BMC Geriatrics

RESEARCH

Open Access

Risk of falls or fall-related injuries associated with potentially inappropriate medication use among older adults with dementia

Arum Moon[1,2], Suhyun Jang[1,2], Jung-Ha Kim[3] and Sunmee Jang[1,2*]

Abstract

Background Potentially inappropriate medications (PIMs) are prevalent in older adults with dementia and subsequent falls or fall-related injuries. The present study determined the risk of falls or fall-related injuries associated with PIM use in older adults with dementia.

Methods The National Health Insurance Service-Elderly Cohort Database 2.0 (NHIS-ECDB 2.0) was used for this self-controlled case series (SCCS) study. This study included 1430 participants who went through exposure and non-exposure periods of PIM application among patients with dementia and experienced outcome events of falls or fall-related injuries between January 2016 and December 2019. The incidence of falls or fall-related injuries during the exposure and post-exposure periods was compared with that during the non-exposure period. Beers Criteria were used to define PIMs in patients with dementia. Negative binomial regression was conducted. The incidence rate ratio (IRR) was used to determine the risk of falls or fall-related injuries.

Results During the exposure periods in which falls or fall-related injuries occurred, the mean number of PIMs among patients with dementia was 3.76 (SD = 2.99), and the most commonly used PIMs among patients with dementia were first-generation antihistamines (n = 283; 59.1%). Compared to the non-exposure period, the adjusted IRR during the exposure period was 1.57 (95% CI = 1.39–1.76). The risk of falls or fall-related injuries was increased when PIM use in patients with dementia was initiated (1–14 days: IRR = 2.76, 95% CI = 2.31–3.28; 15–28 days: IRR = 1.95, 95% CI = 1.48–2.56; ≥ 29 days: IRR = 1.17, 95% CI = 1.01–1.35). Especially, an increased risk of falls or fall-related injuries was associated with greater PIM use among patients with dementia.

Conclusion Among older adults with dementia, PIMs significantly increase the risk of falls and fall-related injuries. Therefore, strategies should be developed to manage PIM prescriptions in patients with dementia to prevent falls.

Keywords Dementia, Falls, PIM, Antipsychotics, Anticholinergics, Benzodiazepines, Z-drugs

Background

Globally, the burden of dementia increases with its incidence. According to the fact sheet on dementia published by the World Health Organization (WHO), over 55 million people worldwide will suffer from dementia by 2023, with 10 million new patients diagnosed annually [1]. Dementia is a geriatric syndrome characterized by cognitive, behavioral, and psychological symptoms [2], and it leads to disability and dependency among

*Correspondence:
Sunmee Jang
smjang@gachon.ac.kr
[1] College of Pharmacy, Gachon University, 191 Hambakmoe-Ro, Yeonsu-Gu, Incheon 21936, Republic of Korea
[2] Gachon Institute of Pharmaceutical Sciences, Incheon, Republic of Korea
[3] Department of Family Medicine, Chung-Ang University Medical Center, College of Medicine, Chung-Ang University, Seoul, Republic of Korea

older adults, thus reducing their quality of life. Additionally, it ranks seventh among the causes of mortality [1]. In 2019, the estimated annual global cost of dementia amounted to 1.3 trillion USD. Approximately 50% of this cost was attributed to informal care provided by family and friends [1]. Consequently, the demand for dementia care has increased worldwide.

Older adults with dementia have multiple medical conditions [3] and often consume multiple medications along with anti-dementia drugs [4, 5]. As dementia mostly occurs among older adults, they experience age-related changes in their pharmacokinetic and pharmacological properties [6, 7]. Furthermore, cognitive impairment makes it challenging for them to manage their medications appropriately [8]. Therefore, medication management in patients with dementia requires caution. Potentially inappropriate medications (PIMs) are medications whose potential risks outweigh the therapeutic benefits in older adults, and it is recommended to switch to a different medication or discontinue their use [9, 10]. Some countries, like some European countries, the United States, and Canada, have developed explicit tools, such as the Beers Criteria, the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP), Screening Tool to Alert to Right Treatment (START), and PRISCUS, to identify PIM use among older adults [11]. In addition, these tools specify the PIMs for each condition. For example, the 2003 Beers criteria define anticholinergics, antipsychotics, benzodiazepines, and Z-drugs as PIMs for older adults with cognitive impairment [12]. These medications can increase the risk of adverse events associated with the central nervous system, such as cognitive impairment, which can result in an extended risk of falls in people with dementia [13–17]. Among older adults with dementia in the United States, PIM use has been associated with an increased risk of falls or fall-related injuries [18]. Among older adults with dementia living in nursing facilities, an increased risk of falls has been reported with antipsychotics use, concomitance, and escalation [19, 20]. In a study of hospitalized patients, the risk of falls increased with the concomitant use of five or more psychotropic medications [21]. Falls and fall-related injuries are critical healthcare problems because they are major causes of mortality, disability, morbidity, and hospitalization among older adults [22, 23]. Interventions can help prevent this problem, and many countries are working to prevent it.

Older adults with dementia are especially prone to falling than those without cognitive impairment, and they require greater attention considering fall prevention [17, 24, 25]. Although PIMs are associated with cognitive impairment and cause falls in older adults with dementia, they are still frequently used. The Beers Criteria identified the prevalence of PIM use among institutionalized and community-dwelling older adults with dementia as 34.1% in Sweden [26], 56% in Australia [27], 66.7% in Brazil [28], and 39.4% in China [29]. Among community-dwelling older adults with dementia, PIM use was 32.7% and 21.4% in the United States [30] and Australia [31], respectively.

It is crucial to gather evidence on the risks associated with PIM use among older adults with dementia to prevent associated falls and fall-related injuries. This study aimed to determine the risk of adverse events associated with PIM use among older adults with dementia by employing representative data and a self-controlled case series (SCCS) study design to reduce bias due to differences between study participants. The study also aimed to examine the relationship between the risk of adverse events and the duration and number of PIMs used in older adults with dementia, and to provide evidence for managing their medications.

