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Original

Risk of Drug-Induced Accidents and Injuries in Elderly Patients Treated with Specific Drugs Rather than Polypharmacy : Analyses of the Japanese Adverse Drug Event Report Database

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Abstract : One of the reasons the health care system requires long-term nursing care for elderly patients is the risk of falls and fractures. In this study, we sought to identify risk factors for drug-induced falls and fractures in elderly patients in Japan. Risk factors for drug-induced falls and fractures in the elderly were analyzed by searching for the Standardised Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) "accidents/injuries" in the Japanese Adverse Drug Event Report database (JADER), as this SMQ was the most well suited for evaluating data on falls and fractures. For elderly patients in Japan, the risk factors for drug-induced accidents/injuries include age ≥ 70 years old, female sex, and treatment with specific drugs, but not polypharmacy. Among the risk factors with the 10 highest reporting odds ratios (RORs) were treatment with : anti-osteoporosis agents such as bisphosphonates (e.g., minodronic acid), eldecalcitol and bazedoxifene ; dementia therapeutic agents such as rivastigmine and memantine ; antiparkinsonian agents such as entacapone and pramipexole ; and neuropathic pain relievers such as pregabalin. Although various geriatric syndromes were generally caused by polypharmacy, it has been posited that individual medications such as those mentioned above have a more significant association with drug-induced accidents and injuries in the elderly than polypharmacy. These drugs should be used cautiously while considering drug interruption, dose reductions, and switching to alternative therapies with lower risks. An association between accidents/injuries and drugs targeting the central nervous system (such as hypnotics, sedatives, anxiolytics, and antidepressants) has previously been reported. However, in the present study, no elevated risks in association with triazolam, zopiclone, flunitrazepam, diazepam, rilmazafone, estazolam, etizolam, or paroxetine were detected. Using RORs for risk detection for drugs in the JADER database is accessible and useful, and enables sensitive risk detection.

Key words : fracture, risk factor, elderly, Japanese adverse drug event report database (JADER)

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Introduction

In Japan, life expectancy at birth for male and female individuals is 81.09 and 87.26 years, respectively, and has reached the highest level to date[1]. The total population ≥ 75 years old is estimated to increase by 1.3 times from 16.32 million people (13.0% aged ≥ 75 years) in 2015 to 21.7 million people (18.1% aged ≥ 75 years) in 2025[2]. Healthy life expectancy (the average period of life during which health problems do not restrict daily life) in 2016 for males and females was 72.14 and 74.79 years, respectively[3]. Smaller differences between life expectancy and healthy life expectancy would likely lead to healthier daily life in the population. The top four reasons for requiring long-term nursing care among elderly users of long-term care insurance in 2016 were dementia (18.0%), cerebrovascular disease (stroke) (16.6%), age-related frailty (13.3%), and a fall or fracture (12.1%)[4]. Furthermore, fractures decrease quality of life[5]. Fracture prevention could therefore extend healthy life expectancy and curb rising medical costs.

Drugs are known as one of the factors responsible for falls and fractures, and a guideline on appropriate use of drugs in the elderly was issued in May 2018 by the Ministry of Health, Labour and Welfare. The guideline states that drug-induced geriatric syndromes are indicated by dizziness, falls, memory impairment, and delirium, and reports that high-risk drugs include antihypertensive agents, hypnotics, anxiolytics, antidepressants, antiepileptics, phenothiazines, antiparkinsonian agents, antihistamines, and memantine[6].

Several studies on drug-induced falls and fractures in elderly patients, including studies on the use of multiple medications (polypharmacy), have been conducted worldwide. However, the results are not consistent — they vary from study to study, and by country. Moreover, in Japan, only sparse data have been collected at a nationwide level.

The Pharmaceuticals and Medical Devices Agency (PMDA) controls the Japanese Adverse Drug Event Report database (JADER), which includes spontaneous reports of adverse drug reactions (ADRs) from the pharmaceutical industry, medical institutions, and clinical trials since April 2004. This database is accessible to the general public following agreement with the user policy. Reports in JADER consist of the following four fields: "demographics (demoCCYYMM)," "drug information (drugCCYYMM)," "adverse event (reacCCYYMM)," and "disease name (histCCYYMM)," which are each associated with the same patient identification (ID) number[7].

Several studies in the elderly have been conducted using JADER, such as analyses of high-risk drugs causing adverse events (AEs), non-benzodiazepine-induced AEs, the prognosis of AEs, and the relationships between polypharmacy and factors such as multi-morbidity, renal function disorders and liver function disorders[8,9]. However, despite drug-induced falls and fractures being a considerable health-related issue for the elderly in Japan, no previous reports have analyzed the risk factors for such events using JADER. One advantage of analyses performed using JADER is that the odds ratios (ORs) for specific drug/AE combinations can be calculated. Another advantage is that relative risk level can be compared by OR to each specific drug and event of interest in the setting of Japan. Thus, the purpose of this study was to explore relevant fac-

tors and specific types of drugs that are associated with a high risk of a fall or fracture in the elderly using JADER.

