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ORIGINAL RESEARCH ARTICLE

Association Between Use of Multiple Psychoactive Medicines and Hospitalization for Falls: Retrospective Analysis of a Large Healthcare Claim Database

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Abstract

Background Little is known about the impact of taking multiple psychoactive medicines on the risk of hospitalization for falls.

Objective To identify the association between multiple psychoactive medicine use and hospitalization for falls.

Methods A retrospective cohort study was conducted between July 2011 and June 2012 in the Australian veteran population who had been dispensed at least one psychoactive medicine within the previous year. Psychoactive medicines with sedative properties included antipsychotics, anxiolytics, hypnotics, antidepressants, opioids, anti-epileptics, anti-Parkinson medicines and medicines for migraine. The associations between falls and the number of psychoactive medicines used or the number of doses were analysed in comparison with falls that occurred when no psychoactive medicine was used.

Results The adjusted results showed a significantly increased risk of falls when patients were on one or more psychoactive medicines or were receiving 0.1–0.9 defined daily dose (DDD) or more per day. The incident rate ratios (IRRs) were 1.22 (95 % confidence interval [CI] 1.08–1.38) for those on one psychoactive medicine, 1.70 (95 % CI 1.45–1.99) for those on two, 1.96 (95 % CI 1.58–2.43) for those on three or four, and 3.15 (95 % CI 1.90–5.23) for those on five or more. A similar result was observed when the data were analysed by dose, with the highest risk being found for those taking three or more DDD per day (adjusted IRR 4.26, 95 % CI 2.75–6.58).

Conclusion Increased numbers or increased doses of psychoactive medicines are associated with an increased risk of hospitalization for falls in older adults. Strategies to reduce the psychoactive medicine burden are likely to translate into significant health benefits.

Key Points

Use of three to four psychoactive medicines concurrently doubled the risk of falls resulting in hospitalization, while concurrent use of five or more tripled the risk

Use of psychoactive medicines at any dose increased the risk of hospitalization for falls. There was a fourfold increased risk of hospitalization for falls on days when patients were taking three or more defined daily doses

Strategies to reduce the psychoactive medicine burden are likely to translate into significant health benefits

1 Introduction

Falls are a major public health problem and are responsible for considerable morbidity and mortality among the elderly population [1–3]. More than 30 % of community-dwelling older people have at least one fall each year [4]. For some,

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the fall results in hospitalization due to injury or leads to institutional care as a result of post-fall immobility, anxiety and depression [1, 2, 5–8]. Falls and fall-related complications are the fifth leading cause of death in the developed world [9]. In Australia, falls accounted for 55 % of injury deaths and 73 % of all hospitalized injuries among older people in 2001–2002 [10]. By 2011, the total cost associated with fall injuries in persons aged 65 years and over in Australia was estimated to be AU$604 million [11]. The incidence of falls increases sharply with age [10]. As the proportion of elderly people in the Australian population is expected to rise to 20 % by 2050 [12], there is likely to be an increased health burden from falls in the future.

Given the increasing public health concern about falls and their consequences, a substantial body of research has identified the risk factors for falls and opportunities for prevention. The contributing factors for falls may be divided into intrinsic factors (e.g. cognitive impairment, balance problems, vision problems, gait problems or muscle strength problems) and extrinsic risk factors or environmental hazards (e.g. slippery flooring or poor lighting) [8, 13, 14]. Medication use, which can be categorized as either an intrinsic factor or an extrinsic factor [14], is an important risk factor for falls in elderly people [9]. Medication use is also considered one of the most easily modifiable risk factors for falls [2], and medicines review is recommended in most guidelines for the prevention of falls in the elderly [8, 15–17].

Among many medicines with the potential to increase the risk of falls, psychoactive medicines are most commonly prescribed for older people [18, 19]. While some psychoactive medicines, such as antidepressants and anticonvulsants, are sometimes clinically essential, others (e.g. benzodiazepines and other sedatives) are often prescribed inappropriately and unnecessarily [19, 20]. Many psychoactive medicines, including antipsychotics, anxiolytics, hypnotics and antidepressants, have been found to be associated with a 50–70 % increased risk of falls [9]. Previous studies have examined the association between use of individual medicines and falls [21]. Use of multiple psychoactive medicines, however, is common among the elderly [22], and few studies have investigated the effect of the total burden of psychoactive medicines on the risk of falls. A prospective longitudinal study, involving annual data collection, assessed the effect of the number and dosage of psychoactive medicines on recurrent falls in community-dwelling older people and found that use of multiple central nervous system medicines doubled or trebled the risk of falls [23]. Self-reported falls were analysed in association with medicine use during the prior data collection period, which was a year earlier. Two limitations of this method are that medicines used at baseline may have been discontinued or changed by the time of falling, and the outcome measure may be affected by patient recall. Our current study used administrative health claims data to determine psychoactive medicine use across the entire study period and the association between multiple medicine use and hospitalization where a fall was recorded as contributing to the admission.

