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Medication use as a risk factor for inpatient falls in an acute care hospital: a case-crossover study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Benzodiazepines, antidepressants, antipsychotic agents, anti-arrhythmic agents, opioid analgesics and antihypertensive agents including α-receptor antagonists and β-receptor antagonists, but not angiotensin II receptor antagonists, have been implicated as risk factors for falls among community dwelling elderly people, and those in aged care hospitals and nursing homes.

WHAT THIS STUDY ADDS

- Using a case-crossover design, the study's findings provide the first evidence suggesting that newly initiating treatment using an angiotensin II receptor antagonist, candesartan, or etizolam, biperiden and zopiclone may be potential risk factors for falls in acute hospitals.

AIMS

The present study aimed to evaluate the associations between medication use and falls and to identify high risk medications that acted as a trigger for the onset of falls in an acute care hospital setting.

METHODS

We applied a case-crossover design wherein cases served as their own controls and comparisons were made within each participant. The 3-day period (days 0 to –2) and the 3-day periods (days –6 to –8, days –9 to –11 and days –12 to –14) before the fall event were defined as the case period and the control periods, respectively. Exposures to medications were compared between the case and control periods. Odds ratios (OR) and 95% confidence intervals (CI) for the onset of falls with respect to medication use were computed using conditional logistic regression analyses.

RESULTS

A total of 349 inpatients who fell during their hospitalization were recorded on incident report forms between March 2003 and August 2005. The initial use of antihypertensive, antiparkinsonian, anti-anxiety and hypnotic agents as medication classes was significantly associated with an increased risk of falls, and these ORs (95% CI) were 8.42 (3.12, 22.72), 4.18 (1.75, 10.02), 3.25 (1.62, 6.50) and 2.44 (1.32, 4.51), respectively. The initial use of candesartan, etizolam, biperiden and zopiclone was also identified as a potential risk factor for falls.

CONCLUSIONS

Medical professionals should be aware of the possibility that starting a new medication such as an antihypertensive agent, including candesartan, and antiparkinsonian, anti-anxiety and hypnotic agents, may act as a trigger for the onset of a fall.

Introduction

Falls are the most common type of inpatient hospital accident, reportedly accounting for up to 70% of all inpatient accidents [1]. Fall rates per 1000 patient-days vary from 2.2 in large tertiary university hospitals to 9.1 in geriatric hospitals [1–8]. Approximately 30% of falls in hospitals lead to physical injury, with 4–6% being serious [6, 9]. For inpatients, falls are associated with serious physical and emotional injury, poor quality of life, increased length of hospital stay, admission to a long-term care facility and increased cost [10–14]. Therefore, it is important to identify and characterize triggers for risk factors for falls in hospitals to assure the quality of hospital care and patient safety.

While many studies on falls in elderly populations have been conducted in community and long-term care facilities, less is known about falls in acute care hospitals. The frequency of falls is higher in institutions such as nursing homes and hospitals than in the community setting [15]. Contributing factors for falls can be divided into two main categories: those specific to the individual (intrinsic) and those related to the environment (extrinsic) [16–31]. Intrinsic factors include age-related changes such as a decline in vision, hearing, musculoskeletal functioning, mobility, and physical activity, and health status-related factors such as the presence of a variety of chronic and acute illnesses, e.g. diabetes, cognitive deficits and Parkinson's disease. Extrinsic factors include poor lighting, loose carpets, slippery flooring and a lack of handrails. Although previous studies have identified risk factors for falls, comparative studies on falls in hospitals have had limitations including variations in study design, setting, patient population, definition of risk factors and care-related factors such as patient-to-nurse ratio. These problems significantly decrease the quality, consistency, and comparability of observational studies on falls in hospital.

Medications related to an increased risk of falls include benzodiazepines, antidepressants, antipsychotic agents, antihypertensive agents, anti-arrhythmic agents and opioid analgesics. In elderly people receiving multiple medications, polypharmacy itself is a risk factor for falls [18, 19]. Yet, many observational studies on falls in hospitals fail to focus on medication use as a risk factor for falls because the majority of falls in hospital settings have a multifactorial aetiology. For example, in acute care hospitals a variety of medications are often prescribed to patients and new medications are frequently added as required by additional symptoms. It is quite possible that the initial use of a newly initiated medication rather than the long-term use of the same medication presents a higher risk for falls. Thus we hypothesized that newly initiated medications are associated with a greater risk for falls than ongoing medications.

