Drug-related falls in older patients: implicated drugs, consequences, and possible prevention strategies

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Abstract: Falls are the leading cause of injuries among older adults, aged 65 years and older. Furthermore, falls are an increasing public health problem because of ageing populations worldwide due to an increase in the number of older adults, and an increase in life expectancy. Numerous studies have identified risk factors and investigated possible strategies to prevent (recurrent) falls in community-dwelling older people and those living in long-term care facilities. Several types of drugs have been associated with an increased fall risk. Since drugs are a modifiable risk factor, periodic drug review among older adults should be incorporated in a fall prevention programme.

Keywords: accidental falls, aged, drugs, falls, risk factors

Introduction

Falls among the older population are associated with a high morbidity and mortality [Kannus *et al.* 1999; Tinetti, 2003]. Due to ageing of societies worldwide, it is expected that falls and their related injuries will become a more prominent public health issue in the coming decades. In this paper the epidemiology of falls, as well as known risk factors including the use of (fall risk increasing) drugs will be highlighted.

Epidemiology

Approximately a third of community-dwelling people aged 65 years and older fall at least once per year. About half (15%) fall at least twice or more times per year [Stel *et al.* 2004]. Fall accidents are even more common in older people residing in nursing homes with an incidence approaching 50% [Rubenstein *et al.* 1994]. The incidence of falls is age related and increases with age. The highest incidence of falls is seen in very old people [Hartholt *et al.* 2011b; Campbell *et al.* 1990]. Campbell and colleagues showed that the incidence rate of falls (number of falls per 100 person years) increased from 47 in people aged 70–74 years to 121 in those aged 80 years [Campbell *et al.* 1990]. Age-related problems, including falls, are expected to increase in the

coming decades due to ageing societies worldwide. With the predicted ageing of societies and fall-related injuries increasing in older adults [Hartholt *et al.* 2011b; Kannus *et al.* 1999], falls are expected to become one of the major public health problems in communities worldwide [Kannus *et al.* 1999].

Consequences

Falls among older people have a major impact on the society and the individual patient. Falls are the leading cause of injury among older people and consequently result in high healthcare demand (Table 1), including direct medical treatment, long-term rehabilitation and social consequences [Hartholt *et al.* 2010b, 2011b; Kannus *et al.* 1999].

The majority of falls result in minor injuries, such as bruises and superficial injuries, and require no medical attention or are fully treated in the primary care setting. In approximately one-tenth of all falls medical treatment in an emergency department (ED) is required. The most common injuries seen in the ED after a fall are fractures (59.6%), superficial injuries (20.9%) and head injuries (8.7%) [Hartholt *et al.* 2011b]. The three most frequently diagnosed fractures are fractures

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Table 1. Fall-related healthcare consumption in older adults (≥65 years), United States, 2008.

	Number
Population aged ≥65 years	38,870,000
No. emergency department visits	2,200,000
Men:women (injured)	1:1.58
No. hospitalizations	581,000
Mortality	19,700
Annual healthcare costs	US$28.2 billion
Centers for Disease Control and Prevention *et al.* [2008].	

of the hip (27.5%), wrist (19.8%) and upper arm (7.2%) [Hartholt *et al.* 2011b]. In about a third of all patients presenting at the ED, hospitalization is required [Hartholt *et al.* 2011b]. In the United States, 559,355 people aged 65 years and older are admitted every year due to an injurious fall [Hartholt *et al.* 2011a]. The hospitalization rates, expressed per 1000 older people, are comparable to those of other countries: 14.1 in The Netherlands, 14.0 in Finland and 14.4 in the United States [Hartholt *et al.* 2010b, 2011a; Kannus *et al.* 1999]. The reasons for admission include surgery, optimizing the general health situation, and sometimes to facilitate arranging suitable home care directly after the incident. In the United States (2008), over 12,900 older adults died as a result of an unintended fall [Centers for Disease Control and Prevention, 2003] The World Health Organization estimated that, worldwide, approximately 392,000 people died due to an unintended fall in 2004 [World Health Organization, 2004].

The total healthcare costs spent on falls are high, partly due to the high incidence of falls, but also because of the high costs per incident [Hartholt *et al.* 2012; Scuffham *et al.* 2003]. The direct healthcare costs per patient with a hip fracture exceeds €20,000 [Hartholt *et al.* 2012]. The total healthcare costs on falls (fatal and nonfatal) in the United States in 2000 were US$19.2 billion [Stevens *et al.* 2006]. Fractures are the most expensive type of injury, accounting for 61% of costs [Stevens *et al.* 2006]. A systematic review by Heinrich and colleagues analyzed all fall-related injuries in people aged 60 years and older in several countries. The authors estimated that the national fall-related healthcare costs were between 0.85% and 1.5% of the total healthcare expenditures, which corresponded to 0.07–0.20% of the gross domestic product [Heinrich *et al.* 2009].