2 Methods

2.1 Setting

The Australian Government Department of Veterans' Affairs (DVA) claims database was used for this study. The database contains details of all prescription medications, medical services, allied health services and hospitalizations provided to veterans for which DVA pays a subsidy. In the dataset, medications are coded according to the Anatomic, Therapeutic and Chemical Classification (ATC) [24] and the Pharmaceutical Benefits Schedule (PBS) item codes [25]. Hospitalizations are coded according to the International Classification of Diseases, Version 10, Australian Modification (ICD-10-AM) [26]. DVA also maintains a client file, which contains information on sex, date of birth, date of death and family status for the treatment population, which in September 2011 was 242,000 people [27].

2.2 Study Design and Participants

A retrospective cohort study was conducted between 1 July 2011 and 30 June 2012 to identify the effect of the psychoactive medicine burden on hospitalizations for falls. Eligible subjects were community-dwelling veterans who were alive and aged 65 years or over at study entry, were eligible for all DVA-subsidized services for at least 12 months prior to study entry, had at least one chronic condition at baseline and had been dispensed at least one psychoactive medicine with sedative properties in the previous year. Veterans receiving palliative care in the 6 months prior to the study were excluded; this was defined as any dispensing of palliative care medicines subsidized under the Australian Pharmaceutical Benefit Scheme or a palliative care service claim under the Australian Medicare Benefits Scheme.

Psychoactive medicines with sedative properties included in the study were antipsychotics (ATC code N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), opioids (N02A), anti-epileptics (N03), anti-Parkinson medicines (N04) and medicines for migraine (N02C) [28]. Patients on anti-dementia medicines (N06DA) were excluded, as dementia is an independent risk factor for falling [29].

2.3 Exposure and Measurements

The total burden of psychoactive medicines taken was defined in two ways: (1) the total number; and (2) the cumulative daily dose standardized to the international defined daily dose (DDD) per day [30]. Using the waiting time distribution approach, which has been described elsewhere [31], the duration of each prescription was calculated from the data and was defined by the time within which 75 % of individuals obtained a refill prescription. Subjects were considered exposed during this time, and at other times they were treated as unexposed. The dose on each day was calculated by the formula:

$$\text{Dose} = (\text{strength} \times \text{quantity}/\text{duration estimate})/\text{DDD}.$$

The cumulative daily dose (in DDD/day) was the sum of all individual standardized medicine doses.

The effect of the psychoactive medicine burden on fall risk was examined by stratifying the total number and cumulative DDD/day of all psychoactive medicines taken on each day of the study and the risk of falling on the subsequent day. Fall risk was determined on the subsequent day to avoid exposure misclassification for medicines that were started on the day of hospital admission and were started as a consequence of the fall. The estimated daily number of medicines and DDD/day for psychoactive medicines were expressed in the following categories in the analyses: 0 (no medicine), 1, 2, 3–4, and 5 or more medicines; and 0 (0 DDD), 0.1–0.9, 1–1.9, 2–2.9, and 3 or more DDD/day. Periods of time when subjects were not taking any psychoactive medicines (i.e. 0 medicine and 0 DDD/day) were used as the reference period.

2.4 Outcome Variables and Follow-Up Period

Given that falls were only recorded in the database as a secondary diagnosis for hospitalization, the primary end-point for the study was any hospitalization with a secondary diagnosis of a fall from the same level (ICD-10-AM: W18, W19, W0). To ensure that the hospitalization was associated with the fall and to reduce the chance that these were within-hospital falls, the fall code was only included where it was the second code in the series (i.e. immediately after the primary diagnosis, indicating that the fall was a contributing factor to the cause of admission). Subjects were followed up until the primary end-point or the end of the study period (30 June 2012), whichever occurred first. Subjects were censored at their first hospitalization event for any reason other than the outcome of interest, upon entering residential aged care facilities, upon receiving their first prescription of palliative care medicines or making a palliative care service claim, or if they died during the study period.

