidity and mortality (2). Cholinesterase inhibitors can improve cognitive function, and antipsychotic medications can control neuropsychiatric symptoms. Therefore, they are commonly prescribed for patients with major neurocognitive disorders. Previous studies have suggested that the use of cholinesterase inhibitors (3, 4) and antipsychotic medications (10-22) may be associated with the risk of falls and fractures due to some side effects like hypotension, syncope, or extrapyramidal symptoms. However, confounding

by indication should be considered since patients may have already been at high risk of falls and fractures before the treatment started. In our study, we found a surge in the risk of falls and fractures during the pre-exposure period, which was mitigated after patients received treatment. However, the risks during exposures to medications remained higher than during the non-exposure period. These findings suggest that close monitoring of any early signs of falls and prevention strategies remain necessary during the treatment.

From our sensitivity analyses, we identified subgroups that might have a higher risk of outcomes at baseline. For example, patients of advanced age or male sex had a higher risk of falls and fractures. Consistent with previous studies in which the anticholinergic effect in the elderly was found to increase the likelihood of falls and cognitive deterioration (54, 55), we observed a much higher risk during the pre-exposure period in patients with a higher anticholinergic burden. One of the likely explanations for the higher risk with haloperidol could be its greater extrapyramidal symptoms, compared with other antipsychotic medications. Confounding by indication could be another explanation because patients with positive symptoms (e.g., agitation) may be more likely to receive haloperidol. Furthermore, we tested various lengths of the pre-exposure period from 7 days to 28 days. The incidence rate ratio was the highest when the length of the pre-exposure period was defined as 7 days (incidence rate ratio: 9.49), and it decreased as the duration of the pre-exposure period lengthened - 14 days (incidence rate ratio: 6.17), 21 days (incidence rate ratio: 4.91), and 28 days (incidence rate ratio: 4.43). Based on these results, it can be concluded that a 7-day pre-exposure period probably represents a period of rapid deterioration. On the other hand, a duration of more than 21 days possibly captures a relatively stable status. Therefore, our decision to use 14 days appears to be appropriate. The sensitivity analyses not only examined the robustness of the results and identified the impacts of various definitions, but also provided parameters for future studies. Moreover, the incidence rate ratio within 14 days after treatment initiation was higher than during other exposure periods, suggesting that a minimum duration of exposure might be required to stabilize these patients. The incidence rate ratio within 14 days after discontinuation of treatment was higher than during the non-exposure period, suggesting that clinical attention is still necessary for the initial stage after patients discontinue their treatments.

Unanswered Questions and Future Research

While the reason for the elevated risk during the pre-exposure period may lie in the relatively unstable condition of patients, this will need to be elucidated by further studies. The risk during the exposure to treatment could reflect a composite consequence of patients' unstable disease status, effects of medications on relieving neuropsychiatric symptoms, and side effects of medications. For example, some side effects of antipsychotic medications such as orthostatic hypotension, sedation, and extrapyramidal symptoms could increase the risk of falls and fractures, while others such as immobility, drowsiness, or being bedridden could reduce the risk. However, these explanations are based mainly on clinical observations, and could not be exhaustively tested in the current study. Future studies considering the severity of major neurocognitive disorders (e.g., Mini Mental State Examination scale or Clinical Dementia Rating scale) and patient-reported information might provide a better platform to address these issues.

CONCLUSION

The incidence of falls and fractures was especially high in the pre-exposure period, suggesting that some factors other than the medications, such as underlying diseases, should be taken into consideration when evaluating the association between the risk of falls and fractures, and the use of cholinesterase inhibitors and antipsychotic medications. The exposure periods were also associated with a higher risk of falls and fractures, compared with the non-exposure period, although the magnitude was much lower than during the pre-exposure period. Prevention strategies and close monitoring of the risk of falls are still necessary until there is evidence that patients have regained a steady condition.

SUMMARY BOX

What is already known on this topic?

- Both antipsychotic medications and cholinesterase inhibitors have been reported to increase the incidence of falls and fractures in patients with major neurocognitive disorders.
- Confounding by indication should be carefully considered while evaluating the association between drugs and adverse reactions because cognitive impairment and neuropsychiatric symptoms of major neurocognitive disorders may lead to a high risk of falls and fractures.

What this study adds?

