Medication-related inpatient falls: a critical review

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Falls are the second leading cause of accidental and unintentional injury deaths worldwide. Inpatient falls in hospital settings are likely to prolong the length of stay of patients in nearly 6.3 days, leading to increased hospitalization costs. The causes of fall incidents in healthcare facilities are multifactorial in nature and certain medications use could be associated with these incidents. This review seeks to critically evaluate the available literature regarding the relationship between inpatient falls and medication use. A comprehensive search was performed on MEDLINE, EMBASE and Lilacs with no time restriction. The search was filtered using English, Spanish or Portuguese languages. Our study evaluated medication use and inpatients falls that effectively happen, considering all ages and populations. An assessment of bias and quality of the studies was carried out using an adapted tool from the literature. The drugs were classified according to the Anatomic Therapeutics Chemical Code. The search strategy retrieved 563 records, among which 23 met the eligibility criteria; ninety three different pharmacological subgroups were associated with fall incidents. Our critical review suggests that the use of central nervous system drugs (including anxiolytics; hypnotics and sedatives; antipsychotics; opioids; antiepileptics and antidepressants) has a greater likelihood of causing inpatient falls. A weak relationship was found between other pharmacological subgroups, such as diuretics, cardiovascular system-related medications, and inpatient fall. Remarkably, several problems of quality were encountered with regard to the eligible studies. Among such quality problems included retrospective design, the grouping of more than one medication in the same statistical analysis, limited external validity, problems related to medication classifications and description of potential confounders.

Keywords: Accidental Fall/hospitals. Therapeutic Uses. Inpatients. Central Nervous System Agents.

INTRODUCTION

Falls are the second leading cause of accidental and unintentional injury deaths in Brazil and worldwide (CDC, 2014; DataSUS, 2014; WHO, 2004). In healthcare facilities, this adverse event is a prevalent patient safety problem. The reduction of injuries stemming from fall incidents is one of the six main goals of the Worldwide Alliance for Patient Safety (WHO, 2008). The World Health Organization (WHO) defines fall as "inadvertently coming to rest on the ground, floor, or other lower level, excluding intentional change in position" (WHO, 2007).

As of 2012, the fall rate of adult inpatients in the USA was 3.56 per 1,000 patients/day (pd), out of which 26.1% resulted in injury (Bouldin *et al.*, 2012). Inpatient falls in hospital settings are likely to prolong the length of stay of patients in nearly 6.3 days, leading to increased direct and indirect hospitalization costs of $13,316 in three American hospitals (Wong *et al.*, 2011). There are few data on adult inpatient falls in Brazil, and most of the studies conducted on the issue restricted their focus to elderly patients. In a study carried out in three large general hospitals in a single state in Brazil, the rate of fall among elderly inpatients was 12.6 per 1,000 patients a day (Abreu *et al.*, 2015).

The fall risk factors are multifactorial in nature and are conventionally classified into intrinsic and extrinsic factors (Ferreira, Yoshitome, 2010, Severo *et al.*, 2014).

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The intrinsic factors are associated with the individual and are essentially related to factors such as the illness of the patient, elderly physiological changes, cognitive decline, gait alteration and medication use (Buksman *et al.*, 2008). These factors are found to be transitory, and include orthostatic hypotension, syncope after anesthesia (Spoelstra *et al.*, 2012) or polypharmacy (Richardson, Bennett, Kenny, 2014). The extrinsic factors are related to external conditions including environmental hazards (such as bedrails or footwear) and low levels of nursing care (Severo *et al.*, 2014; Hignett, Masud, 2006).

While current research studies have devoted their attention to understanding the causes of inpatient fall risks, the huge challenge lies in devising efficient strategies for the prevention of falls in healthcare facilities (Miake-Lye *et al.*, 2013; Brasil, 2013b; Rezende, Gaede-Carrillo, Sabastião, 2012, Boushon *et al.*, 2012). Medication use is cited as one of the main causes of inpatient falls (Rubenstein, 2006; Boyle, Naganathan, Cumming, 2010). Some studies point out the need for the revision of inpatient medical prescriptions and the inclusion of a clinical pharmacist into the multi-professional team so as to increase patient safety and reduce the risk of fall (Zermansky *et al.*, 2006; Haumschild *et al.*, 2003; Browne, Kingston, Keane, 2014). Most of the drugs classified as high risk for fall are categorized in this manner as a result of the adverse events that these medications can cause. Among these adverse effects include orthostatic hypotension due to antihypertensives use or hypoglycemia by virtue of the use of antidiabetics (Rubenstein, 2006; Boushon *et al.*, 2012).

Most of the reviews published in the literature on this subject sough to analyze the underlying relationship between medication use and fall incidents in different settings including community settings, long-term facilities and hospitals. The sample population investigated was often restricted to elderly patients and the studies mostly considered only few medication subgroups (Park *et al.*, 2015; Zang, 2013; Bloch *et al.*, 2010; Boyle, Naganathan, Cumming, 2010; Woolcott *et al.,* 2009; Hegeman *et al.*,

2009; Campbell, 1991). To date, no reports have been published in the literature involving specific medications related to inpatient falls without age restriction. Clearly, in a hospital setting, patients are exposed to a wide range of medications and specific conditions that may contribute towards altering the risk of falling (Matarese *et al.,* 2014). The aim of this study is to carry out a thorough assessment of the literature available regarding the relationship between medication and inpatient falls, regardless of the age of patients. The paper will also undertake a critical review in this context.

METHODS

Data sources and search

A comprehensive literature review was conducted by the author, T.B.R, on MEDLINE (by Pubmed), EMBASE (by Elsevier), and Lilacs (by Virtual Health Library website) (last search on August 4, 2016), with no time restriction and filtered by English, Spanish or Portuguese languages. The medical subject heading (MESH) terms used included "inpatient", "accidental fall", and "therapeutic uses" (linked with "AND"). The term "therapeutic uses" was chosen by virtue of the fact that it indexed all medication classes. A similar search was done on EMBASE using the Emtree terms "hospital", "falling" and "drug therapy". All terms were expanded to capture all relevant articles using relevant synonyms including hospital*, drug*, medicat* and fall*. All potentially eligible studies were included with the exception of reviews. The search strategy is presented in Table I. Some bibliographical references in the eligible studies were evaluated. In some cases, these references were either withdrawn or included based on our search strategy.

Study selection

Studies were considered eligible for inclusion once

TABLE I - Search strategy

Database	Search Strategy
PUBMED.MEDLINE	((((((inpatients[MeSH Terms]) OR inpatient*[Title]) OR hospital*[Title])) AND (((therapeutic uses[MeSH Terms]) OR drug*[Title]) OR medicat*[Title])) AND ((accidental falls[MeSH Terms]) OR fall*[Title])
EMBASE	inpatient*:ti OR 'hospital patient':de,ti OR hospital:ti AND (drug*:ti OR 'drug therapy'/exp OR medicat*:de,ti) AND ('fall risk':de OR falling:de OR fall*:ti)
BVS.LILACS	(mh:inpatients OR ti:inpatient* OR ti:hospital*) AND (mh:"therapeutic uses" OR ti:drug* OR ti:medicat* OR mh:drug* OR mh:medicat*) AND (mh:"accidental falls" OR ti:fall*)

they contained original data based on the association between medication use and inpatient falls, were exclusively conducted in a hospital setting, and included all ages and special populations. The author thoroughly read and assessed all titles and abstracts and selected the studies of interest in line with the inclusion criteria. Reviews and studies that considered pre-hospitalization falls, facilities different from hospital (community or long-term care facilities), and those that did not evaluate medication or falls that effectively happen in a hospital setting were all excluded. All studies retrieved in the search were included in our investigation without regard to quality limitations. The excluded studies were not categorized.