We used a case-crossover design to overcome many of the difficulties involved selecting an appropriate control series for cases. The case-crossover design is an observational design characterized by self-matching, such that case and control data are obtained from the same subject [32]. In this design, cases serve as their own controls, and a participant's exposure at the time of the event of interest (case period) is compared with another period when the participant was not a case (control period). Therefore the sampling of additional control participants is not required. In the analysis, each participant is considered as a stratum in a case-control study and comparisons are made within each participant. Therefore, possible confounding effects including age, sex, personality and other stable patient-specific covariates from differences between individuals are eliminated, and the focus of the analysis is on the variable of interest. Thus, the case-crossover method is an optimal study design to assess high risk medications that act as triggers for the onset of falls among hospitalized patients.

The present case-crossover study aimed to evaluate associations between medication use and falls among hospitalized patients and to identify high risk medications that could act as triggers for the onset of falls.

Methods

Setting, participants and data collection

This retrospective, case-crossover study was conducted at Fukuoka Tokushukai Medical Centre, a 600-bed acute care hospital in Japan. Fifteen clinical departments were included in the study: Internal Medicine, General Surgery, Cranial Nerve Surgery, Plastic Surgery, Orthopaedic Surgery, Urology, Psychosomatic Medicine, Rehabilitation, Cardiovascular Medicine, Dialysis, Nephrology, Otorhinolaryngology, Anesthesiology, Cardiovascular Surgery and Ophthalmology. An inpatient fall was defined as an incident in which a patient suddenly and involuntarily came to rest upon the ground or another surface and was registered with an incident report form submitted by a nurse or another hospital employee who discovered the fall. Data were collected from incident report forms and medical records during the 30 months between March 1 2003 and August 31 2005. Incident report forms included clinical department, patient demographics, date, time, location, circumstances surrounding falls and the severity of injuries. Medical records included patient demographics such as sex, age, weight, height, admission date, concurrent disease, medication history and clinical laboratory test results such as blood urea nitrogen (BUN), serum creatinine and liver enzymes (AST and ALT). Specifically, medication history during the 2 weeks prior to any fall event was carefully investigated. The present study was reviewed and approved by the Fukuoka Tokushukai Medical Centre Institutional Review Board. The need for written informed consent from patients who had fallen was waived because the present study was part of a hospital-based quality

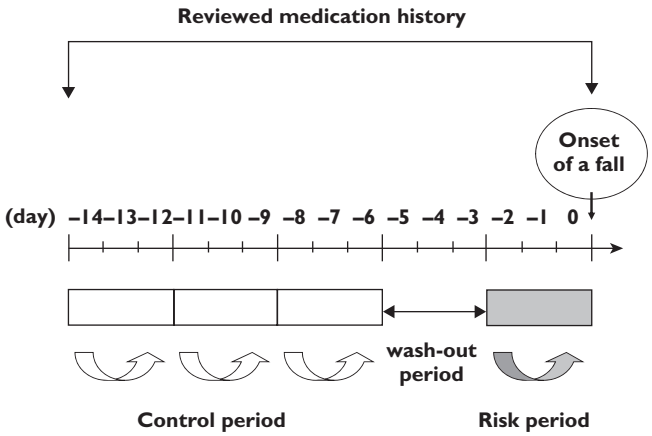

Figure 1

Definition of risk, control and wash-out periods in the present case-crossover study. The 3-day period (days 0 to –2) just before any fall event was defined as the case period based on the elimination half-life of the prescribed medications. The three control periods for each case were estimated to increase the consistency of comparable controls and to enhance the robustness of the analyses. The 3-day periods (days –6 to –8, days –9 to –11 and days –12 to –14) before the fall event were defined as the control period. The 3-day period (days –3 to –6) before the fall event between the case period and the control period was assigned as the wash-out period

improvement project and posed no risk to patients or to their privacy.

Study design

A case-crossover design was used to assess the association between exposure (medication use) and transient outcome (fall). In the present study, we defined the case period (risk period) as the 3-day period (days 0 to –2) just before the fall event based on the elimination half-life of the prescribed medications. To increase the consistency of comparable controls and to enhance the robustness of the analyses, we estimated three control periods for each case and defined control periods as days –6 to –8, days –9 to –11 and days –12 to –14 before the fall event. The 3-day period (days –3 to –6) before the fall event between the case period and the control period was estimated as the wash-out period (Figure 1). The living status of all patients was hospitalization during the period investigated, including both control and case periods.