2.5 Statistical Analysis

Hospitalization rates were calculated as the cumulative number of hospitalizations in each exposure category divided by the number of days at risk. Incidence rate ratios (IRRs) were calculated using Poisson regression with a robust error variance adjusting for age at study entry, sex, socioeconomic index for area [32], number of medicines used, number of prescribers and specialist visits (assessed quarterly in the 12 months prior to the study), number of hospitalizations (for any diagnosis) in the 3 months prior to the study, and number of co-morbidities (as measured by the Australian adaption of Rx-Risk-V) [33].

A sensitivity analysis was undertaken, which excluded patients who were prescribed an anti-Parkinson medicine (ATC code N04) within the 12 months prior to the study, given that patients with Parkinson disease are twice as likely to fall as patients with other neurological conditions [34]. All analyses were performed using SAS Version 9.1.2 software (SAS Institute, Cary, NC, USA).

3 Results

Overall, 73,690 patients were included in the cohort. Patient characteristics are reported in Table 1. At the time of study entry, the average age of the patients was 83 years, and 46 % were male.

Table 2 presents the effect of the total number of psychoactive medicines on fall risk. In comparison with hospitalization for falls that occurred when no psychoactive medicine was used, the risk of hospitalization for falls was slightly increased when one psychoactive medicine was used, increasing to a threefold increased risk when five or more psychoactive medicines were taken concurrently. Sensitivity analysis with exclusion of patients who were prescribed anti-Parkinson medicines within the year prior to the study showed a similar trend (Table 2).

When the data were analysed by dose (Table 3), a similar trend between the cumulative combined dose of psychoactive medicines and the fall risk was observed. All doses were associated with an increased risk of hospitalization for falls. Patients on three or more DDD per day had a fourfold increased risk (Table 3). A similar trend was observed when patients on anti-Parkinson medicines were excluded from the analysis (Table 3).

4 Discussion

This study examined time-varying use of psychoactive medications in older patients and found that concurrent use of multiple psychoactive medicines was associated with an

Table 1 Baseline demographic characteristics of the study cohort

Characteristic	Cohort [n = 73,690]
Age [years; mean (SD)]	82.6 (7.8)
Male sex [n (%)]	33,501 (45.5)
Number of medicines used [median (IQR)][a]	9 (6–12)
Number of prescribers [median (IQR)][a]	2 (1–3)
Number of specialist visits [median (IQR)][a]	1 (0–3)
Number of prior hospitalizations [median (IQR)][b]	0 (0–1)
Number of co-morbidities [median (IQR)][c]	5 (4–7)
Patients receiving anti-Parkinson medicines [n (%)][a]	2,691 (3.7)

IQR interquartile range, *SD* standard deviation

[a] Values for 12 months prior to study entry

[b] Values for 3 months prior to study entry

[c] Values for time-varying every 4 months

increased risk of hospitalization for falls. Additionally, the total daily dosage of psychoactive medicines was a risk factor for falls. We observed a significantly increased risk of falls when people were on one or more psychoactive medicines or were on a dose of 0.1–0.9 DDD or more per day. The strong dose-relationship observed in our study suggests that increased exposure, either by increased numbers of medicines or increased dose, does contribute to the fall risk.

Systematic reviews and meta-analyses of observational and randomized controlled trials have found significant associations between use of psychoactive medicines and falls [9, 35, 36]. Higher doses of psychoactive medicines (e.g. diazepam, benzodiazepines, neuroleptics) were also found to be associated with an increased risk of falls [37–40]. Using the Drug Burden Index (DBI) to measure the burden of medicines with sedative and anticholinergic effects, a number of studies have found that the higher the DBI, the greater the risk of functional impairment and falls [41–43]. Prior research (using a different method) on multiple psychoactive medicine use and falls found that patients taking two or more psychoactive medicines were at increased risk of falls, compared with those taking only one medicine [35]. Using direct comparison of pairwise estimates, another study found an increased risk of recurrent falls in patients taking psychoactive medicines with high combined doses (i.e. more than three standard daily doses [SDD]), compared with those taking medium doses (1–3 SDD) or low doses (<1 SDD) [23]. Previous research