Methods

Data sources

Data from the Version 2.0 of the National Health Insurance Service-Elderly Cohort database (2002–2019) (NHIS-ECDB 2.0) were used in this study. This is a sample research database that provides health insurance claims information for individuals older than 60 years in the Republic of Korea. It comprises approximately 1 million participants, representing 8% of the approximately 6.4 million older adults selected by stratified random sampling using sex, age, insurance fee, and region. The database contains demographic variables, including disability and death, medical use, and long-term care services for older adults. This study was approved by the Institutional Review Board of Gachon University (IBN No. 1044396–202111-HR-236–01).

Study design and Outcomes

Study design

The SCCS design was used to assess the risk of falls or fall-related injuries associated with the use of PIMs in older adults with dementia. This study compared the incidence of outcome events during the exposure and post-exposure periods to that during the non-exposure period as a baseline in the same individual. Therefore, this study only included individuals with non-exposure and exposure periods to PIMs among patients with dementia and outcome events of falls or fall-related injuries between January 2016 and December 2019.

Study participants (Fig. 1)

The inclusion criteria were 1) individuals aged ≥ 65 years with dementia who experienced

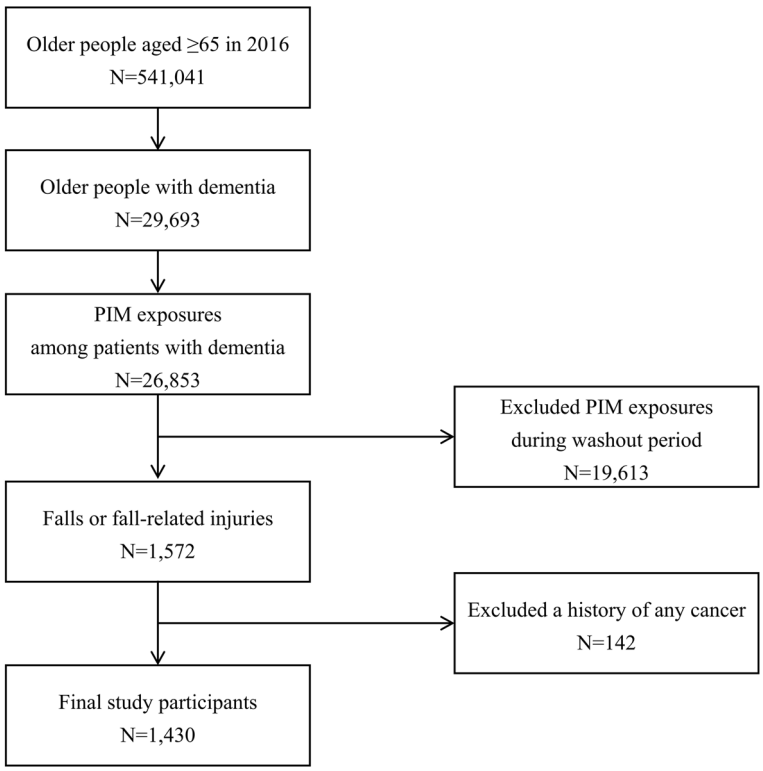

Fig. 1 Flowchart of the study participants' selection

outcomes events and had at least one prescription of PIM during the study period (Jan 2016-Dec 2019), 2) no PIM among patients with dementia prescriptions 6 months before the study period (Jul 2015-Dec 2015), and 3) no history of cancer during the study period. Older adults with dementia were defined as those with at least one prescription for indications of dementia a month before the study period (Dec 2015). The antidementia medications included Donepezil, Rivastigmine, Galantamine, Tacrine, and Memantine. A washout period of 6 months was established before the cohort enrollment to eliminate carryover effects from previous PIM use among patients with dementia [32]. Considering the complex disease characteristics and treatment regimens, older adults with history of cancer were excluded from this study.

Outcome events, exposure, and non-exposure periods

Outcome events included falls and fall-related injuries. Falls and fall-related injuries were identified using the International Classification of Diseases, 10th Revision (ICD-10) (Falls: W00-S19; Fractures as fall-related injuries: S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, and T02). The use of the same diagnostic code for a claim that occurred 6 months ago was not considered a different event.

The 2023 Beers Criteria were used to identify PIMs among patients with dementia. The Beers Criteria identify PIMs that should be avoided in older adults with dementia and consist of drugs with strong anticholinergics, antipsychotics, benzodiazepines, and Z-drugs (Supplementary Table 1).

As shown in Fig. 2, the overall observation period comprised exposure, post-exposure, and non-exposure periods. The exposure period was segmented into 1–14 days, 15–28 days, and ≥ 29 days considering the duration of PIM prescription among patients with dementia after the initiation of the study. As the effects of PIMs among patients with dementia might persist for some time after the medication is discontinued, a post-exposure period of 14 days was included after the end of PIM use among patients with dementia. To eliminate carryover effects, the duration of the post-exposure period was defined by considering the half-life of PIMs in patients with dementia [32–34]. The follow-up period continued until December 2019; however, patients who died before the completion of the study were monitored until the date of death.