- The risk of falls and fractures is the highest before patients receive cholinesterase inhibitors and antipsychotic medications, implying that factors other than the medications may have a huge impact on the incidence of falls and fractures.
- Although the high risk in the pre-exposure period was mitigated after patients received treatment, our results indicated that the patients might not have regained a steady condition.

AUTHOR STATEMANTS

Contributors: GHMW and ECCL initiated the collaborative project, developed the research question, designed the study protocol, and drafted the manuscript. GHMW and ECCL are the guarantors. GHMW, KKCM, WHC, and ECCL edited the study protocol, interpreted the results, and reviewed the manuscript. TCL wrote the statistical analysis plan and conducted the statistical analysis. The authors thank Dr. Swu-Jane Lin for her critical comments on the manuscript. We are grateful to the Health Data Science Center, National Cheng Kung University Hospital for providing administrative and technical support. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: The study protocol has been approved by the Institutional Review Board of National Cheng Kung University Hospital (protocol number: B-ER-107-012).

Data sharing: We remotely accessed the data from the data center of the Ministry of Health and Welfare. Individual-level data is forbidden to be taken out from the data center. No additional data is available.

Transparency: The lead authors (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We plan to submit our accepted manuscript to the National Cheng Kung University Hospital, National Cheng Kung University College of Medicine, and Taiwan Food and Drug Administration to apply for publication on their press releases. We will also write a post on the official website of the National Cheng Kung University School of Pharmacy, which will tag all members in the research groups on Facebook and Twitter.

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TABLES

Table 1: Patient characteristics

Variables	Study population (n=15,278)
Sex, n (%)	
Female	10,190 (66.7)
Male	5,088 (33.3)
Age, years, mean (standard deviation)	74.5 (5.5)
Age group, years, n (%)	
65-74	7,685 (50.3)
75-84	6,966 (45.6)
85+	627 (4.1)
Subtype of major neurocognitive disorders, n (%)	
Alzheimer's disease	3,339 (21.9)
Parkinson's dementia	990 (6.5)
Vascular dementia	230 (1.5)
Mixed type (more than one subtype)	149 (1.0)
Others or unspecified	10,570 (69.2)
Drug sequence, n (%)	
Cholinesterase inhibitors before antipsychotic medication	6,688 (43.8)
Antipsychotic medication before cholinesterase inhibitors	8,289 (54.2)
Used concomitantly	301 (2.0)
Comorbidities, n (%)	
Depression	932 (6.1)
Parkinson's disease	287 (1.9)
Epilepsy	60 (0.4)
Hypertension	7,776 (50.9)
Diabetes mellitus	3,347 (21.9)
Hyperlipidaemia	3,353 (21.9)
Coronary artery disease	3,229 (21.1)
Atrial fibrillation	217 (1.4)
Heart failure	589 (3.9)
Ischemic stroke	1,573 (10.3)
Osteoarthritis	4,703 (30.8)
Osteoporosis	1,553 (10.2)
Cataract	4,261 (27.9)
Co-medications, n (%)	
Antidepressants	1,947 (12.7)
Psychostimulants	861 (5.6)
Anxiolytics	7,904 (51.7)
Hypnotics and sedatives	3,337 (21.8)
Antiparkinsonian agents	6,51 (4.3)
Anticonvulsants	1,178 (7.7)
Muscle relaxants	6,730 (44.1)
Vasodilators	4,993 (32.7)
Antihypertensive drugs	1,651 (10.8)
Diuretics	3,461 (22.7)
Renin–angiotensin–aldosterone system inhibitors	4,377 (28.6)
Beta-blockers	4,841 (31.7)
Calcium channel blockers	5,988 (39.2)
Anti-diabetic drugs	2,801 (18.3)
Lipid modifying agents	2,631 (17.2)
Antiarrhythmic agents (class 1 and 3)	435 (2.8)
Antithrombotic agents	5,018 (32.8)
Steroid (systemic use)	4,238 (27.7)
Non-steroidal anti-inflammatory drug	11,430 (74.8)
Bisphosphonates	199 (1.3)
Parasympathomimetic drugs	314 (2.1)
Antihistamines	9,734 (63.7)

Table 1: Patient characteristics (continued)

