

Correlation between fall risk increasing drugs (FRIDs) and fall events at a rehabilitation hospital

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Abstract. *Background and aim:* Falls and fall-related injuries are a major public health issue which needs global attention due to its clinical and socioeconomic impact. Important risk factors for falls are polypharmacy and the assumption of so-called *Fall Risk Increasing Drugs* (FRIDs). Aims of our study were to investigate the associations between falls and the use of medications among inpatients by conducting a retrospective case-control study in a rehabilitation hospital in Northern Italy in 2018. *Methods:* A Conditional Logistic Regression was performed to analyze the impact that 13 types of FRIDs individually and the number of administered FRIDs had on the risk of falling. A second regression model was obtained adjusting the case-control matching for CIRS, Morse and Barthel scores. *Results:* We identified 148 cases and 444 controls. 3 types of FRIDs were significantly correlated ($p < 0,05$) with an increased risk of falling: Antipsychotics, Antidepressants, Diuretics. Antidepressants were the only type of FRID significantly correlated ($p=0,008$) even in the model adjusted for CIRS, Morse and Barthel scores. The unadjusted model showed that the addition of one type of FRID to therapy was significantly associated with the fall event ($p<0.05$). *Conclusion:* Assumption of drugs, in particular antidepressant and polypharmacy, can play a role in hospital falling. The fall risk assessment tools available, suffer from low specificity and sensitivity and do not assess these risk factors. A holistic approach with a multidimensional evaluation of the patient through screening tools, functional assessment tools and a full medical evaluation should be pursued to improve prediction. (www.actabiomedica.it)

Key words: Falls, FRIDs, rehabilitation.

Introduction

Falls and fall-related injuries, especially among elderly people, are a major public health issue which needs global attention due to its clinical and socioeconomic impact (1-3). In the last decades, this problem has increased progressively in importance due to the ageing of the population (3).

Falls and their consequences involve a large amount of preventable direct and indirect health care

costs. The estimated costs of falls account for approximately \$50 billion in the USA (1). A systematic review assessed that national fall-related costs constitute 0.85-1.5% of total healthcare expenditures (2).

Falls in people living in community can result in fractures, hospital admission, "post-fall syndrome" (dependence, loss of autonomy, confusion, immobilization, depression and restriction in daily activities) (4) and increased mortality (5). Furthermore, many persons who fall develop a deep fear of falling (4) leading

to loss of confidence, loss of balance, restriction in daily activities (6) and an increased likelihood of falls in the future (7,8). Fear of falling occurs among 30% of those who have never fallen and 60% for those who have fallen previously (8).

Older people staying in hospital or in long term care facilities fall more frequently than those living in the community. Inpatient falls are the most common adverse event in hospital and approximately one in three hospital falls lead to an injury, with 4-6% resulting in serious injuries (9).

The identified risk factors for falls in hospitalized patients are similar to those observed in community studies (10). The scientific literature has identified several risk factors for falls which can be categorized as intrinsic or patient-related factors and extrinsic or environmental-behavioral factors (11,12).

Among community-dwelling people, about one in three adults over 65 years of age falls annually (4,13,14) and 15% falls twice or more (14); this percentage increases with age, reaching 50% in the adults over the age of 80 (4,15). Aging is characterized by greater co-morbidity and reduction in several physiological systems (e.g. musculoskeletal, cardiovascular, visual, vestibular, coordination, cognitive function) which all increase the likelihood of falls (16). Women have a higher likelihood of falls (17,18) and to be hospitalized than men (19) while there is no univocal evidence about the role of racial differences (20). Gait and balance disorders and muscle weakness are typical problems of patients admitted for rehabilitation and are one of the strongest risk factors for falls (11,21) followed by visual impairment (22), incontinence (17,23) and mood disorders (17).

Among extrinsic factors, poor lighting, objects around the home or room and type of footwear may increase the likelihood of falls (24)

In inpatients, falls could result in increased mortality and morbidity, longer hospital stays, additional treatment and higher rates of discharge from hospitals to long term care facilities compared with patients who do not fall (25).

Important risk factors for falls both in people living in community and in inpatients are polypharmacy, irrespective of type (17,26,27), and the assumption of so-called *Fall Risk Increasing Drugs* (FRIDs). In the scientific literature, there is no consensus in defining

polypharmacy (27), but the most used definition is four or more medications that is the cutoff above which the risk of falls increases exponentially (27,28). Until now, the majority of researches studying the association between falls and medication have predominantly focusing on those acting on the central nervous system (such as narcotics, sedatives, benzodiazepines, antipsychotics, antidepressants and antiepileptics) and cardiac drugs, with no univocal results (27-30). In addition, to the best of our knowledge, none of them analyzed FRIDs in inpatients admitted for rehabilitation.