Data extraction and quality assessment

Data were extracted and summarized in a spreadsheet with the main study information including the following: author/year, country, number of fallers/ number of control group and special sample condition, median age of fallers, follow-up period, other factors related to fall, medication and measure of association. The type of the studies design (cohort, case-control, etc.) was classified by the authors.

Medications that were related to inpatient fall, those ones which were statistically significant according to univariate and/or multivariate analysis, were classified based on the Anatomical Therapeutic Chemical (ATC) classification. These medications were graded in the pharmacological groups (3rd level). It is worth noting that those medications that could not be classified as 3rd

level (due to the absence of author specification) were catalogued according to the therapeutic subgroup (2nd level).

Data were extracted on the most cited pharmacological subgroups and details were provided regarding the studies that mentioned these subgroups. The data details included the special populations and medications involved.

All studies were evaluated using a quality tool adapted from von Elm (2007) and Young and Solomon (2009) proposals on "how to critically appraise an article". This tool evaluates the main factors that can induce study bias. Among such factors include the following: clear population definition and representation; selection of control and case groups (criteria and sample); full identification of potential confounders; accurate outcome measures; confounders and relevant exposure; and adequate statistical analysis (Table III). These factors were classified under the following categories: "high risk of bias", "low risk of bias" and "not clear". This classification was based on the completion of the topics about the assessment of the risk of bias included in Table III.

RESULTS

The search strategy retrieved 563 records, 34 of which were considered for full-text screening while 23 met the eligibility criteria (Figure 1).

A summarized presentation of the studies data can be found in Table III. Most of the studies (87%) included were published after 2004. Sixty one percent (14/23)

TABLE II - Bias Analysis Tool adapted from Strobe (2007) and Young and Solomon (2009) proposals on "how to critically appraise an article"

Clear definition and representation of population	-The population, the eligibility criteria and methods of selection were clearly described; -The sample was representative of the population or group studied
Adequate selection of cases and control (or comparative group)	-The case and control(or comparative group) selection criteria were clearly described; -The control (in case it is control case) reflects the case population (characteristics and number); - The same indicators were evaluated for both groups.
Full identification of potential confounders	- All confounders (or at least 80%) were identified (we considered the main confounders to fall: history of fall, age, ambulatory aid, gait, mental status (dementia, confusion, disorientation, impulsivity), symptomatic depression), according to Hendrich II Fall Risk Model and Morse Fall Scale.
Accurate measure of all important relevant exposure, potential confounders and outcomes	-Accurate measure and description of the relevant exposure, potential confounders and outcomes, sample characteristics, follow-up period and clear outcomes.
Adequate statistical analysis	-Description and accurate analysis of the statistical methods chosen.

TABLE III - Eligible studies data

Author, publication year	Country	n fallers/ n control group (or comparative group); Special sample condition	Median age (fallers)	Follow-up period	Type of study	Other factors related to fall (statistically significant)	ATC - Pharmacological subgroup	Medication	P value Univariate analysis (UA) and Multivariate analysis (MA)	Odds ratio Univariate analysis (UA) and Multivariate analysis (MA)
O'Neil et al. (2015)	US	228 fallers/ 678 control; NA	61.5	4.5 months	Case control	Underweight, history of falls, fall was the reason for admission, weak gait, assistive device, person assistance, incontinence, syncope, dizziness and confusion.	Anxiolytics	lorazepam, diazepam, clonazepam (as antiepileptics)	UA: S MA: NS	UA: OR: 2.65 (CI:1.88-3.73); MA: NI
							Antidepressants	amitriptyline, nortriptyline, clomipramine, doxepin, desipramine, phenylpiperazine	UA: S UA for antidepressant phenylpiperazines: S	UA: OR: 1.37 (CI: 0.98-1.90),
							Antiepileptics	Phenytoin (hydantoins)	UA: S MA: NI	UA: OR: 4.93 (CI:2.27-10.70), M A: OR: 3.25 (CI: 1.33–7.95)
							Centrally-acting Antiadrenergic agents	clonidine and methyldopa	UA: S MA: NI	UA: OR: 1.89 (CI:1.01-3.52) MA: NI
							Antipropulsives	loperamide	UA:S MA: NI	UA: OR: 2.31 (CI: 1.02-5.48) MA: NI
							Insulin and analogues	insulin	UA: NS MA: NI	UA:NI MA: OR: 1.46 (CI: 1.01-2.13)
Tapper et al. (2015)	US	55 fallers/ 1749 controls; Cirrhotic	55	3.5 years	Retrospective Cohort	Score MELD (hepatic disease), hepatic encephalopathy and length of stay.	Anxiolytics	diazepam, lorazepam, clonazepam, alprazolam, zolpidem, chlordiazepoxide and zolpidem	UA: S MA: NI	UA: ORa: 6.59 (CI: 3.76 -11.59) MA: NI
							Antipsychotics	olanzapine, risperidone, quetiapine and haloperidol.	UA: S MA: NI	UA: ORa:3.72 (CI:1.9-7.06) MA: NI
Hayakawa et al. (2014)	Japan	230 fallers/ 9240 controls; NA	60.5	2 months	Prospective Cohort	History of falls, cognitive dysfunction, wheelchair use, needs help to move, rehabilitation and need help with activities of daily life .	Antipropulsives	Antipropulsives NE	UA: S MA: NS	UA: N MA NI
							Psychotropics[1]	Psychptropics NE*	UA: S MA: S	UA: N MA: OR 3.64 (men)
							Hypnotics and sedatives	hypnotics NE	UA: S A; S	UA: N MA: ; OR 1.65 (women)
Dauphinot et al. (2014)	France	21 fallers/ 317 controls; Exposure to anticholinergic and sedative Drugs	85.33 +- 6.68	11.6 months	Prospective Cohort	Dementia and Parkinson disease.	Opioids	tramadol	UA with increased DDD: S MA: NI	UA: OR: 2.59; (CI: 1.05-6.35) MA: NI
							Anxiolytics	alprazolam e oxazepam	UA with increased DDD for alprazolam and oxazepam: S UA with increased DDD for meprobamate (without BZD): S MA: NI	UA with increased DDD for alprazolam and oxazepam: OR: 2.59 (CI: 1.05-6.35) UA with increased DDD for meprobamate (without BZD): OR: 2.59 (CI: 1.05-6.35) MA: NI
							Hypnotics and sedatives	zopiclone e zolpidem	UA with increased DDD: S MA: NI	UA with increased DDD: OR: 2.59 (CI: 1.05-6.35) MA: NI
							Antipsychotics	olanzapine. risperidone. amisulpiride. tiaprida. ciamemazine	UA with increased DDD: S MA: NI	UA with increased DDD: OR: 2.59 (CI: 1.05-6.35) MA: NI
							Antiepileptics	Phenobarbital	UA with increased DDD: S MA: NI	UA with increased DDD: OR: 2.59 (CI: 1.05-6.35) MA: NI
Costa-Dias et al. (2014)	Portugal	214 falls (193 fallers); Elderly	75	3.5 years	Retrospective Cohort	Age, oncologic patient, neurodegenerative disease, male gender, chronic and palliative inpatient wards	Antiepileptics	Antiepileptics (clonazepam 19%)	UA for fall CNS meds: S UA for recurrent fall with valproic acid: S UA for recurrent fall with levetiracetam: S MA: NI	UA for fall CNS meds: OR 7.14 (CI:NI) UA for recurrent fall with valproic acid: OR 3.33 (CI: 1.39-5.4) UA for recurrent fall with levetiracetam: OR 5.67 (CI: 1.91-13.53) MA: NI

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TABLE III - Eligible studies data (cont.)

