UNIVERSIDADE D
COIMBRA

Rita Bárbara Cardoso Gomes

Polypharmacy as an Independent Risk Factor for Serious Adverse Drug Reactions

A Systematic Review

Dissertação no âmbito do Mestrado em Farmacologia Aplicada, orientada pelo Professor Doutor Carlos Miguel Costa Alves e pelo Doutor Diogo Manuel de Jesus Mendes e apresentada à Faculdade de Farmácia da Universidade de Coimbra.

Fevereiro de 2020

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“As you grow older, you will discover that you have two hands, one for helping yourself, the other for helping others”

- **Audrey Hepburn**

Aos meus pais, porque tudo.

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Não poderia iniciar os agradecimentos sem começar por agradecer à cidade de Coimbra e à imperiosa Faculdade de Farmácia da Universidade de Coimbra. Aquela que me conheceu menina e tornou mulher. Que me limou e me tornou mais um dos seus filhos. Agora sim entendo a magia de Coimbra e tudo o que ela implica. "Segredos desta cidade levo comigo para vida".

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Abstract

Background: Polypharmacy is becoming currently common, particularly among the elderly, and has an increasing support from the disease-specific clinical guidelines recommendations. Although the simultaneous use of multiple drugs is beneficial, particularly among patients with multi-morbidities, it has been associated with negative health outcomes. However, a systematic review dedicated to assess whether polypharmacy increased the risk of serious adverse drug reactions has not yet been published in the scientific literature.

Objective: The main goal of this thesis is to evaluate if polypharmacy is an independent risk factor for serious Adverse Drug Reactions. The secondary objectives of this study are to identify and characterize studies evaluating the risk of serious ADRs associated with polypharmacy and to assess their methodological quality.

Methods: A systematic review was conducted in EMBASE and PUBMED, from January 2008 to May 2019, in order to identify both observational and experimental studies assessing the risk of serious Adverse Drug Reactions among patients under polypharmacy versus non-polypharmacy. The methodological quality of the studies was assessed using the Newcastle-Ottawa Scale (observational studies) and the Cochrane Handbook of Systematic Review of Interventions on assessing adverse effects (experimental studies). The EndNote® software tool was used to manage the citations retrieved from the literature search.

Results: Sixteen observational studies were included in this systematic review. Eleven studies evaluated the risk of hospitalization, of which 10 considered polypharmacy as a risk factor for serious ADRs; Three evaluated the risk of death, but the results are conflicting; One study evaluated the risk of the composite outcome of hospitalization or death, One the risk of the composite outcome of hospitalization or death or life-threatening events, one the risk of disability and one study evaluated the risk of any serious Adverse Drug Reactions, and all of these have identifying statistical significant increased risks. Six studies were assessed as having high methodological quality, nine as having moderate methodological quality and one as having poor methodological quality.

Conclusion: According to the results, polypharmacy seems to be a risk factor for serious adverse drug reactions, particularly hospitalization. However, there is a lack of a homogeneous methodology across the studies, mainly due to significant differences among the polypharmacy and non-polypharmacy terms adopted.

Keywords: serious adverse drug reactions, pharmacovigilance, multiple drug exposure, polypharmacy.

Resumo

Introdução: A polimedicação tem-se tornado cada vez mais comum, principalmente entre a população idosa, e a sua utilização tem sido recomendada por *guidelines* específicas para cada doença. Apesar de o uso simultâneo de vários medicamentos trazer benefícios, particularmente em doentes que apresentem múltiplas comorbidades, a sua utilização tem sido associada com resultados negativos que afetam a saúde. No entanto, ainda não existe na literatura científica publicada na atualidade, uma revisão sistemática que se dedique a estudar se a polimedicação aumenta efetivamente o risco de reações adversas graves.

Objetivo: O principal objetivo deste estudo é avaliar se a polimedicação é um fator de risco independente para a ocorrência de Reações Adversas Medicamentosas graves. Os objetivos secundários deste estudo são identificar e caracterizar estudos que avaliem o risco de Reações Adversas Medicamentosas graves associados à polimedicação e realizar avaliação metodológica da qualidade dos mesmos.

Métodos: Nesse contexto, foi realizada uma revisão sistemática na EMBASE e MEDLINE, desde janeiro de 2008 até maio de 2019, de maneira a identificar estudos observacionais e experimentais que estudassem o risco do Reações Adversas Medicamentosas graves em pacientes polimedicados versus pacientes não-polimedicados. A qualidade metodológica dos estudos foi realizada através do uso da NewCastle-Ottawa Scale (estudos observacionais) e a Cochrane Handbook of Systematic Review of Interventions (estudos experimentais). A ferramenta de *software* utilizada para gerir as citações utilizadas na literatura foi o EndNote®.

Resultados: Dezasseis estudos observacionais foram incluídos nesta revisão sistemática. Onze estudos avaliaram o risco de hospitalização, dos quais 10 consideraram a polimedicação como fator de risco para RAMs graves; Três avaliaram o risco de morte e os dados referentes a esse desfecho são heterogéneos; Um estudou o resultado composto de hospitalização/morte, outro o resultado composto de hospitalização/morte/risco de vida, um estudo avaliou o risco de incapacidade e um estudo avaliou o risco de ocorrência de qualquer tipo de reação adversa grave e em todos estes estudos identificaram relação estatisticamente significativa. Seis estudos foram avaliados como tendo uma alta qualidade metodológica, nove foram avaliados como moderada e um apresentou baixa qualidade metodológica.

Conclusão: Os resultados obtidos sugerem que a polimedicação parece ser um fator de risco para o aparecimento de Reações Adversas Medicamentosas graves, particularmente na hospitalização. No entanto, há uma falta de homogeneidade da metodologia entre os estudos, isto deve-se principalmente ao facto de existirem diferenças significativas no que diz respeito às definições de polimedicação/não-polimedicação.

Palavras-chave: reações adversas graves, farmacovigilância. exposição a múltiplos medicamentos, polimedicação.

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List of Abbreviations

ADLs: Activities of the Daily Living Scale

ADR: Adverse Drug Reaction

AE: Adverse Event

AR: Adverse Reaction

AUC: Area Under the Curve

CI: Confidence Interval

CT: Clinical Trials

DRPs: Drug Related Problems

ED: Emergency Department

EMA: European Medicine Agency

ESC: European Society of Cardiology

ESH: European Society of Hypertension

FDA: Food and Drug Administration

HR: Hazard Ratio

IDU: Inappropriate Drug Use

NA: Not Available

OR: Odds Ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RAM: Reação Adversa Medicamentosa

ROC: Receiver Operating Characteristics

RR: Risk Ratio

SR: Systematic Review

UK: United Kingdom

US: United States

USA: United States of America

WHO: World Health Organization

CHAPTER I

INTRODUCTION

Introduction

Adverse drug reactions

An adverse drug reaction is defined as a "response to a medicinal product which is noxious and unintended" (EMA, 2017). Adverse drug reactions may occur when the drug is used either within or outside the authorized marketing conditions (EMA, 2017). Besides the unintended effects developing at doses normally used for the prophylaxis, diagnosis or therapy of diseases, the off-label use, overdose, misuse, abuse and medication errors are also considered to be adverse drug reactions (EMA, 2017). Contrasting to an adverse event, an adverse drug reaction is characterized by the fact that a causal relationship between the drug and the event is suspected (EMA, 2017).

The "detection, assessment, understanding and prevention" of adverse drug reactions is carried out within the Pharmacovigilance activities (WHO, 2004). The aim of the pharmacovigilance is to assess and reduce the risk of adverse drug reactions at the time of granting a market authorization and throughout the product's lifecycle (Pitts *et al.,* 2016).

Adverse drug reactions are a major public health concern. They are a leading cause of death (Lazarou, 1998; Wester *et al.,* 2008). It is estimated that around 197.000 deaths occurring in the European Union result from adverse drug reactions (Giardina *et al.,* 2018). A systematic review of the literature found that the prevalence of mortality among patients due to adverse drug reactions leading to hospital admission is 0.2% (Patel & Patel, 2019). A recently published Spanish study estimated that the rate of drug related death among all hospital admissions was 0.34%, and the rate of drug-related death among the inpatients was 7% (Montané *et al.,* 2018). A similar study, based on the reviewing of the clinical records of 1388 patients who died during a 22-month period in a tertiary hospital, reported that 256 (18.4 %) cases were suspected of being related to drugs (Pardo Cabello *et al.,* 2016).

Adverse drug reactions are also one of the main reasons for hospital admission (Davies *et al.,* 2009). A systematic review of observational studies was performed aiming to estimating the epidemiology of adverse drug reactions in the hospital setting in Europe (Bouvy *et al.,* 2015). According to the results, the median rate of patients admitted to the hospital due to adverse drug reactions was 3.6%, ranging from 0.5% to 12.8% (Bouvy *et al.,* 2015). Moreover, almost 12% of the patients had at least one adverse drug reaction during the hospital stay [range: 1.7% to 50.9%], with the highest percentage of fatal adverse drug reactions being 0.52% of all admitted patients (Bouvy *et al.,* 2015).

The number of serious adverse drug reactions spontaneously reported to regulatory authorities have increased consistently over the years (Moore *et al.,* 2007). According to

Moore and colleagues (2007), from 1998 through 2005, the reported serious adverse drug events to the US FDA Adverse Event Reporting System increased 2.6-fold (Moore *et al.,* 2007). Such reporting of serious events increased 4 times faster than the total number of drug prescriptions. This increasing trend remained over the years, since a recently published study observed a 2-fold increase in serious adverse drug reactions reported to the US FDA from 2006 through 2014 by (Sonawane *et al.,* 2018).

The economic burden of adverse drug reactions is significant, as well. In the European Union, the total societal cost of adverse drug reactions was estimated at €79 billions per year (European Comission, 2008). Watanabe and colleagues (2018) estimated an annual cost of prescription drug-related morbidity and mortality in the US of $528.4 billion (Watanabe *et al.,* 2018). A systematic review reported that the direct costs resulting from adverse drug reactions range from €702.21 to €40,273.08 per event in ambulatory care, and from €943.40 to €7,192.36 per event in hospital care (Marques *et al.,* 2016).

Polypharmacy

Among the circumstances that seem to increase the risk of adverse drug reactions, which include age-related changes in pharmacokinetics and pharmacodynamics and genetic predisposition of patients, there is also polypharmacy (Hoigné *et al.,* 1990; Lavan & Gallagher, 2016).

Polypharmacy is often referred as the simultaneous use of multiple drugs in the same individual (Organization, 2019). However, there is not standard definition of polypharmacy and the terms found in the published literature are largely heterogeneous and have different meanings (Hoffman *et al.,* 2011). A systematic review found 138 definitions of polypharmacy, where the simultaneous daily use of five or more drugs is the most commonly reported term (Masnoon *et al.,* 2017). Some definitions may incorporate the duration of therapy and terms like minor, moderate, major and excessive may be used to refer to the level of polypharmacy (Masnoon *et al.,* 2017).

The population ageing, the growth in the number of individuals with multi-morbidities and the improvement of the access to healthcare services and the complying with the recommendations of the disease-specific clinical guidelines are often associated with the increasing of polypharmacy (Molokhia & Majeed, 2017) (Payne, 2016). Elderly patients are often under polypharmacy since they have multi-morbidities (Marengoni *et al.,* 2011). A literature review found that 55 to 98% of the older patients have, at least, 2 concurrent diseases (Marengoni *et al.,* 2011). It is also estimated that between 2015 and 2035, the

prevalence of multi-morbidity in England will increase among the elderly, with the proportion of individuals with at least four diseases almost doubling (Kingston *et al.,* 2018). A cross-sectional analysis showed that the prevalence of polypharmacy among elderly patients in Europe ranges from 26% to 40% (Midão *et al.,* 2018). A Swedish prospective cohort study found that such prevalence can reach up to 44%, and that excessive polypharmacy was estimated at almost 12% (Morin *et al.,* 2018). A longitudinal observational study characterized the changes in the prevalence of medication use, including concurrent use of drugs, among a sample of community-dwelling older individuals aged 62 to 85 years old (Qato *et al.,* 2016). The results showed that the concurrent use of 5 or more drugs has grown over the years, with the prevalence increasing from 30.6% in 2005-2006 to 35.8% in 2010-2011 (Qato *et al.,* 2016). There are strategies that can be used to reduce polypharmacy, although there are not convincing evidence that this strategies may be effectiveness. A systematic review and meta-analysis including 25 studies, considering a total of 10 980 participants, explored the impact of strategies to reduce polypharmacy on clinical relevant outcomes, such as mortality, hospital admission and change in number of drugs used by patients (Johansson *et al.,* 2016). The majority of the included studies aimed at improving quality/appropriateness of prescribing by eliminating inappropriate drugs, through the use of 3 main categories of interventions: pharmacist-led interventions, physician-led interventions or multidisciplinary team-led interventions. The results demonstrate that the strategies to reduce polypharmacy had no impact on mortality (OR 1.02; 95% CI 0.84 to 1.23) and only one study found evidence that the intervention reduced the hospital stay (Johansson *et al.,* 2016). The simultaneous use of multiple medicines may be necessary and beneficial, particularly when the patient is diagnosed with multi-morbidities requiring more than one drug class or when monotherapy provides insufficient control (Hoffman *et al.,* 2011). The 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guidelines for the management of arterial hypertension recommend two drugs as initial treatment for most patients in order to improve the effectiveness of blood pressure control (Williams *et al.,* 2018). An initial therapy with, at least, three drugs is recommended for patients with hypertension and heart failure with reduced ejection fraction (Williams *et al.,* 2018). The post-myocardial infarction routine long-term pharmacological therapy should consider, at least, four drugs in order to reduce the risk of a secondary event and increase patients' survival (Ibanez *et al.,* 2018).

Polypharmacy has been, however, associated with negative health outcome. There is evidence suggesting that polypharmacy leads to unnecessary use of drugs, particularly among

the elderly. An observational study was conducted aiming at assessing the prevalence of unnecessary drug use among elderly patients in ambulatory care with 5 or more self-administered medications (Rossi *et al.,* 2007). The analysis showed that 58.6% of the patients had at least 1 unnecessary prescribed drug.

The risk of adverse effects increases with the number of drugs used (Payne, 2016). There is a considerable body of evidence assessing the risk of adverse drug reactions associated with polypharmacy. A cross-sectional study found that the elderly patients who experienced adverse drug reactions used more drugs (n=14) than the other elderly patients (n=8) (Veehof *et al.,* 1999). A prospective cohort study aimed to document the adverse drug reaction leading to hospitalization admission of residents of a nursing facility (Cooper, 1999) the results of this study showed that the number of medications per hospitalized patient (n=8) due to an adverse reaction was higher than the number of medications per patient (n=3) without adverse reactions, despite both groups of patients had the same number of baseline comorbidities (Cooper, 1999). A retrospective cohort study concluded that subjects using ≥9 different drugs were 2.33 times more likely to experience an adverse drug reaction (95% CI 1.54-3.52) than control, in a population from a geriatric nursing home (Nguyen *et al.,* 2006). Moreover, evidence suggests that patients taking multiple drugs simultaneously have an increased risk of developing specific serious adverse reactions, such as bleeding and renal failure (Dörks *et al.,* 2016; Leiss *et al.,* 2015).