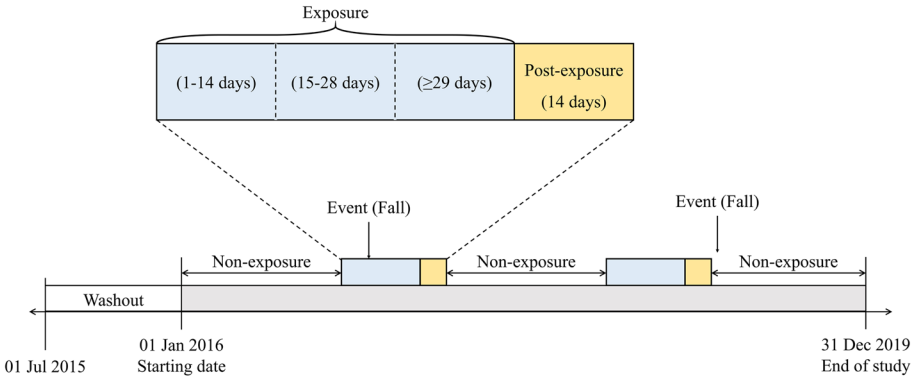

Fig. 2 Overall illustration of the self-controlled case series study design

Statistical analysis and covariates definition

Participants' baseline characteristics were represented using descriptive statistics, including frequencies and percentages for discrete variables and means and standard deviations (SDs) for continuous variables. The risk of falls or fall-related injuries was estimated using negative binomial regression, and crude incidence rate ratios (IRRs) and 95% confidence intervals (95% CIs) were presented. Poisson regression is commonly used to model count data; however, the risk was not equi-dispersed. Therefore, negative binomial regression was used as an appropriate model for overdispersion. IRRs were calculated by dividing the number of events by the sum of person–years multiplied by each period, and 95% CIs were calculated using a negative binomial distribution. Crude IRRs were adjusted for sex, age, living setting, insurance type, disability, Charlson comorbidity index (CCI) score, comorbidities, history of previous falls, and number of comedications, and were presented as adjusted IRRs. According to the Act on Welfare of Persons with Disabilities, a participant with a disability was defined as a person whose daily life or social activity is substantially hampered by physical or mental disabilities over a long period of time and who is registered with the Korea Social Security Information Service [35]. A history of falls was defined as falls or fall-related injuries that occurred from 1 year prior to baseline up to each period. Comorbidity information was identified based on a previous 1 year history of ICD-10 (Supplementary Table 2) or two or more prescriptions specific to hyperlipidemia. The number of co-medications was calculated, excluding PIMs, among patients with dementia during a previous 1 month history.

Subgroup analysis was conducted based on the number of PIMs administered to patients with dementia during each period. The risk of falls or fall-related injuries were estimated by comparing the incidence rates of the outcome between 1, 2, or ≥ 3 PIMs among patients with dementia during the exposure and non-exposure periods within the same individuals using a negative binomial regression. The model was adjusted for sex, age, living setting, insurance type, disability, CCI score, comorbidities, and history of falls.

A key assumption in SCCS studies is that the occurrence and recurrence of outcome events are independent of previous exposure and outcome events [36]. Falls or fall-related injuries may increase mortality and affect the recurrence of adverse events [37, 38]. Therefore, two sensitivity analyses were performed to assess the robustness of the study results: 1) one analysis was restricted to the first fall or fall-related injury during the study period to check the assumption of event independence, and 2) the main analysis was repeated after excluding individuals who died during the study period to account for possible biases from observation censoring.

All analyses were performed using SAS version 9.4. Statistical significance was determined with a two-sided 95% CI and a p-value < 0.05.

Results

Baseline characteristics (Table 1)

This study included 1430 participants. The mean age was 80.13 years (SD = 5.41), and 84.1% (n = 1,202) were female. Community-dwelling participants were 87.5% (n = 1,251). About 88.5% (n = 1,265) of the participants had National Health Insurance (NHI). Approximately, 345 patients (24.1%) died during the study period. People with disabilities accounted for 26.8% of the total population (n = 383). Participants with CCI scores ≥ 1 accounted for 61.2% (n = 875). Among the comorbidities, hypertension was the most prevalent (n = 769; 53.8%), followed by hyperlipidemia (n = 503; 35.2%) and cerebrovascular disease (n = 491; 34.3%). Participants with a history of falls accounted for 10.4% (n = 149). The mean number of

Table 1 Baseline characteristics of the study participants ($N = 1,430$)

Variables	
Age, mean (SD)	80.13 (5.41)
Female, n (%)	1 202 (84.1)
Living setting, n(%)	
Community	1 251 (87.5)
Facility	174 (12.2)
Hospitalization	5 (0.4)
Insurance, n (%)	
National Health Insurance	1 265 (88.5)
Medical care	165 (11.5)
Disability, n (%)	383 (26.8)
Death, n (%)	345 (24.1)
Charlson comorbidity index, n (%)	
0	555 (38.8)
1	421 (29.4)
2	243 (17.0)
≥ 3	211 (14.8)
Comorbidities, n (%)	
Hypertension	769 (53.8)
Atrial fibrillation	39 (2.7)
Ischemic heart disease	137 (9.6)
Heart failure	84 (5.9)
Cerebrovascular disease	491 (34.3)
Diabetes mellitus	320 (22.4)
Chronic kidney disease	20 (1.4)
Chronic obstructive pulmonary disease	141 (9.9)
Parkinson's disease	76 (5.3)
Arthritis (rheumatoid and osteoarthritis)	382 (26.7)
Osteoporosis	252 (17.6)
Depression	252 (17.6)
Hyperlipidemia	503 (35.2)
A history of previous falls, n (%)	149 (10.4)
Number of comedications, n (%)	
≤ 2	456 (31.9)
3–4	217 (15.2)
5–9	396 (27.7)
≥ 10	361 (25.2)
mean (SD)	5.53 (4.40)
Duration of each periods (days), mean (SD)	
Total observation periods	1 324.52 (286.84)
Non-exposure periods	1 010.73 (396.48)
Exposure periods	255.52 (345.13)
Post-exposure periods	58.28 (53.9)
Number of outcome events, mean (SD)	1.46 (0.93)

comedications was 5.53 (SD = 4.40). The mean duration was 1325 days (3.63 years) (SD = 287) for the total observation period, and 256 days (SD = 345) for the exposure period. The mean number of falls or fall-related injuries during the total observation period was 1.46 (SD = 0.93).