Table 2 Effect of total number of psychoactive medicines taken on fall risk

Cohort	Script category	Number of falls	Person-years	Rate per 10 years (95 % CI)	IRR (95 % CI)	P value
Whole cohort						
Unadjusted	0	518	20,448	0.25 (0.23–0.28)	1.00 (1.00–1.00)	–
	1	527	16,945	0.31 (0.29–0.34)	1.23 (1.09–1.39)	0.001
	2	246	5,231	0.47 (0.41–0.53)	1.85 (1.59–2.16)	<0.001
	3–4	108	1,946	0.55 (0.46–0.67)	2.18 (1.78–2.69)	<0.001
	≥5	16	189	0.84 (0.51–1.37)	3.32 (2.02–5.47)	<0.001
Adjusted[a]	0	518	20,448	0.17 (0.13–0.23)	1.00 (1.00–1.00)	–
	1	527	16,945	0.21 (0.16–0.28)	1.22 (1.08–1.38)	0.002
	2	246	5,231	0.29 (0.22–0.40)	1.70 (1.45–1.99)	<0.001
	3–4	108	1,946	0.34 (0.24–0.48)	1.96 (1.58–2.43)	<0.001
	≥5	16	189	0.55 (0.31–0.96)	3.15 (1.90–5.23)	<0.001
Cohort after exclusion of patients with anti-Parkinson medicines in the previous year						
Unadjusted	0	514	20,258	0.25 (0.23–0.28)	1.00 (1.00–1.00)	–
	1	500	16,424	0.30 (0.28–0.33)	1.20 (1.06–1.36)	0.004
	2	219	4,849	0.45 (0.39–0.51)	1.78 (1.52–2.08)	<0.001
	3–4	90	1,673	0.54 (0.44–0.66)	2.11 (1.69–2.65)	<0.001
	≥5	9	147	0.61 (0.32–1.17)	2.41 (1.24–4.66)	0.009
Adjusted[a]	0	514	20,258	0.17 (0.13–0.23)	1.00 (1.00–1.00)	–
	1	500	16,424	0.21 (0.15–0.28)	1.19 (1.05–1.35)	0.006
	2	219	4,849	0.29 (0.21–0.39)	1.63 (1.39–1.93)	<0.001
	3–4	90	1,673	0.33 (0.23–0.47)	1.89 (1.50–2.39)	<0.001
	≥5	9	147	0.40 (0.20–0.82)	2.30 (1.18–4.47)	0.01

CI confidence interval, *IRR* incidence rate ratio

[a] Adjusted for age, sex, socioeconomic index for area, time-varying co-morbidities, and numbers of medicines, prescribers, specialist visits and prior hospitalizations

Table 3 Effect of cumulative defined daily doses of psychoactive medicines on fall risk

Cohort	DDD category	Number of falls	Person-years	Rate per 10 years (95 % CI)	IRR (95 % CI)	*P* value
Whole cohort						
Unadjusted	0	524	20,538	0.25 (0.23–0.28)	1.00 (1.00–1.00)	–
	0.1–0.9	613	17,745	0.35 (0.32–0.37)	1.35 (1.20–1.52)	<0.001
	1–1.9	198	5,409	0.37 (0.32–0.42)	1.43 (1.22–1.69)	<0.001
	2–2.9	58	1,136	0.51 (0.39–0.66)	2.00 (1.52–2.62)	<0.001
	≥3	22	274	0.80 (0.53–1.22)	3.15 (2.05–4.82)	<0.001
Adjusted[a]	0	524	20,538	0.17 (0.12–0.22)	1.00 (1.00–1.00)	–
	0.1–0.9	613	17,745	0.21 (0.15–0.28)	1.24 (1.10–1.39)	<0.001
	1–1.9	198	5,409	0.26 (0.19–0.36)	1.58 (1.33–1.86)	<0.001
	2–2.9	58	1,136	0.38 (0.26–0.56)	2.29 (1.74–3.02)	<0.001
	≥3	22	274	0.71 (0.43–1.17)	4.26 (2.75–6.58)	<0.001
Cohort after exclusion of patients with anti-Parkinson medicines in the previous year						
Unadjusted	0	519	20,321	0.26 (0.23–0.28)	1.00 (1.00–1.00)	–
	0.1–0.9	570	17,048	0.33 (0.31–0.36)	1.31 (1.16–1.47)	<0.001
	1–1.9	174	5,033	0.35 (0.30–0.40)	1.35 (1.14–1.61)	<0.001
	2–2.9	52	1,025	0.51 (0.39–0.66)	1.98 (1.49–2.64)	<0.001
	≥3	17	239	0.71 (0.44–1.14)	2.78 (1.72–4.50)	<0.001
Adjusted[a]	0	519	20,321	0.17 (0.13–0.22)	1.00 (1.00–1.00)	–
	0.1–0.9	570	17,048	0.20 (0.15–0.27)	1.20 (1.06–1.35)	0.004
	1–1.9	174	5,033	0.25 (0.18–0.35)	1.51 (1.27–1.80)	<0.001
	2–2.9	52	1,025	0.39 (0.26–0.57)	2.30 (1.72–3.08)	<0.001
	≥3	17	239	0.65 (0.38–1.14)	3.90 (2.39–6.35)	<0.001