Author, publication year	Country	n fallers/ n control group (or comparative group); Special sample condition	Median age (fallers)	Follow-up period	Type of study	Other factors related to fall (statistically significant)	ATC - Pharmacological subgroup	Medication	P value Univariate analysis (UA) and Multivariate analysis (MA)	Odds ratio Univariate analysis (UA) and Multivariate analysis (MA)
Costa-Dias *et al.* (2014)	Portugal	214 falls (193 fallers); Elderly	75	3.5 years	Retrospective Cohort	Age, oncologic patient, neurodegenerative disease, male gender, chronic and palliative inpatient wards	Antiepileptics	Antiepileptics (clonazepam 19%)	UA for fall - psychotropic meds: S UA for recurrent fall: S MA:NI	UA for fall - psychotropic meds: OR 8.68 (CI:NI) UA for recurrent fall: OR: 2.74 (CI: 1.36-43.29) MA: NI
							Hypnotics and sedatives	Hypnotics and sedatives NE	UA for fall - psychotropic meds: S UA for recurrent fall: S MA: NI	UA for fall - psychotropic meds: OR 8.68 (CI: NI) UA for recurrent fall: OR: 2.74 (CI 1.36-43.29) MA: NI
							Antipsychotics	Antipsychotics (haloperidol 53%)	UA for falls: S UA for recurrent falls: S UA for recurrent fall with haloperidol: NI UA for recurrent fall with clozapine: NI MA: NI	UA for falls: OR: 7.27 UA for recurrent falls: OR: 5.08 (CI: 2.24-10.84) UA for recurrent fall with haloperidol: OR: 3.32 (IC 2.62-10.50) UA for recurrent fall with clozapine: OR: 7.67 (CI:1.81-8.74) MA: NI
							Antidepressants	Antidepressants NE	UA for fall: S UA for recurrent falls: S UA for recurrent fall with trazadone: NI MA: NI	UA for fall: OR: 6.34 (CI: NI) UA for recurrent falls: OR:4.93 (CI: NI) UA for recurrent fall with trazadone OR:5.25(CI: NI) MA: NI
							Opioids	Opioids (tramadol 40%)	UA for falls: S UA for recurrent falls: S UA for recurrent fall with tramadol: S MA:NI	UA for falls:OR: 7.14(CI: NI) UA for recurrent falls: OR:3.97 (CI 1.36-43.29) UA for recurrent fall with tramadol: OR:3.10 (CI: NI) MA: NI
							Diuretics[2]	Diuretics (furosemide 59%)	UA for recurrent falls: S MA:NI	UA for recurrent falls: OR 2.37 (CI: NI) MA:NI
							Agents acting on the renin-angiotensin	Angiotensin-converting-enzyme inhibitor inhibitors (captopril 30%)	UA for recurrent falls: S MA: NI	UA for recurrent falls: OR 7.67 (CI: NI) MA:NI
							Blood glucose lowering drugs. excluding insulin	Oral Antidiabetic drugs (metformin 15%)	UA for recurrent falls: S UA for recurrent fall with metformin: S UA for recurrent fall with gliclazide: S MA:NI	UA for recurrent falls: OR: 2.54 (CI 1.21-5.34) UA for recurrent fall with metformin: OR 2.82 (CI: 1.27-6.20) UA for recurrent fall with gliclazide: OR: 5.36 (CI 2.07-13.90) MA:NI

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Author, publication year	Country	n fallers/ n control group (or comparative group); Special sample condition	Median age (fallers)	Follow-up period	Type of study	Other factors related to fall (statistically significant)	ATC - Pharmacological subgroup	Medication	P value Univariate analysis (UA) and Multivariate analysis (MA)	Odds ratio Univariate analysis (UA) and Multivariate analysis (MA)
Kolla *et al.* (2013)	US	151 falls; NA	56.84 +- 17,24	12 months	Retrospective Cohort	Insomnia, Delirium, age, Charlson index ,Hendrich's fall risk score and zolpidem dose.	Hypnotics and sedatives	zolpidem	UA: S MA: S	UA: OR: 4.37 (CI: 3.33 -5.74) MA: OR: 6,39 (CI: 3.34-5.76)
Pierce *et al.* (2013)	US	251 fallers; NA	NM	12 months	Retrospective Cohort	Pre-fall confusion. Other not evaluated.	Opioids	Opioids NE	UA: S MA: S	UA: OR: 5,12 (CI: 1.96-13.41) MA: OR: 5.38 (CI: 2.07–13.98)
Obayashi *et al.* (2013)	Japan	116 fallers / 3.683 control ; NA	64.7 ± 19.5	3 months	Case control	Age. Others not evaluated.	Hypnotics and sedatives	Zolpiclone, brotizolam, estazolam	UA: NI MA for hypnotics: S MA for zopiclone: NS MA for brotizolam: S MA for estazolam: NS	UA: NI MA for hypnotics: OR: 2.17 (CI: 1.44–3.28) MA for zopiclone: OR: 3.773 (CI: 1.36–10.4); MA for brotizolam: OR: 2.43 (1.61- 3.68) MA for estazolam: OR: 4.027 (1.35–12.1)
							Antiepileptics	Antiepileptics NE	UA: NI MA: S	UA: NI MA: OR 5.06 (CI: 2.70–9.46)
							Anti-dementia drugs	Anti-Alzheimer NE	UA: NI MA: S	UA: NI MA: OR: 3.08 (CI:1.63–5.84)
							Anti-Parkinson drugs[2]	Anti-Parkinson drugs NE	UA: NI MA: S	UA: NI MA: OR: 5.06 (CI:1.58–16.24)
							Diabetic drugs [2]	Diabetic drugs NE	UA: NI MA: S	UA: NI MA: OR: 5.06 (CI:1.58–16.24)
							Drugs for Cardiovascular system[2]	Antihypertensives NE	UA: NI MA: S	UA: NI MA: OR: 2.24 (CI: 1.41–3.56)
							Antiarrhythmic drugs class I and III	Antiarrhythmic drugs class I and III NE	UA: NI MA: S	MA: p=0.005; OR: 2.82 (CI:1.36–5.86)
Lamis *et al.* (2012)	US	96 fallers/ 96 control; NA	70 +- 13,9	12 months	Case control	Not mentioned or evaluated	Other Analgesics e Antipyretics	Analgesics e Antipyretics NE	UA for CNS meds: S MA for CNS meds: S	UA for CNS meds: NI MA: OR:1.4 (CI: 1.09-1.71)
							Antiepileptics	Antiepileptics NE	UA for CNS meds: S MA for CNS meds: S	UA for CNS meds: NI MA: OR:1.4 (CI: 1.09-1.71)
							Antidepressants	Antidepressants NE	UA for CNS meds: S MA for CNS meds: S	UA for CNS meds: NI MA: OR:1.4 (CI: 1.09-1.71)
							Antipsychotics	Antipsychotics NE	UA for CNS meds: S MA for CNS meds: S	UA for CNS meds: NI MA: OR:1.4 (CI: 1.09-1.71)
							Anxiolytics	Anxiolytics NE	UA for CNS meds: S MA for CNS meds: S	UA for CNS meds: NI MA: OR:1.4 (CI: 1.09-1.71)
							Hypnotics and sedatives	Hypnotics and sedatives NE	UA for CNS meds: S MA for CNS meds: S	UA for CNS meds: NI MA: OR:1.4 (CI: 1.09-1.71)
Chang *et al.* (2011)	Taiwan	165 fallers/ 165 controls; Elderly	76.2	12 months	Case control	Oncologic patients. Others not evaluated.	Anxiolytics	Benzodiazepines NE	UA: S MA: S	UA: OR: 2.26 (CI:1.21–4.23) MA: OR: 2.63 (CI:1.55–4.46)

