Age-dependent physiological changes, medicines and sex-influenced types of falls

Aging, medicines and falls

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ABSTRACT

Background/Study context: We investigated various parameters related to falls including age-dependent physiological changes, regular medicine use and different types of falls experienced. There is a lack of research investigating the impact of health status, sex, polypharmacy and ageing on different types of falls such as unspecified fall on the same level, mechanical fall on the same level relating to slipping, tripping or losing balance, fall from a chair, vehicle and fall as a result of syncope, fall from steps or stairs, and fall from the height.

Methods: The study included a random sample of 250 older patients, which comprised 10% of the total number of patients (n=2,492), admitted to a large scale academic hospital following a fall. Patients' medicine and illness history, types of falls, liver, renal, and sensory function were collected. Univariate analysis was used to examine associations between the type of fall and explanatory variables, followed by multinomial logistic regression analysis.

Results: There was a significant association between the type of fall and sex, $p=0.01$, and between the type of fall and regular medicine use, $p=0.002$. The multinomial logistic regression analysis revealed that the full model, which considered all explanatory variables together, was statistically significant, $p<0.001$. The strongest predictor of all types of falls except 'fall from the height' was female sex followed by the regular medicine use.

Conclusion: This study identified predictors for various types of falls in older people; the strongest predictor being a female sex followed by regular medicine use. Based on these findings, the medicine prescribing practice in this older population must be carefully reviewed.

INTRODUCTION

Falls in older people (65 years of age and over) have been recognised as a major public health issue for more than past two decades (Hill & Wee, 2012). Following a fall, the majority of older people are faced with lengthy periods of disability, requiring admission to geriatric rehabilitation services for a prolonged period of time (Hilmer et al., 2007). Past research has focused predominantly on psychotropic medicines as an intrinsic or endogenous risk factor for falls (Bloch et al., 2011; Hill & Wee, 2012; Hilmer et al., 2007; Landi et al., 2005; Payne, Abel, Simpson, & Maxwell, 2013). Traditionally, risk factors for falls have been categorised as extrinsic or exogenous (uneven or slippery floors, unsafe foot wear, poor lighting and loose rugs), intrinsic (co-morbidities, sensory changes, high risk medicines, polypharmacy) and behavioural (Hill & Wee, 2012). Psychotropic medicines were identified as the leading cause of falls and previous studies have found that the risk of falls in older patients taking benzodiazepines is 44% higher than in patients not taking any psychotropic medicines (Ballokova et al., 2014; Mangoni & Jackson, 2004). Mood stabilising agents, such as lithium and antipsychotic medicines, have also been reported to contribute to falls in older people (Chatterjee, Chen, Johnson, & Aparasu, 2012; Ensrud et al., 2002). A recent study has found that cardiovascular medicines that affect blood pressure and the cardiac conducting system significantly increase the chance of falls in older people (Payne et al., 2013). One of the common adverse effects of psychotropic and antihypertensive agents is orthostatic hypotension. Thus, orthostatic hypotension may be an important risk factor for falls (Heitterachi, Lord, Meyerkort, McCloskey, & Fitzpatrick, 2002); however, previous studies failed to demonstrate a correlation between falls and this adverse effect.

Our study takes a different approach by examining the link between exogenous (medicines/polypharmacy and health status) and endogenous (age-dependent physiological changes and sex) factors that can be associated with falls in older people. Endogenous factors, including age-dependent decline in hepatic, renal and sensory function, appear to be more challenging to predict than exogenous factors, thus requiring more focus and attention to detail. In accordance with our model of assessing falls, it has been shown that effectiveness of the hepatic and renal system may play a crucial role in determining the incidence of falls. For example, medicines that are more easily metabolised by the liver and excreted through the renal system do not maintain concentration of drug metabolites in circulation for a long period of time (Rasmussen, Steentoft, Rasmussen, Kristensen, & Moller, 1999). These metabolites that remain in the circulatory system can have adverse effects on the patient particularly in the case of psychotropic medicines (Ballokova et al., 2014). However, with an age-dependent decline in hepatic and renal function, the body's ability to remove drug metabolites is diminished, thus these metabolites can prolong the adverse effects of certain medicines and in turn lead to falls.