Prevalence of PIM use among patients with dementia during the exposure periods (Table 2)

The study participants experienced 6608 exposure periods. Falls or fall-related injuries occurred during 479 (7.2%) exposure periods. During all exposure periods, the mean number of PIMs among patients with dementia was 1.77 (SD = 1.43). The participants using one PIM was 61.0% ($n = 4031$). However, the mean number of PIMs among patients with dementia was 3.76 (SD = 2.99) during the exposure periods in which falls or fall-related injuries occurred, which was higher than all exposure periods. The most commonly used PIMs among patients with dementia were drugs with strong anticholinergic properties (all: $n = 5312$, 80.4%; falls: $n = 403$, 84.1%), especially first-generation antihistamines (all: $n = 4196$, 63.5%; falls: $n = 283$, 59.1%) during all exposure periods and periods in which falls or fall-related injuries occurred.

Risk of falls or fall-related injuries associated with PIM use among patients with dementia (Table 3)

Compared with the non-exposure period, the adjusted IRR in the exposure period was 1.57 (95% CI = 1.39–1.76). Considering the segmented exposure periods, the risk of falls or fall-related injuries was higher closer to an initiation of PIM use among patients with dementia (1–14 days: IRR = 2.76, 95% CI = 2.31–3.28; 15–28 days: IRR = 1.95, 95% CI = 1.48–2.56; ≥ 29 days: IRR = 1.17, 95% CI = 1.01–1.35). For the post-exposure period, the adjusted IRR was 1.15 (95% CI = 0.92–1.43), which was statistically insignificant.

Risk of falls or fall-related injuries associated with the number of PIMs among patients with dementia (Table 4)

An increased risk of falls or fall-related injuries were observed when a higher number of PIMs among patients with dementia were used (1 PIM among patients with dementia: IRR = 1.45, 95% CI = 1.19–1.77; 2 PIMs: IRR = 1.52, 95% CI = 1.20–1.91; ≥ 3 PIMs: IRR = 1.62, 95% CI: 1.39–1.89), compared with periods during which PIMs among patients with dementia were not used.

Sensitivity analyses (Table 5)

The sensitivity analyses were consistent with the results of the main analyses, supporting the robustness of the main analyses.

Table 2 Number and classes of PIMs among patients with dementia

Variables	All Exposure periods	Falls or fall-related injuries
Total number of exposure period, n	6608	479
Number of PIMs among patients with dementia, n (%)		
1	4 031 (61.0)	118 (24.6)
2	1 442 (21.8)	94 (19.6)
3–4	816 (12.4)	118 (24.6)
≥ 5	319 (4.8)	149 (31.1)
mean (SD)	1.77 (1.43)	3.76 (2.99)
PIM categories among patients with dementia, n (%)		
Antipsychotics	1 260 (19.1)	231 (48.2)
Benzodiazepines	1 384 (20.9)	208 (43.4)
Z-drugs	459 (7.0)	72 (15.0)
Strong anticholinergics	5 312 (80.4)	403 (84.1)
Antidepressants	195 (3.0)	44 (9.2)
Antihistamines (1st generation)	4 196 (63.5)	283 (59.1)
Antimuscarinics (urinary incontinence)	517 (7.8)	92 (19.2)
Antiparkinsonian agents	41 (0.6)	16 (3.3)
Antispasmodics	1 008 (15.3)	187 (39.0)
Skeletal muscle relaxants	171 (2.6)	40 (8.4)

Table 3 Risk of falls or fall-related injuries associated with PIM use among patients with dementia (*N* = 1,430)

Periods	No. of events	Person-years	crude IRR (95% CI)	adjusted IRR (95% CI)
Non-exposure period	1 448	3 957	1.00 (ref)	1.00 (ref)
Exposure period	549	1 000	1.45 (1.30, 1.62)	1.57 (1.39, 1.76)
1–14 days	163	162	2.56 (2.16, 3.03)	2.76 (2.31, 3.28)
15–28 days	57	83	1.75 (1.34, 2.29)	1.95 (1.48, 2.56)
≥ 29 days	329	756	1.11 (0.97, 1.28)	1.17 (1.01, 1.35)
Post-exposure period	95	228	1.06 (0.85, 1.31)	1.15 (0.92, 1.43)

Table 4 Risk of falls or fall-related injuries associated with the number of PIMs among patients with dementia (*N* = 1,430)

No. of PIMs	No. of events	Person-years	crude IRR (95% CI)	adjusted IRR (95% CI)
0	1 543	4 185	1.00 (ref)	1.00 (ref)
1	121	242	1.30 (1.07, 1.58)	1.45 (1.19, 1.77)
2	97	182	1.41 (1.13, 1.76)	1.52 (1.20, 1.91)
≥ 3	331	576	1.54 (1.34, 1.77)	1.62 (1.39, 1.89)

Discussion

This study used the SCCS design to investigate negative health outcomes of PIM use in older adults with dementia. The results revealed that the risk of falls or fall-related injuries during periods of PIM use among patients with dementia was 1.57 times higher compared than during periods without PIM use. Cautious use of PIMs among older adults with dementia may decrease the risk of falls and fall-related injuries. Sterke et al. (2012) examined the risk of falls among older adults with dementia residing in nursing homes in the Netherlands and found an association with antipsychotics (HR = 2.78; 95% CI = 1.49–5.17), anxiolytics (HR = 2.58; 95% CI = 1.42–4.68) and antidepressants (HR = 2.84; 95% CI = 1.93–4.16) [19].