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Chang *et al.* (2011)	Taiwan	165 fallers/ 165 controls; Elderly	76.2	12 months	Case control	Oncologic patients. Others not evaluated.	Opioids	Opioids NE	UA: NI	UA: NI
									MA: S	MA: OR: 2.13 (CI:1.16–3.94)
							Antihistamines for systemic use	Antihistamines NE	UA: NI	UA: NI
									MA: S	MA: OR: 3.00 (CI:1.19–7.56)
							Hypnotics and sedatives	zolpidem	UA: NI	UA: NI
									MA: S	MA: OR: 2.38 (CI: 1.04–5.43)
Cashin, Yang (2011)	Canada	151 falls; NA	73.5	12 months	Cross sectional study	Not mentioned or evaluated	Anxiolytics	Alprazolam, bromazepam, chlordiazepoxide, clobazam. Clonazepam, clorazepate. Diazepam,flurazepam. Lorazepam,midazolam, nitrazepam,oxazepam, temazepam,triazolam	UA: NI	UA: NI
									MA: NI	MA: NI
Bun, Serby, Friedmann (2011)	US	15 fallers/ 233 control; Psychiatric population with hyponatemia	55,8	12 months	Case control	Age and hyponatermia. Others not evaluated.	Antipsychotics	Antipsychotics NE	UA: S	UA: OR: 3.85 (CI: 1.17 -12.73)
									MA: NI	MA: NI
Shuto *et al.* (2010)	Japan	349 fallers	71.5± 14.8	2,5 years	Case-crossover	Not mentioned or evaluated	Antihypertensives	amlodipine, atenolol , benidipine ,betaxolol, bisoprolol, candesartan, captopril, carvedilol, clonidina , diltiazem, doxazosin, efonidipine, enalapril, imidapril losartan, etoprolol, nicardipine, nifedipine, nilvadipine, nisoldipine, perindopril, prazosin, propranolol, temocapril, valsartan, verapamil	UA: NI MA: S MA for candersartan: S	UA: NI MA: OR: 8.42 (CI: 3.12-22.72) MA for candersartan: OR: 13.92 (CI: 1.71 - 113.69)
							Anti-Parkinson drugs[2]	amantadine, biperiden, cabergoline, droxidope, levodopa, pergolid), pramipexole,selegiline, tiapride, trihexifenidil	UA: NI MA: S MA for biperiden: S	UA: NI MA: OR: 4,18 (CI: 1.75 -10.02) MA for biperiden: OR: 4.34 (IC: 1.57 - 11.99)
							Anxiolytics	alprazolam, bromazepam, clotiazepam,cloxazolam, diazepam, etil loflazepate, etizolam, lorazepam, tandospirona	UA: NI MA: S MA for etizolam: S	UA: NI MA: OR: 3.25 (IC: 1.62 - 6.50) MA for etizolam: OR: 6.83 (IC: 1.92 - 24.26)
							Hypnotics and sedatives	brotizolam, flunitrazepam, lormetazepam),midazolam, nitrazepam, quazepam, rilmazafone, triazolam, zolpidem, zopiclone	UA: NI MA: S MA for zopiclone: S	UA: NI MA:;OR:2.44 (CI: 1.32 - 4.51) MA for zopiclone: OR: 4.20 (CI: 1.55 - 11.40)
Mamun, Lim (2009)	Singapore	298 fallers/ 298 control; Asian elderly	75.8	12 months	Case control	Normal mental state on admission, length of stay, Morse scale, history of falls, walking independently and number of medications	Anxiolytics	benzodiazepines and anxiolytics	UA: S	UA: NI
									MA: S	MA: NI
							Cough supressant	Cough preparations NE	UA: S	UA: NI
									MA: S	MA: NI
							Antithrombotic agents	Anti-platelet agents NE	UA: S	UA: NI
									MA: S	MA: NI
							Vasodilators used for treating heart-related diseases	Nitrates	UA: S	UA: NI
									MA: NI	MA: NI
							Calcium channel blockers[2]	Calcium channel blockers	UA: S	UA: NI
									MA: NI	MA: NI
							Opioids	Weak opioids	UA: S	UA: NI
									MA: NI	MA: NI
							Diuretics[2]	Diuretics NE	UA: S	UA: NI
									MA: NI	MA: NI

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Mamun, Lim (2009)	Singapore	298 fallers/ 298 control; Asian elderly	75.8	12 months	Case control	Normal mental state on admission, length of stay, Morse scale, history of falls, walking independently and number of medications	Lipid- modifying agents. plain	Lipid -regulating drugs NE	UA: S MA: NI	UA: NI MA: NI
							Beta-blocking Agents	Beta-blockers	UA: S MA: NI	UA: NI MA: NI
							Alpha and beta adrenoreceptor agonist	Alpha-agonist	UA: S MA: NI	UA: NI MA: NI
							Corticosteroids for systemic use	Steroides	UA: S MA: NI	UA: NI MA: NI
Tanaka et al. (2008)	Japan	65 fallers/ 4084 control; NA	68.1±13.1	7 months	Case control	Age >70 years . Other non-specified conditions.	Anxiolytics	Anxiolytics NE	UA: S MA: S	UA: OR: 3.35 (CI: 1.83-5.82) MA: OR: 2.36 (CI: 1.24-4.28)
							Anti-Parkinson drugs	Anti-Parkinson drugs NE	UA: NI MA: S	UA: OR: 5.7 (CI: 1.71 -14.80) MA: OR: 5.04 (CI: 1.44-13.43)
							Hypnotics and sedatives	Hypnotics and sedatives NE	UA: S MA: NS	UA: OR:2.12 (CI: 1.25-3.52) MA: NI
							Opioids	Opioids NE	UA: NI MA: NS	UA: OR: 3.08. (CI: 1.06 -7.11) MA: NI
							Diuretics[2]	Diuretics NE	UA: NI MA: NI	UA: OR: 2.39 (CI: 1.42- 3.95) MA: NI
Angalakuditi, Gomes, Coley (2007)	US	635 fallers/ 1270 control; With chronic kidney disease	68 ± 15	5.5 years	Case control	Dementia, diabetes and pneumonia.	Antiepileptics	Anticonvulsant NE	UA: S MA: S	UA: NI MA: OR: 1.52 (CI: 1.13-2.03)
							Antidepressants	Antidepressants NE	UA: NI MA: S	UA: NI MA: OR: 1.65 (CI: 1.32-2.08)
							Anxiolytics	Benzodiazepines NE	UA:S MA: S	UA: NI MA: OR: 0.69 (CI: 0.55- 0.86)
Vassalo et al. (2006)	UK	825 falls; Confused patients	81.9	17 months	Case control	Confused patients. Others not evaluated.	Anxiolytics	Benzodiazepines NE	UA for falls on tranquilizers (benzodiazepines and antipsychotics): S UA for recurrent falls in confused: S MA: NI	UA for falls on tranquilizers (benzodiazepines and antipsychotics): OR: 0.63 (CI: 047-0.82) UA for recurrent falls in confused: NI MA: NI
							Antipsychotics	Antipsychotics NE	UA for falls on tranquilizers (benzodiazepines and antipsychotics): S UA for recurrent falls in confused: S MA: NI	UA for falls on tranquilizers (benzodiazepines and antipsychotics): OR: 0.63 (CI: 047-0.82) UA for recurrent falls in confused: NI MA: NI
Walker (2005)	US	62 fallers/ 62 control; NA	74.54 ± 6.03	12 months	Case control	Mean ± S.D. no. medications received within 24 hr preceding fall and Dementia.	Other Analgesics e Antipyretics	Aspirin 85 e 325 (77%). aspirin+celecoxibe. aspirin+ibuprofen, celecoxib, ibuprofen, ketorolac, indometacin	UA: S MA: NI	UA: OR: 10.02 (2.6–38.58) MA: NI
							Opioids	Opioids NE	UA: S MA: NI	UA:OR: 0.33 (IC: 0.11–0.96) MA: NI