Materials and methods

Data in JADER that were collected from April 2004 to June 2017 were used. Reported AEs are coded using the Preferred Term (PT) in the Medical Dictionary for Regulatory Activities (MedDRA), developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and stored in JADER[10]. Notably, MedDRA is used by regulatory agencies and pharmaceutical industries worldwide. However, directly and comprehensively searching for AEs in MedDRA is challenging because MedDRA consists of System Organ Classes (SOCs) with four sublevels of hierarchical organization, and PTs belong to different SOCs depending on the AE code. Therefore, identical AEs may be grouped under different SOCs. For example, a discrepancy could arise if the target AE is a "Renal disorder", which belongs to the "Renal and urinary disorders" SOC, because "Blood urea nitrogen (BUN) increase" belongs to the "Investigations" SOC. Even if AEs have the same meaning, they can be classified into different SOCs. Standardised MedDRA Queries (SMQs) are tools developed to facilitate the retrieval of MedDRA-coded data and are used to support signal detection and monitoring. SMQs comprise PTs in MedDRA related to specific medical conditions, and there are currently nearly one hundred SMQs. The accidents and injuries SMQ ("accidents/injuries") is defined as accidents and injuries associated with the use of medications, which include terms such as accidents, injuries, burns, trauma, falls, fractures, wounds, crush, and contusions[11]. However, terms that refer to risk factors for accidents and injuries (e.g., sudden onset of sleep) are excluded[11]. Also, accidents/injuries is a single term and cannot be separated. Although accidents/injuries covers a broader range of AEs than just falls and fractures, this SMQ was selected for our study because it provides sensitive signal detection for drug-induced falls and fractures, and such events can be individuated comprehensively.

Individual case reports and post-marketing surveillance by pharmaceutical companies are the main reported sources in JADER, so reported AEs are almost always caused by drugs. Therefore all AEs in the present study are referred to as ADRs.

Reported ADR events with a clear age range (including 0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90–99 and ≥ 100 years) were extracted from JADER. ADRs were encoded by MedDRA/J Version 20.1, and ADRs matched to accidents/injuries were identified. Next, we checked whether ADRs corresponded to accidents/injuries in the database. Missing sex data were treated as "unknown". Duplicate drugs (those with the same ID number) were excluded. The numbers of drugs were counted and categorized as "1–5 drugs" and "≥ 6 drugs." The numbers of ADRs and numbers of ADRs corresponding to accidents/injuries were counted by age group and sex, and we determined whether the risks of ADRs corresponding to accidents/injuries differed according to sex and age. The World Health Organization's definition of elderly is ≥ 65 years old, but age groups are categorized in 10-year increments in JADER, so elderly patients in the present study were defined as those categorized as ≥ 70 years old. Fac-

tors relevant to ADRs which correspond to accidents/injuries for those aged 70 years or older were analyzed. Drugs were categorized into small therapeutic categories, because there was a large number of drugs in the database[12]. Signals relating to small therapeutic categories, and ADRs corresponding to accidents/injuries were examined. Reports that included unknown drug names or over-the-counter medications were excluded from our analysis. For signal detection, the reporting odds ratio (ROR) was used, and a 95% confidence interval (CI) was calculated. Each ROR was calculated using the following formula:

$$ROR = (N11 / N21) / (N12 / N22) = (N11 \times N22) / (N12 \times N21)$$

Where, N11 and N12 are the numbers of certain and uncertain ADRs for the target drug, respectively, and N21 and N22 are the numbers of certain and uncertain ADRs for other drugs, respectively[13].

In the small therapeutic categories where signals were detected, the ROR was calculated for individual drugs. The proportional relationship between the drug and detected accidents/injuries was calculated. JMP Pro 14 (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analyses.

Results

A total of 749,054 ADR events (483,152 patients) were reported, including 696,794 events with a clear age range. The population used for the risk factor analysis is shown in Fig. 1. The number of ADRs and the number of ADRs corresponding to accidents/injuries categorized by age group and sex are shown in Fig. 2A and B, respectively. The proportion of ADRs by age group was 24.4%, 23.1%, and 13.1% in patients in their 70s, 60s, and 50s, respectively. Furthermore, the proportion of ADRs corresponding to accidents/injuries was 28.2%, 23.7%, and 19.8% in patients in their 70s, 80s, and 60s, respectively. The average number of drugs used in individual patients was 5.1–5.4 for patients aged 50–90 years (data not shown). In patients in their 70s, the proportion of ADRs was 44.8% and 54.6% in female and male patients, respectively, whereas the proportion of ADRs corresponding to accidents/injuries was 63.9% and 34.9% in female and male patients, respectively, and there were more female than male patients listed in the database.

