Comparison of medication-related fall risk in hospitalized adults and older people: systematic review and probable meta-analysis protocol*

Comparación de medicamentos de riesgo para las caídas entre adultos y ancianos hospitalizados: un protocolo de revisión sistemática y un probable metanálisis

Comparação dos medicamentos de risco para queda entre adultos e idosos hospitalizados: protocolo de revisão sistemática e provável metanálise

Amanda Pestana da Silva
Carla Helena Augustin Schwanke
Thiana Sebben Pasa
José Francisco Secorun Inácio
Ana Laura Olsefer Rotta
Janete de Souza Urbanetto

ABSTRACT: The proposed study aims to verify whether drugs, drug classes, and polypharmacy related to the occurrence of falls are the same for hospitalized adults and older people. The present protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42020208624). The search for articles will be carried out in PubMed, Embase, and in Latin American and Caribbean Literature on Health Sciences (Lilacs) databases. If quantitative analysis is not possible, a synthesis of the present information will be carried out.

Keywords: Aged; Drug Therapy; Accidental Falls.

RESUMEN: *El objetivo del estudio propuesto será verificar si los fármacos, clases de fármacos y polifarmacia relacionados con la ocurrencia de caídas son los mismos para adultos y ancianos hospitalizados. Este protocolo se registró en el International prospective register of systematic reviews (PROSPERO) (número de registro: CRD42020208624). La búsqueda de artículos se realizará en las bases de datos PubMed, Embase y Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs). Si el análisis cuantitativo no es posible, se realizará una síntesis de la información presente.*
Palabras clave: *Personas Mayores; Quimioterapia; Accidentes por Caídas.*

RESUMO: *O objetivo do estudo proposto será verificar se os medicamentos, classes medicamentosas e a polifarmácia relacionados à ocorrência de queda são os mesmos para adultos e idosos hospitalizados. O presente protocolo foi registrado no International prospective register of systematic reviews (PROSPERO) (número de registro: CRD42020208624). A busca de artigos será realizada nas bases de dados PubMed, Embase, e Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs). Se a análise quantitativa não for possível, será realizada uma síntese das informações presentes.*
Palavras-chave: *Idoso; Tratamento Farmacológico; Acidentes por Quedas.*

Introduction

Fall is widely known for the potential damage deriving from its occurrence, and it is one of the most notified incidents during hospitalization (National Academies of Sciences, 2018). The older population were identified as the individuals who mostly experience falls inside the hospital environment (Silva *et al*., 2019). In Brazil, falls were the fourth most frequently notified safety incident between August 2019 and July 2020 and the third incident resulting in death (Agência Nacional de Vigilância Sanitária, 2019).

Falls can be one of the consequences of the use of risky drugs and/or of drug interactions, and hospitalization, which considerably increases the risk among the older population (Associação Nacional de Hospitais Privados, 2018). Some drug classes may increase significantly the occurrence of fall, as it happens with opioids, hypnotics, anxiolytics, antidepressants, antipsychotics and sedatives (Associação Nacional de Hospitais Privados, 2018).

Orthostatic hypotension, cognitive dysfunction, balance disorders, dizziness, drowsiness, motor dysfunction, and visual changes are effects caused by certain drugs that may lead to fall. Polyuria and nocturia, caused by the use of diuretics, may indirectly contribute for falls (Dyks, & Sadowski, 2015; Instituto para práticas seguras no uso de medicamentos, 2017).

Three systematic reviews and meta-analysis (de Vries *et al*., 2018; Seppala, Wermelink, de Vries, Ploegmakers, van de Glind, Daams, van der Velde, & EUGMS task and Finish group on fall-risk-increasing drugs, 2018; Seppala, Wermelink, de Vries, Ploegmakers, van de Glind, Daams, van der Velde, & EUGMS Task and Finish Group on Fall-Risk-Increasing Drugs, 2018), which purposes were to provide a comprehensive view of the association between drugs and the risk of fall for elders, were identified. However, the mentioned studies do not focus on the hospital environment and most of the meta-analysis resulted in substantial heterogeneity.