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TABLE III - Eligible studies data (cont.)

Author, publication year	Country	n fallers/ n control group (or comparative group); Special sample condition	Median age (fallers)	Follow-up period	Type of study	Other factors related to fall (statistically significant)	ATC - Pharmacological subgroup	Medication	P value Univariate analysis (UA) and Multivariate analysis (MA)	Odds ratio Univariate analysis (UA) and Multivariate analysis (MA)
Walker (2005)	US	62 fallers/ 62 control; NA	74.54 ± 6.03	12 months	Case control	Mean ± S.D. no. medications received within 24 hr preceding fall and Dementia.	Urological drugs	Oxybutynin and tolterodine	UA for other medication that can produce sedation or postural hypotension: S MA: NI	UA for other medication that can produce sedation or postural hypotension: OR: 13.85 (IC:3.6–52.83) MA: NI
							Blood glucose lowering drugs, excluding insulin	glimepiride, glipizide, insulin, rosiglitazone	UA for other medication that can produce sedation or postural hypotension: S MA: NI	UA for other medication that can produce sedation or postural hypotension: OR: 13.85 (IC:3.6–52.83) MA: NI
							Antiepileptics	carbamazepine, gabapentin, lamotrigine, oxcarbazine, phenytoin, topiramate, valproate.	UA for other medication that can produce sedation or postural hypotension: S MA: NI	UA for other medication that can produce sedation or postural hypotension: OR: 13.85 (IC:3.6–52.83) MA: NI
							Antihistamines for systemic use	cyclizine, fexofenadine	UA for other medication that can produce sedation or postural hypotension: S MA: NI	UA for other medication that can produce sedation or postural hypotension: OR: 13.85 (IC:3.6–52.83) MA: NI
							Drugs for alimentary tract and metabolism[2]	dolasetron, metoclopramide, omeprazole, ondansetron, ranitidine	UA for other medication that can produce sedation or postural hypotension: S MA: NI	UA for other medication that can produce sedation or postural hypotension: OR: 13.85 (IC:3.6–52.83) MA: NI
							Drugs for Cardiovascular system[2]	Amlodipine, diltiazem, nitrates	UA for other medication that can produce sedation or postural hypotension: S MA: NI	UA for other medication that can produce sedation or postural hypotension: OR: 13.85 (IC:3.6–52.83) MA: NI
Krauss et al. (2005)	US	98 fallers/ 318 controls; NA	ND (50-69 years - 37.8%) and >=70 (38.8%)	6 weeks	Case control	Age>50 years, gait/balance deficit or lower extremity, incontinence, diabetes, fallen in the past 6 months, depression, impaired memory, confused, and care-related factors (assistance, patient-to-nurse ration)	Hypnotics and sedatives	Hypnotics and sedatives NE	UA: NI MA: NI	UA: OR: 2.1 (CI: 1.2 – 3.7) MA: OR: 4.3 (CI: 1.6 - 11.5)
							Antiarrhythmics class I and III	Antiarrhythmics class I and III NE	UA: NI MA: NI	UA: OR: 2.1 (CI :1.2 - 3.7) MA: NI
							Diabetic drugs[2]	Diabetic drugs NE	UA: NI MA: NI	UA: OR: 2.1 (CI: 1.2 - 3.5) MA: OR: 3.2 (CI: 1.3 - 7.9)
							Other Analgesics e Antipyretics	Non-narcotic analgesics - NE	UA: NI MA: NI	UA: OR:2.0 (CI:0.9 - 3.3) MA: NI
Vassalo et al. (2004)	UK	136 fallers/ 463 control ; With unsafe-safe gait	81.9	12 months	Prospective Cohort	Unsafe gait, previous fall and confusion .	Anxiolytics	Tranquilizers NE	UA: S MA: NI	UA: OR: 1.73 (CI:1.08–2.75) MA: NI
Frels (2002)	UK	181 fallers/ 181 controls; Elderly	73.3	4 months	Case control	Stroke, previous fall, disoriented in time/place or person and needs maximum assistance.	Anxiolytics	Benzodiazepines NE	UA: S MA: S	UA: NI MA: OR: 2.3 (CI:1.4-3.7)
							Diuretics[2]	Diuretics NE	UA: S MA: NS	UA: NI MA: NI

TABLE III - Eligible studies data (cont.)

Author, publication year	Country	n fallers/ n control group (or comparative group); Special sample condition	Median age (fallers)	Follow-up period	Type of study	Other factors related to fall (statistically significant)	ATC - Pharmacological subgroup	Medication	P value Univariate analysis (UA) and Multivariate analysis (MA)	Odds ratio Univariate analysis (UA) and Multivariate analysis (MA)
Mendelson (1996)	US	253 falls/ 84 control; NA	57.4±1.3	12 months	Case control	Not mentioned or evaluated.	Antidepressants	Amitriptyline.clomipramine, doxepin, fluoxetine, imipramine, nortriptyline and sertraline	UA for antidepressants: S UA for Nortriptyline: S UA for sertraline: S MA: NI	UA: NI UA for Nortriptyline: NI UA for sertraline: NI MA: NI
							Hypnotics and sedatives	Chloral hydrate, temazepam andtriazolam	UA for hypnotics: S UA for temazepam:S MA: NI	UA for hypnotics: NI UA for temazepam:NI MA: NI
							Anxiolytics	Alprozolam,chlordiazepoxide, Chlorazepate, diazepam e lorazepam	UA for benzodiazepines: S UA for alprozolam. diazepam and lorazepam: S MA: NI	UA for benzodiazepines: NI UA for alprozolam. diazepam and lorazepam: NI MA: NI
							Antipsychotics	Clorpromazine, droperidol. Haloperidol,prochlorperazinam, Tioridazinam,tiotixene and trifluoerazine	UA for general: S UA for haloperidol and prochlorperazine: S	UA for general: NI UA for haloperidol and prochlorperazine: NI
Aisen, Deluca, Lawlor (1992)	UK	33 falls (17 fallers)/ 30 control; Geropsychiatry inpatients	75.3±7	12 months	Case control	Length of stay, dementia, history of falls and assistance required	Anxiolytics	Benzodiazepines NE	UA: S MA: NI	UA: NI MA: NI
							Antipsychotics	Neuroleptics NE	UA: S MA: NI	UA: NI MA: NI