Aims of our study were to investigate the occurrence of falls and to identify predictors of falls examining the associations between falls and the use of medications and polypharmacy among inpatients of a rehabilitation hospital by conducting a retrospective case-control study. To achieve these goals, we compared hospitalized patients who had a fall (cases) to hospitalized patients who did not have fall (control).

Materials and Methods

The study was conducted in accordance with international guidelines and the Declaration of Helsinki.

Study setting

The study was conducted in a rehabilitation hospital in Northern Italy with an average yearly admission of about 3000 patients. The facility has 315 inpatient beds and provide medical, rehabilitative and diagnostic clinical services in cardiac, respiratory and neuro-motor areas.

In this hospital, the risk of falls for each patient is established at the admission using fall risk assessment tools such as *Morse Fall Scale* (MFS) (31) and *St. Thomas Risk Assessment Tool* (STRATIFY) (32) predictive scales. The data, were registered on the hospital's medical data warehouse together with patients' demographic characteristics, date of hospitalization, hospital ward, comorbidity, intrinsic and extrinsic risk factors for falls (using *Cumulative Illness Rating Scale* and *Barthel Index*), fall-risk scores, fall event characteristics (date, time and place of the fall, modalities and consequences of falling) and patients' drug therapy the day before falling (number,

type of medications and ATC (Anatomical Therapeutic Chemical Classification System) codes ((Opioids (ATC class N02A), Antipsychotics (ATC class N05A), Anxiolytics (ATC class N05B), Hypnotic and sedatives (ATC class N05C), Antidepressants (ATC class N06A), Vasodilators (ATC class C01D), Anti-hypertensives (ATC class C02), Diuretics (ATC class C03), Beta blocking agents (ATC class C07), Calcium channel blockers (ATC class C08), Renin-angiotensin system inhibitors – ACE-Inhibitors (ATC class C09), Alpha-adrenoceptor antagonists (ATC class G04CA) and Dopaminergic agents (ATC class N04B)) (33).

All patients' data used in this retrospective study were extracted from the hospital's medical data warehouse and anonymized.

Study population

In our study, we considered a fall as the event in which a patient inadvertently came to rest on the floor, ground or lower level (3,34,35).

All inpatients for whom a fall occurred between 01/01/2018 and 31/12/2018 were considered eligible for the study. For the purposes of this study, in the period under examination we considered only the first fall event both in patients who experienced more than one fall during a single hospitalization and in patients who have fallen more than once in multiple hospitalizations.

Patients for whom fall risk assessment at the admission was missing totally or partially were excluded.

Inpatients who had a fall were identified and three unique control for each faller, matched by age, sex and hospitalization ward, were selected from patients hospitalized between 01/01/2018 and 31/12/2018.

Data analyses

Continuous data were expressed as means and medians with standard deviations (SD). Qualitative data were converted in categorical variables and expressed as numbers and frequencies.

We analyzed the impact that 13 types of FRIDs had on the risk of falling by performing a Conditional Logistic Regression and matching cases and controls by Age, Sex, and hospital ward (Model 0). Cases with missing data were excluded from the analyses. A second regression model was obtained by further adjusting the case-control matching for CIRS, Morse and Barthel scores (Model 1) (31,36,37).

Data analyses were carried out using R software (38).

In addition, we evaluated the existence of associations between number of administrated FRIDs and fall events through a logistic regression model, adjusting for the same confounders. Results are presented as odds ratio (ORs) with 95% confidence intervals (CIs). Variables with P-value < 0,05 were considered significant.

Results

We identified 173 fallers (Table 1) on a sample of 2711 inpatients. 25 cases were excluded from the analyses due to lack of medical data. The total sample was therefore composed of 147 cases and 441 controls (Table 1). Patients that fell were on average 76,1 years old (\pm 9,71 SD), and were slightly more likely to be men (52%, n = 90). Regarding location, cardiology and physical medicine and rehabilitation (PMR) wards presented the highest rate of falls.