Statistical analysis

We first performed univariate analysis to select covariates, adjusting for multivariable analysis. All variables with a significant association with falls, P value < 0.05, in univariate analysis, were entered into a staged multivariable analysis. The strength of association between medication use and falls was evaluated using odds ratios (OR) and 95% confidence intervals (CI). To estimate the OR of falls with respect to medication use, we used conditional logistic regression analyses for 1–3 matching. The 98 medications prescribed were classified into nine groups: hypnotic, anti-anxiety, antipsychotic, antihistamine, antidiabetic, antihypertensive, antiparkinsonian, anti-ulcer agents and diuretics (Table 1). Results were categorized by medication class or by specific medication. In the first analysis, we evaluated the associations between medication classes and falls. In the second analysis, we identified the specific medications that act as triggers for the onset of falls. The analysis was done separately for patients under and over 75 years of age. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Inc., Cary, NC).

Table 1

List of nine classes of medication and 98 specific medications prescribed to cases in this study

Medication classes	Specific medication (*n*)
Hypnotic agents	brotizolam (25), flunitrazepam (25), lormetazepam (3), midazolam (8), nitrazepam (12), quazepam (3), rilmazafone (1), triazolam (16), zolpidem (40), zopiclone (41)
Anti-anxiety agents	alprazolam (2), bromazepam (12), clotiazepam (2), cloxazolam (4), diazepam(21), ethyl loflazepate (3), etizolam (42), lorazepam (5), tandospirone (2)
Antipsychotic agents	chlorpromazine (8), haloperidol (31), prochlorperazine (1), promethazine (21), quetiapine (2), risperidone (7), sulpiride (3), thioridazine (2), timiperone (1)
Antihistamines	cetirizine (1), *d*-chlorpheniramine (6), clemastine (1), cyproheptadine (0), epinastine (4), fexofenadine (1), homochlorcyclizine (0), hydroxyzine (10), ketotifen (1), mequitazine (3), olopatadine (4), oxatomide (2), promethazine (1)
Antidiabetic agents	glibenclamide (8), gliclazide (4), glimepiride (10), insulin (8), metformin (8), nateglinide (3), pioglitazone (1), voglibose (14)
Antihypertensive agents	alprenolol (0), amlodipine (48), atenolol (8), benidipine (6), betaxolol (1), bisoprolol (2), candesartan (41), captopril (0), carvedilol (10), clonidine (1), delapril (0), diltiazem (26), doxazosin (8), efonidipine (1), enalapril (19), imidapril (11), losartan (22), metoprolol (1), nicardipine (6), nifedipine (35), nilvadipine (6), nisoldipine (16), nitrendipine (0), perindopril (4), prazosin (7), propranolol (1), temocapril (1), valsartan (25), verapamil (3)
Diuretics	azosemide (6), canrenoate (0), furosemide (37), spironolactone (23), trichlormethiazide (5)
Antiparkinsonian agents	amantadine (11), biperiden (25), cabergoline (7), droxidopa (3), levodopa (13), pergolide (5), pramipexole (1), selegiline (2), tiapride (15), trihexyphenidyl (4)
Anti-ulcer agents	cimetidine (4), famotidine (14), lafutidine (20), ranitidine (41), roxatidine (1)

Results

A total of 349 inpatient falls were recorded on incident report forms during the 30 months between March 1 2003 and August 31 2005. Tables 2 and 3 show the characteristics and the admitting diagnoses of fallers (cases) in the

Table 2

Characteristics of cases in this study (n = 349)

Characteristic	n (%)		n (%)
Gender		Clinical departments	
Male	194 (55.6)	Internal Medicine	120 (34.4)
Female	155 (44.4)	Cardiovascular Medicine	48 (13.8)
Age (years)		Cranial Nerve Surgery	36 (10.3)
20–29	5 (1.4)	General Surgery	33 (9.5)
30–39	6 (1.7)	Orthopaedic Surgery	33 (9.5)
40–49	9 (2.6)	Rehabilitation	24 (6.9)
50–59	34 (9.7)	Psychosomatic Medicine	18 (5.2)
60–69	69 (19.8)	Plastic Surgery	14 (4.0)
70–79	109 (31.2)	Urology	12 (3.4)
80–89	96 (27.5)	Nephrology	3 (0.9)
90–99	21 (6.0)	Anesthesiology	2 (0.6)
		Ophthalmology	2 (0.6)
		Cardiovascular Surgery	1 (0.3)
		Dialysis	1 (0.3)
		Otorhinolaryngology	1 (0.3)
		Unknown*	4 (1.2)