Legend: ATC: Anatomical Therapeutic Chemical Code; CI: confidence interval 95%; CNS meds: Central nervous system medication; MA: multivariate analysis; "n": number of participants; NA: not applicable; NE: nonspecified; NI: not informed; OR: odds ratio; UA: univariate analysis. "¹":Psychotropics could not be classified according to pharmacological subgroup; "²":These medications were classified according to ATC Therapeutic Subgroup (2nd level).
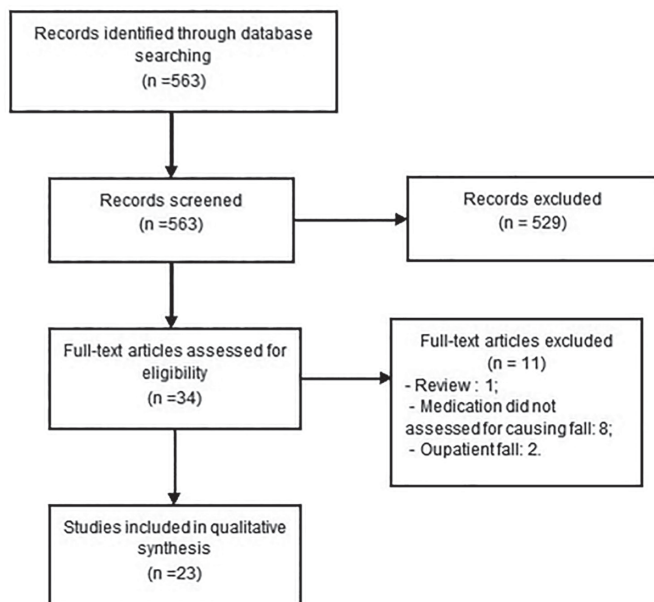
FIGURE 1 - Flowchart of studies selection according to PRISMA, 2009.

of the study designs covered case controls, 18% dealt with retrospective cohorts (4/23), 13% were focused on prospective cohorts (3/23), one study was cross-sectional and the remaining one was case-crossover. The retrospective studies represented 87% (20/23) of the total number of eligible full studies. No randomized controlled trial (RCT) was found. Studies performed in a single institution represented 91% (21/23) of the total number of studies under investigation.

The follow-up period for patient observation in almost half of the studies lasted 12 months; in 30% (7/23) of the studies the follow-up period was less than 12 months; and four studies reported follow-up periods longer than one year (1.5 to 5.5 years).

The total number of inpatients in the studies amounted to 27,449; this consisted of 4,474 fallers and 22,975 classified as control or comparative group. The median age of the fallers was 69 years. Another fact that deserves mentioning is that in four studies (17%) the population was restricted to only elderly patients. Six other studies included special population: cirrhotic patient, patients with unsafe gait, patients who are exposed to anticholinergic and sedatives drugs, psychiatric patients with hyponatremia, geropsychiatric patients and those with chronic kidney disease.

Fifty seven percent of the studies did not specify the medication, class or substances included in the

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group (only mentioned, for instance, sedative hypnotics, without indicating any specific drug) (Costa-Dias *et al.*, 2014; Pierce Jr. *et al.*, 2013; Obayashi *et al.*, 2013; Lamis *et al.*, 2012; Chang *et al.*, 2011; Bun, Serby, Friedmann, 2011; Mamun, Lim, 2009; Tanaka *et al.*, 2008; Angalakuditi, Gomes, Coley, 2007; Vassalo *et al.*, 2006; Krauss *et al.*, 2005; Vassalo *et al.*, 2004; Aisen, Deluca, Lawlor, 1992). Some articles focused their studies on all central nervous system medications (Lamis *et al.*, 2012) (without establishing any distinction between the pharmacological groups). Some studies grouped more than one pharmacological group (Costa-Dias *et al.*, 2014; Vassalo *et al.*, 2006). Walker (2005) evaluated a broad class of medications and identified it as "other medications that can cause sedation and postural hypotension". They also included different pharmacological groups in their analysis (urological drugs; blood glucose lowering drugs excluding insulin; antiepileptics; antihistamines for systemic use; drugs for alimentary tract and metabolism; drugs for cardiovascular system). Dauphinot *et al.* (2014) evaluated defined daily dose (DDD) of anticholinergic and sedative agents. They found that DDD increase was related to fall, but made no assessment of the relation between the medication and the falling incidents.

Only six studies presented all confounders correctly (Figure 2). Other risk factors for inpatient fall were evaluated. These included age, oncologic patient, neurodegenerative disease, male gender, chronic/palliative inpatient wards, previous falls, cognitive dysfunction, wheelchair use, patients in need of help to move, rehabilitation, patients in need of help with daily life activities, incontinence, diabetes, depression and impaired memory.

A decreasing list was made based on the studies and pharmacological subgroups (Table III). Some drugs were not classified in the pharmacological subgroup due to the fact that the study failed to specify the group to which these drugs belong. Hence, these drugs were exceptionally classified under the therapeutic subgroup (2nd level by ATC classification) category: calcium channel blockers, diuretics, anti-parkinson drugs, antihypertensives, antidiabetic drugs, drugs for alimentary tract and metabolism, and drugs used for treating the cardiovascular system. Remarkably, there was only one study that used a classification which had no designation under the ATC classification system. The classification was that of unspecified psychotropic drugs.

In seventy-four percent of the studies (17/23), the inpatient falls were attributed to anxiolytics, hypnotics and sedatives accounted for 48% (11/23), antipsychotics represented 35% (8/23), opioids and antiepileptics

Bias analysis / Author, year	Clear population definition and representativity	Selection of control and cases (adequate criteria and sample)	Full identification of potential confounders	Accurate measure of all relevant exposure, potential confounders and outcomes	Adequate statistical analysis
O'Neil *et al.*, 2015	+	-	+	+	+
Tapper *et al.*, 2015	+	-	-	+	?
Hayakawa *et al.*, 2014	+	-	+	+	+
Dauphinot *et al.*, 2014	+	-	+	+	?
Costa-Dias *et al.*, 2014	?	?	-	+	-
Kolla *et al.*, 2013	+	+	+	+	?
Pierce Jr *et al.*, 2013	+	-	-	-	+
Obayashi *et al.*, 2013	+	-	-	-	+
Lamis *et al.*, 2012	-	+	-	+	+
Chang *et al.* 2011	+	+	-	+	+
Cashin *et al*, 2011	+	-	-	-	-
Bun *et al.*, 2011	-	+	-	?	-
Shuto *et al.*, 2010	-	?	-	+	?
Mamun *et al.*, 2009	+	+	+	-	?
Tanaka *et al.*, 2008	+	-	-	+	+
Angalakuditi *et al.*, 2007	+	+	-	-	+
Vassalo *et al.*, 2006	+	-	-	-	?
Walker *et al.*, 2005	+	-	-	+	-
Krauss *et al.*, 2004	+	+	+	+	?
Vassalo *et al.*, 2004	+	+	+	+	+
Frels *et al.*, 2002	+	-	-	+	?
Mendelson *et al.*, 1996	+	+	-	-	-
Aisen *et al.*, 1992	-	+	+	?	-

Legend:
- (+) Low risk of bias
- (-) High risk of bias
- (?) Uncertain risk of bias

FIGURE 2 - Studies bias analysis (Tool adapted from STROBE (2007) and Young and Solomon (2009) proposition for critically appraise an article).

accounted for 30% (n=7) while antidepressants represented 22% (5/23). Diuretics (4/23), anti-parkinson drugs (3/23), other analgesics and antipyretics (3/23) were mentioned in less than 20% of the studies. The other subgroups accounted for less than 10% of inpatient falls in the studies.