Table 1 Fallers and non-fallers characteristics (logistic regression sample)

	FALLERS (n=147)	NON FALLERS (n=441)
Sex		
Male	48,3 % (n=71)	48,3 % (n=213)
Female	51,7 % (n=76)	51,7 % (n=228)
Mean age		
Total	77,13 (\pm 8,86 SD)	75,95 (\pm 11,14 SD)
Male	75,86 (\pm 8,69 SD)	74,30 (\pm 10,53 SD)
Female	78,32 (\pm 8,92 SD)	77,50 (\pm 11,49 SD)

Table 1 (Continued)

Table 1 Fallers and non-fallers characteristics (logistic regression sample) (*Continued*)

	FALLERS (n=147)	NON FALLERS (n=441)
Ward		
Cardiology	45,59 % (n =67)	45,58 % (n=201)
PMR	36,73 % (n=54)	36,73 % (n=162)
Pneumology	17 % (n=25)	17 % (n=75)
Neurorehabilitation	0,68 % (n=1)	0,68 % (n=3)
Scores		
CIRS	4,53 (± 2,12 SD)	3,99 (± 2,24 SD)
MORSE	40,75 (± 18,86 SD)	33,16 (± 19,67 SD)
BARTHEL	57,72 (± 26,59 SD)	64,69 (± 29,97 SD)

Table 2 reports the fall characteristics. Falls occurred in every setting, mainly in the patient room, but also in the restroom or walking down the aisle. Moreover, falls occurred more frequently during the day shift, between 8:00 am and 16:00 pm. Most falls had not injurious consequences for the patients and only 23,7% led to an injury. Regarding seasonality, there was a slight increase in the rate of falling during warmer months with 56,1% of the episodes occurring in spring and summer. The rate of falls was almost constant during the whole year, peaking in November and plunging in February, making falling an endemic illness among elderly people (Figure 1).

The unadjusted model (Model 0 in Table 3) identified 3 types of FRIDs significantly correlated (p -value < 0,05) with an increased risk of falling, specifically: N05A (Antipsychotics) [OR: 1,98; CI 95%: 1,01 - 3,89], N06A (Antidepressants) [OR: 2,18; CI 95%: 1,32 - 3,59], and C03 (Diuretics) [OR: 1,71; CI 95%: 1,09 - 2,68].

The N06A (Antidepressants) was the only type of FRID significantly correlated even in the model adjusted for CIRS, Morse and Barthel scores (Model 1 in Table 3) with an odds ratio of 2,00 [CI 95%: 1,20 - 3,34] and p -value of 0,008.

The analysis of associations between the number of administrated FRIDs and fall events (unadjusted model) showed that the addition of one type of FRID to therapy was significantly associated with the fall event (p -value <0.05) [OR: 1.21; CI 95%:

Table 2 Falls characteristics

FALLS (n=173)	
Ward	Cardiology: 39,3% (n= 68)
	FRR: 31,8% (n= 55)
	Pneumology: 15,6% (n= 27)
	Neurorehabilitation: 13,3% (n= 23)
Time	Day shift (7:00 AM to 6:59 PM): 60,1% (n= 104)
	Night shift (7:00 PM to 6:59 AM): 39,9% (n=69)
Seasonality	Spring: 31,2% (n= 54)
	Summer: 24,9% (n= 43)
	Autumn: 20,8% (n= 36)
	Winter: 23,1% (n= 40)
Hours	08:00 AM to 3:59 PM: 48% (n= 83)
	4:00 PM to 11:59 PM: 24,8% (n= 43)
	00:00 AM to 7:59 AM: 27,2% (n= 47)
Location	Room: 66,5% (n= 115)
	Aisle: 6,8% (n= 12)
	Bathroom: 23,1% (n= 40)
	Bar: 0,6% (n= 1)
	Gym: 1,2% (n= 2)
	Outdoor: 0,6% (n= 1)
	Other: 1,2% (n= 2)

Table 2 (*Continued*)

Table 2 Falls characteristics (*Continued*)

FALLS (n=173)	
Fall mechanism	Off the bed: 13,3% (n= 23)
	Off the bed with bed rail: 9,8% (n= 17)
	Off the WC: 2,3% (n= 4)
	From standing position: 41% (n= 71)
	Off the chair: 6,9% (n= 12)
	Off the wheelchair: 18,5% (n= 32)
	Nd: 8,2% (n= 14)
Outcome	Injurious fall: 23,7% (n= 41)
	Not injurious fall: 75,8% (n=131)
	Nd: 0,5% (n= 1)

1.05 - 1.40]. This significance was lost in the second analysis adjusted for the CIRS, Morse and Barthel scores (p-value <0.05) [OR: 1.14; CI 95%: 0.98 -1.33].