Polypharmacy seems to increase the risk of death as well. A systematic review and meta-analysis including 47 studies found a significant association between polypharmacy and mortality risk (OR 1.08; 95% CI 1.04-1.12) (Leelakanok *et al.,* 2017). Excessive polypharmacy (≥10 drugs) was also associated with death (OR 1.96; 95% CI 1.42-2.71) (Leelakanok *et al.,* 2017). However, the findings from this meta-analysis must be considered with caution. Although the risk estimates had been highly consistent across the sensitivity analyses and the different definitions of polypharmacy evaluated, the risk estimates were usually associated with high between-studies heterogeneity (I^2>50%).

The studies dedicated to assess the risk of adverse drug reactions associated to polypharmacy are significantly heterogeneous. As previously described, different definitions have been used to define "polypharmacy". The control groups used in the studies may not be comparable as well, since patients classified as under "no polypharmacy" may be using anything from none to several drugs (ex: 0 to 1; 1 to 2; or 1 to 4 drugs) (Fried *et al.,* 2014). Furthermore, many studies may not provide clear information on the treatment duration, type of pharmacological drug classes, or whether over-the-counter products are used or not

(Leelakanok *et al.,* 2017). Such limitations appear to have impact in the methodological quality of the studies. A systematic review aimed to summarize the evidence regarding the health outcomes associated with polypharmacy concluded that not all studies have good methodological quality, with some failing to properly adjust the results for relevant confounding, like comorbid conditions or patient's age (Fried *et al.,* 2014).

A recently published article reviewed the results from four systematic reviews which have evaluated the risk of negative health outcomes associated with polypharmacy (Wastesson *et al.,* 2018). Of those, two assessed specific outcomes, such as frailty (Gutiérrez-Valencia *et al.,* 2018) and mortality (Leelakanok *et al.,* 2017), while the remaining evaluated the risk of various health outcomes in simultaneous (Fried *et al.,* 2014; Maher *et al.,* 2014). However, a systematic review focused on assessing whether polypharmacy changes the risk of serious adverse drug reactions has not yet been published in the scientific literature. Understanding the risk of developing clinically relevant adverse effects due to polypharmacy is relevant in order to assure the best treatment for patients and to develop strategies aiming to prevent harms.

CHAPTER II

OBJECTIVES

Objectives

The main goal of this study is to investigate if polypharmacy is an independent risk factor for serious adverse drug reactions.

The secondary objectives of this study are the following:

- To identify studies published in the scientific literature assessing the risk of serious adverse drug reactions in polypharmacy patients compared to non-polypharmacy patients;
- To characterize the studies that evaluate the risk of serious adverse drug reactions associated with polypharmacy;
- To perform the methodological quality assessment of the studies included in this systematic review.

CHAPTER III

METHODS

Methods

This systematic review conforms to standard guidelines and it is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher *et al.,* 2009). The PRISMA guideline is composed of a checklist of 27 items. The purpose of this guideline is to improve the quality of systematic reviews through the minimization of potential bias. The PRISMA checklist is available in Appendix 1.

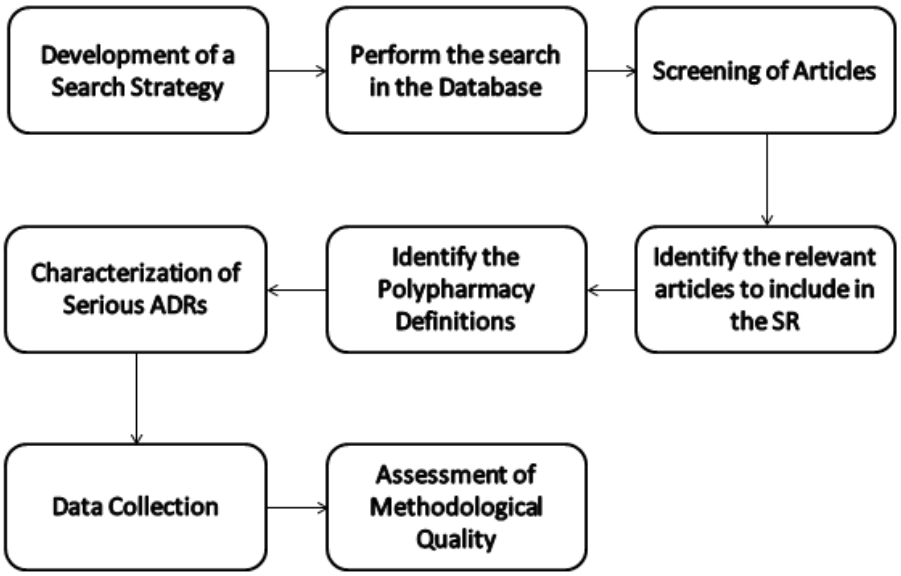

Figure 1: Study Design

Search Strategy

PubMed and EMBASE databases were searched in order to identify studies (published between 1 January 2008 and 30 May 2019) evaluating the association between polypharmacy and serious adverse drug reactions. Bibliographic reference lists of all relevant studies and systematic reviews were hand searched to identify additional eligible articles. Only literature published in English language was considered for inclusion. The search strategy is available in Appendix 2.

Study Selection

The EndNote® software tool was used to manage the citations which were retrieved from the literature search, including the detection and exclusion of duplicates. Titles and abstracts of all retrieved citations were screened by two independent reviewers (R.G. and D.M.) to identify potentially relevant publications. Articles clearly not meeting the established inclusion criteria were immediately excluded. Full texts were retrieved for relevant citations and were grouped into 2 different groups: "relevant" and "irrelevant". Those that were

selected as irrelevant by both investigators were automatically deleted. Discrepancies were resolved by majority decision (two of three) involving a third investigator (C.A.).

Inclusion Criteria

Observational (cohort, case-control, and cross-sectional) and experimental studies (clinical trials and pragmatic trials) assessing the risk of serious adverse drug reactions among patients under polypharmacy versus non-polypharmacy were eligible for inclusion. According to the WHO criteria, a serious adverse drug reaction is a reaction that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or congenital anomaly or requires intervention to prevent permanent impairment or damage (WHO, 2002). Only studies published as full-papers in peer-reviewed journals were considered. Case reports, physician and patient surveys, narrative reviews and conference abstracts were not eligible for inclusion.

Exclusion Criteria

Studies were excluded if they:

a) were designed to assess the appropriateness of medication use (e.g. drugs review using START/ STOP, BEERS or PRISCUS criteria);

b) did not provide a definition of serious adverse drug reaction;

c) were aimed to study drug related problems (DRP) other than adverse drug reactions (e.g. assessing drugs' effectiveness, drug-disease, drug-food, drug-alcohol or drug-nutritional status interactions);

d) studied only a given disease (e.g. diabetes mellitus), drug (e.g. anti-psychotics) or specific adverse drug reactions (e.g. falls).

Methodological Quality Assessment

The Newcastle-Ottawa Scale was used to assess the methodological quality of the included case-control and cohort studies (GA Wells, B Shea, D O'Connell, J Peterson, V Welch, M Losos, 2006). An adapted version of the Newcastle-Ottawa Scale was used to assess the methodological quality of the cross-sectional studies (Alshabanat *et al.,* 2015). The two Newcastle-Ottawa Scale versions used according to the specific study design (cohort and case-control or cross-sectional) are described in the Appendix 3, 4 and 5.

The Newcastle-Ottawa Scale was selected because it is recommended to assess the methodologic quality of observational studies (Well *et al.,* 2000). It is composed by 3

subscales: "Selection", "Comparability" and "Exposure/Outcome" and uses a star system that allows semi-quantitative assessments of study quality.

In the Newcastle-Ottawa Scale, each topic of the "Selection" and "Exposure" sections could be awarded with a maximum of 1 star. For the "Comparability" section a maximum of 2 stars could be awarded. The maximum overall score of this scale is 9 stars.

In the Newcastle-Ottawa Scale adapted for cross-sectional studies, each topic of the "Selection" section could be awarded with a maximum of 1 star (except the "Ascertainment of the exposure (risk factor)" sub-section, which could receive 2 stars). For the "Comparability" section, a maximum of 2 stars could be awarded and for the "Outcome" section a maximum of 3 stars could be awarded. The maximum overall score of this scale is 10 stars.

Observational studies scoring ≥7 stars were considered to have high methodological quality. Studies scoring <7 and ≥5 stars were considered to have moderate methodological quality and studies scoring <5 stars were considered to have poor methodological quality.

The methodological quality of the experimental studies (clinical trials and pragmatic trials) was assessed using the recommendations of the Cochrane Handbook of Systematic Review of Interventions on assessing adverse effects (Loke *et al.,* 2008). According to this Cochrane tool, the value of clinical trial data on adverse effects relies on two characteristics: the rigor of monitoring for the adverse effects during the study and the completeness of reporting. The allocation concealment and withdrawal rates were also evaluated.

Two investigators assessed the methodological quality of the studies (R.G. and D.M.). Discrepancies were resolved by majority decision (two of three) with the help of a third investigator (C.A.).

Data Extraction

The following information was extracted from each study included in the systematic review:

- Bibliographic reference, first author, year of publication and country where the study was conducted;
- Study design;
- Definition of polypharmacy;
- Population characteristics: number, gender and age of patients;
- Outcome;
- Identified risk factors;

- Risk Ratio (e.g. Odds Ratio; Hazard Ratio)
- Incidence of polypharmacy;
- Mean number of drugs used.

If the studies presented more than one risk estimate or incidence rate, the most adjusted ones would be used.

Data analysis and presentation

Data were analyzed using descriptive statistics. Statistical analyses were conducted with Microsoft Excel 2016® (Microsoft Corporation, Santa Rosa, CA, USA).

CHAPTER III

RESULTS

Results

Study Selection

Figure 2 presents the search strategy flowchart. The literature search returned 9113 citations. After excluding duplicates (n=102) and reviewing titles and abstracts of 9011 records, 109 potentially relevant articles were selected for full-text evaluation. Sixteen studies met the inclusion criteria. The reasons for excluding 93 articles are detailed in the Appendix 6.

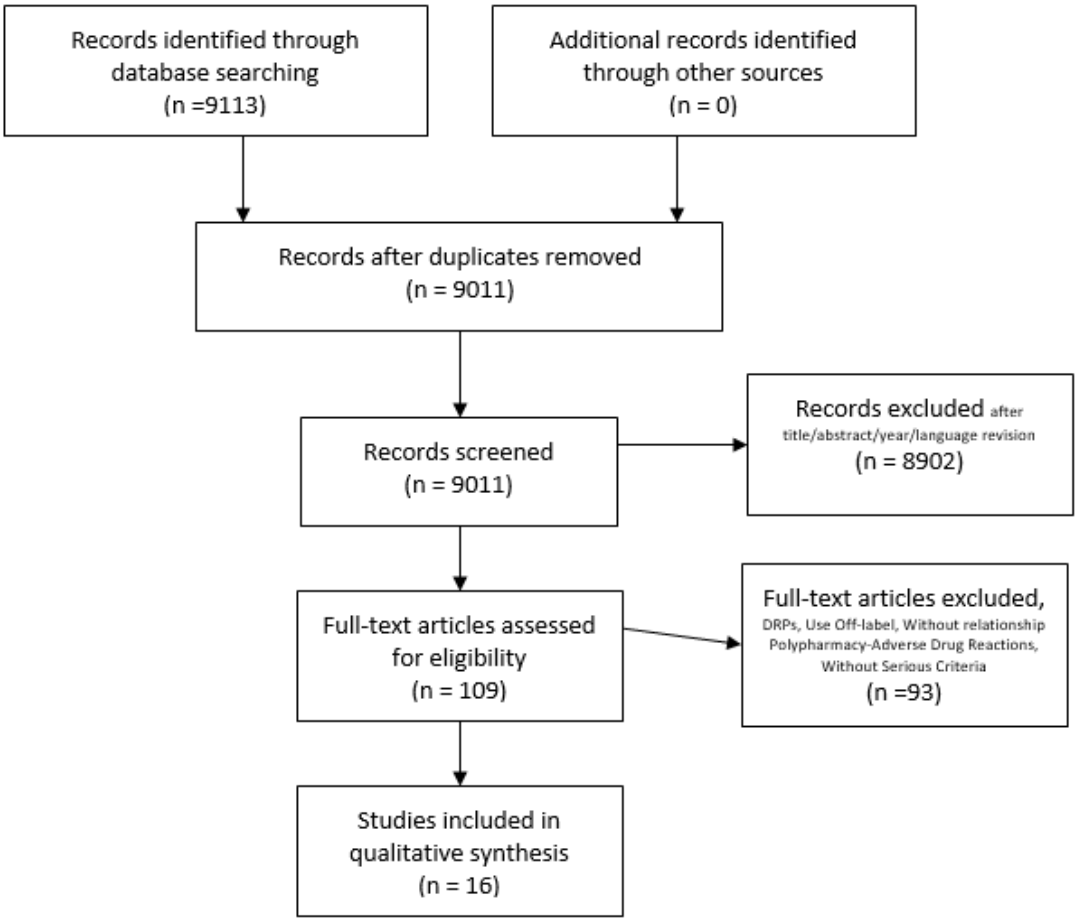

Figure 2: PRISMA flowchart of study selection in the systematic review

Characteristics of the included studies

The main characteristics of the studies included in the systematic review (n=16) are summarized in Table 1. The design, country, definition of polypharmacy and comparators, sample sizes, patients' characteristics (age and sex) and outcomes are described for each study.

Seven were cohort (Abe *et al.,* 2016; Bourgeois *et al.,* 2010; Gnjidic *et al.,* 2012; Marcum *et al.,* 2012; Payne *et al.,* 2014; Salvi *et al.,* 2017; Schöttker *et al.,* 2017), 5 case-control (Chen *et al.,* 2014; Leendertse *et al.,* 2008; Macedo *et al.,* 2011; Olivier *et al.,* 2009; Rausch *et al.,* 2017) and 4 cross-sectional studies (Laatikainen *et al.,* 2016; Pedrós *et al.,* 2014; Sevilla-Sanchez *et al.,* 2017; Varallo *et al.,* 2014). No experimental studies (clinical trials or pragmatic trials) were included in this systematic review.

Ten studies were conducted in Europe (Spain, n=2; Netherlands, n=1; France, n=1; Portugal, n=1; Finland, n=1; UK, n=1; Italy, n=1; Sweden, n=1; Germany, n=1), two in the USA (n=2), two in Asia (Taiwan, n=1; Japan, n=1), one in Brazil and one in Australia.

The sample size ranged from 235 to 4,335,990 participants across the included studies. The proportion of women included in the studies ranged from 0% to 69.1%. The mean age of the participants ranged from 49 years old (Payne *et al.,* 2014) to 90 years old (Abe *et al.,* 2016). Nine studies included only patients aged ≥65 years old (Abe *et al.,* 2016; Chen *et al.,* 2014; Gnjidic *et al.,* 2012; Laatikainen *et al.,* 2016; Marcum *et al.,* 2012; Olivier *et al.,* 2009; Pedrós *et al.,* 2014; Salvi *et al.,* 2017; Sevilla-Sanchez *et al.,* 2017).

Methodological Quality Assessment

The methodological quality assessment scores for the case-control, cohort and cross-sectional studies are presented in the tables 2, 3 and 4, respectively. The methodological quality was found to be poor in 1 study (Leendertse *et al.,* 2008), moderate in 9 studies (Bourgeois *et al.,* 2010; Chen *et al.,* 2014; Laatikainen *et al.,* 2016; Macedo *et al.,* 2011; Marcum *et al.,* 2012; Olivier *et al.,* 2009; Payne *et al.,* 2014; Pedrós *et al.,* 2014; Rausch *et al.,* 2017) and high in 6 studies (Abe *et al.,* 2016; Gnjidic *et al.,* 2012; Salvi *et al.,* 2017; Schöttker *et al.,* 2017; Sevilla-Sanchez *et al.,* 2017; Varallo *et al.,* 2014).