Long acting benzodiazepines as well as lithium can remain in circulation for long periods of time between doses (Berdot et al., 2009). When the ability to metabolise and eliminate these drugs decreases, their effects are prolonged causing dizziness, vertigo and other associated catalysts to falls. While this effect is most commonly associated with psychotropic medicines it is also prevalent in patients taking cardiovascular medicines. Therefore, parameters such glomerular filtration rate and liver enzyme values could provide valuable insight into the link between drug metabolism, elimination and falls (Berdot et al., 2009). Age-dependent physiological changes affecting renal and hepatic function have not previously been investigated in association with falls despite the evidence showing that a decline in drug metabolism leads to

retention of drug metabolites in the circulation (Sproule, Naranjo, Brenner, & Hassan, 1997). Furthermore, the past studies focusing on the type of falls and predictors are limited (Gassmann, Rupprecht, & Freiburger, 2009; Morris, 2007) and no links were made to whether a fall occurred on the flat/same level surface, height or steps or stairs. To the best of our knowledge, there are no studies that have investigated different types of falls in the context of age-dependent physiological changes.

The aim of this study is therefore to make a broad-spectrum analysis of older patients with falls by encompassing several possible factors such as health status, sex, polypharmacy and age-related changes in order to establish links between type of falls in older people and medicine use. Previous studies have attributed falls most commonly to the use of psychotropic medicines and no clinical audits were conducted to assess the dynamic relationship between age related factors, combination drug therapies and the type of falls that patients had. This study of older patients with falls takes into account the background factors related to their age such as glomerular filtration rate, liver function tests, and sensory function including any visual, vestibular or auditory changes and compare these factors to the use of different classes of medicines.

METHODS

Study population and design

Using a retrospective observational study design, the medical records of older patients admitted to a large scale academic hospital in Melbourne, Australia following a fall were examined. The study population included a random sample of 250 patients which comprised a 10% of the total number of patients (n=2,492) admitted to the hospital following a fall between

January 2013 and August 2014. The study was approved by the Human Research Ethics Committee of Melbourne Health, Australia (QA Number: QA2014053). Comprehensive data regarding patients' medicine history, health status and types of falls were collected from medical records. Data were collected using a hard copy of the data collection tool based on the following inclusion criteria: the patient was 65 years of age and over and the patient has experienced a fall related to hospital admission. The following details were documented and grouped as explanatory variables: age, sex, health conditions, and medicine history at the time of hospital admission which included all regular medicines taken by patients to manage their chronic condition, liver and renal function, and sensory function. These explanatory variables were then compared to the outcome variable which is the type of fall (unspecified/mechanical fall on the same level, fall from steps/stairs or height).

Record of data

Liver function was evaluated by reviewing the first set of test results during an older person's admission for three enzymes. Gamma-glutamyl transferase (GGT), aspartate transaminase (AST) and alanine transaminase (ALT) are commonly used as markers of liver dysfunction (Kunutsor, Apekey, & Khan, 2014). Renal function was recorded as patients' estimated glomerular filtration rate (eGFR), which reflects the quantity of glomerular filtrate produced each minute by all nephrons in both kidneys (Zaman, Filipowicz, & Beddhu, 2013). Sensory function data were obtained from falls risk assessment (FRA) records which indicated the ability of a patient to use sensory information to successfully perform day to day tasks such as vision, hearing and balance. Based on the exclusion criteria, which were patients with incomplete medicine history and patients with falls that resulted in fatality, data from 12 patients were excluded from the study, thus the total number of patients included in the study was 238.