A multivariate analysis was performed using the total population, including the variables of sex, age group (< 70 years or ≥ 70 years), and drug usage (≥ 6 or 1–5 drugs) (Table 1). The factors associated with ADRs corresponding to accidents/injuries were female sex (OR [95% CI], 1.73 [1.65–1.82]), age ≥ 70 years (OR [95% CI], 2.16 [2.06–2.27]), and 1–5 drugs used (OR [95% CI], 1.52 [1.44–1.60]).

Similarly, a multivariate analysis was performed using the elderly population (Table 2). The factors associated with ADRs corresponding to accidents/injuries were female sex (OR [95% CI], 2.17 [2.02–2.32]), age 80–89 years (OR [95% CI], 1.65 [1.54–1.76]), age 90–99 years (OR [95% CI], 1.73 [1.51–1.98]) and 1–5 drugs used (OR [95% CI], 1.60 [1.49–1.71]). There was no relationship between multiple medications (polypharmacy) and accidents/injuries.

Of the 171,218 patients with reported ADRs in the age group ≥ 70 years, 59 small therapeutic

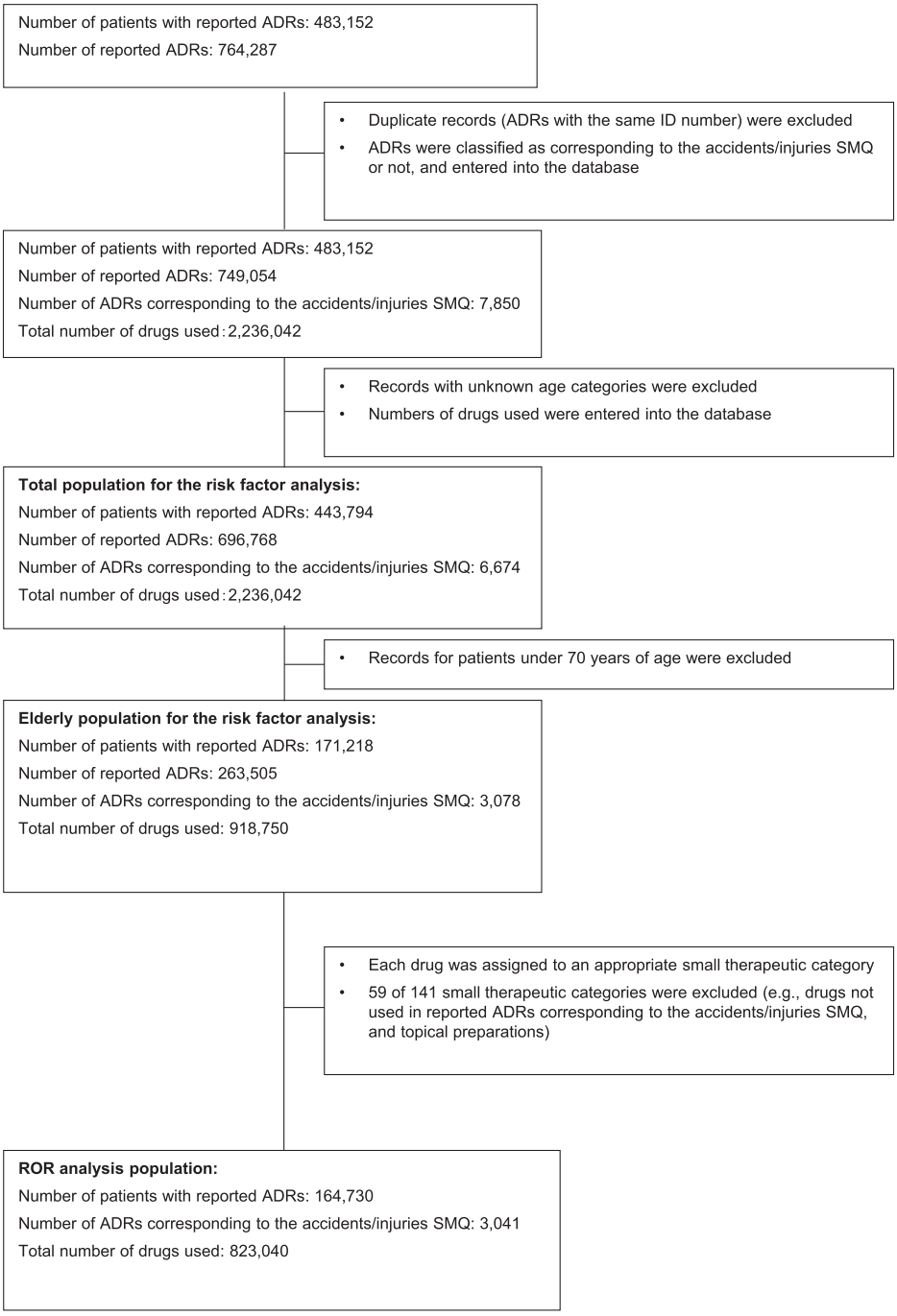
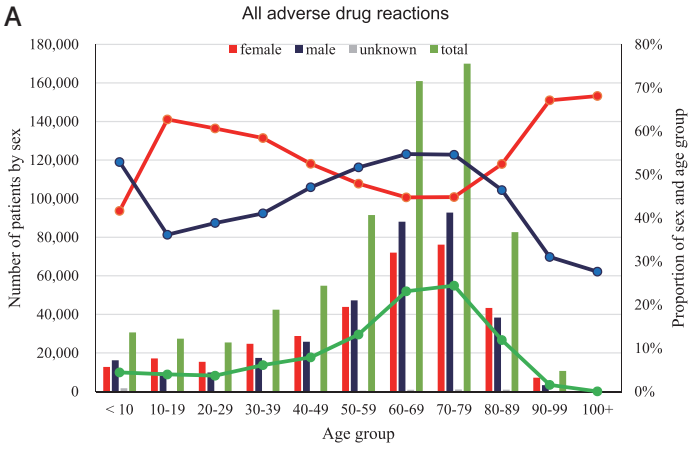
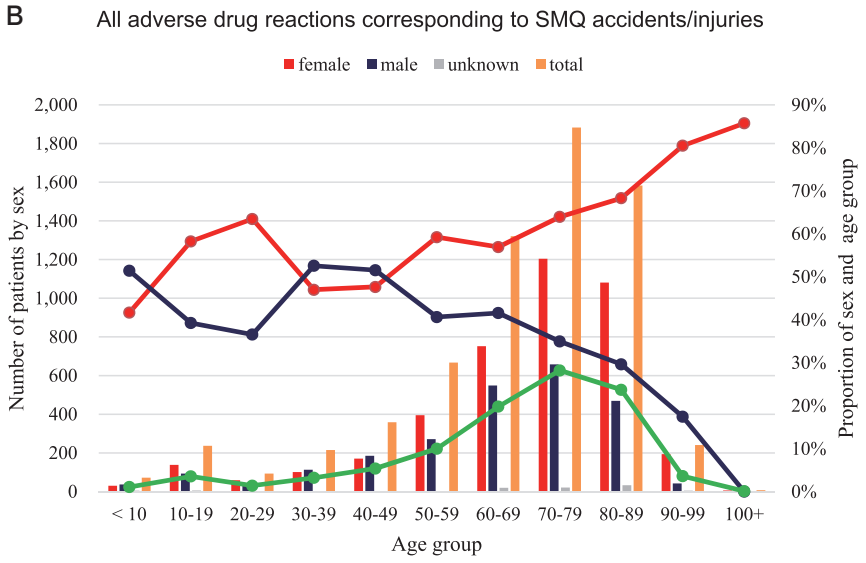