Besides the large burden of healthcare consumption and costs, falls may have a major impact on the individual patient. Patients seen in the ED after a fall reported a reduction in their quality of life (QoL) up to 9 months after the fall [Hartholt *et al.* 2011b]. Admitted patients reported problems with 'mobility' (70%), 'self care' (41%), 'usual activities' (64%) and 'anxiety/depression' (28%) up to 9 months after the fall. Nonadmitted patients mainly reported problems with 'self care' (22%) and 'usual activities' (41%) [Hartholt *et al.* 2011b]. Furthermore, a fall may generate fear of falling. Studies have shown that fear of falling is associated with negative health effects, including recurrent falls, reduced physical activity, restriction or avoidance of social activities, depression and a reduction in self-reported QoL [Scheffer *et al.* 2008].

Risk factors

Because of the possible severe consequences of a low-energetic fall, prevention of falls has become a major topic. To create an effective falls prevention programme, risk factors should be identified. Numerous studies have been performed over the last decades on falls and risk factors [de Vries *et al.* 2011; Gillespie *et al.* 2001; Hartholt *et al.* 2011c; van der Velde *et al.* 2007]. By now, over 20 risk factors for recurrent falls among older adults have been identified (Box 1). Although some falls in the older population have a single cause, the majority have a multifactorial aetiology. Risk factors can be categorized as intrinsic (e.g. impairment in balance, gait or vision) [Nevitt *et al.* 1989] and extrinsic factors (e.g. improper use of assistive devices, slippery flooring, poor light, or carpets).

Major risk factors include history of one or more previous falls, mobility impairments, cognitive impairment, use of fall-risk increasing drugs and old age [Graafmans *et al.* 1996]. Box 1 summarizes the most frequent risk factors for recurrent falls (at least two falls annually). Recently, Hartholt and colleagues showed that people aged 65 years or older who visited the ED due to a fall had a mean age of 78.8 years and were mostly women (76%) [Hartholt *et al.* 2011b]. Older adults are also at increased risk of serious injuries, even after a relatively minor trauma such as a fall, because of the number and severity of comorbidities, which makes this age group more vulnerable to fractures and head injuries [O'Neill and Roy, 2005]. Compared with men, women are

Risk factor
Age
Female gender
History of previous falls
Fear of falling
Mobility impairment
Low level of activity
Arthritis
Joint disorder
Parkinson's disease
Vision impairment
Hearing problems
Cognitive impairment
Postural hypotension
Depression
Urinary incontinence
Stroke
Cardiovascular disease
Drug use
Dizziness
Chronic disease (at least one disease)
Pain

more likely to fall and are more prone to related injuries. Why women are at increased risk of falls is not clear yet.

Drugs and falls

Drug use among the older population has increased in the past decades. The majority (72%) of people aged at least 55 years use at least one drug. In this age group, 20.3% are taking four or more drugs [Ziere *et al.* 2006]. Consequently, adverse drug reactions (ADRs) may occur, resulting in significant morbidity and mortality. Two-thirds of all ADR-related hospitalizations occur in the over 60 age group [Hartholt *et al.* 2010a]. Recent studies have shown that ADR-related hospital admissions are increasing in western societies [Patel *et al.* 2007]. ADR-related hospitalizations account for approximately 3.4–16.6% of all hospital admissions in older people [Beijer and de Blaey, 2002; Onder *et al.* 2002] with a high in-hospital mortality rate of 8–10% [van der Hooft *et al.* 2006]. Older people in particular are at increased risk of developing an ADR due to their social setting [Barat *et al.* 2001; Leendertse *et al.* 2008], polypharmacy [Barat *et al.* 2001;

Budnitz *et al.* 2007; Fialova *et al.* 2005; Leendertse *et al.* 2008], comorbidities,[Zhang *et al.* 2009], cognitive impairment [Barat *et al.* 2001; Fialova *et al.* 2005] and physiological changes affecting the pharmacokinetics and pharmacodynamics of many drugs [Leendertse *et al.* 2008; Spinewine *et al.* 2007]. The exact number of falls caused by drugs or drug intoxication is not known because falls are not officially recognized as an ADR.

Several types of drugs are associated with a significant risk of falls, the so-called 'fall risk increasing drugs'. In 1999 Leipzig and colleagues published a meta-analysis of observational studies that assessed the association between falls and the use of psychotropic, cardiac and analgesic drugs in the older population [Leipzig *et al.* 1999a, 1999b]. In 2009, Woolcott and colleagues updated this meta-analysis [Woolcott *et al.* 2009]. Table 2 presents nine unique drug classes that were included in the analysis: antihypertensive agents, diuretics, β blockers, sedatives and hypnotics, neuroleptics and antipsychotics, antidepressants, benzodiazepines, narcotics and nonsteroidal anti-inflammatory drugs. The authors presented a significant association between falls and the use of sedatives and hypnotics, antidepressants and benzodiazepines. The use of antidepressants had the strongest association with falls. Other drug classes have also been associated with an increased fall risk. In studies which were considered to have good medication and falls ascertainment, an increased likelihood of falling was estimated with the use of neuroleptics and antipsychotics, and nonsteroidal anti-inflammatory drugs [Woolcott *et al.* 2009].