Discussion

This retrospective study was conducted to investigate the intercurrent relationship between medications and fall events in order to help improving the management of this very actual problem in a rehabilitation setting.

Our study showed that about 25% of falls led to an injury; this data is quite congruent with the literature (9).

Table 3 Odds Ratios (OR) for the occurrence of a fall during hospitalization according to the type of FRID (Fall Risk Inducing Drugs) medication. Study estimates were obtained with Conditional Logistic Regression.

	ATC	OR	(95% CI)	P-value	
Model 0 a)					
	N02A	0,72	(0,31 - 1,64)	0,431	
	N05A	1,98	(1,01 - 3,89)	0,047	*
	N05B	1,24	(0,79 - 1,93)	0,348	
	N05C	1,02	(0,50 - 2,09)	0,952	
	N06A	2,18	(1,32 - 3,59)	0,002	**
	C01D	1,07	(0,52 - 2,19)	0,849	
	C02	1,28	(0,57 - 2,87)	0,542	
	C03	1,71	(1,09 - 2,68)	0,020	*
	C07	0,82	(0,54 - 1,27)	0,381	
	C08	0,85	(0,51 - 1,42)	0,545	
	C09	1,10	(0,74 - 1,65)	0,640	
	G04CA	1,53	(0,73 - 3,23)	0,260	
	N04B	0,78	(0,24 - 2,58)	0,689	
Model 1 b)					
	N02A	0,59	(0,25 - 1,35)	0,210	
	N05A	1,70	(0,83 - 3,45)	0,145	
	N05B	1,23	(0,78 - 1,94)	0,371	
	N05C	0,93	(0,45 - 1,93)	0,847	
	N06A	2,00	(1,20 - 3,34)	0,008	**
	C01D	0,88	(0,42 - 1,88)	0,749	
	C02	1,13	(0,49 - 2,62)	0,773	
	C03	1,43	(0,89 - 2,30)	0,134	

Table 3 (*Continued*)

Table 3 Odds Ratios (OR) for the occurrence of a fall during hospitalization according to the type of FRID (Fall Risk Inducing Drugs) medication. Study estimates were obtained with Conditional Logistic Regression. (*Continued*)

	ATC	OR	(95% CI)	P-value
	C07	0,83	(0,53 – 1,29)	0,412
	C08	0,77	(0,46 – 1,31)	0,342
	C09	1,14	(0,75 – 1,73)	0,532
	G04CA	1,53	(0,70 – 3,34)	0,290
	N04B	0,73	(0,22 – 2,36)	0,596

a) unadjusted. Matched for age, sex, and hospital ward. $R^2 = 0,039$.

b) adjusted for CIRS, Morse and Barthel. Matched for age, sex, and hospital ward. $R^2 = 0,065$. * $p < ,05$. ** $p < ,01$.

An important intrinsic risk factor for falls is the assumption of medications and in particular of the so called FRIDs. The main finding of our study is that a statistically significant association between falls and three classes of FRIDs: N05A (Antipsychotics), N06A (Antidepressant) and C03 (Diuretics). However, considering the adjusted model for CIRS, Morse and Barthel score, there is no statistical significance for N05A and EC03, while it persists for N06A (antidepressant). This result is in agreement with recent literature findings relating administration of antidepressants to increased falls rates (39,40). Other psychotropic drugs, such as antipsychotics and benzodiazepines, have been associated with increased risk of falling (41,42). As highlighted before, in our study antipsychotics were significantly related to fall events in the rough model but not in the adjusted one. This outcome is partly in line with what has been highlighted by a recent English cohort study that revealed how the risk of falling of the subjects enrolled was significantly associated with antidepressants and benzodiazepines, but not with antipsychotics; a probable explanation can be found in a more responsible use of these drugs in subjects at risk (43). As suggested by two different meta-analyses, cardiovascular medications, mainly including antihypertensives and diuretics, could be involved in fall risk, too (44). Nevertheless, there were no similar significances in our study.

A similar remark can be made referring to medications' number assessment. In the adjusted model we found no relationship between the number of FRIDs assumed and increasing fall risk, consistently with previous studies (33,45,46). At the opposite, other authors found significant relationships of this kind (47).

Differences underlined above and the heterogeneity of literature findings may be explained by several factors. First of all, the different definitions of FRIDs often led to a great variability in study settings. At the same time, the lack of specific assessments of active substances, as well as their dosages and pharmacokinetics characteristics, may represent another important variable.