Statistical analysis

Hard copy data were transferred and stored in a Microsoft Excel spreadsheet. Statistical analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS, Version 22, Chicago, IL, USA). Descriptive statistical analyses were conducted on patients' age, sex, health status, types of falls, number and type of regular medicines used, sensory function, renal and hepatic function. Associations between explanatory variables and the outcome variable (type of fall) were investigated by running univariate analyses (Chi-square analysis) between each explanatory variable and the type of fall. Most explanatory variables were categorical in nature which related to their presence or absence (i.e. regular medicine use, prescription of analgesic, antihypertensive, psychotropic medication) whereas the following were continuous variables (i.e. age, eGFR, liver function tests – GGT, AST, ALT). This process was followed by performing multinomial logistic regression analysis between the variables showing associations at $p < 0.1$ in univariate analysis and the outcome variable (type of fall). In multinomial logistic regression analysis, a $p \leq 0.05$ was used as a statistically significant value to identify independent associations between specific explanatory variables and the type of fall. Demographic data are presented as mean and standard deviation (SD) results.

RESULTS

Demographic characteristics: age, sex and health status

The mean age of patients was 81.06 years (SD = 8.3 years) of age. The youngest patient was 65 years of age (the threshold for the study) while the oldest patient was 104 years old. Of the 238 patients, 104 (44%) were male while 134 (56%) were female patients. The health conditions patients suffered from were grouped into cardiovascular, hepatic, musculoskeletal,

psychiatric, renal and other disorders. Of the 238 patients, 112 (47%) did not have any pre-existing psychiatric or cognitive disorder, while the remaining 126 (53%) suffered from depression, anxiety, dementia and delirium. The most common psychiatric disorder was depression, affecting the largest proportion of the population with every 1 in 4 patients being affected. Additionally, of the 238 patients, 46 (19%) did not have any cardiovascular, hepatic or renal disorder. The remaining 192 patients suffered from a range of conditions including hypertension (77 %), dyslipidaemia (41%), atrial fibrillation and ischemic heart disease (20%), and renal impairment (21%). There were 129 patients who suffered from one or more pre-existing musculoskeletal disorders while the remaining 109 patients did not have any musculoskeletal comorbidity. Of the 129 patients with musculoskeletal disorders, osteoarthritis and osteoporosis were the most common with 46% and 36% incidence respectively. Other disorders included type 2 diabetes mellitus (26%) and thyroid gland abnormalities, such as hypothyroidism and hyperthyroidism (6%).

Medicine use

Of the 238 patients, 229 (96%) were on regular medicines. The mean number of medicines used was 6.08 (SD = 2.78 medicines), with a minimum number used by a patient being one (1) and a maximum being 16. There were 8 classes of medicines commonly prescribed to 22 or more patients and these included analgesics, anti-platelets, anti-hypertensives, medicines affecting bone density, lipid lowering and oral hypoglycaemic drugs, proton pump inhibitors and psychotropics (Table 1). Anti-hypertensives were the most commonly prescribed with 162 (68%) patients using multiple classes of anti-hypertensive medicines. Angiotensin (AT₁) receptor blockers such as irbesartan, candesartan and telmisartan were the most commonly used anti-

hypertensives, followed by beta blockers (atenolol and metoprolol), and calcium channel blockers such as amlodipine and diltiazem (Table 1). Angiotensin converting enzyme (ACE) inhibitors and loop diuretics were prescribed to 45 and 36 patients, respectively. Paracetamol was the most commonly used analgesic to manage pain, followed by statins such as atorvastatin and simvastatin for dyslipidaemia. Medicines affecting bone such as alendronate and colecalciferol were prescribed to 74 patients whereas 89 patients were on psychotropic medicines with antidepressant use noted in 60 patients (67%), followed by anxiolytics and hypnotics such as benzodiazepines (Table 1).

Types of falls and associations with age and sex

Using comprehensive clinical notes, the falls were categorized into five (5) types which were labelled from 1 to 5 as follows: 1-unspecified fall on the same level, 2-mechanical fall on the same level relating to slipping, tripping or losing balance, 3-other unspecified fall on/from unspecified level such as fall from a chair, vehicle and fall as a result of syncope, 4-fall from steps or stairs, and 5-fall from the height (ladder, roof). The most common type of fall was the mechanical fall (35%), followed by the unspecified fall on the same level (31%), other type of fall (19%), fall from steps or stairs (9%) and fall from the height (6%) (Table 2).