*A lack of description in an incident report.

present case-crossover study, respectively. The mean ± SD age of cases was 71.5 ± 14.8 years. Table 4 shows the classes and numbers of medications prescribed in the present case-crossover study. The median numbers of medications prescribed during the case and the control period were 7 and 6, respectively.

Medication classes and falls

In the analysis concerning medication classes, the results using data without patients aged <75 years old were similar to those from all patients. For univariate analysis, antihypertensive, antiparkinsonian, anti-anxiety and hypnotic agents were selected as covariates adjusting for multivariable analysis. For multivariable analysis, the initial use of antihypertensive, antiparkinsonian, anti-anxiety and hypnotic agents was significantly associated with an increased risk of falls, and these ORs (95% CI) were 8.42 (3.12, 22.72), 4.18 (1.75, 10.02), 3.25 (1.62, 6.50) and 2.44 (1.32, 4.51), respectively (Table 5).

Specific medication and falls

For univariate analysis, candesartan cilexetil, etizolam, biperiden and zopiclone were selected as covariates adjusting for multivariable analysis. For analysis concerning specific medications, the results using data from patients aged <75 years old were somewhat different from those using data from patients aged ≥75 years old. The results of the multivariate analysis were as follows. In all age groups, the initial use of candesartan cilexetil, etizolam, biperiden and zopiclone was significantly associated with an increased risk of falls, and these ORs (95% CI) were 13.92 (1.71, 113.69), 6.83 (1.92, 24.26), 4.34 (1.57, 11.99) and 4.20 (1.55, 11.40), respectively. In the age group <75 years of age, the initial use of candesartan cilexetil and biperiden were significantly associated with an increased risk of falls; these ORs (95% CI) were 11.23 (1.22, 103.04) and 10.68 (1.24, 92.24), respectively. In the age group ≥75 years of age, the initial use of biperiden and zopiclone were significantly associated with an increased risk of falls; these ORs (95% CI) were 3.75 (1.01, 13.97) and 5.40 (1.63, 17.93), respectively (Table 5).

Table 3

Admitting diagnosis of cases in this study

Diagnosis	n	Diagnosis	n
Cerebral infarction	73	Gastrointestinal bleeding	3
Cerebral haemorrhage	33	Herpes zoster	3
Chronic renal failure	30	Hydrocephalus	3
Diabetes mellitus	22	Intestinal perforation	3
Parkinson's disease	21	Pancreatic cancer	3
Depression	17	Urine tube cancer	3
Congestive heart failure	14	Aortic dissection	3
Pneumonia	14	Asthma	2
Angina pectoris	13	Cholecystitis	2
Gastric cancer	10	Chronic pancreatitis	2
Burn	9	Diabetic retinopathy	2
Ileus	9	Eating disorder	2
Liver cirrhosis	9	Hypoglycaemia	2
Epilepsy	8	Sepsis	2
Hypertension	8	Transient ischaemic attack	2
Arteriosclerosis obliterans	7	Aortic stenosis	2
Brain contusion	7	Aplastic anaemia	1
Colorectal cancer	7	Cataract	1
Dementia	7	Chorea	1
Lung cancer	7	Diabetic nephropathy	1
Subarachnoid haemorrhage	7	Dilated cardiomyopathy	1
Subdural haematoma	7	Duodenal ulcer	1
Benign prostatic hyperplasia	6	Oesophageal varices	1
Gastric ulcer	6	Fever of unknown origin	1
Alcoholic hepatitis	5	Fibroid lung	1
Head injury	5	Hypokalaemia	1
Hernia	5	Infectious endocarditis	1
Myocardial infarction	5	Myelodysplastic syndrome	1
Alcohol withdrawal syndrome	4	Nephrotic syndrome	1
Alcoholic psychoses	4	Osteoarthritis	1
Cellulitis	4	Pancreatitis	1
Cholelithiasis	4	Panic disorder	1
Hepatocellular carcinoma	4	Pyelonephritis	1
Prostate cancer	4	Renal tumour	1
Traumatic injury	4	Respiratory failure	1
Atrial fibrillation	3	Schizophrenia	1
Bile duct cancer	3	Thoracic aortic aneurysm	1
Bladder cancer	3	Thrombocytopenic purpura	1
Breast cancer	3	Thyroid cancer	1
Chronic obstructive pulmonary disease	3	Trigeminal neuralgia	1
Diabetic acidosis	3	Ventricular tachycardia	1
Drug intoxication	3		