Table 1: Characteristics of the studies included in the SR (n=16)

Study	Study Design	Mean Age and Age Inclusion Criteria	Definition of Polypharmacy	Comparator	Total No of Subjects	Female (%)	Outcome
Sevilla-Sanchez, D et al. (2017) - Spain	Cross-Sectional	87; ≥65 years	≥5 drugs Extreme Polypharmacy: ≥10 drugs	0-4 drugs	235	65.50%	Hospitalization
Leendertse, A et al. (2008) - Netherlands	Case-Control	60; ≥18 years	≥5 drugs	<5 drugs	664	Cases: 49.4%; Controls: 49.4%	Hospitalization
Abe, T. et al. (2016) - Japan	Cohort	90; ≥85 years	≥5 drugs	<5 drugs	347	Cases: 62%; Controls: 60%	Hospitalization
Varallo, F. et al. (2014) - Brazil	Cross- Sectional	NA; ≥18 years	≥5 drugs	<5 drugs	248	Cases: 50.7%; Controls: 49.3%	Hospitalization
Chen, Y. et al. (2014) - Taiwan	Case-Control	Cases: 81; Controls: 80; ≥65 years	Simultaneous use of Multiple Drugs	0-2 drugs	590	Cases: 31.5%; Controls: 30.8%	Hospitalization
Gnjidic, D et al. (2012) - Australia	Cohort	77; ≥70 years	6 to 9 drugs; Extreme Polypharmacy: ≥10 drugs	xdrugs	1705	0%	i) Death; ii) Disability
Bourgeois, F. et al. (2010) - USA	Cohort	NA; ≥0 years	Simultaneous use of Multiple Drugs	1-2 drugs	4335990	Outpatient Clinics: 59.9%; ED: 64%	Hospitalization
Olivier, P. et al. (2009) - France	Cases-Control	Cases: 80; Controls: 80; ≥65 years	Average of five drugs	0 drugs	789	Cases: 59.1%; Controls: 55%	Composite: Hospitalization or Life Threatening or Death
Macedo, A F et al. (2011) - Portugal	Case-Control	55; ≥0 years	Simultaneous use of Multiple Drugs	1 drug; <2 drugs; and <3 drugs	1482	69.1%	Any Serious ADR
Laatikainen, O. Et al. (2016) - Finland	Cross- Sectional	Cases: 79; Controls: 76; ≥65 years	Simultaneous use of multiple drugs	≤ 1 drug	290	Cases: 59.7%; Controls: 47,9%	Hospitalization
Payne, Rupert A. Et al. (2014) - UK	Cohort	49; ≥20 years	Simultaneous use of Multiple Drugs	1-3 drugs	180915	50.7%	Hospitalization
Salvi, F. et al. (2017) - Italy	Cohort	82; ≥65 years	6 to 9 drugs; Extreme Polypharmacy: ≥10 drugs	≤ 5 drugs	2057	60%	i) Hospitalization; ii) Death
Rausch, C. et al. (2017) - Sweden	Case-Control	NA; ≥50 years	≥5 drugs	1 drug	26680	Cases: 56.2% ; Controls: 56.2%	Composite: Hospitalization or Death
Schottker, B. et al. (2017) - Germany	Cohort	70; 50-74 years	≥5 drugs Extreme Polypharmacy: ≥10 drugs	0-4 drugs	2687	≈50%	Death
Marcum, Zachary A. et al. (2012) - USA	Cohort	76; ≥65 years	Simultaneous use of multiple drugs	0-4 drugs	678	1.5%	Hospitalization
Pedrós, C. et a.l (2014) - Spain	Cross-Sectional	Cases: 75; Controls: 66; ≥65 years	Simultaneous use of Multiple Drugs	≤2 drugs	4403	Cases: 44.1%; Controls: 39.4%	Hospitalization

Table 2: Methodological quality assessment of the case-control studies

	Selection				Comparabilit		Exposure			Total Score	
	Case definition adequate	Representativeness of cases	Selection of controls	Definition of controls	Comparability: age and sex	Comparability: additional factors	Ascertainment of exposure	Case and controls: same ascertainment	Case and controls: same		
Case-control studies											
Leendertse, A et al (2008)	0	0	0	1	0	1	0	1	1	4	4/9
Chen, Y. et al (2014)	0	0	0	1	1	1	0	1	1	5	5/9
Olivier, P. et al (2009)	1	0	0	1	0	1	0	1	1	5	5/9
Macedo, A F et al (2011)	1	0	0	1	0	0	1	1	1	5	5/9
Rausch, C. et al (2017)	0	0	1	1	1	1	0	1	1	6	6/9

Table 3: Methodological quality assessment of the cohort studies

	Selection				Comparability		Exposure				
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest not present at start	Comparability: age and sex	Comparability: additional factors	Ascertainment of outcome	Follow-up long enough (5 years)	Adequacy of follow-up	Total Score	
Cohort studies											
Abe, T. et al (2016)	0	1	0	1	1	1	1	0	1	6	6/9
Gnjidic, D et al (2012	0	1	1	1	0	1	1	0	1	6	6/9
Bourgeois, F. et al (2010)	1	1	1	1	1	1	1	1	0	8	8/9
Payne, Rupert A. Et al (2014)	1	1	0	0	1	1	1	0	1	6	6/9
Salvi, F. et al (2017)	0	1	1	1	1	1	0	0	1	6	6/9
Schottker, B. et al (2017)	0	1	1	1	1	1	0	1	1	7	7/9
Marcum, Zachary A. et al (2012)	0	1	0	0	1	1	1	0	1	5	5/9

Table 4: Methodological quality assessment of the cross-sectional studies

	Selection				Comparability		Exposure		Total Score	
	Representativeness of the sample	Sample size	Ascertainment of exposure	Non-respondent	The subjects in different outcome	The study control for any additional factor (*)	Ascertainment of outcome	Statistical test		
Cross-sectional studies										
Sevilla-Sanchez, D et al (2017)	0	0	2	1	1	1	2	1	8	8/10
Varallo, F. et al (2014)	0	0	2	1	1	1	2	1	8	8/10
Laatikainen, O. Et al (2016)	0	0	2	1	1	1	1	1	7	7/10
Pedrós, C. et al (2014)	0	1	1	1	1	1	2	1	8	8/10

Definition of polypharmacy

The definition of polypharmacy differed between the included studies. Seven studies provided a quantitative definition for polypharmacy: concurrent use of ≥5 drugs in six studies (Abe *et al.,* 2016; Leendertse *et al.,* 2008; Rausch *et al.,* 2017; Schöttker *et al.,* 2017; Sevilla-Sanchez *et al.,* 2017; Varallo *et al.,* 2014) or ≥6 drugs in two others (Gnjidic *et al.,* 2012; Salvi *et al.,* 2017). Seven studies defined polypharmacy as the concurrent use of multiple drugs (Bourgeois *et al.,* 2010; Chen *et al.,* 2014; Laatikainen *et al.,* 2016; Macedo *et al.,* 2011; Marcum *et al.,* 2012; Payne *et al.,* 2014; Pedrós *et al.,* 2014), but did not provide an objective threshold. A definition for polypharmacy was not explicitly provided in one study, but the authors reported that the patients used an average of five drugs in simultaneous (Olivier *et al.,* 2009).

Four studies defined extreme polypharmacy as the concurrent use of ≥10 drugs (Gnjidic *et al.,* 2012; Salvi *et al.,* 2017; Schöttker *et al.,* 2017; Sevilla-Sanchez *et al.,* 2017).

The mean number of drugs used in simultaneous by patients on polypharmacy regimens ranged from 2.9 (Macedo *et al.,* 2011) to 9.46 (Sevilla-Sanchez *et al.,* 2017).

The number of drugs used by patients allocated to control groups (i.e. non-polypharmacy) ranged from 0 to 5 drugs.

Outcomes: seriousness criteria of adverse drug reactions

The association between polypharmacy and serious adverse drug reactions resulting in:

a) hospitalization was evaluated in eleven studies (Abe *et al.,* 2016; Bourgeois *et al.,* 2010; Chen *et al.,* 2014; Laatikainen *et al.,* 2016; Leendertse *et al.,* 2008; Marcum *et al.,* 2012; Payne *et al.,* 2014; Pedrós *et al.,* 2014; Salvi *et al.,* 2017; Sevilla-Sanchez *et al.,* 2017; Varallo *et al.,* 2014);

b) death in three studies (Gnjidic *et al.,* 2012; Salvi *et al.,* 2017; Schöttker *et al.,* 2017);

c) hospitalization or death in one study (Rausch *et al.,* 2017);

d) hospitalization, life-threatening or death in one study (Olivier *et al.,* 2009);

e) patient's disability in one study (Gnjidic *et al.,* 2012);

f) and any serious outcome (i.e. death, life-threatening, hospitalization, disability, congenital anomaly/birth defect, or other medically important event) in one study (Macedo *et al.,* 2011).

The relative risk (e.g. OR and HR) of serious adverse reactions in polypharmacy groups versus control groups was adjusted to several covariates, excepting for 3 studies (Bourgeois *et al.,* 2010; Laatikainen *et al.,* 2016; Pedrós *et al.,* 2014) (Supplementary Appendix 8).

Polypharmacy and risk of hospitalization

The results of the studies evaluating the risk of hospitalization due to polypharmacy are described in Table 5. Ten out of 11 studies identified an increased risk of hospitalization due to polypharmacy (Abe *et al.,* 2016; Bourgeois *et al.,* 2010; Chen *et al.,* 2014; Laatikainen *et al.,* 2016; Leendertse *et al.,* 2008; Marcum *et al.,* 2012; Payne *et al.,* 2014; Pedrós *et al.,* 2014; Salvi *et al.,* 2017; Varallo *et al.,* 2014). One out of 11 studies did not identify an increased risk of hospitalization associated with polypharmacy (Sevilla-Sanchez *et al.,* 2017).

Furthermore, 5 out of 11 studies evaluated the risk of hospitalization associated with extreme polypharmacy; all identified statistically significant increased risks (Marcum *et al.,* 2012; Payne *et al.,* 2014; Pedrós *et al.,* 2014; Salvi *et al.,* 2017; Sevilla-Sanchez *et al.,* 2017).

Polypharmacy versus the use of 0-4 drugs

The use of ≥5 drugs versus the use of 0-4 drugs was associated with an increased risk of hospital admissions in 5 out of 6 studies: OR=2.7 (95% CI 1.6-4.4) (Leendertse *et al.,* 2008); AOR=2.85 (95% CI 1.03-7.85) (Marcum *et al.,* 2012); OR=1.14 95% CI (1.03-1.26) (Varallo *et al.,* 2014); OR=2.12 (1.03-4.43) (Abe *et al.,* 2016); HR=1.49 (95% CI 1.42-1.80) (Salvi *et al.,* 2017). Polypharmacy (5-9 drugs) was not associated with an increased risk of hospitalization (univariate OR=1.73; 95% CI 0.22-13.73) in the study by Sevilla-Sanchez et al. (2017).

Polypharmacy versus the use of 1-3 drugs

Payne *et al.* (2014) found that the number of unplanned hospitalizations increased as the number of medications used by patients tended to be higher (i.e. 5.2%, 10.3%, and 24.8% of patients were using 1-3, 4-6, and ≥10 drugs before hospital admission, respectively). Compared to the use of 1-3 drugs at baseline, the use of 4-6 drugs (adjusted OR=1.33; 95% CI 1.12–1.57), and 7-9 drugs (adjusted OR=2.28; 95% CI 1.80–2.89) were associated with increased risks of hospitalization.

Polypharmacy versus the use of ≤2 drugs

The findings from Chen *et al.* (2014) revealed that using 3-7 drugs (OR=4.1; 95% CI 2.4-6.9) or >8 drugs (OR=6.4; 95% CI 3.7-11.0) versus the use of 0-2 drugs was associated with an increased risk of hospitalization. According to Pedrós *et al.* (2014), the use of 3-5 drugs (OR=5.07; 95% CI 2.71–9.50), and of 6-9 drugs (OR=5.90; 95% CI 3.16–11.01) increased the risk of hospitalization versus the use of 0-2 drugs. The results from Bourgeois *et al.* (2010) showed an increased risk of hospitalization among patients using 3-4 drugs (OR=1.44; 95% CI 1.24–1.67) and ≥5 drugs (OR=1.88; 95% CI 1.56–2.24) versus the use of 1-2 drugs at baseline.

The study by Laatikainen *et al.* (2016) compared the risk of hospital admissions between patients receiving ≥2 drugs (polypharmacy) versus those using ≤1 drug and estimated an adjusted OR of 3.3 (95% CI 1.5–6.9).

Extreme polypharmacy versus the use of 0-4 drugs

Extreme polypharmacy was found to increase the risk of hospitalization in the study by Sevilla-Sanchez *et al.* (2017) (≥10 drugs vs. 0-4 drugs; OR=3.36; 95% CI 1.07–10.59), in the study of Marcum *et al.* (2012) (≥9 drugs vs. 0-4 drugs; OR=3.90; 95% CI 1.43–10.61), and in the study of Salvi *et al.* (2017) (≥10 drugs vs. 0-4 drugs; HR= 2.11; 95% CI 1.72–2.58).

Extreme polypharmacy versus the use of 1-3 drugs

According to Payne *et al.* (2014), the use of ≥10 drugs versus 1-3 drugs was associated with an increased risk of hospitalization (adjusted OR=4.19; 3.11–5.65).

Extreme polypharmacy versus the use of ≤2 drugs

The results from Pedrós *et al.* (2014) showed that patients using ≥10 drugs were more likely to be hospitalized than those using 0-2 drugs before admission (OR=8.94; 95% CI 4.73–16.89).

Polypharmacy and risk of death

The results of the three studies that evaluated the association between polypharmacy and the risk of death are conflicting (Table 6) (Gnjidic *et al.,* 2012; Salvi *et al.,* 2017; Schöttker *et al.,* 2017).

Polypharmacy versus the use of an indeterminate number of drugs

The study by Gnjidic *et al.* (2012) determined the optimal discriminating number of medications associated with mortality in community-dwelling men aged ≥70 years old. Receiver operating characteristic (ROC) curve analyses were used to calculate the area under the curve (AUC) for the association of the number of concomitant medications with mortality. The authors found that the highest value of the Youden Index (i.e. summary measure of the ROC curve that represents the maximum potential effectiveness of the marker) for mortality was obtained for a cutoff point of 4.5 medications. For every one increase in number of medications, the adjusted OR was 1.09 (95% CI 1.04–1.15) for mortality (Gnjidic *et al.,* 2012).

Polypharmacy and Extreme Polypharmacy versus the use of ≤5 drugs

The study by Salvi *et al.* (2017) assessed whether polypharmacy (6-9 drugs) and extreme polypharmacy (≥10 drugs) are independent risk factors for in-hospital mortality and mortality in a 6-month follow-up after an emergency department visit. The non-polypharmacy group included individuals using ≤5 drugs concomitantly.–After adjusting data for covariates, polypharmacy was an independent risk factor for in-hospital mortality at the limit of significance (adjusted OR=1.63; 95% CI 1.00–2.65; $p<0.05$), but not for 6-month mortality (adjusted HR=1.24, 95% CI 0.93–1.67); and extreme polypharmacy was no longer an independent risk factor for in-hospital mortality (adjusted OR=1.58; 95% CI 0.92–2.72), but it still increased the risk of 6-month mortality (adjusted HR=1.74; 95% CI 1.28–2.36) (Salvi *et al.,* 2017).