Table 5 Sensitivity analysis

Periods	No. of events	Person-years	crude IRR (95% CI)	adjusted IRR (95% CI)
Restricted to first outcome events (*N* = 1,430)				
Non-exposure period	1 046	1 955	1.00 (ref)	1.00 (ref)
Exposure period	323	294	1.33 (1.11, 1.59)	1.27 (1.06, 1.53)
1–14 days	98	60	1.49 (1.17, 1.89)	1.41 (1.11, 1.80)
15–28 days	28	28	0.88 (0.59, 1.32)	0.83 (0.55, 1.25)
≥ 29 days	197	206	1.39 (1.08, 1.80)	1.35 (1.04, 1.76)
Post-exposure period	61	82	0.65 (0.49, 0.86)	0.63 (0.47, 0.84)
Excluding deaths (*N* = 1,085)				
Non-exposure period	1 136	3 268	1.00 (ref)	1.00 (ref)
Exposure period	448	846	1.49 (1.32, 1.68)	1.62 (1.43, 1.83)
1–14 days	130	137	2.60 (2.16, 3.13)	2.80 (2.32, 3.39)
15–28 days	48	69	1.90 (1.42, 2.54)	2.12 (1.58, 2.85)
≥ 29 days	270	640	1.15 (0.99, 1.34)	1.23 (1.06, 1.44)
Post-exposure period	83	189	1.20 (0.96, 1.51)	1.29 (1.02, 1.62)

Additionally, Yip et al. (1994) reported an increased risk of falls associated with antipsychotic use among older adults in Australia, with an odds ratio of 4.4 (95% CI = 1.2–16.5) [20]. A recent study by Tan et al. (2021) reported an increased risk of falls with the use of anticholinergic medications among hospitalized patients with dementia in Australia, with an incidence rate ratio of 2.2 ($p < 0.001$) [21]. Richardson et al. (2020) reported an increased risk of falls (HR = 1.33; 95% CI = 1.06–1.66) and fractures (HR = 1.67; 95% CI = 1.13–2.46) with the initial use of Z-drugs among people with dementia [39]. These previous studies either restricted the study population based on residency in nursing homes or hospitalizations, or focused on the initial use of PIMs among patients with dementia. Furthermore, the studies included different drugs and statistical methods, which may have resulted in varying risk magnitudes. However, the use of PIMs among patients with dementia increases the risk of falls, and fall-related injuries are consistent with the findings. This study identified an elevated likelihood of falls or fall-related injuries in all individuals with dementia aged 65 years or older who used PIMs, irrespective of their living settings or prior PIM use. Furthermore, the risk of falls was higher when PIM use among patients with dementia when PIM use was initiated. These results are comparable to those of Lim et al. (2023) who reported a higher risk of hospitalization and emergency department visits when PIM use was initiated [40]. Therefore, it is important to pay more attention to the occurrence of falls during the initiation of PIM use in older adults with dementia.

The present study not only identified higher concurrent use of PIMs among patients with dementia during the period in which falls or fall-related injuries occurred but also demonstrated that the risk of falls or fall-related injuries increased with the number of concurrent uses. These findings are similar to those of Sterke et al. (2012), who reported that the concomitant use of antipsychotics, anxiolytics, hypnotics, sedatives, and antidepressants increased the risk of falls among nursing home residents with dementia [19], and Tan et al. (2021), who found that falls in hospitalized patients with dementia were associated with the concomitant use of five or more psychotropic medications [21]. Additionally, the concomitant use of low-scoring anticholinergic medications increases the risk of falls in patients with dementia [18]. A similar association was reported in a previous study examining the general older adult population, in which first-generation antihistamines increased the risk of falls and fall-related injuries [41]. Thus, the use of PIMs among older adults with dementia should be cautious and used only when necessary, at low doses, and for short periods.

Paired cohort methods are commonly used to study the risk of adverse events associated with medication use [42–44]. The observation period of this study was 4 years, which was longer than that of previous studies. In a baseline analysis of older adults with dementia, 90.4% ($n = 26{,}853$) used PIMs at least once during the study period; therefore, the number of controls was insufficient. Moreover, individuals with dementia have a wide range of comorbidities and symptoms [45], resulting in a high degree of inter-individual variations [2]. The SCCS is an appropriate study method for outcomes of interest for which the exact time of occurrence is known [36]. It aims to estimate the relative incidence by comparing the incidence of an outcome event during the period of risk exposure with that during all other periods [46]. Confounding variables due to interindividual differences

could be controlled because only the patient population was studied.

While the characteristics of the SCCS study make it difficult to entirely eliminate biases arising from a study population comprising solely participant-experience exposures and outcomes [47], the sociodemographic characteristics and health status of the study participants were not significantly different from those reported in previous studies among older adults with dementia [5, 26, 30, 48–52]. The population in these studies was predominantly female (84.1%), with a mean age of 80.13 years. According to the 2016 dementia statistics released by the South Korean government, women comprise approximately 64% of patients aged 65 years and older with dementia [53]. The prevalence of dementia increases with age, with a prevalence of 32.2% among those aged 85 years.

The most frequently used PIMs among patients with dementia during the exposure periods were strong anticholinergics (80.4%), benzodiazepines (20.9%), and antipsychotics (19.1%), with an average of 1.77 PIMs. This utilization pattern aligns with that of previous studies examining PIM use among patients with dementia [30, 31]. Notably, in the present study, we observed a higher rate of drug utilization with strong anticholinergic properties. During the observation period, all PIMs among patients with dementia that were used at least once were measured while considering the broad use of strong anticholinergics for conditions such as seasonal allergies, colds, urinary disorders, and depression [54]. The high frequency of use of first-generation antihistamines suggests that older adults with dementia commonly consume these drugs.