Discussion

Our results suggested that the initial use of the medication classes of antihypertensive, antiparkinsonian, anti-anxiety

Table 4

Classes and number of medications prescribed to cases (n = 349) in this study

Periods	Case n (%) Day before a fall event 0 to –2	–6 to –8	Control n (%) –9 to –11	–12 to –14
Classes of medications				
Hypnotic agents	134 (38.4)	122 (35.0)	113 (32.4)	108 (31.0)
Anti-anxiety agents	77 (22.1)	66 (18.9)	63 (18.1)	59 (17.0)
Antipsychotic agents	58 (16.6)	63 (18.1)	56 (16.1)	51 (14.6)
Antihistamines	25 (7.2)	26 (7.5)	21 (6.0)	18 (5.2)
Antidiabetic agents	40 (11.5)	37 (10.6)	39 (11.2)	37 (10.6)
Antihypertensive agents	190 (54.4)	176 (50.4)	169 (48.4)	166 (47.6)
Diuretics	52 (14.9)	53 (15.2)	51 (14.6)	49 (14.0)
Antiparkinsonian agents	65 (18.6)	59 (16.6)	51 (14.6)	50 (14.3)
Anti-ulcer agents	76 (21.8)	72 (20.6)	67 (19.2)	67 (19.2)
Number of medications				
0–5	131 (37.5)	152 (43.6)	161 (46.1)	168 (48.1)
6–10	141 (40.4)	140 (40.1)	138 (39.5)	129 (37.0)
11–15	66 (18.9)	48 (13.8)	43 (12.3)	45 (12.9)
16–20	10 (2.9)	9 (2.6)	7 (2.0)	7 (2.0)
21–25	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Median (min–max)	7 (0–21)	6 (0–18)	6 (0–18)	6 (0–18)

Table 5

Odds ratios and 95% confidence intervals for the onset of a fall with respect to medication classes and specific medication computed by conditional logistic regression

Variable	Odds ratio	95% confidence interval	P value
Medication class			
All age groups			
Antihypertensive agents	8.42	3.12, 22.72	<0.001
Antiparkinsonian agents	4.18	1.75, 10.02	0.004
Anti-anxiety agents	3.25	1.62, 6.50	0.001
Hypnotic agents	2.44	1.32, 4.51	0.004
Specific medication			
All age groups			
Candesartan cilexetil	13.92	1.71, 113.69	0.014
Etizolam	6.83	1.92, 24.26	0.003
Bipereiden	4.34	1.57, 11.99	0.005
Zopiclone	4.20	1.55, 11.40	0.005
Age group <75 years			
Candesartan cilexetil	11.23	1.22, 103.04	0.033
Bipereiden	10.68	1.24, 92.24	0.031
Age group ≥75 years			
Bipereiden	3.75	1.01, 13.97	0.049
Zopiclone	5.40	1.63, 17.93	0.006

and hypnotic agents were significantly associated with the onset of falls with eight-, four-, three- and two-fold higher risks, respectively. The initial use of candesartan, etizolam, biperiden and zopiclone were identified as a potential risk factor for falls. To our knowledge, the present study is the first case-crossover study to evaluate the association between medication use and falls and to identify high risk medications that act as triggers for the onset of falls in an acute care hospital setting. Our results are further confirmation that medications that act on the central nervous system are significantly associated with an increased risk of falls. However, we are the first to show that the initial use of candesartan may act as trigger for the onset of falls in acute care hospitals.