The studies were also subjected to quality assessment using the bias analysis tool (Figure 2). The results obtained showed that only 26% (n=8) of the studies presented full identification of potential confounders, 52% had high risk of bias for selection of control and intervention cases and only 39% exhibited low risk of bias for statistical analysis. The pharmacological subgroups that were cited more

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frequently (in more than 20% of the eligible studies) are described below.

Anxiolytics

Seventeen studies attributed inpatient falls to anxiolytics use (Tapper, Risech-Neyman, Segupta, 2015; O'Neil *et al.*, 2015; Mamun, Lim, 2009; Lamis *et al.*, 2012; Frels, 2002; Dauphinot *et al.*, 2014; Costa-Dias *et al.*, 2014; Tanaka *et al.*, 2008; Chang *et al.*, 2011; Angalakuditi, Gomes, Coley, 2007; Shuto *et al.,* 2010; Cashin, Yang, 2011; Vassalo *et al.*, 2004; Mendelson,

TABLE IV - Distribution of pharmacological subgroups according to ATC classification for medications related to inpatient falls

Pharmacological Subgroup related to inpatient fall	Studies "n"	% based on total number of studies n=23
Anxiolytics	17	74
Hypnotics and sedatives	11	48
Antipsychotics	8	35
Opioids	7	30
Antiepileptics	7	30
Antidepressants	5	22
Diuretics[2]	4	17
Anti-Parkinson drugs[2]	3	13
Other Analgesics e Antipyretics	3	13
DiabetIC drugs[2]	2	8,7
Drugs for cardiovascular system[2]	2	8,7
Antipropulsives	2	8,7
Antihistamines for systemic use	2	8,7
Antiarrhythmic drugs - class I and III	2	8,7
Agents acting on the renin-angiotensin system	1	4,3
Urological drugs	1	4,3
Blood glucose lowering drugs, excluding insulin	1	4,3
Beta-blocking agentes	1	4,3
Drugs for alimentary tract and metabolism[2]	1	4,3
Alpha and beta adrenoreceptor agonist	1	4,3
Centrally-acting antiadrenergic agents	1	4,3
Anti-dementia drugs	1	4,3
Antihypertensives[2]	1	4,3
Antithrombotic agents	1	4,3
Blood glucose lowering drugs, excluding insulin	1	4,3
Calcium channel blockers [2]	1	4,3
Corticosteroids for systemic use	1	4,3
Cough supressant	1	4,3
Insulin and analogues	1	4,3
Lipid modifying agents, plain	1	4,3
Psychotropics[1]	1	4,3
Vasodilators used for treating heart-related diseases	1	4,3
Total	93	-

Captions: "[1]":Psychotropics could not be classified according to the pharmacological subgroup; "[2]":These medications were classified according to ATC Therapeutic Subgroup (2nd level).

1996; Vassalo *et al*., 2006; Aisen, Deluca, Lawlor, 1992). Four studies consisted of only elderly patients while five others included special population. The medication in this subgroup included all benzodiazepines. Ten studies did not specify the chemical substance (eg. Benzodiazepines NE or Anxiolytics NE). The reports mentioned the following medications: alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, clotiazepam, cloxazolam, diazepam, ethyl loflazepate, etizolam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam and triazolam.

Hypnotics and sedatives

Data on the use of hypnotics and sedatives were collected from 11 studies. Among these studies, two study populations were, however, restricted to elderly patients. Most of the studies did not specify the medication employed in their investigation (Hayakawa *et al*., 2014; Kolla *et al*., 2013; Costa-Dias *et al*., 2014; Tanaka *et al*., 2008; Chang *et al*., 2011; Krauss *et al*., 2005) while four others mentioned the following medications: zolpidem, zopiclone (Kolla *et al*., 2013; Dauphinot *et al*., 2014; Chang *et al*., 2011), brotizolam, flunitrazepam, lormetazepam, midazolam, nitrazepam, quazepam, rilmazafone, triazolam (Shuto *et al*., 2010; Obayashi *et al*., 2013; Mendelson, 1996).

Antipsychotics

Eight studies attributed inpatient falls to antipsychotics. Most of the studies were devoted to special populations (Tapper *et al.,* 2015; Costa-Dias *et al*., 2014; Vassalo *et al*., 2006; Aisen, Deluca, Lawlor, 1992; Bun, Serby, Friedmann, 2011) and only three placed no restrictions on the study population (Lamis *et al*., 2012; Dauphinot *et al*., 2014; Mendelson, 1996). The chemical substances included: olanzapine, risperidone, amisulpride, tiaprida, ciamemazine, quetiapine and haloperidol. Four studies did not specify the medication involved.

Opioids

Seven studies analyzed the use of opioids and the incidence of accidental falls (Walker, 2005; Pierce *et al*., 2013, Tanaka *et al*., 2008). Four of these studies contained special populations (Mamun, Lim, 2009; Chang *et al*., 2011**;** Dauphinot *et al*., 2014; Costa-Dias *et al*., 2014). Tramadol was the only substance specified in a single study. The other studies mentioned opioids, yet without specifying them.

Antiepileptics

Data on the use of antiepileptics were collected from seven studies (O'Neil *et al*., 2015; Lamis *et al*., 2012; Dauphinot *et al*., 2014; Walker, 2005; Obayashi *et al.,* 2013). Two of these studies focused their investigation on elderly patients and patients with chronic kidney disease (Costa-Dias *et al*., 2014; Angalakuditi, Gomes, Coley, 2007). The chemical substances cited were carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, topiramate, valproate and phenobarbital. Four studies did not specify the drugs employed in their investigation.

Antidepressants

Five studies associated inpatient falls with antidepressants (O'Neil *et al*., 2015; Lamis *et al*., 2012; Mendelson, 1996), two of which focused their investigation on elderly patients and patients with chronic kidney disease (Costa-Dias *et al*., 2014; Angalakuditi, Gomes, Coley, 2007). The chemical substances cited included amitriptyline, fluoxetine, nortriptyline, clomipramine, doxepin, desipramine, phenylpiperazine, imipramine and sertraline.

DISCUSSION

Our critical review shows that the use of central nervous system drugs (including anxiolytics; hypnotics and sedatives; antipsychotics; opioids; antiepileptics and antidepressants) is likely to induce inpatient fall incidents.

To the best of our knowledge, there are no reports in the literature concerning the analysis of particular medication related to fall incidents involving hospitalized patients. The studies that have been published recently were aimed at different patient settings such as community and long-term facilities. Interestingly, the findings of these studies were quite similar to ours. Wolcott (2009) conducted a systematic search and a meta-analysis aiming at updating the study carried out by Leipzig, Cumming and Tinetti (1999). They evaluated all FRIDS (Fall Risk Increasing Medication) in different settings (community, long-term facilities and hospital care). The investigation included 22 observational studies and the outcome was based on the Bayesian random effects-model. The result of their investigation pointed out an association between the elderly who use sedatives/ hypnotics, antidepressants and benzodiazepines and accidental falls. Park *et al.* (2015) reported the results of a systematic investigation they carried out which associated the use of sedatives/hypnotics

and antidepressants with an increased risk of fall among the elderly. The critical review of Hartikainen, Lonnroos and Louhivuori (2007) associated central nervous system medications with fall incidents among older people. The researcher also suggested some topics that could help improve the quality of observational studies employed towards examining medication use as a risk factor for falling. All the above-mentioned researchers have pointed out the underlying limitations of their studies with regard to quality, consistency, and comparability. They acknowledged the need for well-designed studies such as those related to prospective cohorts. It is worth noting that our study encountered similar limitations.