Polypharmacy and Extreme Polypharmacy versus the use of 0-4 drugs

According to the most adjusted results of a propensity score analysis, Schottker *et al.* (2017) found that neither polypharmacy (5-9 drugs) (adjusted HR=1.26; 95% CI 0.70– 2.28) nor extreme polypharmacy (≥10 drugs) (adjusted HR=1.08; 95% CI 0.49–2.40) were independently associated with an increased risk of non-cancer mortality among a cohort of German older adults (aged 50-74 years) (Schottker *et al.,* 2017).

Polypharmacy and risk of disability

The association between polypharmacy and disability was evaluated in only one study (Table 7). Disability was defined as needing help with one or more activities included in the activities of daily living scale (ADLs) (Gnjidic *et al.,* 2012). The highest value of the Youden Index for disability was obtained for a cutoff point of 5.5 medications. For every one increase in the number of medications, the adjusted OR was 1.08 (95% CI 1.00–1.15; p=0.04) for disability (Gnjidic *et al.,* 2012).

Polypharmacy and risk of hospitalization or death

The study by Rausch *et al.* (2017) evaluated the risk of a composite outcome of hospitalization or death for polypharmacy versus non-polypharmacy (i.e. the use of only one drug) (Table 8). According to the results (OR adjusted for several covariates and excluding indicators of inappropriate drug use [IDU]), an increased risk for the outcome of interest was found in association with the use of ≥3 drugs (adjusted OR=1.5; 95% CI 1.2–2.0) (Rausch *et al.,* 2017).

Polypharmacy and risk of hospitalization, life-threatening events or death

Olivier *et al.* (2009) carried out a prospective cohort study aimed to estimate the incidence of ADRs and associated factors resulting in hospitalization of patients aged ≥65 years old (Table 9). Patients admitted to the emergency department because of ADRs were compared to those admitted due to other reasons regarding the characteristics of both groups. The mean number of drugs used before hospital admission was significantly higher in patients with ADRs than in those without ADRs (5.9 ± SD 2.9 vs. 4.5 SD ± 2.8; p<0.0001). The number of drugs used by patients before hospital admission was found to be an

independent risk factor associated with ADRs (adjusted OR=1.18; 95% CI 1.08–1.29) (Olivier *et al.,* 2009).

Polypharmacy and risk of any serious adverse drug reaction

Macedo *et al.* (2011) used data from spontaneous reports of ADRs to determine if polypharmacy was an independent risk factor for any type of serious ADRs (i.e. any untoward medical occurrence that results in death, is life-threatening, requires hospitalization, results in disability or congenital anomaly or any other medically important consequence) (Table 10). The authors found that the use of ≥3 drugs was associated with an increased risk for serious ADRs (adjusted OR=1.23; 95% CI 1.02–1.51) (Macedo *et al.,* 2011).

Table 5: Polypharmacy and risk of hospitalization

Study	Study Type	Polypharmacy	Comparator	Risk Ratio (95% CI)	Incidence	Mean Drugs Used	Risk Factors
Sevilla-Sanchez, D *et al.* (2017)	Cross-Sectional	5-9 drugs	0-4 drugs	OR = 1.73 (0.22 - 13.73)	No polypharmacy: 8.10%; Moderate Polypharmacy (5-9): 45.10%; Extreme Polypharmacy (≥10): 46.80%	Mean Polypharmacy: 9.46 (SD=3.77; Rank = 1-22)	Extreme Polypharmacy, High Anticholinergic Burden, Inappropriate Medication and Excessive Treatment Complexity
		≥10 drugs (extreme)	0-4 drugs	OR= 3.36 (1.07 - 10.59)			
Leendertse, A *et al.* (2008) - Netherlands	Case-Control	≥5 drugs	<5 drugs	OR= 2.7 (1.6 - 4.4)	Polypharmacy+related hospitalization (vs. Non-polypharmacy): 54.2%; Polypharmacy+non-related hospitalization (vs. Non-polypharmacy): 28.9%	–	Impaired cognition, 4 or more diseases in the patient medical history, dependent living situation, impaired renal function before admission, nonadherence to the medication regimen, polypharmacy.
Abe, T. *et al.* (2016)	Cohort	≥5 drugs	<5 drugs	OR=2.12, (1.03 - 4.43) p=0.042	Polypharmacy = 72%; Non-polypharmacy = 28%	Mean number of prescriptions = 6.8 ± 3.9	Polypharmacy and Increased heart rate
Varallo, F. *et al.* (2014)	Cross-Sectional	≥5 drugs	<5 drugs	OR= 1.14, (1.03 - 1.26) p=0.05	–	Median nr of Drugs: With ADE = 5 (1-14); Without ADE = 4 (1-13)	Polypharmacy
Chen, Y. *et al.* (2014)	Case-Control	3-7 drugs	0-2 drugs	OR= 4.1 (2.4 - 6.9)	–	Patients with ADEs= 8.0 ± 3.9 (1-21); Patients without ADEs= 5.2 ± 4.2 (0-21)	Higher Charlson Comorbidity Index Score, Polypharmacy, Longer ED stay and Increased serum creatinine
		≥8 drugs	0-2 drugs	OR= 6.4 (3.7 - 11.0)			
Bourgeois, F. *et al.* (2010)	Cohort	3-4 drugs	1-2 drugs	OR= 1.44 (1.24 - 1.67)	Outpatient Clinics: 1-2 Medications = 64.6%; 3-4 Medications = 19.4%; 5 or more Medications = 16.0%. ED: 1-2 Medications = 64.6%; 3-4 Medications = 23.0%; 5 or more Medications = 12.4%	–	Increased Age and Polypharmacy
		≥5 drugs	1-2 drugs	OR= 1.88 (1.56 - 2.24)			
Laatikainen, O. *Et al.* (2016)	Cross-Sectional	≥2 drugs	≤1 drugs	OR= 3.3, (1.5 - 6.9) p=0.001	Polypharmacy: Related with Hospital Admission = 28.2%; Non-Related with Hospital Admission = 71.8%. No Polypharmacy: Related with Hospital Admission = 10.7; Non-Related with Hospital Admission = 89.3%	Mean Nr of Regular Medication: Related with Hospital Admission = 9.1 ± 4.0 (0-22); Non-Related with Hospital Admission = 6.8 ± 4.5 (0-22). Mean Nr of Medications Used "as needed": Related with Hospital Admission = 2.8 ± 2.2 (0-11); Non-Related with Hospital Admission = 2.0 ± 2.3 (0-15).	Polypharmacy
Payne, Rupert A. *Et al.* (2014)	Cohort	4-6 drugs	1-3 drugs	OR= 1.33 (1.12 - 1.57), p-value= 0.001	0 medications = 53.3%; 1-3 medications = 25.2%; 4-6 medications = 11.0%; 7-9 medications =5.9%; ≥10 medications = 4.6%	–	Number of clinical conditions, number of medications, male Gender, increased age and socioeconomic deprivation
		7-9 drugs	1-3 drugs	OR= 2.28 (1.80 - 2.89), p-value= 0.001			
		≥10 drugs (extreme)	1-3 drugs	OR= 4.19 (3.11 - 5.65), p-value= 0.001			
Salvi, F. *et al.* (2017)	Cohort	6-9 drugs	≤5 drugs	HR= 1.49 (1.42 - 1.80), p-value <0.0001	Excessive polypharmacy = 17.8%; Polypharmacy = 30.3%; Non-Polypharmacy = 51.8%	Mean number of prescriptions = 5.7 ± 4.3(range 0-25)	Polypharmacy and Excessive Polypharmacy are both independent risk factors
		≥10 drugs	≤5 drugs	HR= 2.11 (1.72 - 2.58) p-value <0.0001			

Table 5: Polypharmacy and risk of hospitalization (Cont.)

Marcum, Zachary A. *et al.* (2012)	Cohort	5-8 drugs	0-4 drugs	AOR= 2.85, (1.03 - 7.85) p-value=0.04	Polypharmacy (≥9) = 44.8%; Polypharmacy (5-8) = 35.4%	—	Polypharmacy
		≥9 drugs	0-4 drugs	AOR = 3.90, (1.43-10.61) p-value <0.01			
Pedrós, C. *et al.* (2014)	Cross-Sectional	3-5 drugs	≤2 drugs	OR = 5.07, (2.71 - 9.50) p= < 0.001	ADR related admission: 0 Drugs = 0%; 1-2 Drugs = 7.0%; 3-5 Drugs = 26.3%; 6-9 Drugs = 35.0%; ≥10 Drugs = 31.7% Non ADR related admission: 0 Drugs = 18.2%; 1-2 Drugs = 18.6%; 3-5 Drugs = 23.7%; 6-9 Drugs = 25.0%; ≥10 Drugs = 14.5%	Median nr of Drugs: ADR related admission = 7 (1-20); Non ADR related admission = 4 (0-24)	Polypharmacy, Advanced Age, Female Gender, Specific Therapeutic Groups
		6-9 drugs	≤2 drugs	OR = 5.90, (3.16 - 11.01) p= <0.001			
		≥10 drugs (extreme)	≤2 drugs	OR = 8.94, (4.73 - 16.89) p= <0.001			

Table 6: Polypharmacy and risk of death

Study	Study Type	Polypharmacy		Comparator	Risk Ratio (95% CI)	Incidence	Mean Drugs Used	Risk Factors
Gnjidic, D *et al.* (2012) - Australia	Cohort	x drugs+1		x drugs	OR= 1.09, (1.04 - 1.15) p=0.0009	Medication Exposure = 90%; No Medication Exposure = 10%.	Mean number of prescriptions = 4.0 ± 2.9	Use of more than 4 medications.
Salvi, F. *et al.* (2017)	Cohort	In-Hospital Mortality	6-9 drugs	≤5 drugs	HR=1.63 (1.00 - 2.65), p <0.05	Excessive polypharmacy = 17.8%; Polypharmacy = 30.3%; Non-Polypharmacy = 51.8%	Mean number of prescriptions = 5.7 ± 4.3(range 0-25)	In-hospital Mortality: Slightly associated with polypharmacy. Not related to excessive polypharmacy 6 Months-Hospital Mortality: Associated with excessive polypharmacy but not polypharmacy.
			≥10 drugs (extreme)	≤5 drugs	HR=1.58 (0.92 - 2.72), p= 0.15			
		Mortality (6 months follow-up)	6-9 drugs	≤5 drugs	HR=1.24 (0.93 - 1.67), p=0.15			
			≥10 drugs (extreme)	5 drugs	HR=1.74 (1.28 - 2.36), p <0.0001			
Schottker, B. *et al.* (2017)	Cohort	5-9 drugs		0-4 drugs	HR=1.26, (0.70 - 2.28) p=0.786	Hyperpolypharmacy (≥10) = 8.6%; Polypharmacy (5 - 9) = 38.8%; No Polypharmacy = 52.6%	Mean number of prescriptions = 4.6 ± 3.4	No risk Factors identified
		≥10 drugs (extreme)		0-4 drugs	HR = 1.08, (0.49 - 2.40) p=0.019			
		x drugs+1		x drugs	HR = 1.07, (0.91 - 1.06) p=0.007			

Table 7: Polypharmacy and risk of disability

Study	Study Type	Polypharmacy	Comparator	Risk Ratio (95% CI)	Incidence	Mean Drugs Used	Risk Factors
Gnjidic, D *et al.* (2012) - Australia	Cohort	x drugs+1	x drugs	OR= 1.08, (1.00 - 1.15) p=0.04	Medication Exposure = 90%; No Medication Exposure = 10%.	Mean number of prescriptions = 4.0 ± 2.9	Use of more than 4 medications.

Table 8: Polypharmacy and risk of hospitalization or death

Study	Study Type	Polypharmacy	Comparator	Risk Ratio (95% CI)	Incidence	Mean Drugs Used	Risk Factors
Rausch, C. *et al.* (2017)	Case-Control	2 drugs	1 drug	RR = 1.3, (0.9 - 1.6)	**Cases:** 0 medications= 5.1%; 1 medications= 2.8%; 2 medications = 3.5%; 3 medications = 4.1%; 4 medications = 5.5%; 5-9 medications = 32.2%; ≥10 medications = 46.9%. **Controls:** 0 medications= 26.1%; 1 medications= 9.4%; 2 medications = 8.7%; 3 medications = 8.6%; 4 medications = 7.9%; 5-9 medications = 26.7%; ≥10 medications =12.7%	–	≥3 medications
		3 drugs	1 drug	RR = 1.5, (1.2 - 2.0)			
		4 drugs	1 drug	RR = 2.1, (1.7 - 2.7)			
		5-9 drugs	1 drug	RR= 2.8, (2.3 - 3.5)			
		≥10 drugs (extreme)	1 drug	RR = 3.8, (3.0 - 5.7)			

Table 9: Polypharmacy and risk of hospitalization or life threatening events or death

Study	Study Type	Polypharmacy	Comparator	Risk Ratio (95% CI)	Incidence	Mean Drugs Used	Risk Factors
Olivier, P. *et al.* (2009)	Cases-Control	5.9 drugs	4.5 drugs	OR= 1.18, (1.08-1.29) p=0.0003	Patients taking ≥1 drug before admission: With ADR = 98.5%; Without ADR = 92.3%	With ADR = 5.85 ± 2.89 (1-16) ; Without ADR = 4.49 ± 2.82 (1-15)	Polypharmacy, Self-Medication, Use of Antithrombotics, Use of Bacterial Drugs

Table 10: Polypharmacy and risk of any serious ADR

Study	Study Type	Polypharmacy	Comparator	Risk Ratio (95% CI)	Incidence	Mean Drugs Used	Risk Factors
Macedo, A F *et al.* (2011)	Observational	≥2 Drugs	1 drug	OR= 1.17, (0.86 - 1.33), p-value <0.05	1 Drug = 33.2% (46.4% serious ADRs; 53.8% non-serious); ≥2 Drugs = 66.8% (48.0% serious ADRs; 52.0% non-serious); ≥3 Drugs = 46.5% (50.1% serious ADRs; 49.9% non-serious); ≥4 Drugs = 31.4% (51.9% serious ADRs; 48.1% non-serious)	Mean number of prescriptions = 2.9 ± 2.0 (range 1-14)	Polypharmacy, Male Gender
		≥3 Drugs	1 Drugs	OR= 1.23, (1.02-1.51), p-value <0.05			
		≥4 Drugs	1 Drugs	OR= 1.30, (1.04-1.62) , p-value <0.05			

CHAPTER IV

DISCUSSION

Discussion

There is some evidence suggesting that the use of multiple drugs in simultaneous is associated with an increased risk of adverse drug reactions, most of them preventable. (Fried *et al.,* 2014; Gutiérrez-Valencia *et al.,* 2018; Leelakanok *et al.,* 2017; Maher *et al.,* 2014). However, most of those studies do not discriminate results according to the seriousness of adverse drug reactions. As such, it is not possible to ascertain whether those reactions are clinically important or not based on current available evidence.