Variables	Study population (n=15,278)
Age on the event date, years, mean (standard deviation)	79.7 (6.1)
Age group on the event date, years, n (%)	
65-74	3,137 (20.5)
75-84	8,703 (57.0)
85+	3,438 (22.5)
Outcome events, n (%)	
Falls	766 (5.0)
Falls from a different level	200
Falls from the same level	310
Fractures	14,874 (97.4)
Hip fractures	2,863
Settings of the event being diagnosed, n (%)	
Outpatient	7,857 (51.4)
Inpatient	4,644 (30.4)
Emergency room	2,777 (18.2)
Died during the study period, n (%)	5,198 (34.0)
Died within 3 months after event	264
Anticholinergic burden, anticholinergic drug scale, median (interquartile range)	1.0 (3.0)
Cumulative dose of antipsychotic medications, ratio of prescribed daily dose to defined daily dose, median (interquartile range)	12.3 (49.0)
Type of exposure on the event date, n (%)	
Combination	1,270 (8.3)
Cholinesterase inhibitors alone	1,960 (12.8)
Donepezil	1,826
Rivastigmine (oral)	974
Rivastigmine (patch)	242
Galantamine	195
Antipsychotic medications alone	1,374 (9.0)
Haloperidol (oral)	116
Haloperidol (parenteral)	154
Risperidone	401
Olanzapine	110
Quetiapine	1,901
Dose on the event date, ratio of prescribed daily dose to defined daily dose, median (interquartile range)	
Cholinesterase inhibitors	
Donepezil	0.9 (0.6)
Rivastigmine (oral)	0.7 (0.4)
Rivastigmine (patch)	0.9 (0.4)
Galantamine	1.0 (0)
Antipsychotic medications	
Haloperidol (oral)	0.1 (0.2)
Haloperidol (parenteral)	0.1 (0.2)
Risperidone	0.2 (0.1)
Olanzapine	0.5 (0.3)
Quetiapine	0.1 (0)
Time from the closest prescription to the event (weeks), median (interquartile range)	
Cholinesterase inhibitors	
Donepezil	64.1 (104.3)
Rivastigmine (oral)	59.7 (123.0)
Rivastigmine (patch)	59.4 (83.4)
Galantamine	80.9 (146.5)
Antipsychotic medications	
Haloperidol (oral)	7.9 (44.0)
Haloperidol (parenteral)	0 (2.3)
Risperidone	31.4 (66.0)
Olanzapine	29.2 (51.0)
Quetiapine	45.6 (88.9)