The systematic evaluation of the relationship between drugs, drug classes and polypharmacy and the occurrence of fall during hospitalization of adults and older people is still a gap in the literature that needs to be filled. Therefore, the proposed systematic review and probable meta-analysis aims at answering the research question "The drugs, drug classes, and polypharmacy related to the occurrence of fall are the same in older patients compared to hospitalized adults?". The purpose is to verify whether drugs, drug classes, and polypharmacy related to the occurrence of falls are the same for hospitalized adults and older people.

Methods

The present protocol was registered in the International prospective register of systematic reviews (PROSPERO) (ID: CRD42020208624). This study is reported according to the recommendations of Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) (Shamseer *et al.,* 2015).

This systematic review and probable meta-analysis will be conducted according to the recommendations of Preferred reporting items for systematic review and meta-analysis (PRISMA) (Liberati *et al.,* 2009).

Eligibility criteria

Observational studies (prospective and retrospective of cohort, cross-sectional, case-control and nested case-control). Clinical trials, reviews (systematic reviews and meta-analysis, integrative reviews, narrative reviews, literature reviews), case series, case reports, errata of publications not related to included articles and letters to the editor will be excluded.

Studies with adult subjects (age ≥ 18 years-old) and olders (age ≥ 60 years-old) will be included. The index prognostic factors of interest are the use of drugs, drug classes and polypharmacy and the prognostic factors of age, gender and fall history will be considered the comparator prognostic factors. The analyzed outcome will be occurrence of falls. Drugs prescribed during hospitalizations will be considered, with inclusion of studies carried out in hospital settings.

An option to include materials published from the year 2000 was made. Such period is justified because the report To Err is Human (Kohn *et al.,* 2000), which is considered a milestone for the development of several studies related to patient safety and changes in practices of incident prevention, was published. There will be no restriction regarding language and geographic location and published and non-published studies, as well as conference abstracts, will be included.

Information sources and search strategy

Descriptors registered in the Medical Subject Headings (MeSH), Embase subject headings (Emtree), Descriptors in Health Sciences (DECs) and words related to drugs with potential risk of fall for hospitalized adults, and older adults will be used.

The search will be carried out in PubMed, Embase, and in Latin American and Caribbean Literature on Health Sciences (Lilacs) databases. Grey literature will be searched in the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) theses and dissertations catalog, Open Access Theses and Dissertations and Google Scholar. The reference list of included studies and identified reviews will be reviewed, in order to guarantee that all relevant material was found.

The descriptors "hospitals", "hospitalization", "inpatients", "pharmaceutical preparations", "therapeutic uses", "drug therapy", "polypharmacy" and "accidental falls", indexed in MeSH, and the respective entry terms were searched and adapted for the other databases. Search date was limited between 01/01/2000 and 10/06/2020. The main strategy was submitted to peer review from another researcher with experience in search strategies, according to the guidelines of Peer Review of Electronic Search Strategies (PRESS) (McGowan *et al*., 2016). The search strategy in PubMed database is presented supplementary Table 1. The searches will be updated before the final analysis.

Supplementary Table 1: Search strategy in PubMed database. Porto Alegre/RS, Brazil. 2020

Search	Query	Results	PICOTS
#4	#1 AND #2 AND #3 Filters: from 2000 - 2020	2,803	
#3	"Accidental Falls"[Mesh] OR Fall [Title/Abstract] OR Falls [Title/Abstract] OR Falling [Title/Abstract]	177,593	O
#2	"Pharmaceutical Preparations"[Mesh] OR "Pharmaceutical Preparation" [Title/Abstract] OR "Pharmaceutic Preparations" [Title/Abstract] OR Pharmaceuticals[Title/Abstract] OR Drugs[Title/Abstract] OR Drug[Title/Abstract] OR Medication[Title/Abstract] OR Medications[Title/Abstract] OR "Therapeutic Uses"[Mesh] OR "Therapeutic Uses"[Title/Abstract] OR "Uses, Therapeutic"[Title/Abstract] OR "Therapeutic Effects"[Title/Abstract] OR "Effects, Therapeutic"[Title/Abstract] OR "Drug Therapy"[Mesh] OR "Drug Therapies"[Title/Abstract] OR Pharmacotherapy[Title/Abstract] OR Pharmacotherapies[Title/Abstract] OR Polypharmacy [Title/Abstract] OR Polymedication [Title/Abstract]	4,790,896	I
#1	"Hospitals"[Mesh] OR Hospitals [Title/Abstract] OR Hospital [Title/Abstract] OR "Hospitalization"[Mesh] OR Hospitalization [Title/Abstract] OR Hospitalizations [Title/Abstract] OR "Inpatients"[Mesh] OR Inpatients [Title/Abstract] OR Inpatient [Title/Abstract]	1,482,444	P