In this context, it is important to clarify if polypharmacy is an independent risk factor for serious adverse drug reactions. In order to accomplish this objective, a systematic review of the literature was carried out to identify published studies assessing the risk of serious adverse reactions between polypharmacy and non-polypharmacy patients.

The conduction of the present study is particularly relevant in the light that prescription patterns are changing and the number of patients using multiple drugs in simultaneous has been increasing over time (Kantor *et al.,* 2016). This is due to the fact that current treatment guidelines often recommend the prescription of more than one drug to initiate therapy in several diseases and also because of the fact that populations are getting older, having therefore several comorbidities which need to be addressed through the concurrent use of several drugs. This systematic review includes studies published over the past 10 years (2008-2018) with the aim of aggregating results that best reflect the most current standards of clinical practice. In addition, with the search strategy being restricted to the last few years, it was expected that the studies would have better methodological quality than the older ones, which in turn would contribute to more robust conclusions.

According to the inclusion/exclusion criteria applied to this systematic review, studies focused on a particular disease or condition, a given drug and/or a specific adverse drug reaction were not considered. The main objective of using this pre-established condition was to consider only studies reporting results obtained from populations with a broad spectrum of clinical characteristics, and therefore to avoid comparisons between populations that are not comparable at the baseline and that are at different risks to develop adverse events over time. For example, patients with type 2 diabetes are at an increased risk for macrovascular adverse events (e.g. cardiovascular disease, and heart failure (Hippisley-Cox & Coupland, 2016b), and microvascular complications (e.g. blindness, kidney disease, and amputation) (Hippisley-Cox & Coupland, 2016a), while patients with rheumatoid arthritis have a higher

risk of developing malignancies compared with the general population (Simon *et al.,* 2015). Thus, studies assessing the association between polypharmacy and the risk of hospitalization among patients with rheumatoid arthritis (Filkova *et al.,* 2017), or cancer patients (Park *et al.,* 2016), for example, were excluded. Others estimating the impact of using several drugs versus monotherapy within a given pharmacological class, such as the risk of death among schizophrenic individuals on multiple anti-psychotics, antidepressants or benzodiazepines versus monotherapy (Tiihonena *et al.,* 2012), were also excluded. In addition, studies that addressed only a particular adverse outcome, for example constipation and diarrhea (Fosnes *et al.,* 2011), fall-related hospitalization (Ryan-Atwood *et al.,* 2017), or indicators of patient frailty (Ballew *et al.,* 2017) were not considered. Furthermore, the objective of the present work was to estimate an overall risk. In the future, other systematic reviews should be performed to explore the impact of polypharmacy versus non-polypharmacy in patients with particular diseases.

The analysis of the results was still challenging due to few reasons. First, the concept of polypharmacy varied considerably between studies and, as such, it is difficult to analyze the results in an aggregate way. There is not a consensual and widely-accepted definition of polypharmacy (Masnoon *et al.,* 2017). Some of the studies have defined polypharmacy in a qualitative manner as the "simultaneous use of multiple drugs" (i.e. ≥2 drugs), while others used an objective threshold of ≥5 drugs, or ≥6 drugs. Furthermore, there were studies that defined "excessive" or "extreme" polypharmacy as the concurrent use of ≥9 or ≥10 drugs. Similarly, the number of drugs used by patients included in the control groups ranged significantly (between 0 and 5). Therefore, some of the patients included in the control groups of given studies (e.g. patients using 5 drugs in the control group of the study by Salvi *et al.,* (2017) would have been classified as polypharmacy patients in other studies (e.g. polypharmacy was defined as using ≥2 drugs by Laatikainen et al. 2016, or ≥3 drugs by Chen, *et al.,* 2014, Bourgeois *et al.,* 2010, and Pedrós *et al.,* 2014). Second, while some studies were objectively designed to compare the risk of adverse drug reactions between polypharmacy and non-polypharmacy patients (Payne *et al.,* 2014; Salvi *et al.,* 2017; Schöttker *et al.,* 2017; Marcum *et al.,* 2012), with three of those also aiming to determine an objective threshold for the number of medications that increases such risk (Macedo *et al.,* 2011; Gnjidic *et al.,* 2012; Rausch *et al.,* 2017); others were aimed to identify risk factors (e.g. polypharmacy, age, gender) associated with adverse drug reactions through the comparison of the characteristics of patients affected by such reactions with those of unaffected patients (Sevilla-Sanchez *et al.,* 2017; Leendertse *et al.,* 2008; Abe *et al.,* 2016; Varallo *et al.,* 2014;

Chen *et al.,* 2014; Bourgeois *et al.,* 2010; Olivier *et al.,* 2009; Laatikainen *et al.,* 2016; Pedrós *et al.,* 2014). This is an important point because it is possible that this systematic review did not have enough power to identify other studies aimed at identifying risk factors for adverse reactions, but in which polypharmacy has not been identified as being one of those. This is a limitation of the present study.

Despite the challenges that have been pointed out, the results of this systematic review are, in general, sufficiently robust to answer the research question. The methodological quality of the included studies was moderate to high, with the exception of one study which was of poor quality. Out of the 16 studies included in the analysis, the study by Schottker *et al.* (2017) was the only one in which no association was found between polypharmacy (including extreme polypharmacy) and serious adverse drug reactions (mortality in that study). The methodological approach used in the study by Schottker *et al.* (2017) is different from the other studies. Schottker and colleagues addressed confounding for indication through the adjustment of the model for a propensity score for polypharmacy. Although they have initially found an association between polypharmacy and non-cancer mortality in a model adjusted for comorbidity and other factors, that association lost statistical significance after an additional adjustment for a propensity score for polypharmacy. They concluded that statistical significant associations reported in other studies are probably affected by confounding by indication. In addition Schottker *et al.* (2017) found an interaction between extreme polypharmacy and multi-morbidity, which is expected given than patients with multiple medical conditions need to be treated with a high number of drugs. Thus, extreme polypharmacy may only be harmful to patients without multi-morbidity (i.e. patients who do not have indication to receive several drugs), while those with several comorbidities may benefit from the concurrent use of multiple drugs (Schottker *et al.,* 2017).Polypharmacy has been described in previously published studies as one of the major risk factors for hospital admission, particularly among older people (Fushiki *et al.,* 2014; Lalic *et al.,* 2016). The 11 studies assessing this association in the present systematic review indicated that polypharmacy increased the risk of hospitalization, but one of those studies only find a statistically significant association when the number of drugs used was ≥10 versus <5 (Sevilla-Sanchez *et al.,* 2017). These findings are in line with the available literature, since polypharmacy patients are usually more likely to be hospitalized than the others.

Some authors have argued that few drug-related problems, such as drug-drug interactions, non-compliance, adverse drug reactions and inappropriate prescribing, may contribute to increase the risk of mortality among patients under treatment with multiple

drugs in simultaneous (Hajjar *et al.,* 2007; Pasina *et al.,* 2014; Salvi *et al.,* 2012). The results from other studies published in the scientific literature have not found a causal relationship between polypharmacy and mortality (Díez-Manglano *et al.,* 2015; Nobili *et al.,* 2011; Schöttker *et al.,* 2018). The results of the studies included in our systematic review do not allow drawing definitive conclusions on this topic. Nevertheless, the analyzed evidence is possibly not robust enough to establish an association between polypharmacy and an increased risk of death. First, the study by Gnjidic *et al.* (2012) was not designed to compare the risk of mortality between polypharmacy and non-polypharmacy patients, but rather to determine the number of medications which is associated with mortality. They used Youden Index (J), which is usually used in other studies to indicate the performance of a diagnostic test (the larger the better) at a given cutoff. When both sensitivity and specificity equals 1 at the same time, the maximum value of the Youden Index (J = sensitivity + specificity – 1) is reached (*J* = 1), which indicates a perfect test, i.e. the false positive rate (1 – specificity) is zero (0) (Kallner, 2018). Thus, the results obtained by Gnjidic *et al.* (2012) simply allow to conclude that a cutoff of 4.5 medications is a marker for mortality among elderly men. Second, according to the most adjusted analysis (Cox proportional hazards regression model) in the study by Salvi *et al.* (2017), polypharmacy (concurrent use of 6 to 9 drugs) slightly increased the risk of in-hospital mortality (lower limit of the 95% CI was estimated at 1.00, $p<0.05$), while extreme polypharmacy (≥10 drugs) was linked to an increased risk of 6-month mortality, but not in-hospital mortality. Lastly, Schottker *et al.* (2017) have not found any relationship between polypharmacy and mortality based on the results from a propensity score analysis. Noteworthy, both Salvi *et al.* (2017) and Schottker *et al.* (2017) have found statistically significant associations between polypharmacy and mortality based on crude relative risks (i.e. OR and HR) that lost statistical significance after they have adjusted the analysis for several potential confounders. These examples illustrate the importance of addressing the covariates that can contaminate the results obtained from observational data and consequently lead to misleading conclusions.

Interestingly, Rausch *et al.* (2017) excluded indicators of inappropriate drug use (IDU) (e.g. prescription of ≥2 drugs of the same pharmacological group [i.e. duplicate therapy], multiple psychoactive drugs, or several medications with known drug-drug interactions) before analyzing the relationship between the number of prescribed drugs and the composite outcome of hospitalization or death. They found that indicators of IDU were absent in approximately half of the adverse events analyzed, and among those cases the risk for the outcome of interest increased with the increasing number of the prescribed drugs

(Rausch *et al.,* 2017). The methodological approach used in this study may be a good example to be followed in further studies aimed to study polypharmacy in the light of the rationality of the prescription.

The study performed by Macedo *et al.* (2011) was the only one that used data from spontaneous reports of suspected adverse drug reactions, and which have considered any criteria of seriousness to classify the reactions. The authors found that the likelihood of a spontaneous report being classified as serious was higher when the patient used ≥3 drugs compared to one drug.

The results of this systematic review should be interpreted in the light of the following. The search strategy was performed within only two databases (EMBASE and MEDLINE), and restricted to articles published in English. Searches in the grey literature were not carried out. Therefore, there is the possibility that some studies have not been captured by the search strategy.

Although the aim of the present systematic review was to examine whether polypharmacy is associated or not with an increased risk of serious adverse drug reactions among the general population, nine out of the 16 studies included only patients aged ≥65 years old. This means that there is lack of evidence on the effects of polypharmacy among younger patients. However, the prevalence of multi-morbidity and polypharmacy among the young and adult populations is considerable (Barnett *et al.,* 2012; Menditto *et al.,* 2019). As an example, the results of a Scottish cross-sectional study of a database of 1,751,841 individuals revealed that the absolute number of people with multi-morbidity was higher than in those younger than 65 years of age (210,500 vs. 194,996) (Barnett *et al.,* 2012). As another example, six multi-morbidity/polypharmacy patterns (i.e. respiratory, mental health, cardiometabolic, endocrinological, osteometabolic, and mechanical-pain) were identified in a cross-sectional study conducted in Spain, which analyzed electronic medical databases and pharmacy dispensing data for 887,572 patients aged ≤65 years old (Menditto *et al.,* 2019). Therefore, further studies are needed to evaluate the association between polypharmacy and the risk of serious adverse drug reactions in the non-elderly population.

This systematic review allowed assessing the risk of serious adverse drug reactions according to the number of drugs used by patients, but it does not take into account the rationality of the prescription. Although the results suggest that the risk of serious adverse drug reactions is as high as the greater the number of drugs used by patients, it should not be concluded that polypharmacy is harmful in itself. There are patients who have several

comorbidities and, as such, need to use several drugs simultaneously. Thus the main problem with polypharmacy is not polypharmacy in itself, but probably the lack of an effective adjustment of the therapeutic schemes to the needs of the individual patient, which can assure that the benefits of the treatment outweigh its risks. In future studies it would be important to assess the influence of polypharmacy on the risk of serious adverse drug reactions from a qualitative point of view, i.e. taking into account the rationality of the prescribed therapy. On the other hand, it would be important to clarify whether the possible risks that arise from polypharmacy outweigh its benefits, including those of long term (e.g. stroke, retinopathy, etc.). From this point of view, observational studies, including patient records, will be needed to allow long-term outcome assessments to be adjusted with various variables and risk factors.

CHAPTER V

CONCLUSIONS

Conclusions

This thesis was aimed to identify studies assessing the risk of serious adverse drug reactions associated with polypharmacy. In order to the initial research question, a systematic review of the literature was conducted. The most relevant conclusions obtained from this work are the following:

- Sixteen studies were included in this systematic review, most of which (n=11) using hospital admission as the outcome of interest. Two additional studies assessed the risk of hospital admission due to polypharmacy as part of a composite outcome (hospital admission or death; hospital admission or life-threatening events or death).
- The results of the studies suggest that polypharmacy may increase the risk of i) hospital admission and ii) disability. The findings of the studies evaluating composite outcomes suggest that polypharmacy is associated with an increased risk of i) hospital admission or death; ii) hospital admission or life-threatening events or death; and iii) any serious adverse drug reaction.
- The three studies evaluating the risk of death due to polypharmacy present conflicting results. Thus, it is not possible to reach a definitive conclusion.
- The methodological quality of the majority of the studies (n=9) was assessed as being moderate. Only 6 studies were judged as having good methodological quality, while one has high risk of bias. However, the characteristics and the methodology of the studies seem to be heterogeneous, despite the strict inclusion/exclusion criteria adopt for this systematic review.
- The studies used different definitions of polypharmacy, which varied from a quantitative (n=8) threshold to a qualitative description using a mean number of drugs (n=7); one study did not provide an explicit definition of polypharmacy. The number of drugs used by patients allocated to control groups (i.e. non-polypharmacy) also varied significantly between the studies, ranging from 0 to 5 drugs. Additionally, the covariates used to adjust the results differ across the studies.

In conclusion, although polypharmacy seems to be a risk factor for serious adverse drug reactions, particularly hospitalization, there is a lack of homogeneous methods across the studies, mainly regarding the polypharmacy definition and the number of drugs used to define in the comparators used.