Fig. 1. Flowchart showing the process of selecting patients for inclusion in the analyses of ADRs corresponding to the accidents/injuries SMQ.

categories such as drugs that were not used in patients who had experienced the ADRs corresponding to accidents/injuries (e.g., topical preparations, drugs used for diagnosis, and unknown drugs) were excluded. Subsequently, the RORs for the remaining 164,730 patients were analyzed. A total of 823,040 drugs were used to calculate the RORs. The small therapeutic



Age group	< 10	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100+
Female	41.6%	62.7%	60.6%	58.4%	52.5%	47.9%	44.7%	44.8%	52.4%	67.1%	68.1%
Male	52.9%	36.1%	38.8%	41.0%	47.1%	51.6%	54.7%	54.6%	46.4%	31.0%	27.6%
Total	4.4%	3.9%	3.7%	6.1%	7.9%	13.1%	23.1%	24.4%	11.9%	1.5%	0.0%



Age group	< 10	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100+
Female	41.7%	58.2%	63.4%	47.0%	47.6%	59.2%	56.9%	63.9%	68.3%	80.5%	85.7%
Male	51.4%	39.2%	36.6%	52.6%	51.5%	40.6%	41.6%	34.9%	29.6%	17.4%	0.0%
Total	1.1%	3.5%	1.4%	3.2%	5.4%	10.0%	19.8%	28.2%	23.7%	3.6%	0.1%

Fig. 2. Distribution of ADRs reported in patients by sex and age group (A), and distribution of ADRs corresponding to accidents/injuries by sex and age group (B). On each graph, the bars show numbers of patients by sex, and the lines show proportions of patients by sex and age group. The table below each graph shows the proportions of female and male patients within each age group (excluding patients for whom sex was unknown), and the proportions of total patients (female, male or unknown sex) within each age group.

Table 1. Multivariate model estimates for risk of ADRs corresponding to accidents/injuries in the total population

Variable		Odds ratio (95% CI)	P (based on χ^2 test)
Sex	Male	1*	< 0.0001
	Female	1.73 (1.65-1.82)	
Age group	< 70	1*	< 0.0001
	≥ 70	2.16 (2.06-2.27)	
Drug usage	≥ 6	1*	< 0.0001
	1-5	1.52 (1.44-1.60)	

*Reference category.