This study had certain limitations. Although medications were identified as PIMs among patients with dementia, their appropriateness may depend on the patient's clinical condition. Considering that most PIMs among patients with dementia are associated with medications prescribed for psychiatric disorders and that the data source utilized in this study was incapable of offering personal information relating to psychiatric diseases, regarded as highly confidential in Korea, sufficient information indicating PIM usage rationales among patients with dementia could not be considered. Additionally, outcome events were determined based on diagnostic codes from insurance claims data, which may not precisely reflect clinical symptoms. Considering that falls are used as a criterion for evaluating medical institutions and long-term care facilities, some individuals may attempt to classify falls as fall-related injuries and attribute them to a primary diagnosis. Therefore, codes for both falls and fall-related injuries were included to account for falls that may occur in daily life, as well as those resulting from injuries caused by falls. Lastly, the present study utilized the NHIS-ECDB 2.0, which are based on health insurance claims data and only consists of records for reimbursed medications. Non-reimbursed and over-the-counter medications were excluded. Additionally, it is impossible to confirm whether all prescribed medications were administered, considering the clinical nature of patients with dementia, even if prescription records exist.

Despite these limitations, this study has several strengths. Using the highly representative NHIS-ECDB 2.0, this empirical analysis examined whether adverse reactions occurred more frequently among individuals with dementia who used PIMs among patients with dementia by studying a randomly sampled cohort of approximately 540,000 Korean older adults longitudinally. Previous studies have analyzed PIM usage patterns among patients with dementia; however, only a few have investigated negative health outcomes associated with overall PIM usage among patients with dementia rather than individual PIM use among patients with dementia. Additionally, considering that the older adult population exhibits significant physiological variations and diverse medical utilization behaviors, particularly in patients with dementia and various clinical symptoms, this study employed the SCCS design to control for confounding factors associated with interpersonal clinical differences and conducted intrapersonal comparisons. Furthermore, the use of PIMs among older adults with dementia increased the risk of falls or fall-related injuries. Therefore, the present study provides evidence for the development of effective strategies to reduce the PIM use among patients with dementia.

Conclusions

Falls and fall-related injuries among older adults with dementia increased with PIM use, as did concurrent use of PIMs among patients with dementia. Therefore, it is crucial to monitor PIM use among older adults with dementia and develop a standardized management protocol.

Abbreviations

CCI	Charlson comorbidity index
CIs	Confidence intervals
IRR	Incidence rate ratio
NHI	National Health Insurance
NHIS-ECDB 2.0	National Health Insurance Service-Elderly Cohort Database 2.0
PIMs	Potentially inappropriate medications
SCCS	Self-controlled case series study
SDs	Standard deviations
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older Persons' potentially inappropriate Prescriptions
ICD-10	International Classification of Diseases 10th Revision
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-024-05300-x.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements
We would like to thank Dr. Jaeok Lim for his help with data analysis.

Authors' contributions
AM and Sunmee J conceived and designed the study. AM analyzed and interpreted all analyses and was a major contributor to writing the manuscript. Suhyun J, JK and Sunmee J revised the manuscript. JK and Sunmee J acquired funding. All authors made substantial contributions to the conception and read and approved the final manuscript.

Funding
This study was supported by a grant from the Patient-Centered Clinical Research Coordinating Center funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HC21C0069).

Availability of data and materials
The data were third-party data managed by the Korea National Health Insurance Service (KNHIS) as requested for political and academic research purposes. These datasets are not publicly available due to privacy and ethical issues under the current KNHIS policy. The National Health Information Data Request Review Committee of the KNHIS approved this study (approval number: NHIS-2022–2–374). The authors have no special access privileges for the data. Interested and qualified researchers can request access to the data by contacting the KNHIS National Health Information Data Request Review Committee (https://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do).

Declarations

Ethics approval and consent to participate
This retrospective study utilized the National Health Insurance Service-Elderly Cohort Database 2.0 (NHIS-ECDB 2.0), a dataset managed by the Korea National Health Insurance Service (KNHIS) for governmental and academic research purposes. The NHIS-ECDB 2.0 is designed to ensure the privacy of individuals by excluding personally identifiable information. As a result, researchers cannot identify or access personal data of any specific individuals, negating the need for obtaining individual consent. Approval for this study was obtained from the Institutional Review Board of Gachon University, confirming that formal informed consent was not required for utilizing this database (IBN No. 1044396–202111-HR-236–01). The certificate of IRB review exemption is provided for documentation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 25 October 2023 Accepted: 13 August 2024
Published online: 23 August 2024