There was a significant association between the type of fall and sex, $\chi^2 (4) = 13.3$, $p=0.01$, (Table 3) with females having more falls than males in each category except category 5; fall from the height (Table 2). Furthermore, there was no significant association between the type of fall and age, $\chi^2 (4) = 8.1$, $p=0.089$. The highest number of falls occurred in the 65-85 age group (Table 2) and the most common type of fall was category 2 falls (mechanical fall on the same level relating to slipping, tripping or losing balance).

Associations between the type of fall, age-dependent physiological changes and medicines

Age-dependent physiological changes affecting patients in this study were placed under three (3) categories: sensory, renal and hepatic changes (Table 2). Sensory information data revealed that 59% of patients had normal sensory function whereas 41% of patients showed some form of sensory impairment with no significant association between the type of fall and sensory impairment. Furthermore, there was no significant association between the type of fall and eGFR with a minimum eGFR being 8 and maximum 95. Finally, there was no significant association between the type of fall and hepatic function as measured by GGT, ALT and AST (Table 3).

Chi-square analysis showed no association between the type of fall and medical conditions patients suffered from. In contrast there was a significant association between the type of fall and regular medicine use, $\chi^2 (4) = 16.7$, $p=0.002$ (Table 3). Additionally, there were significant associations between the type of fall and psychotropic medicines, $\chi^2 (4) = 10.8$, $p=0.029$ and the medicines affecting the bone and type of fall, $\chi^2 (4) = 10.5$, $p=0.033$ (Table 3). In regards to bone medicine use, 73 patients or 31% of the cohort was regularly taking one bone medicine and these patients had less falls in each category when compared to patients who were not taking bone medicines. Out of 238 patients, 89 (37%) were taking psychotropic medicines, with a minimum being one and maximum being 4. Only one patient was taking 4 whereas 61/89 (69%) were on one, 20/89 (23%) were on two and 7/89 (8%) were on three psychotropic medicines.

Multinomial logistic regression model of type of falls and explanatory variables

The result of the multinomial logistic regression analysis showed that the full model which considered all the five explanatory (independent) variables together was statistically significant, $\chi^2(20) = 55.8$, $p < 0.001$. This result implied that the odds for a different type of fall were related to the five independent variables; sex, age, regular medicine use, bone and psychotropic medicines. The strongest predictor of all types of falls except 'fall from the height' was female sex with odds ratios (OR) being 5.3 for unspecified fall on the same level, 7.7 for mechanical fall on the same level relating to slipping, tripping or losing balance, 7.6 unspecified fall on/from unspecified level such as fall from a chair, vehicle or syncope, and 9.0 for fall from steps or stairs (Table 4). The second predictor that made significant contribution to the model was the regular medicine use. Regular medicine use predicted an increased incidence of falls, $p < 0.001$. Thus, older individuals taking regular medicines were at increased risk of experiencing any type of fall identified in this study.

DISCUSSION

This study found that 96% of patients were on regular medicines, and the most commonly used were anti-hypertensive, analgesic and psychotropic medicines. This finding is in line with previous studies showing that older people regularly take multiple medicines daily (Kerse et al., 2008) as co-morbidities become more prevalent with aging, thus the number of medicines increases. Females had more falls than males in each category except category 5, which includes a fall from the height. This finding suggests that males were possibly more likely to engage in risky behaviours or activities that require use of ladders, and that their decision making process and thus judgement could be possibly affected by use of multiple medicines. As

shown here, there was a significant association between regular medicine use and falls, specifically bone and psychotropic medicines. Patients taking the medicines affecting bone had fewer falls than patients not taking these medicines with unspecified fall on the same level being the most common type of fall. This finding is in line with literature reporting that vitamin D supplementation can prevent falls, particularly in the vitamin D deficient older individuals (Winzenberg, van der Mei, Mason, Nowson, & Jones, 2012). Additionally, bone medicines can prevent osteoporotic changes in postmenopausal women that could contribute to falls (Sanders & Geraci, 2013). However, more research needs to be done in relation to prescribing practices around bone medicine group. Future studies should include details regarding the dose, frequency, length of administration, ethnicity, sex and a family history of bone disease. This information can provide an insight into the possibility of using this medicine group prophylactically much earlier in life in patients exhibiting strong predictors for falls.