Table 2: Risk of falls and fractures in different study periods

	Events, n	Follow-up time, person-years, sum	Follow-up time, years, median (interquartile range)	Incidence rate (95% confidence interval), /100 person-years	Crude incidence rate ratio (95% confidence interval) compared with non-exposure	Adjusted incidence rate ratio (95% confidence interval) compared with non- exposure	Adjusted incidence rate ratio (95% confidence interval) compared with pre-exposure*
All events **(n=15,278)**							
Non-exposure	10,208	122,963.00	8.55 (4.01)	8.30 (8.14, 8.46)	Reference	Reference	0.16 (0.15, 0.18)
Pre-exposure	657	1,254.90	0.07 (0.03)	52.35 (48.46, 56.47)	6.31 (5.83, 6.82)	6.17 (5.69, 6.69)	Reference
Cholinesterase inhibitor alone	1,790	19,018.33	0.96 (1.92)	9.41 (8.98, 9.86)	1.13 (1.08, 1.19)	1.17 (1.10, 1.24)	0.19 (0.17, 0.21)
Antipsychotic medication alone	1,353	13,087.45	0.35 (1.21)	10.34 (9.80, 10.89)	1.25 (1.18, 1.32)	1.33 (1.24, 1.43)	0.22 (0.20, 0.24)
Combination	1,270	12,037.35	0.56 (1.31)	10.55 (9.98, 11.14)	1.27 (1.20, 1.35)	1.35 (1.26, 1.45)	0.22 (0.20, 0.24)
Falls **(n=766)**							
Non-exposure	341	6,750.84	9.28 (3.32)	5.05 (4.54, 5.61)	Reference	Reference	0.10 (0.07, 0.12)
Pre-exposure	84	62.84	0.07 (0.03)	134.70 (107.30, 164.70)	26.46 (20.84,33.60)	10.39 (8.08,13.37)	Reference
Cholinesterase inhibitor alone	120	968.87	1.01 (2.11)	12.39 (10.31, 14.76)	2.45 (1.99, 3.02)	0.91 (0.71, 1.18)	0.09 (0.06, 0.12)
Antipsychotic medication alone	107	554.99	0.28 (0.93)	19.28 (15.88, 23.20)	3.82 (3.07, 4.74)	1.36 (1.02, 1.82)	0.13 (0.09, 0.18)
Combination	114	518.55	0.49 (1.16)	21.98 (18.22, 26.31)	4.35 (3.52, 5.38)	1.55 (1.17, 2.05)	0.15 (0.11, 0.21)
Fractures **(n=14,874)**							
Non-exposure	9,998	119,543.18	8.53 (4.02)	8.36 (8.20, 8.53)	Reference	Reference	0.16 (0.15, 0.18)
Pre-exposure	627	1,222.01	0.07 (0.03)	51.31 (47.41, 55.45)	6.13 (5.66, 6.65)	6.11 (5.62, 6.63)	Reference
Cholinesterase inhibitor alone	1,735	18,491.49	0.96 (1.91)	9.16 (8.74, 9.60)	1.12 (1.07, 1.18)	1.18 (1.11, 1.26)	0.19 (0.18, 0.21)
Antipsychotic medication alone	1,299	12,764.29	0.35 (1.21)	10.18 (9.64, 10.74)	1.22 (1.15, 1.29)	1.34 (1.24, 1.43)	0.22 (0.20, 0.24)
Combination	1,215	11,759.94	0.56 (1.31)	10.33 (9.76, 10.93)	1.24 (1.16, 1.31)	1.35 (1.25, 1.45)	0.22 (0.20, 0.24)
Hospitalized events **(n=7,364)**							
Non-exposure	4,382	58,310.22	8.44 (4.15)	7.51 (7.30, 7.74)	Reference	Reference	0.10 (0.09, 0.11)
Pre-exposure	516	608.77	0.07 (0.04)	84.76 (77.68, 92.32)	11.28 (10.30, 12.36)	10.20 (9.28, 11.21)	Reference
Cholinesterase inhibitor alone	909	9,005.44	0.94 (1.85)	10.09 (9.45, 10.77)	1.34 (1.25, 1.44)	1.27 (1.17, 1.39)	0.12 (0.11, 0.14)
Antipsychotic medication alone	782	6,584.79	0.36 (1.26)	11.88 (11.07, 12.73)	1.58 (1.46, 1.71)	1.55 (1.41, 1.71)	0.15 (0.13, 0.17)
Combination	775	5,905.85	0.57 (1.34)	13.12 (12.22, 14.07)	1.75 (1.62, 1.88)	1.73 (1.57, 1.90)	0.17 (0.15, 0.19)

*Note: we considered the pre-exposure period as reference group and repeated the analysis.