References

1. World Health Organization: Fact sheets, Dementia. 15 March 2023. https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed 2 Aug 2023.
2. Gale SA, Acar D, Daffner KR. Dementia. Am J Med. 2018;131(10):1161–9.
3. Bunn F, Burn AM, Goodman C, Rait G, Norton S, Robinson L, et al. Comorbidity and dementia: a scoping review of the literature. BMC Med. 2014;12:192. https://doi.org/10.1186/s12916-014-0192-4.
4. Park HY, Park JW, Song HJ, Sohn HS, Kwon JW. The association between polypharmacy and dementia: A nested case-control study based on a 12-year longitudinal cohort database in South Korea. PLoS ONE. 2017;12(1):e0169463. https://doi.org/10.1371/journal.pone.0169463.
5. Kristensen RU, Nørgaard A, Jensen-Dahm C, Gasse C, Wimberley T, Waldemar G. Polypharmacy and potentially inappropriate medication in people with dementia: a nationwide study. J Alzheimers Dis. 2018;63(1):383–94. https://doi.org/10.3233/JAD-170905.
6. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem. 2010;17(6):571–84. https://doi.org/10.2174/092986710790416326.
7. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57(1):6–14. https://doi.org/10.1046/j.1365-2125.2003.02007.x.
8. Lim RH, Sharmeen T. Medicines management issues in dementia and coping strategies used by people living with dementia and family carers: a systematic review. Int J Geriatr Psychiatry. 2018;33(12):1562–81. https://doi.org/10.1002/gps.4985.
9. Alhawassi TM, Alatawi T, Alwhaibi M. Prevalence of potentially inappropriate medications use among older adults and risk factors using the 2015 American Geriatrics Society Beers Criteria. BMC Geriatr. 2019;19(1):154. https://doi.org/10.1186/s12877-019-1168-1.
10. Malakouti SK, Javan-Noughabi J, Yousefzadeh N, Rezapour A, Mortazavi SS, Jahangiri R, Moghri J. A systematic review of potentially inappropriate medications use and related costs among the elderly. Value Health Reg Issues. 2021;25:172–9. https://doi.org/10.1016/j.vhri.2021.05.003.
11. Corsonello A, Onder G, Abbatecola AM, Guffanti EE, Gareri P, Lattanzio F. Explicit criteria for potentially inappropriate medications to reduce the risk of adverse drug reactions in elderly people: from Beers to STOPP/START criteria. Drug Saf. 2012;35(S1):21–8. https://doi.org/10.1007/BF03319100.
12. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163(22):2716–24. https://doi.org/10.1001/archinte.163.22.2716.
13. 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023;71(7):2052–2081. https://doi.org/10.1111/jgs.18372.
14. Liu L, Jia L, Jian P, Zhou Y, Zhou J, Wu F, Tang Y. The Effects of Benzodiazepine Use and Abuse on Cognition in the Elders: a systematic review and meta-analysis of comparative studies. Front Psychiatry. 2020;11:00755. https://doi.org/10.3389/fpsyt.2020.00755.
15. Fox C, Smith T, Maidment I, Chan WY, Bua N, Myint PK, Boustani M, Kwok CS, Glover M, Koopmans I, Campbell N. Effect of medications with anticholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. Age Ageing. 2014;43(5):604–15. https://doi.org/10.1093/ageing/afu096.
16. Yoon K, Kim JT, Kwack WG, Kim D, Lee KT, Yang S, Lee S, Choi YJ, Chung EK. Potentially Inappropriate Medication Use in Patients with Dementia. Int J Environ Res Public Health. 2022;19(18):11426. https://doi.org/10.3390/ijerph191811426.
17. Racey M, Markle-Reid M, Fitzpatrick-Lewis D, Ali MU, Gagne H, Hunter S, Ploeg J, Sztramko R, Harrison L, Lewis R, Jovkovic M, Sherifali D. Fall prevention in community-dwelling adults with mild to moderate cognitive impairment: a systematic review and meta-analysis. BMC Geriatr. 2021;21(1):689. https://doi.org/10.1186/s12877-021-02641-9.
18. Green AR, Reifler LM, Bayliss EA, Weffald LA, Boyd CM. Drugs contributing to anticholinergic burden and risk of fall or fall-related injury among older adults with mild cognitive impairment, dementia and multiple chronic conditions: a retrospective cohort study. Drugs Aging. 2019;36(3):289–97. https://doi.org/10.1007/s40266-018-00630-z.
19. Sterke CS, van Beeck EF, van der Velde N, Ziere G, Petrovic M, Looman CW, et al. New insights: dose-response relationship between psychotropic drugs and falls: a study in nursing home residents with dementia. J Clin