CHAPTER VI

REFERENCES

REFERENCES

Abe, T., Tamiya, N., Kitahara, T., & Tokuda, Y. (2016). Polypharmacy as a risk factor for hospital admission among ambulance-transported old-old patients. *Acute Medicine & Surgery*, *3*(2), 107–113. https://doi.org/10.1002/ams2.153

Alshabanat, A., Zafari, Z., Albanyan, O., Dairi, M., & FitzGerald, J. M. (2015). Asthma and COPD overlap syndrome (ACOS): A systematic review and meta analysis. *PLoS ONE*, *10*(9), 1–15. https://doi.org/10.1371/journal.pone.0136065

Ballew, S. H., Chen, Y., Daya, N. R., Godino, J. G., Windham, B. G., McAdams-DeMarco, M., Coresh, J., Selvin, E., & Grams, M. E. (2017). Frailty, Kidney Function, and Polypharmacy: The Atherosclerosis Risk in Communities (ARIC) Study. *American Journal of Kidney Diseases*, *69*(2), 228–236. https://doi.org/10.1053/j.ajkd.2016.08.034

Barnett, K., Mercer, S. W., Norbury, M., Watt, G., Wyke, S., & Guthrie, B. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *The Lancet*, *380*(9836), 37–43. https://doi.org/10.1016/S0140-6736(12)60240-2

Bourgeois, F. T., Shannon, M. W., Valim, C., & Mandl, K. D. (2010). Adverse drug events in the outpatient setting: An 11-year national analysis. *Pharmacoepidemiology and Drug Safety*, *19*(9), 901–910. https://doi.org/10.1002/pds.1984

Bouvy, J. C., De Bruin, M. L., & Koopmanschap, M. A. (2015). Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies. *Drug Safety*, *38*(5), 437–453. https://doi.org/10.1007/s40264-015-0281-0

Chen, Y. C., Fan, J. S., Chen, M. H., Hsu, T. F., Huang, H. H., Cheng, K. W., Yen, D. H. T., Huang, C. I., Chen, L. K., & Yang, C. C. (2014). Risk factors associated with adverse drug events among older adults in emergency department. *European Journal of Internal Medicine*, *25*(1), 49–55. https://doi.org/10.1016/j.ejim.2013.10.006

Cooper, J. W. (1999). *Adverse Drug Reactions-Related Hospitalizations of Nursing Facility Patients: A 4-Years Study*. COOPER, J. W. (1999). Adverse Drug Reaction-Related Hospitalizations of Nursing Facility Patients. Southern Medical Journal, 92(5), 485–490. https://doi.org/10.1097/00007611-199905000-00007

Davies, E. C., Green, C. F., Taylor, S., Williamson, P. R., Mottram, D. R., & Pirmohamed, M. (2009). Adverse drug reactions in hospital in-patients: A prospective analysis of 3695 patient-episodes. *PLoS ONE*, *4*(2). https://doi.org/10.1371/journal.pone.0004439

Díez-Manglano, J., Giménez-López, M., Garcés-Horna, V., Sevil-Puras, M., Castellar-Otín, E., González-García, P., Fiteni-Mera, I., & Morlanes-Navarro, T. (2015). Excessive polypharmacy and survival in polypathological patients. *European Journal of Clinical Pharmacology*, *71*(6), 733–739. https://doi.org/10.1007/s00228-015-1837-8

Dörks, M., Herget-Rosenthal, S., Schmiemann, G., & Hoffmann, F. (2016). Polypharmacy and Renal Failure in Nursing Home Residents: Results of the Inappropriate Medication in Patients with Renal Insufficiency in Nursing Homes (IMREN) Study. *Drugs and Aging*, *33*(1), 45–51. https://doi.org/10.1007/s40266-015-0333-2

EMA. (2017). Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 4). *Heads of Medicine Agencies*, *October*, 1–33. https://doi.org/EMA/876333/2011 Rev. 1*

European Comission. (2008). *REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products f*. 8.

Filkova, M., Carvalho, J., Norton, S., Scott, D., Mant, T., Molokhia, M., Cope, A., & Galloway, J. (2017). Polypharmacy and unplanned hospitalizations in patients with rheumatoid arthritis. *Journal of Rheumatology*, *44*(12), 1786–1793. https://doi.org/10.3899/jrheum.160818

Fosnes, G. S., Lydersen, S., & Farup, P. G. (2011). Constipation and diarrhoea - common adverse drug reactions? A cross sectional study in the general population. *BMC Clinical Pharmacology*, *11*. https://doi.org/10.1186/1472-6904-11-2

Fried, T. R., O'Leary, J., Towle, V., Goldstein, M. K., Trentalange, M., & Martin, D. K. (2014). Health outcomes associated with polypharmacy in community-dwelling older adults: A systematic review. *Journal of the American Geriatrics Society*, *62*(12), 2261–2272. https://doi.org/10.1111/jgs.13153

Fushiki, Y., Kinoshita, K., & Tokuda, Y. (2014). Polypharmacy and Adverse Drug Events Leading to Acute Care Hospitalization in Japanese Elderly. *General Medicine*, *15*(2), 110–116. https://doi.org/10.14442/general.15.110

GA Wells, B Shea, D O'Connell, J Peterson, V Welch, M Losos, P. T. (2006). The Newcastle-Ottawa Scale (NOS). In *The Newcastle-Ottawa Scale (NOS)* (Vol. 13, Issue 2, pp. 110–115). Professor GA Wells, Department of Epidemiology and Commuunity Medicine, University of Ottawa, Room 3227A, 451 Smyth Road, Ottawa, Ontario K1J 8M5, Canada. https://doi.org/10.1207/s15551407vcq1302_4

Giardina, C., Cutroneo, P. M., Mocciaro, E., Russo, G. T., Mandraffino, G., Basile, G., Rapisarda, F., Ferrara, R., Spina, E., & Arcoraci, V. (2018). Adverse drug reactions in hospitalized patients: Results of the FORWARD (facilitation of reporting in hospital ward) study. *Frontiers in Pharmacology*, *9*(APR), 1–12. https://doi.org/10.3389/fphar.2018.00350

Gnjidic, D., Hilmer, S. N., Blyth, F. M., Naganathan, V., Waite, L., Seibel, M. J., McLachlan, A. J., Cumming, R. G., Handelsman, D. J., & Le Couteur, D. G. (2012). Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *Journal of Clinical Epidemiology*, *65*(9), 989–995. https://doi.org/10.1016/j.jclinepi.2012.02.018

Gutiérrez-Valencia, M., Izquierdo, M., Cesari, M., Casas-Herrero, Inzitari, M., & Martínez-Velilla, N. (2018). The relationship between frailty and polypharmacy in older people: A systematic review. *British Journal of Clinical Pharmacology*, *84*(7), 1432–1444. https://doi.org/10.1111/bcp.13590

Hajjar, E. R., Cafiero, A. C., & Hanlon, J. T. (2007). Polypharmacy in elderly patients. *American Journal Geriatric Pharmacotherapy*, *5*(4), 345–351. https://doi.org/10.1016/j.amjopharm.2007.12.002

Hippisley-Cox, J., & Coupland, C. (2016a). Diabetes treatments and risk of amputation, blindness, severe kidney failure, hyperglycaemia, and hypoglycaemia: Open cohort study in primary care. *BMJ (Online)*, *352*. https://doi.org/10.1136/bmj.i1450

Hippisley-Cox, J., & Coupland, C. (2016b). Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality: Cohort study in primary care. *BMJ*

(Online), *354*. https://doi.org/10.1136/bmj.i3477

Hoffman, D. A., Schiller, M., Greenblatt, J. M., & Iosifescu, D. V. (2011). Polypharmacy or medication washout: An old tool revisited. *Neuropsychiatric Disease and Treatment*, *7*(1), 639–648. https://doi.org/10.2147/ndt.s24375

Hoigné, R., Lawson, D. H., & Weber, E. (1990). Risk factors for adverse drug reactions - epidemiological approaches. *European Journal of Clinical Pharmacology*, *39*(4), 321–325. https://doi.org/10.1007/BF00315403

Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H., Caforio, A. L. P., Crea, F., Goudevenos, J. A., Halvorsen, S., Hindricks, G., Kastrati, A., Lenzen, M. J., Prescott, E., Roffi, M., Valgimigli, M., Varenhorst, C., Vranckx, P., Widimský, P., … Gale, C. P. (2018). 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal*, *39*(2), 119–177. https://doi.org/10.1093/eurheartj/ehx393

Johansson, T., Abuzahra, M. E., Keller, S., Mann, E., Faller, B., Sommerauer, C., Höck, J., Löffler, C., Köchling, A., Schuler, J., Flamm, M., & Sönnichsen, A. (2016). Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis. *British Journal of Clinical Pharmacology*, 532–548. https://doi.org/10.1111/bcp.12959

Kantor, E. D., Rehm, C. D., Haas, J. S., Chan, A. T., Giovannucci, E. L., Sloan, M., Cancer, K., Health, P., Sciences, B., Hospital, M. G., Unit, T. E., & Hospital, M. G. (2016). *HHS Public Access*. *314*(17), 1818–1831. https://doi.org/10.1001/jama.2015.13766.Trends

Kingston, A., Robinson, L., Booth, H., Knapp, M., Jagger, C., Adelaja, B., Avendano, M., Bamford, S. M., Banerjee, S., Berwald, S., Bowling, A., Burgon, C., Bustard, E., Comas-Herrera, A., Dangoor, M., Dixon, J., Farina, N., Greengross, S., Grundy, E., … Wittenberg, R. (2018). Projections of multi-morbidity in the older population in England to 2035: Estimates from the Population Ageing and Care Simulation (PACSim) model. *Age and Ageing*, *47*(3), 374–380. https://doi.org/10.1093/ageing/afx201

Laatikainen, O., Sneck, S., Bloigu, R., Lahtinen, M., Lauri, T., & Turpeinen, M. (2016). Hospitalizations due to adverse drug events in the elderly-a retrospective register study. *Frontiers in Pharmacology*, *7*(OCT), 1–8. https://doi.org/10.3389/fphar.2016.00358

Lalic, S., Sluggett, J. K., Ilomäki, J., Wimmer, B. C., Tan, E. C. K., Robson, L., Emery, T., & Bell, J. S. (2016). Polypharmacy and Medication Regimen Complexity as Risk Factors for Hospitalization Among Residents of Long-Term Care Facilities: A Prospective Cohort Study. *Journal of the American Medical Directors Association*, *17*(11), 1067.e1. https://doi.org/10.1016/j.jamda.2016.08.019

Lavan, A. H., & Gallagher, P. (2016). Predicting risk of adverse drug reactions in older adults. *Therapeutic Advances in Drug Safety*, *7*(1), 11–22. https://doi.org/10.1177/2042098615615472

Lazarou, J. (1998). Adverse drug reactions in hospitalized patients. *JAMA : The Journal of the American Medical Association*, *280*(20). https://doi.org/10.1097/01.wox.0000412144.27167.4e

Leelakanok, N., Holcombe, A. L., Lund, B. C., Gu, X., & Schweizer, M. L. (2017). Association between polypharmacy and death: A systematic review and meta-analysis. *Journal of the American Pharmacists Association*, *57*(6), 729-738.e10. https://doi.org/10.1016/j.japh.2017.06.002

Leendertse, A. J., Egberts, A. C. G., Stoker, L. J., & Van Den Bemt, P. M. L. A. (2008). Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Archives of Internal Medicine*, *168*(17), 1890–1896. https://doi.org/10.1001/archinternmed.2008.3

Leiss, W., Méan, M., Limacher, A., Righini, M., Jaeger, K., Beer, H. J., Osterwalder, J., Frauchiger, B., Matter, C. M., Kucher, N., Angelillo-Scherrer, A., Cornuz, J., Banyai, M., Lämmle, B., Husmann, M., Egloff, M., Aschwanden, M., Rodondi, N., & Aujesky, D. (2015). Polypharmacy is Associated with an Increased Risk of Bleeding in Elderly Patients with Venous Thromboembolism. *Journal of General Internal Medicine*, *30*(1), 17–24. https://doi.org/10.1007/s11606-014-2993-8

Macedo, A. F., Alves, C., Craveiro, N., & Marques, F. B. (2011). Multiple drug exposure as a risk factor for the seriousness of adverse drug reactions. *Journal of Nursing Management*, *19*(3), 395–399. https://doi.org/10.1111/j.1365-2834.2011.01216.x

Maher, R. L., Hanlon, J., & Hajjar, E. R. (2014). Clinical consequences of polypharmacy in elderly. *Expert Opinion on Drug Safety*, *13*(1), 57–65. https://doi.org/10.1517/14740338.2013.827660

Marcum, Z. A., Amuan, M. E., Hanlon, J. T., Aspinall, S. L., Handler, S. M., Ruby, C. M., & Pugh, M. J. V. (2012). Prevalence of unplanned hospitalizations caused by adverse drug reactions in older veterans. *Journal of the American Geriatrics Society*, *60*(1), 34–41. https://doi.org/10.1111/j.1532-5415.2011.03772.x

Marengoni, A., Angleman, S., Melis, R., Mangialasche, F., Karp, A., Garmen, A., Meinow, B., & Fratiglioni, L. (2011). Aging with multimorbidity: A systematic review of the literature. *Ageing Research Reviews*, *10*(4), 430–439. https://doi.org/10.1016/j.arr.2011.03.003

Marques, F. B., Penedones, A., Mendes, D., & Alves, C. (2016). A systematic review of observational studies evaluating costs of adverse drug reactions. *ClinicoEconomics and Outcomes Research*, *8*, 413–426. https://doi.org/10.2147/CEOR.S115689

Masnoon, N., Shakib, S., Kalisch-Ellett, L., & Caughey, G. E. (2017). What is polypharmacy? A systematic review of definitions. *BMC Geriatrics*, *17*(1), 1–10. https://doi.org/10.1186/s12877-017-0621-2

Menditto, E., Miguel, A. G., Juste, A. M., Plou, B. P., Pascual-Salcedo, M. A., Orlando, V., Rubio, F. G., & Torres, A. P. (2019). Patterns of multimorbidity and polypharmacy in young and adult population: Systematic associations among chronic diseases and drugs using factor analysis. *PLoS ONE*, *14*(2), 1–18. https://doi.org/10.1371/journal.pone.0210701

Midão, L., Giardini, A., Menditto, E., Kardas, P., & Costa, E. (2018). Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe. *Archives of Gerontology and Geriatrics*, *78*, 213–220. https://doi.org/10.1016/j.archger.2018.06.018

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Altman, D., Antes, G., Atkins, D., Barbour, V., Barrowman, N., Berlin, J. A., Clark, J., Clarke, M., Cook, D., D'Amico, R., Deeks, J. J., Devereaux, P. J., Dickersin, K., Egger, M., Ernst, E., … Tugwell, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7). https://doi.org/10.1371/journal.pmed.1000097

Molokhia, M., & Majeed, A. (2017). Current and future perspectives on the management of polypharmacy. *BMC Family Practice*, *18*(1), 1–9. https://doi.org/10.1186/s12875-017-

0642-0

Montané, E., Arellano, A. L., Sanz, Y., Roca, J., & Farré, M. (2018). Drug-related deaths in hospital inpatients: A retrospective cohort study. *British Journal of Clinical Pharmacology*, *84*(3), 542–552. https://doi.org/10.1111/bcp.13471

Moore, T. J., Cohen, M. R., & Furberg, C. D. (2007). Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. *Archives of Internal Medicine*, *167*(16), 1752–1759. https://doi.org/10.1001/archinte.167.16.1752

Morin, L., Johnell, K., Laroche, M. L., Fastbom, J., & Wastesson, J. W. (2018). The epidemiology of polypharmacy in older adults: Register-based prospective cohort study. *Clinical Epidemiology*, *10*, 289–298. https://doi.org/10.2147/CLEP.S153458

Nguyen, J. K., Fouts, M. M., Kotabe, S. E., & Lo, E. (2006). Polypharmacy as a risk factor for adverse drug reactions in geriatric nursing home residents. *American Journal Geriatric Pharmacotherapy*, *4*(1), 36–41. https://doi.org/10.1016/j.amjopharm.2006.03.002

Nobili, A., Licata, G., Salerno, F., Pasina, L., Tettamanti, M., Franchi, C., De Vittorio, L., Marengoni, A., Corrao, S., Iorio, A., Marcucci, M., & Mannucci, P. M. (2011). Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. *European Journal of Clinical Pharmacology*, *67*(5), 507–519. https://doi.org/10.1007/s00228-010-0977-0

Olivier, P., Bertrand, L., Tubery, M., Lauque, D., Montastruc, J. L., & Lapeyre-Mestre, M. (2009). Hospitalizations because of adverse drug reactions in elderly patients admitted through the emergency department: A prospective survey. *Drugs and Aging*, *26*(6), 475–482. https://doi.org/10.2165/00002512-200926060-00004

Organization, W. H. (2019). Medication Safety in Polypharmacy. *World Health Organization Technical Report Series*, 11–13. https://apps.who.int/iris/bitstream/handle/10665/325454/WHO-UHC-SDS-2019.11-eng.pdf?ua=1