The link between long term psychotropic medicine use and falls in older people has been well documented, however, previous studies have not taken into account the role different classes of medicines and age-dependent physiological changes play in falls. This study found that psychotropic medicines were prescribed to 89 patients. Antidepressant use was the highest at 67% and this finding correlates with the high proportion of patients having a depression as their pre-existing psychiatric disorder. Some classes of antidepressants such as selective serotonin and serotonin-noradrenaline reuptake inhibitors have long been associated with extrapyramidal adverse effects which commonly led to postural hypotension and subsequent falls (van Strien, Koek, van Marum, & Emmelot-Vonk, 2013). Furthermore, psychotropic use is associated with complex regimens that can have an impact on older patients' ability to self-manage their medicines in terms of dose, frequency, and other specific recommendations and precautions

(Bauer et al., 2013). Our study results showed that the patients had 4.7 times increased odds of experiencing a fall on the same level and 5.9 times increased odds of experiencing a fall from steps and stairs if they were on psychotropic medication compared to those who were not taking any psychotropics. However, the confidence intervals for these results were large and therefore the results were not significant. Further research should involve recruitment of patients with and without psychotropic medications to test the patterns in relation to various types of falls.

The ageing process causes various health-related complications and whilst some of these complications result in pathological changes, others can influence the physiology without actually resulting in a named co-morbidity. Hepatic and renal function have been shown to deteriorate with aging (Menkes, 1989) however our study showed no impact of hepatic and renal function on the type of fall experienced. Future studies should consider genetic influences, ethnicity and race, architectural features of people's homes and residential facilities and more specific renal function tests in the context of regular medicine use and the types of falls experienced not just whether the fall has occurred.

Using eGFR as a sole marker for renal function in hospitalised patients may not be true reflection of patients' renal state because eGFR can show day-to-day variability post-admission (Kanaoka et al., 2012). Our study suggests that in addition to eGFR, assessment of renal function in older people should also include more specific tests such as creatinine clearance. Creatinine clearance is calculated by using the Cockcroft-Gault equation that incorporates specific parameters such age, weight and sex into the equation (Fernandez-Prado, Castillo-Rodriguez, Velez-Arribas, Gracia-Iguacel, & Ortiz, 2016). As a result of ageing process, older people have diminished skeletal muscle mass which can affect creatinine levels; creatinine is a by-product of the skeletal muscle (Denison, Cooper, Sayer, & Robinson, 2015; Nowson & O'Connell, 2015).

Therefore, including age, sex and weight when assessing the renal function may control variability between older people and provide true reflection of individuals' renal state.

In conclusion, our study strengthens the evidence that connects psychotropic medicine use and falls in older people and identifies the additional predictors of sex that are related to different types of falls in the study population. These predictors were both exogenous (regular medicine use reflecting health status) and endogenous (sex) in nature. We found an association between sex and regular medicine use and different types of falls. Based on these findings, it is possible to make a recommendation that the prescription of medicines be carefully reviewed for patients with strong predictors for fall types. This review should be based on calculation of creatinine clearance in relation to renal function and the dose adjustment where relevant. Taken together, the findings of this study suggest: a) an urgent need for randomised controlled trials in older people especially with regard to antihypertensive and psychotropic medicine use in individuals with altered hepatic and renal function; and b) a review of the medicine prescribing practices in older people from different ethnic groups. The key limitation of this study is that it was retrospective in design – transition of patients through different points of care could affect the medicine use and management and these discrepancies in medicine use could have affected the incidence of falls. Therefore, future studies must include representative sample of older people from different ethnic groups who reside in different settings.

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CONFLICT OF INTEREST

None. The authors declare that they have no conflict of interest.