Table 3. Summary of sensitivity analysis

	Patients, n	Adjusted Incidence Rate Ratio (95% confidence intervals)*			
		Pre-exposure	Antipsychotic medication alone	Cholinesterase inhibitor alone	Combination use
Main analysis	15,278	6.17 (5.69, 6.69)	1.33 (1.24, 1.43)	1.17 (1.10, 1.24)	1.35 (1.26, 1.45)
Stratified by sex and age					
Male	5,088	7.63 (6.73, 8.65)	1.55 (1.38, 1.75)	1.18 (1.06, 1.30)	1.48 (1.31, 1.67)
Female	10,190	5.35 (4.80, 5.95)	1.24 (1.13, 1.35)	1.16 (1.07, 1.25)	1.29 (1.18, 1.41)
Age group 65-74 years	3,137	2.81 (2.03, 3.90)	1.56 (1.25, 1.93)	1.16 (0.95, 1.40)	1.67 (1.29, 2.16)
Age group 75-84 years	8,703	6.11 (5.49, 6.80)	1.28 (1.17, 1.41)	1.18 (1.09, 1.28)	1.25 (1.14, 1.37)
Age group 85+ years	3,438	8.07 (7.03, 9.26)	1.20 (1.05, 1.37)	1.29 (1.15, 1.45)	1.51 (1.33, 1.72)
Stratified by anticholinergic burden indicators					
Anticholinergic drug scale 2+	6,579	7.41 (6.60, 8.33)	1.76 (1.60, 1.95)	1.35 (1.24, 1.48)	1.67 (1.51, 1.85)
Anticholinergic drug scale 0-1	8,699	5.30 (4.74, 5.94)	1.02 (0.93, 1.13)	1.05 (0.96, 1.13)	1.11 (1.01, 1.23)
Stratified by cumulative dose of antipsychotic medications					
Higher than the median value	3,232	5.73 (4.54, 7.24)	3.80 (3.38, 4.27)	2.04 (1.77, 2.35)	5.38 (4.79, 6.05)
Equal to or lower than the median value	3,247	5.45 (4.54, 6.53)	2.91 (2.54, 3.33)	1.66 (1.48, 1.87)	2.12 (1.82, 2.47)
Restricted to outcomes at outpatient settings only	7,914	2.54 (2.14, 3.01)	1.12 (1.01, 1.25)	1.09 (1.00, 1.19)	1.02 (0.91, 1.13)
Re-selected patients without excluding schizophrenia and bipolar disorder	15,791	6.07 (5.60, 6.57)	1.32 (1.24, 1.42)	1.17 (1.10, 1.24)	1.33 (1.24, 1.43)
Stratified by schizophrenia (yes)	98	2.94 (0.70, 12.37)	1.55 (0.80, 2.99)	0.66 (0.16, 2.72)	1.79 (0.75, 4.28)
Stratified by schizophrenia (no)	15,693	6.08 (5.61, 6.59)	1.32 (1.23, 1.42)	1.17 (1.10, 1.24)	1.33 (1.24, 1.43)
Stratified by bipolar disorder (yes)	426	3.24 (1.76, 5.99)	1.12 (0.80, 1.58)	1.19 (0.79, 1.81)	0.84 (0.55, 1.30)
Stratified by bipolar disorder (no)	15,365	6.15 (5.67, 6.67)	1.33 (1.24, 1.43)	1.17 (1.10, 1.24)	1.35 (1.26, 1.45)
Stratified by depression (yes)	4,743	4.13 (3.49, 4.90)	1.12 (1.00, 1.27)	1.03 (0.91, 1.16)	1.06 (0.93, 1.20)
Stratified by depression (no)	11,048	6.95 (6.34, 7.61)	1.43 (1.32, 1.56)	1.22 (1.14, 1.31)	1.48 (1.37, 1.61)
Removed patients who died during the study period	10,080	6.43 (5.80, 7.12)	1.25 (1.15, 1.37)	1.10 (1.02, 1.19)	1.18 (1.08, 1.30)
Removed patients who died within three months after the events	15,014	6.12 (5.63, 6.64)	1.30 (1.21, 1.40)	1.17 (1.10, 1.24)	1.31 (1.22, 1.41)
Redefined outcome by specific codes, all event	5,458	10.16 (9.10, 11.35)	1.52 (1.36, 1.69)	1.22 (1.11, 1.35)	1.67 (1.49, 1.87)
Falls	621	10.77 (8.19, 14.16)	1.26 (0.91, 1.74)	0.87 (0.65, 1.16)	1.49 (1.09, 2.04)
Fractures	5,149	10.41 (9.29, 11.66)	1.57 (1.40, 1.76)	1.26 (1.13, 1.39)	1.70 (1.51, 1.91)
Counting all episodes of falls and fractures	15,278	5.53 (5.21, 5.88)	1.24 (1.18, 1.31)	1.16 (1.11, 1.21)	1.31 (1.25, 1.38)
Redefined the length of pre-exposure period to					
7 days prior to exposure	15,278	9.49 (8.64, 10.43)	1.30 (1.21, 1.39)	1.17 (1.10, 1.25)	1.32 (1.23, 1.42)
21 days prior to exposure	15,278	4.91 (4.56, 5.30)	1.34 (1.25, 1.44)	1.17 (1.10, 1.24)	1.37 (1.27, 1.47)
28 days prior to exposure	15,278	4.43 (4.14, 4.75)	1.35 (1.26, 1.45)	1.18 (1.11, 1.25)	1.39 (1.29, 1.49)

Focusing on individual antipsychotic medications					
Haloperidol	4,745	12.11 (10.84, 13.54)	3.75 (3.15, 4.47)	1.16 (1.06, 1.27)	4.26 (3.37, 5.37)
Risperidone	5,119	2.74 (2.23, 3.35)	1.15 (0.99, 1.35)	1.23 (1.13, 1.35)	1.32 (1.13, 1.54)
Olanzapine	1,314	3.72 (2.57, 5.37)	1.35 (1.00, 1.82)	1.31 (1.09, 1.56)	1.77 (1.31, 2.39)
Quetiapine	12,851	5.40 (4.91, 5.93)	1.16 (1.07, 1.26)	1.18 (1.11, 1.26)	1.16 (1.07, 1.26)
*Reference group = non- exposure period					