Table 2. Multivariate model estimates for risk of ADRs corresponding to accidents/injuries in the elderly population

Variable		Odds ratio (95% CI)	P (based on χ^2 test)
Sex	Male	1*	< 0.0001
	Female	2.17 (2.02-2.32)	
Age group	70-79	1*	NA
	80-89	1.65 (1.54-1.76)	< 0.0001
	90-99	1.73 (1.51-1.98)	< 0.0001
	100+	2.46 (1.15-5.24)	0.0197
Drug usage	≥ 6	1*	< 0.0001
	1-5	1.60 (1.49-1.71)	

*Reference category.

categories with ROR values > 1 and 95% CIs that do not include 1, and the RORs for the individual drugs with many ADRs corresponding to accidents/injuries, are shown in Table 3. Higher ROR values were obtained for anti-osteoporosis drugs than for other agents, especially bisphosphonates, followed by anti-Alzheimer's disease drugs and antiparkinsonian agents. The 10 highest ROR values included those for anti-osteoporosis agents such as bisphosphonates (minodronic acid ROR [95% CI], 8.7 [7.2-10.3]; eldecalcitol (ROR [95% CI], 4.1 [3.4-5.0]); bazedoxifene ROR, [95% CI], 4.5 [3.0-6.7]), dementia therapeutic agents such as rivastigmine (ROR [95% CI], 5.5 [4.3-7.1]) and memantine (ROR [95% CI], 4.2 [3.2-5.3]), antiparkinsonian agents such as entacapone (ROR [95% CI], 5.0 [3.3-7.6]) and pramipexole (ROR [95% CI], 4.0 [2.9-5.5]), and neuropathic pain relievers such as pregabalin (ROR [95% CI], 3.5 [3.1-4.1]). Approximately 80% of bisphosphonates were determined to be related to accidents/injuries, whereas only 60-70% and 20-30% of anti-Alzheimer's disease drugs and antiparkinsonian agents such as levodopa were associated with accidents/injuries.

Individual drugs with ROR values > 1 and 95% CIs that do not include 1, other than anti-osteoporosis agents, dementia therapeutic agents, antiparkinsonian agents and neuropathic pain relievers, were: limaprost (ROR [95% CI], 2.0 [1.6-2.5]); antihyperphosphatemics such as

Table 3. RORs for drugs with ADRs corresponding to accidents/injuries in the ROR analysis population

Drug names, organized by small therapeutic category	Numbers of ADRs corresponding to accidents/injuries					ROR (95% CI)	Suspected drug*
	Specific drug		Other drugs				
	Yes	No	Yes	No	Total		
Other agents affecting metabolism (miscellaneous)	1,431	28,714	11,721	781,174	823,040	3.3 (3.1–3.5)	NA
Alendronate sodium	437	3,866	12,715	806,022	823,040	7.2 (6.5–7.9)	84.9%
Sodium risedronate hydrate	231	2,260	12,921	807,628	823,040	6.4 (5.6–7.3)	84.8%
Minodronic acid hydrate	139	999	13,013	808,889	823,040	8.7 (7.2–10.3)	84.2%
Zoledronic acid	73	1,638	13,079	808,250	823,040	2.8 (2.2–3.5)	79.5%
Denosumab	54	985	13,098	808,903	823,040	3.4 (2.6–4.5)	83.3%
Raloxifene hydrochloride	32	1,066	13,120	808,822	823,040	1.9 (1.3–2.6)	34.4%
Bazedoxifene acetate	26	356	13,126	809,532	823,040	4.5 (3.0–6.7)	76.9%
Agents affecting central nervous system (miscellaneous)	598	13,296	12,554	796,592	823,040	2.9 (2.6–3.1)	NA
Pregabalin	212	3,736	12,940	806,152	823,040	3.5 (3.1–4.1)	69.3%
Donepezil hydrochloride	103	3,586	13,049	806,302	823,040	1.8 (1.5–2.2)	33.0%
Rivastigmine	71	793	13,081	809,095	823,040	5.5 (4.3–7.1)	94.4%
Memantine	67	998	13,085	808,890	823,040	4.2 (3.2–5.3)	67.2%
Galantamine hydrobromide	44	752	13,108	809,136	823,040	3.6 (2.7–4.9)	72.7%
Pramipexole hydrochloride	39	606	13,113	809,282	823,040	4.0 (2.9–5.5)	64.1%
Calcium preparations	64	1,501	13,088	808,387	823,040	2.6 (2.1–3.4)	NA
Calcium L-aspartate hydrate	41	866	13,111	809,022	823,040	2.9 (2.1–4.0)	13.3%
Calcium lactate hydrate	15	414	13,137	809,474	823,040	2.2 (1.3–3.7)	19.5%
Vitamin A and D preparations	350	8,466	12,802	801,422	823,040	2.6 (2.3–2.9)	NA
Alfacalcidol	183	5,408	12,969	804,480	823,040	2.1 (1.8–2.4)	5.5%
Eldecalcitol	118	1,780	13,034	808,108	823,040	4.1 (3.4–5.0)	30.0%
Calcitriol	33	803	13,119	809,085	823,040	2.5 (1.8–3.6)	9.1%
Vitamins E preparations	13	339	13,218	865,595	823,040	2.4 (1.4–4.1)	NA
Tocopheryl acetate	13	339	13,139	809,559	823,040	2.4 (1.4–4.1)	0.0%
Antiparkinsonian agents	252	6,904	12,900	802,984	823,040	2.3 (2.0–2.6)	NA
Carbidopa hydrate - levodopa mixt	40	1,256	13,112	808,632	823,040	2.0 (1.4–2.7)	22.5%
Levodopa - benserazide hydrochloride mixt	43	730	13,109	809,158	823,040	3.6 (2.7–5.0)	23.6%
Amantadine hydrochloride	36	1,315	13,116	808,573	823,040	1.7 (1.2–2.4)	61.1%
Entacapone	24	296	13,128	809,592	823,040	5.0 (3.3–7.6)	79.2%
Selegiline hydrochloride	18	377	13,134	809,511	823,040	2.9 (1.8–4.7)	27.8%
Vitamins K preparations	29	980	13,123	808,908	823,040	1.8 (1.3–2.6)	NA
Menatetrenone	28	968	13,124	808,920	823,040	1.8 (1.2–2.6)	3.6%
Cardiovascular agents (miscellaneous)	220	9,390	12,932	800,498	823,040	1.5 (1.3–1.7)	NA
Limaprost alfadex	76	2,354	13,152	807,534	823,040	2.0 (1.6–2.5)	5.3%
Tocopherol nicotinate	21	1,246	13,131	808,642	823,040	1.0 (0.7–1.6)	0.0%
Calcium polystyrene sulfonate	21	1,420	13,131	808,468	823,040	0.9 (0.6–1.4)	9.5%
Lanthanum carbonate	17	349	13,135	809,539	823,040	3.0 (1.8–4.9)	29.4%
Iron sucrose	14	480	13,138	809,408	823,040	1.8 (1.1–3.1)	0.0%