Hyposedatives and benzodiazepines
Hyposedative drugs are widely prescribed to older adults. Of all hyposedative medications, benzodiazepines are the most commonly used by community dwelling older people. The prevalence of benzodiazepine use is approximately 10–12% [Blazer *et al.* 2000]. Benzodiazepines are commonly used to treat sleeping disorders and anxiety problems. However, their ability to treat sleeping disorders is generally short lived, not exceeding a few weeks, with sleeping patterns declining towards pretreatment levels over a 2-year period. Nonetheless, in almost 80% of older people treated with benzodiazepines, therapy continues for over 2 years [Lechevallier *et al.* 2003]. Furthermore, benzodiazepines cause psychological dependence, which contributes to difficulties with discontinuation [Heberlein *et al.*

Table 2. Fall risk increasing drugs and odds ratios.

Drug class	Odds ratio	95% CI
Antihypertensive agents	1.24	1.01–1.50
Diuretics	1.07	1.01–1.14
B blockers	1.01	0.86–1.17
Sedatives and hypnotics	1.47	1.35–1.62
Neuroleptics and antipsychotics	1.59	1.37–1.83
Antidepressants	1.68	1.47–1.91
Benzodiazepines	1.57	1.43–1.72
Narcotics	0.96	0.78–1.18
Nonsteroidal anti-inflammatory drugs	1.21	1.01–1.44

Woolcott *et al.* [2009].
CI, confidence interval.

2008]. Multiple studies have evaluated the association between benzodiazepines and falls. Hartikainen and colleagues performed a systematic review of all literature published between 1996 and 2004 on falls, fractures and the association with drug use among older people (aged 60 years and older) [Hartikainen *et al.* 2007]. Most studies showed a significant association between the use of benzodiazepines and falls or fractures. The risk of falling increased after a new prescription of benzodiazepine and with long-term use. Concomitant use of two or more benzodiazepines increased the risk of hip fracture twofold [Pierfitte *et al.* 2001].

Landi and colleagues conducted an observational study in which benzodiazepines were classified into two different groups according to their metabolic pathway: short-acting (<24 h) and long-acting benzodiazepines (>24 h) [Landi *et al.* 2005]. Benzodiazepines with a long elimination half life increased the risk of falling [adjusted odds ratio (OR) 1.45; 95% confidence interval (CI) 1.00–2.19]; similarly to benzodiazepines with short elimination half life (adjusted OR 1.32; 95% CI 1.02–1.72). The authors suggested that the preferential use of benzodiazepines with short elimination half life is unlikely to reduce fall risk among older people taking benzodiazepines [Landi *et al.* 2005]. Besides an increased risk for falls, benzodiazepine exposure in community-dwelling older people has been associated with several negative health consequences, including depressed mood [Patten *et al.* 1996], impaired cognition [Hanlon *et al.* 1998] and loss of physical function [Gray *et al.* 2002].

Antidepressants
Antidepressants have long been recognized as a contributory factor to falls. In 1987, Ray and colleagues published a first large case-control study. A significant association between tricyclic antidepressants (TCAs) and the risk of hip fracture in people aged 65 years and older was shown [Ray *et al.* 1987]. In 1998, Thapa and colleagues demonstrated the association between selective serotonin reuptake inhibitors (SSRIs) and risk of falls in the same age group [Thapa *et al.* 1998]. The ratios were increased for both TCAs and SSRIs after adjustments were made for differences in potential confounding factors: 2.0 (95% CI 1.8–2.2) and 1.8 (95% CI 1.6–2.0) respectively.

TCAs are thought to contribute to falls and hip fractures through several mechanisms, which are attributable to their effects on histamine receptors and α adrenoceptors. These drug classes may cause sedation and sleep disturbance with daytime sleepiness, orthostatic hypotension, confusion and cardiac arrhythmias. SSRIs have fewer anticholinergic side effects and appear to be better tolerated by patients [Martin *et al.* 1997]. Despite another profile on side effects, adverse effects such as impaired balance and sleep disturbance are frequently reported. Ziere and colleagues examined in a prospective study the association between the antidepressants TCAs and SSRIs, and the risk of nonvertebral fractures in older people. They reported that people who use TCAs but also SSRIs have a significantly increased risk of nonvertebral fractures. As the risk diminished progressively with prolonged use of TCAs, it increases over time with the use of SSRIs [Ziere *et al.* 2008]. There is growing evidence that SSRIs increase fracture risk

by causing a reduction in bone mineral density. A reduction of 3.9% of the bone mineral density at the hip and 5.9% at the lumbar spine was found [Haney *et al.* 2007].