Pharmacol. 2012;52(6):947–55. https://doi.org/10.1177/0091270011405665.
20. Yip YB, Cumming RG. The association between medications and falls in Australian nursing-home residents. Med J Aust. 1994;160(1):14–8. https://doi.org/10.5694/j.1326-5377.1994.tb138194.x.
21. Tan SX, Cameron SC, Sam LM, Eigeland H, Hay K, Eeles E, et al. A delicate balance: Psychotropic polypharmacy and anti-cholinergic use are correlated with fall incidence in Australian inpatients with dementia. Aging Med (Milton). 2021;4(3):193–200. https://doi.org/10.1002/agm2.12175.
22. Montero-Odasso M, Van Der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age Ageing. 2022;51(9):afac205. https://doi.org/10.1093/ageing/afac205.
23. Al-Aama T. Falls in the elderly: spectrum and prevention. Can Fam Physician. 2011;57(7):771–6.
24. Beauchet O, Sekhon H, Schott AM, Rolland Y, Muir-Hunter S, Markle-Reid M, Gagne H, Allali G. Motoric Cognitive Risk Syndrome and Risk for Falls, Their Recurrence, and Postfall Fractures: Results From a Prospective Observational Population-Based Cohort Study. J Am Med Dir Assoc. 2019;20(10):1268–73. https://doi.org/10.1016/j.jamda.2019.04.021.
25 Booth V, Logan P, Harwood R, Hood V. Falls prevention interventions in older adults with cognitive impairment: a systematic review of reviews. Int J Ther Rehabil. 2015;22(6):289–96. https://doi.org/10.12968/ijtr.2015.22.6.289.
26. Sönnerstam E, Harlin F, Gustafsson M. Potentially inappropriate medications among elderly people with neurocognitive disorders - a nationwide register-based study using 3 different explicit criteria. Res Social Adm Pharm. 2023;19(5):758–63. https://doi.org/10.1016/j.sapharm.2023.01.010.
27. Ruangritchankul S, Peel NM, Hanjani LS, Gray LC. Drug related problems in older adults living with dementia. PLoS One. 2020;15(7):e0236830. https://doi.org/10.1371/journal.pone.0236830.
28. Ferreira TR, Lopes LC, Motter FR, de Cássia BC. Potentially inappropriate prescriptions to Brazilian older people with Alzheimer disease: a cross-sectional study. Medicine (Baltimore). 2021;100(12):e25015. https://doi.org/10.1097/MD.0000000000025015.
29. Zhao M, Chen Z, Tian F, Xu T. Potentially inappropriate medication among people with dementia in China: a nationwide cross-sectional study. Front Pharmacol. 2022;13:929584. https://doi.org/10.3389/fphar.2022.929584.
30. Bae-Shaaw YH, et al. Potentially inappropriate medication use in community-dwelling older adults living with dementia. J Alzheimers Dis. 2023;93(2):471–81. https://doi.org/10.3233/JAD-221168.
31. Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Ilomäki J, et al. Potentially inappropriate medications and anticholinergic burden in older people attending memory clinics in Australia. Drugs Aging. 2016;33(1):37–44. https://doi.org/10.1007/s40266-015-0332-3.
32. Kyung-Soo K. Clinical trial design and ethics. Korean Journal of Family Medicine. 2002;23(5):573–82.
33. Jeon SM, Park HY, Park S, Chung US, Kwon JW. Association of Treatment With Antipsychotics, Antidepressants, or Both With Movement Disorders and Seizures Among Children and Adolescents With Depression in Korea. JAMA Netw Open. 2022;5(4):e227074. https://doi.org/10.1001/jamanetworkopen.2022.7074.
34. Cleophas TJ. Carry-over biases in clinical pharmacology. Eur J Clin Chem Clin Biochem. 1993;31(12):803–9. https://doi.org/10.1515/cclm.1993.31.12.803.
35. Machinery of Government legislation. Act on Welfare of Persons With Disabilities. Korean Law Information Center. 2023.
36. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016;354:i4515. https://doi.org/10.1136/bmj.i4515.
37. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: a prospective study in older people. PLoS ONE. 2009;4(5):e5521. https://doi.org/10.1371/journal.pone.0005521.
38. van Doorn C, Gruber-Baldini AL, Zimmerman S, Richard Hebel J, Port CL, Baumgarten M, et al. Dementia as a risk factor for falls and fall injuries among nursing home residents. J Am Geriatr Soc. 2003;51(9):1213–8. https://doi.org/10.1046/j.1532-5415.2003.51404.x.
39. Richardson K, Loke YK, Fox C, Maidment I, Howard R, Steel N, et al. Adverse effects of Z-drugs for sleep disturbance in people living with dementia: a population-based cohort study. BMC Med. 2020;18(1):351. https://doi.org/10.1186/s12916-020-01821-5.
40. Lim J, Jeong S, Jang S, Jang S. Hospitalization and emergency department visits associated with potentially inappropriate medication in older adults: Self-controlled case series analysis. Front Public Health. 2023;11:1080703. https://doi.org/10.3389/fpubh.2023.1080703.
41. Cho H, Myung J, Suh HS, Kang HY. Antihistamine use and the risk of injurious falls or fracture in elderly patients: a systematic review and meta-analysis. Osteoporos Int. 2018;29(10):2163–70. https://doi.org/10.1007/s00198-018-4564-z.
42. Pearce N. Analysis of matched case-control studies. BMJ. 2016;352: i969. https://doi.org/10.1136/bmj.i969.
43. Hashimoto Y, Yamana H, Iwagami M, Ono S, Takeuchi Y, Michihata N, et al. Ocular adverse events after coronavirus disease 2019 mRNA vaccination: Matched cohort and self-controlled case series studies using a large database. Ophthalmol. 2023;130(3):256–64. https://doi.org/10.1016/j.ophtha.2022.10.017.
44. Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Connolly AM. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. Lancet. 2021;398(10300):599–607. https://doi.org/10.1016/S0140-6736(21)00896-5.
45. Public Health England. Dementia: Comorbidities in patients - data briefing. 2019. https://www.gov.uk/government/publications/dementia-comorbidities-in-patients/dementia-comorbidities-in-patients-data-briefing. Accessed 2 Aug 2023.
46. Whitaker HJ, Paddy Farrington C, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Stat Med. 2006;25(10):1768–97. https://doi.org/10.1002/sim.2302.
47. Takeuchi Y, Shinozaki T, Matsuyama Y. A comparison of estimators from self-controlled case series, case-crossover design, and sequence symmetry analysis for pharmacoepidemiological studies. BMC Med Res Methodol. 2018;18(1):4. https://doi.org/10.1186/s12874-017-0457-7.
48. Bosboom PR, Alfonso H, Almeida OP, Beer C. Use of potentially harmful medications and health-related quality of life among people with dementia living in residential aged care facilities. Dement Geriatr Cogn Dis Extra. 2012;2(1):361–71. https://doi.org/10.1159/000342172.
49. Harrison SL, Kouladjian O'Donnell L, Milte R, Dyer SM, Gnanamanickam ES, Bradley C, et al. Costs of potentially inappropriate medication use in residential aged care facilities. BMC Geriatr. 2018;18(1):9. https://doi.org/10.1186/s12877-018-0704-8.
50. Montastruc F, Gardette V, Cantet C, Piau A, Lapeyre-Mestre M, Vellas B, et al. Potentially inappropriate medication use among patients with Alzheimer disease in the REAL.FR cohort: Be aware of atropinic and benzodiazepine drugs! Eur J Clin Pharmacol. 2013;69(8):1589–97. https://doi.org/10.1007/s00228-013-1506-8.
51. Hyttinen V, Taipale H, Tolppanen AM, Tanskanen A, Tiihonen J, Hartikainen S, et al. Incident use of a potentially inappropriate medication and hip fracture in community-dwelling older persons with Alzheimer's disease. Ann Pharmacother. 2017;51(9):725–34. https://doi.org/10.1177/1060028017708394.
52. Renom-Guiteras A, Thürmann PA, Miralles R, Klaaßen-Mielke R, Thiem U, Stephan A, et al. Potentially inappropriate medication among people with dementia in eight European countries. Age Ageing. 2018;47(1):68–74. https://doi.org/10.1093/ageing/afx147.
53. Nam HJ, Hwang SH, Kim YJ, Byung SJ, Kim KW. Korean Dementia Observatory 2017. National Institute of Dementia; Ministry of Health and Welfare. 2017.
54. Gerretsen P, Pollock BG. Drugs with anticholinergic properties: a current perspective on use and safety. Expert Opin Drug Saf. 2011;10(5):751–65. https://doi.org/10.1517/14740338.2011.579899.

Publisher's Note