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Selection process and data collection

A manual will be developed for the selection and data extraction steps, and based on it, there will be previous training for reviewers, in order to reduce errors and prevent inconsistencies throughout the process.

Search results will be imported to Rayyan online application, where duplicates will be identified and removed (Ouzzani *et al*., 2016). From this point, screening will be carried out, by two pairs of reviewers, in an independent manner. Titles and abstracts that meet the eligibility criteria or those that cause divergences between the pair of reviewers will be obtained in full. The step of full-text review will be carried out by two reviewers. In the event of disagreement between the reviewers, both will try to reach a consensus or the case will be resolved by a third reviewer. In this phase, articles that do not meet the eligibility criteria will have their exclusion reasons registered.

Articles that are included will have data extraction performed by two reviewers, in an independent manner, using an extraction form and following the manual for the selection and data extraction steps. There will be also previous training for this step. In the event of disagreement between the pair, it will be resolved by consensus or upon consulting a third reviewer. If there are questions or missing data regarding the included studies, the respective authors will be contacted, by e-mail, for clarifications or data request. It will be sought to identify articles that are part of the same study and, whenever possible, the articles will be reviewed as a single study.

There will be extraction of data related to the publication, purpose of the study, design, sample (including recruiting methods), setting (country and hospital sectors), data related to falls and evaluated prognostic factors, missing data, main results and evaluation items of methodological quality.

Risk of bias in individual studies

The risk of bias in individual studies will be assessed with the Quality in Prognosis Studies (QUIPS) tool (Hayden *et al.,* 2013).

Data synthesis

There will be a quantitative analysis (meta-analysis) in the event that three or more identified studies have low to moderate heterogeneity between them and when result combination is appropriate (same outcomes). Data will be grouped according to the measure of effect of each study (odds ratio, hazard ratio, and relative risks). The analysis model will be that of fixed effects. The calculation method (for study weighting) will be the Mantel-Haenszel when few events are identified and inverse-variance when a large number of events are identified. Heterogeneity will be analyzed by I² and visual analysis of the forest plot.

There will be a subgroup analysis with adults (18-59 years-old), older adults (if possible 60-79 years-old and ≥80 years old - longevous), in studies that meet methodological quality and of adjusted and unadjusted data. In case of high heterogeneity, variables suspected to be potential sources of heterogeneity will be analyzed by meta-regression.

If quantitative analysis is not possible, a synthesis of the information in the text will be made in tables, in order to summarize and present the characteristics and the findings of the studies. The results will be categorized by drug and drug class, and differentiated for adults and older persons (if possible 60-79 years-old and ≥80 years old - longevous). Such synthesis will identify individual findings of each study and relate the findings in different studies.

Risk of bias across studies

Risk of bias across studies will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for studies of prognostic factors (Huguet *et al*., 2013).

Discussion/Conclusion

Ageing and the emergence of different diseases make people more susceptible to use some drugs (World Health Organization, 2018). Hospitalization may imply in changing the drugs in use and adding some others, increasing the risk of falls (Associação Nacional de Hospitais Privados, 2018).

It is worth mentioning that falls are one of the most prevalent safety incidents during hospitalization (Agência Nacional de Vigilância Sanitária, 2019; National Academies of Sciences, 2018). Although there are studies investigating the relation of drug use and the occurrence of falls, such incident is still extremely prevalent and there are still blanks to be filled on this topic.