Candesartan cilexetil is an inactive ester prodrug that is completely hydrolyzed to the active form, candesartan, during absorption from the gastrointestinal tract. Candesartan is a potent, highly selective antagonist of the angiotensin II receptor subtype 1 [33]. Candesartan cilexetil has been available in Japan since 1999 and is used for the treatment of hypertension and heart failure (NYHA class II-IV). Antihypertensive agents produce orthostatic hypotension, resulting in an increased risk of falls. There are no studies on the association between the use of angiotensin II receptor subtype 1 antagonists and falls. Studies with a large number of participants are needed to determine whether the use of this class of cardiovascular medication is associated with an increased risk of falls. Biperiden, an anticholinergic agent, has been available in Japan since 1964 and is used as adjunctive therapy for all forms of parkinsonism (e.g. idiopathic, postencephalitic and arteriosclerotic) and the control of extrapyramidal disorders secondary to neuroleptic drug therapy (e.g. phenothiazines). The most troublesome side-effects of anticholinergic medications include sedation and mental confusion. Such responses could contribute to adverse events such as falls, delirium, and cognitive impairment in older patients. Etizolam, a thienodiazepine derivative, has been available in Japan since 1983 and is used for anxiety and sleep disorders, as well as for muscle contraction headaches. Based on the pharmacokinetic profiles (half-life = 3.4 h) of the parent compound and its main active metabo-

lite, α-hydroxyetizolam, etizolam can be regarded as a short-acting benzodiazepine [34]. Zopiclone is a cyclopyrrolone that is chemically unrelated to the benzodiazepines and is thought to act on the GABA A receptor complex at a site distinct from, but closely related to, the benzodiazepine binding site. Based on its pharmacokinetic profile (half-life = 5–6 h), zopiclone can also be regarded as a short-acting nonbenzodiazepine [35]. Zopiclone has been available in Japan since 1989 and is used for the treatment of sleep disorders.

Numerous studies have indicated the importance of benzodiazepines as risk factors for falls in the elderly. However, the findings are potentially contradictory. Some studies demonstrated an association between the use of long-acting benzodiazepines and the risk of falls among community-dwelling elderly [36–38]. Others have shown that the use of short half-life benzodiazepines is also associated with an increased risk of falls [39, 40]. Most such studies have focused on either nursing home residents or on those dwelling in the community [36–38, 41]. Few studies have been conducted in a hospital setting, where other factors such as the presence of acute illnesses and the frequent addition of new medications could increase the risk of iatrogenic complication and falls [4, 6, 8, 29, 42]. Our results showed that the use of short-acting benzodiazepines was significantly associated with falls, compared with the use of long-acting benzodiazepines. On the other hand, it has been reported that the risk of falls was significantly high only among patients exposed to high doses of benzodiazepines, suggesting that dosage rather than half-life is more important in the evaluation of the association between the use of benzodiazepines and falls [40]. It is well known that benzodiazepines produce dose-related impairment of reaction time and psychomotor function, sedation and muscle relaxation, and these responses may lead to falls. To confirm the association between the use of benzodiazepines and falls, dose–response as well as half-life needs to be considered in analysis.

There are several limitations in the present study. First, the case-cross over design did not allow for alterations of behavioural patterns in patients between the exposed and unexposed periods. Because there were no convincing data providing evidence that no change in diagnoses was observed during the 2-week period in hospital, we could not completely rule out the possibility that the same individuals did not behave in the same manner between the case and control periods. Second, since the information on medication use has been obtained from prescription data, not intake data, we could not confirm patients' compliance with the medication regime prescribed by a physician. Third, we collected information on the dose of prescribed medications, but analyses could not be performed because of the small sample size and low statistical power. Fourth, the ability to generalize our results may be limited because of the small sample size in a single centre setting, although hospital-related confounding effects such as poor lighting, loose carpets and slippery flooring were limited.

In summary, our findings suggest that the initial use of angiotensin II receptor antagonists as antihypertensive agents, antiparkinsonian agents, anti-anxiety agents and hypnotic agents are increased risk factors for falls. Physicians and other medical professionals should be aware of the possibility that medications such as candesartan, etizolam, biperiden and zopiclone, when newly administered to patients, may act as triggers for the onset of falls in acute care hospitals. When these medications are introduced to older patients, a low but effective dose should be used taking into consideration the changes possible in pharmacodynamics and pharmacokinetics. Medical professionals including physicians, nurses and pharmacists should carefully monitor patients for an initial 3 days after starting treatment with any of these medications. Appropriate preventive strategies for falls in acute care hospitals should be considered to assure the quality of hospital care and patient safety.

Competing interests

None declared.

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