Concerning polypharmacy, there is no unanimous agreement on the number of FRIDs to be considered, thus determining different cut-offs and consequently inconsistent results.

Most studies about this topic have identified this type of link between drug therapy and the fall event, but there is a lack of reliable studies based on a large sample size and investigating the mechanisms underlying this increased risk.

One of the possible explanations is represented, for example, by the fact that these FRIDs might contribute to falls through significant movement-related side effects which could cause imbalance, and also through other mechanisms such as sedation, orthostatic hypotension and cardiac arrhythmia which lead to a fall that could result in an injury (48). Such mechanisms of action and side effects could also explain the effects of cardiovascular drugs.

This aspect is relevant overall in consideration of the rehabilitation setting where our study was conducted. In fact, most of our patients, especially admission, are characterized by balance, motor control and/or blood pressure problems.

At the same time, the majority of the numerous studies that investigated this issue did not examine in depth some possible approach strategies and solutions.

It is therefore evident that studies on large samples are required to carefully investigate the dynamics of action of these drugs and at the same time to suggest possible solutions. These solutions must be necessarily integrated to a greater attention in FRIDs prescription and in a constant review of these therapies, from hospitalization to patient discharge, with a more dynamic approach in order to ensure primary prevention of the fall event. To this purpose, the rehabilitation setting could be considered the appropriate site to assess and manage the effects of changes to the therapy regimen during the course of rehabilitation.

The primary intervention to prevent accidental falls should consist in evaluating the person, i.e. identifying the patient at risk in order to adopt the most suitable preventive actions. In this sense, it should be emphasized that the strategy of deprescribing FRIDs alone has not proved effective in preventing falls, but must consequently be included in a multidimensional approach, precisely due to the fact that falls almost always depend on multiple overlapping factors (49).

One of the objectives of the Joint Commission's *National Patient Safety Goals Program* is to reduce falls and injury from falls (50). As consequence, several fall risk assessment tools have been developed in recent years. The most frequently used are the St. Thomas Risk Assessment Tool (STRATIFY) (32), the Morse Fall Scale (MFS) (31) and the Hendrich II Fall Risk Model (HFRM II) (51). Despite these tools are widely used in clinical settings, they have some limitations. These instruments do not predict the type of fall for which the patient is at risk, so that it is not possible to establish a tailored fall prevention strategy for each patient. Moreover, they suffer from low specificity and sensitivity and do not assess all the known risk factors that predispose a patient to fall, especially the use of medications and polypharmacy (26,52).

Limitations of our study include that it was performed in a single medical center in northern Italy and is characterized by a relatively small sample size that also had not homogeneous diagnoses at the admission. In addition, it should be taken into account that subjects with a major risk of falling may have been subjected to stricter containment measures.

As a consequence, our conclusions may not be generalizable for facilities with care settings different

from rehabilitation and patient characteristics. Therefore, in order to make more generalizable our findings it would be appropriate to carry out other studies in different care settings. Another limitation could also be the fact that our study includes only the effect of drugs on falls. Adopting a more complex model it will be possible to include other factors such as the function of the lower extremities and the foot, the possible degree of pain of the patient, footwear and other variables.

A holistic approach with a multidimensional evaluation of the patient through screening tools, functional assessment tools and a full medical evaluation should be improved.

It will, therefore, be important to implement adequate strategies to ensure that the drug therapy factor is also taken into account when stratifying the risk of falling for patients; this objective can be achieved thanks to the construction of new more specific assessment tools or thanks to the implementation more reliable predictive models taking into consideration already existing tools in combination with other information related to medications and polypharmacy.

Conclusion

The risk profile of patients who fell in respect to those who did not fall during stay in a rehabilitation hospital can be worsened by the medical therapy and polypharmacy. The analysis we carried out show that the assumption of antidepressants may increase the risk up to two times than that of a control group (non-fallers) matched by CIRS, Morse and Barthel scores.

Because the importance for public health of the fall in hospital issue, mainly due to the significant direct and indirect costs caused by falls and the clinical consequences for patients, more efforts should be made to prevent them and at the same time to develop more reliable predictive models and tools.

Abbreviations: ATC: Anatomical Therapeutic Chemical Classification System; CIRS: Cumulative Illness Rating Scale; FRIDs: Fall Risk Increasing Drugs; HFRM II: Hendrich II Fall Risk Model; MFS: Morse Fall Scale; STRATIFY: St. Thomas Risk Assessment Tool

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: 18 April 2021

Accepted: 28 May 2021

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