Pardo Cabello, A. J., Del Pozo Gavilán, E., Gómez Jiménez, F. J., Mota Rodríguez, C., Luna Del Castillo, J. D. D., & Puche Cañas, E. (2016). Drug-related mortality among inpatients: a retrospective observational study. *European Journal of Clinical Pharmacology*, *72*(6), 731–736. https://doi.org/10.1007/s00228-016-2026-0

Park, J. W., Roh, J. L., Lee, S. wook, Kim, S. B., Choi, S. H., Nam, S. Y., & Kim, S. Y. (2016). Effect of polypharmacy and potentially inappropriate medications on treatment and posttreatment courses in elderly patients with head and neck cancer. *Journal of Cancer Research and Clinical Oncology*, *142*(5), 1031–1040. https://doi.org/10.1007/s00432-015-2108-x

Pasina, L., Djade, C. D., Tettamanti, M., Franchi, C., Salerno, F., Corrao, S., Marengoni, A., Marcucci, M., Mannucci, P. M., & Nobili, A. (2014). Prevalence of potentially inappropriate medications and risk of adverse clinical outcome in a cohort of hospitalized elderly patients: Results from the REPOSI Study. *Journal of Clinical Pharmacy and Therapeutics*, *39*(5), 511–515. https://doi.org/10.1111/jcpt.12178

Patel, P. B., & Patel, T. K. (2019). Mortality among patients due to adverse drug reactions that occur following hospitalisation: a meta-analysis. *European Journal of Clinical Pharmacology*, *75*(9), 1293–1307. https://doi.org/10.1007/s00228-019-02702-4

Payne, R. A. (2016). The epidemiology of polypharmacy. *Clinical Medicine, Journal of the Royal College of Physicians of London*, *16*(5), 465–469. https://doi.org/10.7861/clinmedicine.16-5-465

Payne, R. A., Abel, G. A., Avery, A. J., Mercer, S. W., & Roland, M. O. (2014). Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. *British Journal of Clinical Pharmacology*, *77*(6), 1073–1082. https://doi.org/10.1111/bcp.12292

Pedrós, C., Quintana, B., Rebolledo, M., Porta, N., Vallano, A., & Arnau, J. M. (2014). Prevalence, risk factors and main features of adverse drug reactions leading to hospital admission. *European Journal of Clinical Pharmacology*, *70*(3), 361–367. https://doi.org/10.1007/s00228-013-1630-5

Pitts, P. J., Louet, H. Le, Moride, Y., & Conti, R. M. (2016). 21St Century Pharmacovigilance: Efforts, Roles, and Responsibilities. *The Lancet Oncology*, *17*(11), e486–e492. https://doi.org/10.1016/S1470-2045(16)30312-6

Qato, D. M., Wilder, J., Schumm, L. P., Gillet, V., & Alexander, G. C. (2016). Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Internal Medicine*, *176*(4), 473–482. https://doi.org/10.1001/jamainternmed.2015.8581

Rausch, C., Laflamme, L., Bültmann, U., & Möller, J. (2017). Number of medications and adverse drug events by unintentional poisoning among older adults in consideration of inappropriate drug use: a Swedish population-based matched case-control study. *European Journal of Clinical Pharmacology*, *73*(6), 743–749. https://doi.org/10.1007/s00228-017-2220-8

Rossi, M., Young, a, & Maher, R. (2007). Polypharmacy and health beleafs in older patients. *The American Journal …*, *5*(4), 317–323. http://ukpmc.ac.uk/abstract/MED/18179989

Ryan-Atwood, T. E., Hutchinson-Kern, M., Ilomäki, J., Dooley, M. J., Poole, S. G., Kirkpatrick, C. M., Manias, E., Mitra, B., & Bell, J. S. (2017). Medication Use and Fall-Related Hospital Admissions from Long-Term Care Facilities: A Hospital-Based Case–Control Study. *Drugs and Aging*, *34*(8), 625–633. https://doi.org/10.1007/s40266-017-0472-8

Salvi, F., Marchetti, A., D'Angelo, F., Boemi, M., Lattanzio, F., & Cherubini, A. (2012). Adverse drug events as a cause of hospitalization in older adults. *Drug Safety*, *35*(SUPPL. 1), 29–45. https://doi.org/10.1007/BF03319101

Salvi, F., Rossi, L., Lattanzio, F., & Cherubini, A. (2017). Is polypharmacy an independent risk factor for adverse outcomes after an emergency department visit? *Internal and Emergency Medicine*, *12*(2), 213–220. https://doi.org/10.1007/s11739-016-1451-5

Schöttker, B., Muhlack, D. C., Hoppe, L. K., Holleczek, B., & Brenner, H. (2018). Updated analysis on polypharmacy and mortality from the ESTHER study. *European Journal of Clinical Pharmacology*, *74*(7), 981–982. https://doi.org/10.1007/s00228-018-2445-1

Schöttker, B., Saum, K. U., Muhlack, D. C., Hoppe, L. K., Holleczek, B., & Brenner, H. (2017). Polypharmacy and mortality: new insights from a large cohort of older adults by detection of effect modification by multi-morbidity and comprehensive correction of confounding by indication. *European Journal of Clinical Pharmacology*, *73*(8), 1041–1048. https://doi.org/10.1007/s00228-017-2266-7

Sevilla-Sanchez, D., Molist-Brunet, N., Amblàs-Novellas, J., Roura-Poch, P., Espaulella-Panicot, J., & Codina-Jané, C. (2017). Adverse drug events in patients with advanced chronic conditions who have a prognosis of limited life expectancy at hospital admission. *European Journal of Clinical Pharmacology*, *73*(1), 79–89. https://doi.org/10.1007/s00228-016-2136-8

Simon, T. A., Thompson, A., Gandhi, K. K., Hochberg, M. C., & Suissa, S. (2015). Incidence of malignancy in adult patients with rheumatoid arthritis: A meta-analysis. *Arthritis Research and Therapy*, *17*(1), 1–10. https://doi.org/10.1186/s13075-015-0728-9

Sonawane, K. B., Cheng, N., & Hansen, R. A. (2018). Serious adverse drug events reported to the FDA: Analysis of the FDA adverse event reporting system 2006-2014 Database. *Journal of Managed Care and Specialty Pharmacy*, *24*(7), 682–690. https://doi.org/10.18553/jmcp.2018.24.7.682

Tiihonena, J., Suokas, J. T., Suvisaari, J. M., Haukka, J., & Korhonen, P. (2012). Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. *Archives of General Psychiatry*, *69*(5), 476–483. https://doi.org/10.1001/archgenpsychiatry.2011.1532

Varallo, F. R., Capucho, H. C., Planeta, C. da S., & Mastroianni, P. de C. (2014). Possible adverse drug events leading to hospital admission in a brazilian teaching hospital. *Clinics*, *69*(3), 163–167. https://doi.org/10.6061/clinics/2014(03)03

Veehof, L. J. G., Stewart, R. E., Meyboom-de Jong, B., & Haaijer-Ruskamp, F. M. (1999). Adverse drug reactions and polypharmacy in the elderly in general practice. *European Journal of Clinical Pharmacology*, *55*(7), 533–536. https://doi.org/10.1007/s002280050669

Wastesson, J. W., Morin, L., Tan, E. C. K., & Johnell, K. (2018). An update on the clinical consequences of polypharmacy in older adults: a narrative review. *Expert Opinion on Drug Safety*, *17*(12), 1185–1196. https://doi.org/10.1080/14740338.2018.1546841

Watanabe, J. H., McInnis, T., & Hirsch, J. D. (2018). Cost of Prescription Drug–Related Morbidity and Mortality. *Annals of Pharmacotherapy*, *52*(9), 829–837. https://doi.org/10.1177/1060028018765159

Wester, K., Jönsson, A. K., Spigset, O., Druid, H., & Hägg, S. (2008). Incidence of fatal adverse drug reactions: A population based study. *British Journal of Clinical Pharmacology*, *65*(4), 573–579. https://doi.org/10.1111/j.1365-2125.2007.03064.x

Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D., Coca, A., de Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S., Kreutz, R., Laurent, S., … Erdine, S. (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension. In *European Heart Journal* (Vol. 39, Issue 33). https://doi.org/10.1093/eurheartj/ehy339)(PMID:30165516)

CHAPTER VII

APPENDIX

APPENDIX 1 - PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	11
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	19
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	27
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	34
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	33
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	79
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	33
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	35
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	NA
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	34
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	34
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	39
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	40
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	40
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	43
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	53
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	56
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	61
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

APPENDIX 2 - Search Strategy

Embase Session Results

No.	Query	Results
#12	#10 AND #11	9,113
#11	#5 OR #6 OR #7 OR #8 OR #9	2,715,763
#10	#1 OR #2 OR #3 OR #4	24,692
#9	'risk factor'/exp OR 'risk factor'	1,051,856
#8	'iatrogenic disease'/exp OR 'iatrogenic disease'	812,129
#7	'drug related problem'/exp OR 'drug related problem'	427
#6	'adverse drug reaction'/exp OR 'adverse drug reaction' OR 'adverse effect'/exp OR 'adverse effect' OR 'adverse reaction'/exp OR 'adverse reaction' OR 'side effect'/exp OR 'side effect' OR 'adverse drug effect'/exp OR 'adverse drug effect' OR 'drug reaction adverse'/exp OR 'drug reaction adverse'	1,745,699
#5	'adverse drug reaction'/exp OR 'adverse drug reaction'	1,546,098
#4		14,384

'multiple drug exposure' OR **'multiple drug treatment'**/exp OR **'multiple drug treatment'**

24,583

#3

polypharmac* OR **'poly pharmac*'** OR **polypharmacotherap*** OR **'polypharmaco therap*'** OR **polymedication*** OR **'poly medication*'** OR **polymedicine*** OR **'poly medicine*'** OR **multipharmac*** OR **'multi pharmac*'** OR **multimedication*** OR **'multi medication*'** OR **multimedicine*** OR **'multi medicine*'** OR **comedication*** OR **'co medication*'** OR **polypragmas*** OR **'poly pragmas*'** OR **overprescri*** OR **'over prescri*'** OR **polymedication**

839

#2

'polypharmacology'/exp OR **'polypharmacology'**

17,386

#1

'polypharmacy'/exp OR **'polypharmacy'**

APPENDIX 3 - Methodological Quality Cohort Studies Form

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✱
   b) somewhat representative of the average _____ in the community ✱
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✱
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✱
   b) structured interview ✱
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✱
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✱
   b) study controls for any additional factor ✱ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✱
   b) record linkage ✱
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✱
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✱
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✱
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

APPENDIX 4 - Methodological Quality Case-Control Studies Form

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✱
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✱
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✱
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✱
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✱
   b) study controls for any additional factor ✱ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✱
   b) structured interview where blind to case/control status ✱
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✱
   b) no

3) Non-Response rate
   a) same rate for both groups ✱
   b) non respondents described
   c) rate different and no designation

APPENDIX 5 - Methodological Quality Cross-Sectional Studies Form

Newcastle-Ottawa Scale adapted for cross-sectional studies

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
- a) Truly representative of the average in the target population. * (all subjects or random sampling)
- b) Somewhat representative of the average in the target population. * (non-random sampling)
- c) Selected group of users.
- d) No description of the sampling strategy.

2) Sample size:
- a) Justified and satisfactory. *
- b) Not justified.

3) Non-respondents:
- a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *
- b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
- c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor):
- a) Validated measurement tool. **
- b) Non-validated measurement tool, but the tool is available or described.*
- c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
- a) The study controls for the most important factor (select one). *
- b) The study control for any additional factor. *

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
- a) Independent blind assessment. **
- b) Record linkage. **
- c) Self report. *
- d) No description.

2) Statistical test:
- a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *
- b) The statistical test is not appropriate, not described or incomplete.

This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment of cross-sectional studies for the systematic review, "Are Healthcare Workers' Intentions to Vaccinate Related to their Knowledge, Beliefs and Attitudes? A Systematic Review".

We have not selected one factor that is the most important for comparability, because the variables are not the same in each study. Thus, the principal factor should be identified for each study.

APPENDIX 6 - Exclusion Reasons (n=93)

	Title	Reason for Exclusion
1	*A limited number of prescribed drugs account for the great majority of drug-drug interactions - Holm, J. et al*	Without relationship between polypharmacy-serious ADRs
2	*A Pharmacovigilance Study in Medicine Department of Tertiary Care Hospital in Chhattisgarh (Jagdalpur), India - Singh H et al*	Without relationship between polypharmacy-serious ADRs
3	*A profile of adverse drug reactions in a rural tertiary care hospital - Patil, S. B. et al*	No relationship between polypharmacy and serious ADRs
4	*A qualitative study to explore how patients identify and assess symptoms as adverse drug reactions - Nataporn Chaipichit et al*	Specific Drug Class
5	*A study of adverse drug reactions in patients admitted to intensive care unit of a tertiary care teaching rural hospital - Kathiria, J. M. et al*	Without relationship between polypharmacy-serious ADRs
6	*A study on polypharmacy among elderly medicine in-patients of a tertiary care teaching hospital of North India - Rohini Gupta et al*	Without Serious Criteria
7	*Adverse drug events responsible for hospitalization in the intensive care unit: A single center descriptive study - Arcizet, J. et al*	Without Serious Criteria
8	*Adverse drug reaction monitoring: Support for pharmacovigilance at a tertiary care hospital in Northern Brazil - Lobo, M. G. A. D. A.*	Without Serious Criteria
9	*Adverse drug reaction-related hospitalizations in persons aged 55 years and over: A population-based study in the Netherlands - Ruiter, R. et al*	No relationship between polypharmacy and serious ADRs
10	*Adverse drug reactions caused by drug-drug interactions in elderly outpatients: A prospective cohort study - Obreli-Neto, P. R. et al*	DRPs
11	*Adverse drug reactions in hospitalized pediatric patients of Saudi Arabian University Hospital and impact of pharmacovigilance in reporting ADR - Lateef M. Khan et al*	Without relationship between polypharmacy-serious ADRs
12	*Adverse Drug Reactions in Hospitalized Pediatric Patients: A Prospective Observational Study - J. Kurian et al*	Without Serious Criteria
13	*Adverse drug reactions in medical intensive care unit of a tertiary care hospital - Joshua, L. et al*	Without Serious Criteria