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Table 1 Distribution of regular medicine prescription according to the clinical composition of the sample.

Clinical indication	Medication class	Number of prescriptions
Coronary syndrome	Anti-platelets (Aspirin)	90
Dyslipidaemia	Statins	110
Hypertension	Angiotensin (AT ₁) receptor blockers	72
	Beta blockers	51
	Calcium-channel blockers	48
	ACE inhibitors	45
	Loop diuretics	36
Osteoporosis	Vitamin D	60
	Bisphosphonates	14
Pain	Analgesics (Paracetamol)	133
	Opiod analgesics	59
Psychiatric disorders	Benzodiazepines	28
	Selective serotonin reuptake inhibitors	24
	Tetracyclic antidepressants	15
	Serotonin-noradrenaline reuptake inhibitors	11
Reflux disease	Proton pump inhibitors	91
Type 2 diabetes	Biguanides	27
	Sulfonylureas	19

Table 2 Distribution of explanatory variables according to the type of fall.

Sample characteristics (N=238)	Unspecified fall on the same level (n)	Mechanical fall on the same level (n)	Fall from unspecified level (n)	Fall from steps or stairs (n)	Fall from the height (n)
Gender					
Male	34	32	17	8	13
Female	40	51	29	12	2
Age group					
65-85 y	48	53	30	14	15
86-104 y	26	30	16	6	0
Regular medicine use					
No	1	2	2	4	0
Yes	73	81	44	16	15
Anti-hypertensives					
No	24	27	10	8	7
Yes	50	56	36	12	8
Lipid-lowering					
No	41	41	27	12	10
Yes	33	42	19	8	5
GI medicines					
No	49	54	30	13	9
Yes	25	29	16	7	6
Psychotropics					
No	38	59	28	11	13
Yes	36	24	18	9	2
Bone medicines					
No	54	53	27	17	14
Yes	20	30	19	3	1
Sensory function					
Normal	39	45	19	10	10
Impaired	24	33	18	8	3
eGFR					
Normal	10	2	4	0	1
Impaired	34	34	20	6	3
GGT					
Normal	20	16	10	2	2
Impaired	12	12	8	1	1
ALT					
Normal	29	27	14	2	2
Impaired	9	3	6	1	1
AST					
Normal	25	26	15	1	2
Impaired	11	4	5	2	1

N=total number of subjects in the study

n= number of subjects experiencing specific type of fall

Table 3 Associations between the type of fall, age, gender, age-dependent physiological changes and regular medicine use.

Univariate analysis (Pearson Chi-Square)	Value	df	Asymp. Sig. (2-sided)
<i>Significant</i>			
Gender	13.3	4	0.01
Regular medicine use	16.7	4	0.002
Psychotropics	10.8	4	0.029
Bone medicines	10.5	4	0.033
<i>Non-significant</i>			
Age	8.1	4	0.089
Antihypertensives	4.3	4	0.365
Lipid-lowering	2.3	4	0.674
GI medicines	0.2	4	0.995
Sensory function	2.9	4	0.561
eGFR	6.0	4	0.197
GGT	0.4	4	0.980
ALT	3.8	4	0.428
AST	5.7	4	0.226

Table 4 Multinomial logistic regression predicting the likelihood of different types of falls.

Type of fall	P value	OR	95% CI
Unspecified fall on the same level			
Female	0.04	5.3	1.1-26.4
Regular medicine use	<0.001	2.1×10^7	1.9×10^8 - 2.3×10^6
Psychotropics	0.06	4.7	0.9-23.2
Mechanical fall on the same level			
Female	0.012	7.7	1.6-37.6
Regular medicine use	<0.001	1.3×10^7	1.9×10^8 - 8.9×10^7
Fall from unspecified level			
Female	0.016	7.6	1.5-39.7
Regular medicine use	<0.001	5.5×10^8	7.9×10^9 - 3.8×10^7
Fall from steps or stairs			
Female	0.018	9.0	1.5-55.4
Psychotropics	0.06	5.9	0.9-36.8

Note Fall from a height was taken as a reference point for regression analysis.