CI confidence interval, *DDD* defined daily dose, *IRR* incidence rate ratio

[a] Adjusted for age, sex, socioeconomic index for area, time-varying co-morbidities and numbers of medicines, prescribers, specialist visits and prior hospitalizations

in other settings, such as nursing facilities, has also showed evidence of an association between the psychoactive load and an increased risk of falls [44].

Our study had a number of strengths, including a large sample size and assessment of day-to-day medication exposure. Use of hospitalizations for falls as an outcome was potentially more reliable than self-reported falls because it avoided bias due to inconsistent recording and differential recall of community events that did not result in hospitalization [45]. It also focused on possibly more serious falls (i.e. falls resulting in hospitalization), which may have been more important to study, given the substantial morbidity associated with these events compared with minor falls that did not require hospitalization. However, community events would also result in significant injury, and research focused on community events is also needed. Additionally, our ascertainment of medicine use on each day of the study and the risk of falling on the subsequent day ensured that the medicines were taken before the fall occurred, which is an important concept in the assessment of adverse drug reactions, particularly when many of these medicines may be dispensed in hospital to treat the pain associated with a fall [46].

Although a large number of potential confounders were controlled for in our study, we were unable to control for all potential confounders. The absence of diagnostic information in the dataset meant that disease severity could not be taken into account, nor did we control for all clinical conditions for which the psychoactive medicines might have been prescribed, although we did try to reduce the impact of indication bias by excluding dementia medicines (as a proxy for dementia disease) and patients receiving palliative care, and by undertaking a sensitivity analysis where we excluded patients who were dispensed anti-Parkinson medicines. Although only 3.7 % of our patients received anti-Parkinson medicines in the year before the study, the exclusion of these patients resulted in a slight reduction in the risk estimates. It should also be noted that we used dementia medicines as a proxy to exclude dementia patients, but many patients with dementia may not be treated with specific medicines and thus would not have been excluded on that basis. Other potential confounders may have included concomitant use of some cardiovascular medicines (such as antihypertensives or diuretics) that have been found to be associated with a modest increase in the fall risk [9]. While some

unmeasured confounding may remain, an unknown confounding factor with a prevalence of 20 % would need to have large associations with both the outcome and the exposure (by factors of 4–5) to reduce a relative risk from 1.57 down to 1 [47]. Therefore, the moderate to strong increased risks found in our current study are unlikely to have been due to unknown or unmeasured confounding [46].

The primary disadvantage of using the waiting time distribution approach to assign exposure duration to single prescriptions is that the approach is more relevant for medicines with predominantly chronic use patterns [31]. Our study included medicines that are used short term or as required, including pain relievers and medicines (such as prochlorperazine) for dizziness, nausea and vomiting. As we were unable to determine actual consumption, it is possible that some patients who were classified as being exposed only took the medicine for a few days or did not consume the medicine at all. The use of the veteran population in this study may also be seen as a limitation for generalization of our findings. However, previous research has reported that there was no difference in use of practitioners, health services and treatment between veteran and non-veteran patients in both the primary and tertiary Australian care sectors after adjustment for age, service-related disability and marital status [48]. Our results are therefore likely to be applicable to other elderly Australians.

5 Conclusion

The results of our study demonstrate that an increased number and increased doses of psychoactive medicines are significantly associated with an increased risk of hospitalization for falls in older adults. With up to a third of the elderly on psychoactive medicines, strategies to reduce the psychoactive medicine burden are required and are likely to translate into significant health benefits.

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Conflict of interest Nicole L. Pratt, Emmae N. Ramsay, Lisa M. Kalisch Ellett, Tuan A. Nguyen, John D. Barratt and Elizabeth E. Roughead have no conflicts of interest that are directly relevant to the content of this study.

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