Table 3. RORs for drugs with ADRs corresponding to accidents/injuries in the ROR analysis population

Drug names, organized by small therapeutic category	Numbers of ADRs corresponding to accidents/injuries					ROR (95% CI)	Suspected drug*
	Specific drug		Other drugs				
	Yes	No	Yes	No	Total		
Hypnotics, sedatives, and anxiolytics	460	20,221	12,692	789,667	823,040	1.4 (1.3-1.6)	NA
Zolpidem tartrate	131	4,397	13,021	805,491	823,040	1.8 (1.6-2.2)	37.4%
Brotizolam	118	5,092	13,034	804,796	823,040	1.4 (1.2-1.7)	25.4%
Triazolam	33	1,753	13,119	808,135	823,040	1.2 (0.8-1.6)	18.2%
Alprazolam	29	1,036	13,124	808,852	823,040	1.7 (1.1-2.4)	28.6%
Zopiclone	26	1,767	13,126	808,121	823,040	0.9 (0.6-1.3)	34.6%
Flunitrazepam	23	1,449	13,129	808,439	823,040	1.0 (0.7-1.5)	26.1%
Diazepam	20	1,076	13,132	808,812	823,040	1.1 (0.7-1.8)	5.0%
Rilmazafone hydrochloride hydrate	8	652	13,144	809,236	823,040	0.8 (0.4-1.5)	12.5%
Estazolam	12	561	13,140	809,327	823,040	1.3 (0.7-2.3)	8.3%
Eszopiclone	15	314	13,137	809,574	823,040	2.9 (1.8-4.9)	46.7%
Quazepam	8	156	13,144	809,732	823,040	3.2 (1.6-6.4)	75.0%
Psychotropics	516	23,232	12,636	786,656	823,040	1.4 (1.3-1.5)	NA
Etizolam	24	4,783	13,078	805,105	823,040	1.0 (0.8-1.2)	9.5%
Quetiapine fumarate	40	1,231	13,112	808,657	823,040	2.0 (1.5-2.8)	62.5%
Risperidone	38	1,340	13,114	808,548	823,040	1.8 (1.3-2.4)	50.0%
Paroxetine Hydrochloride Hydrate	30	1,400	13,122	808,488	823,040	1.3 (0.9-1.9)	50.0%
Carbamazepine	27	1,553	13,125	808,335	823,040	1.1 (0.7-1.6)	70.4%
Thyroid and parathyroid hormone preparations	87	4,060	13,065	805,828	823,040	1.3 (1.1-1.6)	NA
Teriparatide	32	536	13,105	806,794	823,040	3.7 (2.6-5.3)	59.4%
Levothyroxine sodium	47	3,094	13,121	807,425	823,040	0.8 (0.5-1.1)	2.1%
Methimazole	7	376	13,145	809,512	823,040	1.2 (0.5-2.4)	14.3%
Propylthiouracil	1	54	13,151	809,834	823,040	1.1 (0.2-8.2)	0.0%
Antipyretics, analgesics, and anti-inflammatory agents	665	32,157	12,487	777,731	823,040	1.3 (1.2-1.4)	NA
Tramadol hydrochloride	27	604	13,125	809,284	823,040	2.8 (1.9-4.1)	48.1%
Neurotropin	45	1,098	13,107	808,790	823,040	2.5 (1.9-3.4)	2.2%
Etodolac	45	1,601	13,107	808,287	823,040	1.7 (1.3-2.3)	6.7%
Ketoprofen	48	1,908	13,104	807,980	823,040	1.6 (1.2-2.1)	2.1%
Tramadol hydrochloride, acetaminophen	50	1,296	13,102	808,592	823,040	2.4 (1.8-3.2)	62.0%
Acetaminophen	51	3,501	13,101	806,387	823,040	0.9 (0.7-1.2)	3.9%
Diclofenac sodium	67	3,467	13,085	806,421	823,040	1.2 (0.9-1.5)	20.9%
Celecoxib	85	3,830	13,067	806,058	823,040	1.4 (1.1-1.7)	18.8%
Loxoprofen sodium hydrate	142	9,150	13,152	800,738	823,040	1.0 (0.8-1.1)	3.5%
Urogenital and anal organ agents (miscellaneous)	249	12,483	12,903	797,405	823,040	1.2 (1.1-1.4)	NA
Tamsulosin hydrochloride	51	3,269	13,101	806,619	823,040	1.0 (0.7-1.3)	17.6%
Imidafenacin	14	447	13,138	809,441	823,040	1.9 (1.1-3.3)	14.3%
Mirabegron	34	755	13,118	809,133	823,040	2.8 (2.0-3.9)	61.8%
Propiverine hydrochloride	24	909	13,128	808,979	823,040	1.6 (1.1-2.4)	4.2%
Solifenacin succinate	33	1,304	13,119	808,584	823,040	1.6 (1.1-2.2)	45.5%