A systematic review synthesizing available evidence regarding the use of drugs by adults and older adults and the propensity of such patients to the event of fall during hospitalization, may guide preventive actions of such safety incident. Systematic reviews are, therefore, a source of information intended to minimize biases, providing more reliable results, which may base the design of guidelines, protocols, and actions possibly to mitigate the occurrence of falls (Liberati *et al*., 2009).

It is expected, at the end of this study, to know the drugs that really create risk of fall in hospitalized adult and older patients. Results achieved in the proposed review may help professionals to identify possible drug interactions in the decision-making process related to drug prescription and drug reconciliation. In addition, it may complement the risk assessment tools for falls and help in the planning of preventive actions to reduce the occurrence of such incident and, consequently, of damage. The results of this study will be disseminated through publication of an article, presentation in events and non-academic scientific disclosure, contributing for popularization of knowledge.

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Amanda Pestana da Silva - Graduation in Nursing, Pontifical Catholic University of Rio Grande do Sul. Master's degree in progress at the Graduate Program in Biomedical Gerontology. Postgraduate Nursing in Intensive Care and Adult Emergency, at Hospital Moinhos de Vento. Member of the Interdisciplinary Patient Safety Research Group. Member of the Artificial Intelligence in Health Group.

ORCID iD: https://orcid.org/0000-0002-8551-6334

E-mail: amanda.pestana@acad.pucrs.br

Carla Helena Augustin Schwanke - Graduated in Medicine, Pontifical Catholic University of Rio Grande do Sul, PUCRS. Specialist in Geriatrics from Hospital São Lucas, PUCRS. Master in Internal Medicine, area of concentration in Geriatrics, PUCRS, CAPES scholarship holder) and PhD in Biomedical Gerontology, PUCRS3, CAPES scholarship holder). Professor at PUCRS since 2002. Adjunct professor TI / 40, at the School of Medicine, permanent professor at the Postgraduate Program in Biomedical Gerontology (PPG-GERONBIO), professor and researcher at the Institute of Geriatrics and Gerontology (IGG).

ORCID iD: https://orcid.org/0000-0002-0397-771X

E-mail: schwanke@pucrs.br

Thiana Sebben Pasa - Graduation in Nursing, Federal University of Santa Maria, UFSM/RS. Master's in Nursing, Graduate Program in Nursing at Federal University of Santa Maria UFSM (PPGEnf/UFSM), Brazil; and Doctoral Student at the Graduate Program in Biomedical Gerontology at the Pontifical Catholic University of Rio Grande do Sul (PUCRS-CAPES scholarship holder). Nurse at the Internal Regulation Nucleus/NIR- Bed Management, at the University Hospital of Santa Maria (HUSM/EBSERH). Professor at the Pontifical Catholic University of Rio Grande do Sul, Brazil. Graduate Program in Biomedical Gerontology.

ORCID iD: https://orcid.org/0000-0003-3931-4149

E-mail: thianasp@hotmail.com

José Francisco Secorun Inácio - Degree in Electrical Engineering, Federal University of Rio Grande do Sul. Master in Health Research and Innovation Processes, Instituto de Cardiologia do Rio Grande do Sul. Currently works as an Engineer at Toth Lifecare, developing and executing tests of standards for electromedical equipment. In the academic field he has experience and publications performing Meta-analyses of Systematic Reviews.

ORCID iD: https://orcid.org/0000-0001-9799-7588

E-mail: francisco.secorun@gmail.com

Ana Laura Olsefer Rotta - Graduation in Nursing, Pontifical Catholic University of Rio Grande do Sul, PUCRS, Brazil. Monitor at the PUCRS.

ORCID iD: https://orcid.org/0000-0003-2747-3580

E-mail: ana.rotta@acad.pucrs.br

Janete de Souza Urbanetto - Graduation in Nursing, Master in Nursing, Doctor in Medicine and Health Sciences, Pontifical Catholic University of Rio Grande do Sul, PUCRS, Brazil. Adjunct Professor at the Pontifical Catholic University of Rio Grande do Sul, Brazil.

ORCID iD: https://orcid.org/0000-0002-4697-1641

E-mail: jurbanetto@pucrs.br