A famous tool recommended by the Agency of Health Research and Quality (AHRQ, 2016) which is based on the study conducted by Beasley and Patatanian (2009) classified drugs according to the risk of falling for patients in hospital settings. This tool evaluates medication-related fall risk on admission based on a score. Analgesics, antipsychotics, anticonvulsants, benzodiazepines were assigned 3 points which denoted high risk of fall; antihypertensives, cardiac drugs, antiarrhythmics and antidepressants scored 2 points (denoting medium risk); and diuretics gained one point (indicating low risk). In our study, the association between inpatient fall and other pharmacological subgroups (unlike the central nervous system drugs) was found to be weak (only less than 20% of the studies showed this relation). Some studies published in the literature included antihypertensives, cardiac drugs, antiarrhythmics and diuretics as having weak risk of causing inpatient falls (Leipizig, Cumming, Tinetti, 1999).

Evidence from healthcare settings is supported by the prominent tool known as the evidence pyramid (Murad *et al.*, 2016). The case control design, represented by 61% of the total eligible studies, is known to have low quality of evidence (it is found at the base of the evidence pyramid). The starting point of this study is the outcome (which in our case is patient falls in hospital settings). Afterwards, an assessment is made regarding the exposure to the risk so as to develop a hypothesis with respect to risk estimation. It is true that this risk estimation does not often reflect the real causality (Nobre, Bernardo, 2006). Moreover, in many studies the control group selection appears to be inadequate and fails to represent the population in an appropriate fashion (Figure 2). No randomized controlled trial (RCT) experiments are found in our investigation. This is attributed to the fact that this type of study design has not been used routinely for the evaluation of adverse effects. The article that reports the new evidence pyramid highlights the critical assessment of the studies taking into account methodological limitations, imprecision,

inconsistency and indirectness. These topics could be analyzed through the tool for assessing risk of bias (Figure 2). Only 8 studies were found to have low risk of bias in three or more items that were considered critical to the quality of the study.

Retrospective studies accounted for 87% (n=20) of the total eligible studies. Several limitations were noted regarding this type of study. These included the inappropriate nature of chart review for study questions or lack of systematic review, the unavailability of important data, the difficulty of establishing cause and effect, the reliability of written information and the problem of missing data (Hess, 2004).

Some studies presented several problems with respect to statistical analysis. In one of the studies, the statistical analysis was not homogeneous for the groups under investigation (some had odds ratio (OR), whereas others did not). Some studies did not present confidence interval (CI) despite having defined an OR value. In many studies, CI was close to 1 (1.01 to 1.09) and the results that were equal or above 1 show no relationship between cause and effect (Bland, 2000). In one study employing cross-sectional design, the statistical analysis was not performed at all. The analysis was restricted to medications that were related to fall incidents which the author found in the literature. As no control group was assessed, causality could also not be evaluated.

One of the study limitations stemmed from the groupings of medication. Some studies grouped different pharmacological subgroups under the same category. For purposes of illustration, the studies employed categories such as "medication that can produce sedation or postural hypotension", "central nervous system medication" or "psychotropic medication". Clearly, this was a relevant weakness inasmuch as the full analysis was performed relative to a broad group, and could not, as a result, be strictly attributed to a specific pharmacological group or medication.

Limitations were likewise observed in most of the studies regarding the evaluation of confounders. The bias analysis tool (Figure 2) showed that only 8 studies had a relatively satisfactory identification. It is a known fact that fall incidents are attributed to multifactorial reasons (Spoelstra, Given, Given, 2012), as such, a complete list of potential confounders is essentially important if one is to appropriately evaluate bias that may exclude the relation between a given medication and inpatient fall.

The external validity of the studies faces constraints in that 91% (n=21) of them were performed in a single institution. A further shortcoming lies in the fact that a significant number of studies focused their investigation

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on specific populations including cirrhotic patients, psychiatric patients, patients suffering from chronic kidney disease, confused patients, elderly patients, patients with altered gait and those suffering from geropsychiatry. The inclusion criteria for one of the studies were restricted to patients exposed to anticholinergic and sedative medications. One will notice that these conditions by themselves could be related to fall incidents (Soriano *et al.*, 2012; Ruxton, Woodman, Mangoni, 2015; Severo *et al.*, 2014; Spoelstra, Given, Given, 2012).

The median age of the fallers was 69 years; this can largely be explained by the fact that elderly patients are more prone to accidental falls and age itself is cited as a single risk factor (WHO, 2007). In Brazil, 33.5% of patients in the Brazilian Public Health Service (known as Sistema Único de Saúde - SUS) are aged 60 and above (Peixoto *et al.*, 2004). The US reported similar percentages of elderly inpatients in 2012, where 34.9% of all hospitalizations represented people aged 65 and above. Indeed, this shows that the elderly population accounts for a significant amount of hospital admissions.

One of our study constraints was related to the use of the quality assessment tool adapted from STROBE and Young and Solomns (2009) instead of the well-known observational assessment tool (like Newcastle-Ottawa Scale). We chose this adapted tool owing to the fact that it provides the possibility of locating all eligible studies in a single table and irrespective of study design. In addition, it gives a clearer exposition of information with self-explanatory icons (the caption was inspired by the Cochrane collaboration tool for assessing risk of bias in randomized trials).

Other study constraints our study encountered were related to ATC classification which could not be fitted to all studies and drugs, considering the indication of some specific medications or group classification. Grey literature was not included and our search was restricted to English, Spanish and Portuguese languages. The review steps were performed by only one of the authors.

The assessment of fall risk in hospital settings is extremely important as it can help prevent inpatient negative outcomes and contribute towards increasing the safety policy of the institution (WHO, 2008). Notwithstanding the weakness of some studies included in this review, our findings were similar to those of the most recent reports published in the literature which also associated central nervous system drugs (namely anxiolytics; hypnotics and sedatives; antipsychotics; opioids; antiepileptics and antidepressants) with inpatient falls. These findings could be used as a tool to help prevent inpatient falls, especially for those patients who exhibit more risk factors for fall incidents. The multi-professional team acting in inpatient healthcare settings can contribute towards improving patient safety and help diminish fall incidents. One of the mechanisms to prevent patient falls in hospitals is assigning a professional pharmacist to the team and allowing him/her to review the medical records and prescriptions of the patients (Zermansky *et al.*, 2006; Haumschild *et al.*, 2003). Similarly, the hospital nursing team can tailor their care planning activities in such a way as to prevent negative outcomes (including inpatient falls) during the stay of the patients in healthcare settings (Severo *et al.*, 2014; Hignett, Masud, 2006).

CONCLUSION

Our study shows that central nervous system medications, particularly in the following order: anxiolytics, hypnotics and sedatives, antipsychotics, opioids, antiepileptics and antidepressants, seem to be associated with an increased risk of inpatient falling. The result of this study is in line with those of recently published reports in the literature on risk of fall incidents in community and other settings. While the results of this critical review are worthy of consideration, one cannot virtually neglect the several methodological limitations that characterize the eligible observational studies that were employed. Among the constraints noted in these eligible studies included failure to provide proper definition, unspecified medication classifications and unsatisfactory description of potential confounders. Better delineated studies are needed if one is to properly assess the relationship between medications and inpatient falls.

ACKNOWLEDGEMENT

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