NA : not applicable. *Proportion of ADRs corresponding to accidents/injuries judged to be due to the specific drug.

lanthanum (ROR [95% CI], 3.0 [1.8–4.9]) ; iron sucrose (ROR [95% CI], 1.8 [1.1–3.1]) ; hypnotics, sedatives and anxiolytics such as the non-benzodiazepines zolpidem (ROR [95% CI], 1.8 [1.6–2.2]) and eszopiclone (ROR [95% CI], 2.9 [1.8–4.9]), and the benzodiazepines brotizolam (ROR [95% CI], 1.4 [1.2–1.7]), alprazolam (ROR [95% CI], 1.7 [1.1–2.4]) and quazepam (ROR [95% CI], 3.2 [1.6–6.4]) ; antischizophrenia agents such as quetiapine (ROR [95% CI], 2.0 [1.5–2.8]) and risperidone (ROR [95% CI], 1.8 [1.3–2.4]) ; antipyretics ; and analgesics. The list also included anti-inflammatory agents such as tramadol (ROR [95% CI], 2.8 [1.9–4.1]), neurotropin (ROR [95% CI], 2.5 [1.9–3.4]) and etodolac (ROR [95% CI], 1.7 [1.3–2.3]), as well as overactive bladder agents such as mirabegron (ROR [95% CI], 2.8 [2.0–3.9]).

Discussion

The novel findings reported in the present study reveal that the risk factors for drug-induced accidents and injuries were age ≥ 70 years old, female sex, and treatment with specific drugs rather than polypharmacy. In addition, the study detected drugs associated with the risk of accidents and injuries in Japan. The number of ADRs corresponding to accidents/injuries was the largest in the 70–79-year-old group, and we posited that accidents/injuries would be one of the causes of health problems. In female patients, the difference in the period between life expectancy (87.26 years) and healthy life expectancy (74.79 years) is higher than that in male patients, and this difference is likely to contribute to accidents/injuries such as fractures.

Several studies on drug-induced falls and fractures in elderly patients have been reported, including small, single-center studies conducted in Japan. Although one group of Japanese researchers reported a risk of falls associated with hypnotic drugs, a second group reported a risk of falls associated with polypharmacy[14, 15]. Moreover, there are limited nationwide data in Japan. JADER is the only database that includes spontaneous reports of ADRs nationwide in Japan. Therefore, the present study has provided robust information on risk factors for accidents and injuries in the elderly.