Neuroleptics and antipsychotics

Until recently, there was limited evidence that neuroleptics and antipsychotics increase the risk of recurrent falls in older adults. Several studies have been performed but the evidence remains inconclusive [Sterke *et al.* 2008]. Recently, Sterke and colleagues evaluated the dose–response relationship between psychotropic drugs and falls in nursing home residents with dementia. The authors showed that fall was increased with the use of antipsychotics (hazard ratio 1.53, 95% CI 1.17–2.00) and found also a significant dose–response relationship for the use of antipsychotics (hazard ratio 2.78; 95% CI 1.49–5.17) [Sterke *et al.* 2012].

Polypharmacy

Fall risk increases with the number of drugs used per day [Ziere *et al.* 2006] and polypharmacy (the use of at least three drugs) is regarded as an important risk factor for falls in older people. A recent cross-sectional study showed that polypharmacy itself is not a risk factor for falling, unless a fall risk increasing drug is part of the drug regimen. Ziere and colleagues stated that polypharmacy remained a significant risk factor for falling [Ziere *et al.* 2006].

Prevention

The majority of falls have a multifactorial origin. With respect to falls prevention, all factors should be analysed and evaluated. Multidisciplinary falls programmes, for example, assessment by a geriatrician, should be implemented and focused on the high-risk groups [Cameron *et al.* 2010]. Drugs are one of the modifiable risk factors for falls and related injuries. With the growing evidence of drugs contributing to fall incidents, and their extensive use, it should be no surprise that prevention is nowadays mainly focused on these so-called 'fall risk increasing drugs'. In a randomized control trial the effectiveness of psychotropic drug withdrawal on the prevention of falls in community-dwelling people aged at least 65 years was assessed [Campbell *et al.* 1999]. A 66% reduction in falls was shown in patients when psychotropic drugs were gradually withdrawn compared with those who continued using psychotropic drugs. However, they also concluded that permanent withdrawal of psychotropic drugs is difficult to

achieve [Campbell *et al.* 1999]. Nonetheless, a more recent study showed that dosage reduction of benzodiazepines can be associated with a high success rate [Joester *et al.* 2010]. The same effect, a significant reduction in falls, was demonstrated with withdrawal (discontinuation or dose reduction) of cardiovascular drugs in a recent prospective cohort study [van der Velde *et al.* 2007]. A review of the safety of drug withdrawal in older people demonstrated that withdrawal of cardiovascular and psychotropic drugs can be done safely with adequate follow up [Iyer *et al.* 2008].

De Vries and colleagues conducted a randomized control trial to assess the effectiveness of a multifactorial fall-prevention programme in older people who are at increased risk of recurrent falls [de Vries *et al.* 2011]. The multifactorial intervention programme consisted of a geriatric assessment after a fall-related ED visit. This extensive assessment did not lead to a reduction of falls. Several explanations have been suggested. One explanation may be that usual care following a fall is equally effective as a multifactorial intervention. Second, increased awareness of their high fall risk after informing patients about the aim of the study may be an effective intervention. Neyens and colleagues implemented a similar kind of falls prevention programme for older adults living in a psychogeriatric nursing home. Their intervention consisted of anticipating the circumstances and causes of falls, critically reviewing and monitoring medication intake (type, number, dose and time of intake), individually designed exercise programmes, carefully (re)assessing the need for assistive and protective aids, and promoting the correct use of these aids. Their randomized controlled trial showed a reduction in the number of falls (intervention group 2.04 *versus* 2.54 falls annually per person). Subgroup analyses showed that fall risk declined further as patients participated longer in the intervention programme. Therefore it seems that specific groups may already benefit from structured falls prevention programmes [Neyens *et al.* 2009].

Although fall incidents are the main mechanism for injuries, underlying medical conditions, such as osteoporosis, places older individuals at higher risk of injurious falls. The prevention of falls is a first and important step, but should be accompanied by optimizing the patient's condition and medication use to reduced injuries due to falls.

Conclusion

Falls are a major public health problem in ageing populations worldwide. Fall-related injuries have large societal and individual consequences. Programmes to prevent falls and fractures should be implemented to reduce the associated injury, mortality, costs and substantial burden on healthcare workers and institutions. Several risk factors have been identified, including the use of fall risk increasing drugs. Drug prescriptions for older patients require close attention, particularly since drug metabolism, efficacy and ADRs vary significantly between older and younger individuals. Future research is necessary to show the best strategies to avoid multiple drug use and their interactions among the increasing older population. Another important aspect is that healthcare professionals are aware of drugs being a potential cause for falls.

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Conflict of interest statement

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