In the present study, the risk of accidents/injuries was significantly higher in patients using 1–5 drugs than in the polypharmacy group (patients using ≥ 6 drugs). In terms of accidents and injuries, the risks posed by individual drugs should be considered rather than the number of drugs used by an individual. Similar findings have been reported by Lawlor *et al*, who found that chronic diseases and multiple co-morbidities are more critical predictors of falls than polypharmacy in the elderly[16]. Iihara et al have pointed out that medication class is a more crucial risk factor for fall-related fractures than a polypharmacy measure that does not take into account medication class[17].

In addition, the present study showed that the risk of drug-induced accidents/injuries is higher in females than males. The number of patients with osteoporosis in Japan is estimated at 12.8 million (3.0 million males, 9.8 million females), and incidence of osteoporosis increases with age[18]. Given the high RORs for osteoporotic drugs, the prevalence of osteoporosis may affect the risk of accidents/injuries in elderly females. In addition, the reason for the high risk in ≥ 70-year-old patients could be due to an increase in co-morbid Parkinson's disease and dementia.

It is also possible that female sex, aging, and prevalence of co-morbidities such as osteoporosis, Parkinson's disease and dementia are confounded.

Drugs associated with the highest risk of accidents/injuries were those used to treat osteoporosis, Alzheimer's disease, and Parkinson's disease. Conversely, antischizophrenia agents, hypnotics, sedatives, and anxiolytics were not associated with high RORs.

Interestingly, the bisphosphonates, which suppress fractures in patients with osteoporosis, had the highest RORs for accidents/injuries. Although it might be posited that the increased fracture incidence could be due to the primary disease, the RORs of other osteoporotic drugs for accidents/injuries are not as high as those for the bisphosphonates. This could be because bisphosphonates are being used for patients with more severe osteoporosis. However, since the risks of osteonecrosis of the jaw and atypical femur fractures increase with long-term bisphosphonate treatment[19, 20], an assessment of drug use (and the potential benefit of a "drug holiday") after treatment for a certain period has been proposed[21]. Essentially, patients with osteoporosis are at high risk of fractures, so careful treatment is needed.

Although pregabalin has been used as a neuropathic pain reliever, its associated ROR was high (3.5 [95% CI, 3.1-4.1]). The package insert for pregabalin includes a caution regarding the potential risk of fractures due to ADRs such as dizziness, somnolence, and loss of consciousness, especially in the elderly[22]. Therefore, drugs such as pregabalin should be carefully selected after weighing the risks and benefits for individual patients.

A cost-effectiveness analysis of a home safety intervention aimed at preventing falls in impaired elderly people showed that this approach could reduce fall-related fractures in elderly females[23]. This is because the incremental cost-effectiveness ratio of the home safety intervention compared to no prevention was €9,580 per quality-adjusted life years (QALY) in females[23]. This finding could apply to elderly Japanese females because the risk factors identified in our study included female sex and aging.

Several studies have used JADER to evaluate the relationships between drugs and AEs. JADER contains causality data, such as the drug suspected to have caused the AE, concomitant drugs, and drug-drug interactions. In some studies, only "suspected drug" data has been extracted for analysis. However, in the present study, drugs identified as contributing to a high risk of a fall or fracture were not always identified as the "suspected drug" in JADER. Therefore, analyses that aim to detect the risk factors for AEs should not rely on suspected causality data.

It has been reported that calculating the RORs from spontaneous report databases has advantages over calculating proportional reporting ratios, and allows for estimation of relative risk[13]. Using RORs for risk detection for drugs in JADER is accessible and useful, and enables sensitive risk detection.

The association between accidents/injuries and drugs targeting the central nervous system, such as hypnotics, sedatives, anxiolytics, and antidepressants, has previously been reported[24-26]. In contrast, in the present study, an elevated risk was not detected in association with triazolam, zopiclone, flunitrazepam, diazepam, rilmazafone, estazolam, etizolam, or paroxetine. Since the information sources contained in JADER are spontaneous reports, pharmaceutical companies

mainly report individual cases to the PMDA, and many events might be serious ADRs as determined by physicians. Indeed, there is a reporting bias as only some ADRs observed in clinical practice are reported, and the level of reporting can vary because of numerous factors[27]. Therefore, the present study may have underestimated risks, particularly those associated with hypnotics, sedatives, anxiolytics, and antidepressants.

In conclusion, we identified the principal risk factors for drug-induced accidents and injuries in the elderly in Japan to be female sex and advanced age. Specific medications have a more significant association with drug-induced accidents and injuries in elderly than polypharmacy. The top 10 ROR values included those for: anti-osteoporosis agents such as bisphosphonates (e.g., minodronic acid), eldecalcitol and bazedoxifene; dementia therapeutic agents such as rivastigmine and memantine; antiparkinsonian agents such as entacapone and pramipexole; and neuropathic pain relievers such as pregabalin. These drugs should be used cautiously while considering drug cessation, dose reductions, and switching to similar therapeutic drugs with lower associated risks as alternative management strategies.

Conflict of interest disclosure

The authors report no conflicts of interest in this study.

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