14	*Adverse drug reactions leading to urgent hospital admission in an elderly population: Prevalence and main features - Pedrós C. et al*	No relationship between polypharmacy and serious ADRs
15	*Adverse drug reactions of spontaneous reports in Shanghai pediatric population - Li, H. et al*	No relationship between polypharmacy and serious ADRs
16	*Adverse drug reactions: Trends in a tertiary care hospital - Rehan, H. S. et al*	No relationship between polypharmacy and serious ADRs
17	*Adverse drug reactions amongst adult patients admitted in lagos state university teaching hospital lagos, Nigeria - Aderemi-Williams, R. I. et al*	No relationship between polypharmacy and serious ADRs
18	*An analysis of adverse drug reactions in extremes of age group at tertiary care teaching hospital - Amin, S.*	Without Serious Criteria
19	*Analysis of polypharmacy effects in older patients using Japanese Adverse Drug Event Report database - Junko Abe et al*	Without relationship between polypharmacy-serious ADRs
20	*Analysis of polypharmacy effects in older patients using Japanese adverse drug event report database - Abe, J. et al*	Without Serious Criteria
21	*Assessment of drug-related problems in pediatric ward of Zewditu Memorial Referral Hospital, Addis Ababa, Ethiopia - Mequanent Kassa Birarra et al*	DRPs
22	*Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population - Johanna Jyrkka¨et al*	Without relationship between polypharmacy-serious ADRs
23	*Case Series Analysis of New Zealand Reports of Rapid Intense Potentiation of Warfarin by Roxithromycin - Ruth L. Savage et al*	Without relationship between polypharmacy-serious ADRs
24	*Causality, Severity and Preventability Assessment of Adverse Cutaneous Drug Reaction: A Prospective Observational Study in a Tertiary Care Hospital - Padmavathi S.et al*	Without Serious Criteria
25	*Characteristics of polymedicated (≥ 4) elderly: A survey in a community-dwelling population aged 60 years and over - Husson, N. et al*	Without relationship between polypharmacy-serious ADRs
26	*Clinical medication reviews in elderly patients with polypharmacy: a cross-sectional study on drug-related problems in the Netherlands - Chau, S. H.*	Without Serious Criteria
27	*Cumulative Anticholinergic Exposure Is Associated with Poor Memory and Executive Function in Older Men - Ling Han et al*	Without Serious Criteria

28	*Diagramming patients' views of root causes of adverse drug events in ambulatory care: An online tool for planning education and research - Brown, M. et al*	No relationship between polypharmacy and serious ADRs
29	*Drug eruptions in the mature patient - Ronni Wolf, Branka Marinovi´c*	Without Serious Criteria
30	*Drug Interactions in Dying Patients: A Retrospective Analysis of Hospice Inpatients in Germany - Sebastian Frechen et al*	DRPs
31	*Drug related problems identified by clinical pharmacist at the internal medicine ward - Abunahlah, N. et al*	DRPs
32	*Drug related problems identified by clinical pharmacist at the Internal Medicine Ward in Turkey - Abunahlah, N. et al*	DRPs
33	*Drug related problems identified by clinical pharmacist at the Internal Medicine Ward in Turkey - Nibal Abunahlah et al*	DRPs
34	*Drug-related problems in the elderly - Bor A et al*	Without Serious Criteria
35	*Effects of Polypharmacy on Adverse Drug Reactions among Geriatric Outpatients at a Tertiary Care Hospital in Karachi: A Prospective Cohort Study - Bilal Ahmed et al*	Without relationship between polypharmacy-serious ADRs
36	*Epidemiology and potential associated risk factors of drug-related problems in hospitalised children in the United Kingdom and Saudi Arabia - Asia N. Rashed et al*	DRPs
37	*Epidemiology and potential risk factors of drug-related problems in Hong Kong paediatric wards - Asia N. Rashed*	DRPs
38	*Epidemiology of Polypharmacy and Potential Drug–Drug Interactions Among Pediatric Patients in ICUs of U.S. Children's Hospitals - Dingwei Dai et al*	Without Serious Criteria
39	*Evaluation of drug-related problems in older polypharmacy primary care patients - Kovačević, S. V. et al*	No relationship between polypharmacy and serious ADRs
40	*Evaluation of Predisposing Factors Associated with Suspected Adverse Drug Reactions of Hospitalized Patients - Manoj K Mudigubba et al*	Without Serious Criteria
41	*Exploring Variation in Rates of Polypharmacy Across Long Term Care Homes - Bronskill, S. E.*	No relationship between polypharmacy and serious ADRs
42	*Frailty, Kidney Function, and Polypharmacy: The Atherosclerosis Risk in Communities (ARIC) Study -Shoshana H. Ballew*	Without relationship between polypharmacy-serious ADRs
43	*Hyperglycemic adverse events following antipsychotic drug administration in spontaneous adverse event reports - Yamato Kato et al*	Without Serious Criteria

44	*Identification of drug related problems by clinical pharmacist in prescriptions with polypharmacy: A prospective interventional study - Greeshma, M. et al*	DRPs
45	*Identification of Drug Related Problems by Clinical Pharmacist in Prescriptions with Polypharmacy: A Prospective Interventional Study - Mohan Greeshma et al*	DRPs
46	*Idiosyncratic Adverse Reactions of Most Frequent Drug Combinations Longterm Use Among Hospitalized patients with polypharmacy - Edisa Trumic et al*	Without Serious Criteria
47	*Impact of pharmaceutical care on adherence, hospitalisations and mortality in elderly patients - Olesen, C.*	No relationship between polypharmacy and serious ADRs
48	*Inappropriate prescribing in an acutely ill population of elderly patients as determined by Beers' Criteria - Paul F. Gallagher et al*	DRPs
49	*Incidence and determinants of medication errors and adverse drug events among hospitalized children in West Ethiopia - Mohammed Gebre Dedefo et al*	Without relationship between polypharmacy-serious ADRs
50	*Incidence and economic burden of adverse drug reactions among elderly patients in Ontario emergency departments: A retrospective study - Wu, C. et al*	Without Serious Criteria
51	*Incidence and Predictors of Adverse Drug Reactions Caused by Drug-Drug Interactions in Elderly Outpatients: A Prospective Cohort Study - Paulo Roque Obreli Neto et al*	DRPs
52	*Incidence of risk factors for developing hyperkalemia when using ACE inhibitors in cardiovascular diseases - Omalhassan Amir et al*	Without relationship between polypharmacy-serious ADRs
53	*Increase of 10% in the Rate of Adverse Drug Reactions for Each Drug Administered in Hospitalized Patients - Marisa Rosimeire Ribeiro et al*	Without Serious Criteria
54	*Investigating polypharmacy and drug burden index in hospitalised older people - O. Best et al*	Without Serious Criteria
55	*Late-life depression and the association with multimorbidity and polypharmacy: a crosssectional study - Floor Holvasta et al*	Without Serious Criteria
56	*Multimorbidity, polypharmacy, referrals, and adverse drug events: are we doing things well? - Amaia Calderón-Larrañaga et al*	Without Serious Criteria
57	*Off-label and unlicensed drug use in children population - Moulis, F. et al*	Off-label
58	*Off-label and unlicensed utilization of drugs in a Brazilian pediatric hospital - Vanessa Pereira Gomes et al*	Off-label

59	*Optimizing Medication Management in the Hospitalized Older Adult - Michele Pisano*	Without Serious Criteria
60	*Patient risk factors for developing a drug-related problem in a cardiology ward - Olatz Urbina et al*	DRPs
61	*Patient-specific risk factors of adverse drug events in adult inpatients – evidence detected using the Global Trigger Tool method - Marja Harkanen et al*	Without relationship between polypharmacy-serious ADRs
62	*Patterns, predictors and preventability of adverse drug reactions in the coronary care unit of a tertiary care hospital - Padmini Devi et al*	Without relationship between polypharmacy-serious ADRs
63	*Perceived adverse drug reactions among non-institutionalized children and adolescents in Germany - Hildtraud Knopf & Yong Du*	Without relationship between polypharmacy-serious ADRs
64	*Pharmacovigilance and drug safety in Calabria (Italy): 2012 adverse events analysis - Giofrè, C. et al*	Without relationship between polypharmacy-serious ADRs
65	*Polypharmacy – we make it worse! A cross-sectional study from an acute admissions - T. M. Betteridge et al*	Without relationship between polypharmacy-serious ADRs
66	*Polypharmacy and adverse outcomes after hip fracture surgery - Maria Härstedt et al*	Without Serious Criteria
67	*Polypharmacy and Patterns of Prescription Medication Use Among Cancer Survivors - Caitlin C. Murphy et al*	Without relationship between polypharmacy-serious ADRs
68	*Polypharmacy cut-points in older people with cancer: how many medications are too many? - Justin P. Turner et al*	Without relationship between polypharmacy-serious ADRs
69	*Polypharmacy in older adults - Kaufman, G.*	Without relationship between polypharmacy-serious ADRs
70	*Polypharmacy profiles and predictors among adults with autism spectrum disorders - Johanna K. Lake et al*	Without relationship between polypharmacy-serious ADRs
71	*Potentially inappropriate medications in geriatric outpatients with polypharmacy: Application of six sets of published explicit criteria - Chang, C. B. et al*	Without Serious Criteria

72	*Prevalence and Covariates of Polypharmacy in Elderly Patients on Discharge from a Tertiary Care Hospital in Oman - Amna Al-Hashar et al*	Without relationship between polypharmacy-serious ADRs
73	*Prevalence and covariates of polypharmacy in elderly patients on discharge from a tertiary care hospital - Al Mahrizi, A. Et al*	No relationship between polypharmacy and serious ADRs
74	*Prevalence of Polypharmacy and Drug Interactions in a Tertiary Care Teaching Hospital - Kumara Swamy RC et al*	DRPs
75	*Prevalence of polypharmacy exposure among hospitalized children in the United States - Feudtner, C. et al*	Without relationship between polypharmacy-serious ADRs
76	*Reduction in the numbers of drugs administered to elderly in-patients with polypharmacy by a multidisciplinary review of medication using electronic medical records - Yuichi Hayashi et al*	Without relationship between polypharmacy-serious ADRs
77	*Relationships between the amount of saliva and medications in elderly individuals - Kana Ichikawa et al*	Without Serious Criteria
78	*Revisit, Subsequent Hospitalization, Recurrent Fall, and Death Within 6 Months After a Fall Among Elderly Emergency Department Patients - Sri-on, J. et al*	No relationship between polypharmacy and serious ADRs
79	*Risk Factors Associated with Adverse Drug Reactions Following Hospital Admission: A Prospective Analysis of 907 Patients in Two German University Hospitals - Yurdaguel Zopf et al*	Without relationship between polypharmacy-serious ADRs
80	*Risk factors associated with adverse drug reactions in hospitalised children: international multicentre study - Asia N. Rashed et al*	Without relationship between polypharmacy-serious ADRs
81	*Risk Factors Associated with Adverse Drug Reactions in hospitalized patients - Manoj K. Mudigubba et al*	Without relationship between polypharmacy-serious ADRs
82	*Risk Factors in Preventable Adverse Drug Events in Pediatric Outpatients - Stephanie O. Zandieh et al*	Without relationship between polypharmacy-serious ADRs
83	*Side Effects from Use of One or More Psychiatric Medications in a Population-Based Sample of Children and Adolescents - Robert J Hilt et al*	Without relationship between polypharmacy-serious ADRs
84	*Social functioning, polypharmacy and depression in older Chinese primary care patients - Chi-pun Bem et al*	Without Serious Criteria
85	*Spontaneous reporting of adverse drug reactions at a department of Internal Medicine - Zorica Jovic et al*	Without relationship between polypharmacy-serious ADRs

86	*The association between polypharmacy and medication regimen complexity and antibiotic use in bronchiectasis - Maureen Spargo et al*	Without relationship between polypharmacy-serious ADRs
87	*The depth, duration, and degree of outpatient pediatric polypharmacy in Colorado fee-for-service Medicaid patients - James A. Feinstein et al*	Without Serious Criteria
88	*The impact of polypharmacy on the health of Canadian seniors - Ben Reason et al*	Without Serious Criteria
89	*The interpersonal adverse effects reported by 1,008 users of antidepressants; and the incremental impact of polypharmacy - John Read et al*	Without relationship between polypharmacy-serious ADRs
90	*The prevalence of polypharmacy in department of medicine of a tertiary care teaching hospital: A pharmacoepidemiological approach - Siddiq, A. et al*	No relationship between polypharmacy and serious ADRs
91	*The risks of polypharmacy following spinal cord injury - Patrick Kitzman et al*	Without relationship between polypharmacy-serious ADRs
92	*Tools in polypharmacy: Current evidence from observational and controlled studies - Dovjak, P.*	Without relationship between polypharmacy-serious ADRs
93	*Using clinical trial data and linked administrative health data to reduce the risk of adverse events associated with the uptake of newly released drugs by older Australians: a model process -Whitstock, M. T. et al*	Without Serious Criteria

APPENDIX 7 - Included Study Aims (n=16)

Study	Aim
Sevilla-Sanchez, D et al (2017) - Spain	"evaluate (i) the prevalence ofADEs at the time of admission to hospital, (ii) the causality, severity, and preventability of the ADEs, and (iii) the clinical and pharmacological characteristics associated with the ADEs."
Leendertse, A et al (2008) - Netherlands	"identifying the frequency and preventability of medication-related hospitalizations in the Netherlands and risk factors for the preventable hospitalizations"
Abe, T. et al (2016) - Japan	"to analyze the relationship between polypharmacy and hospital admission in ambulance-transported old-old patients"
Varallo, F. et al (2014) - Brazil	"to estimate the prevalence of hospitalization due to adverse drug events and to identify the drugs, the adverse drug events, and the risk factors associated with hospital admissions."
Chen, Y. et al (2014) - Taiwan	"to identify risk factors associated with adverse drug events (ADEs) leading to ED visits."
Gnjidic, D et al (2012) - Australia	to determine an optimal discriminating number of concomitant medications associated with geriatric syndromes, functional outcomes, and mortality in community-dwelling older men"
Bourgeois, F. et al (2010) - USA	"to provide national estimates and characterizations of outpatient ADEs and determine risk factors associated with these events"
Olivier, P. et al (2009) - France	"to assess the incidence of ADRs and associated factors leading to hospital admissions in the elderly population"
Macedo, A F et al (2011) - Portugal	"to validate the hypothesis that multiple drug exposure is an independent risk factor for serious adverse drug reactions (ADRs)"
Laatikainen, O. Et al (2016) - Finland	"to determine the number of geriatric medication-related hospitalizations in the Finnish patient population and to discover the potential means of recognizing patients particularly at risk of ADEs."
Payne, Rupert A. Et al (2014) - UK	"Prescribing multiple medications is associated with various adverse outcomes, and polypharmacy is commonly considered suggestive of poor prescribing. Polypharmacy might thus be associated with unplanned hospitalization. We sought to test this assumption."
Salvi, F. et al (2017) - Italy	"verifying the role of polypharmacy as an independent risk factor for adverse health outcomes in older emergency department (ED) patients"
Rausch, C. et al (2017) - Sweden	"to determine the association between the number of prescribed medications and adverse drug events (ADE) by unintentional poisoning and examine this risk when known indicators of inappropriate drug use (IDU) are accounted for"
Schottker, B. et al (2017) - Germany	"to investigate whether the association of polypharmacy with non-cancer mortality is independent from comorbidity and is not a result of confounding by indication."
Marcum, Zachary A. et al (2012) - USA	"To describe the prevalence of unplanned hospitalizations caused by ADRs among older Veterans and examine the association between this outcome and polypharmacy after controlling for comorbidities and other patient characteristics."
Pedrós, C. et al (2014) - Spain	"To assess the prevalence of hospital admission related to adverse drug reactions (ADRs) in a third-level hospital, to analyse the associated factors, and to describe the reactions and the drugs involved."

APPENDIX 8 - Included Study Adjusted Covariates (n=16)

Study	Adjusted for
Sevilla-Sanchez, D *et al.*	Anticholinergic Drug Scale and Medication Appropriateness
Leendertse, A *et al.*	Medication Regimen Adherence
Abe, T. *et al.*	Age, Sex, Initial Vital Signs (Mean Blood Pressure, Respiration Rate, Heart Rate), Requirement of Hospital Admission
Varallo, F. *et al.*	Gender, Age, Ethanol Consumption, Smoking Habit, Length of Stay
Chen, Y. *et al.*	Age, Gender, Charlson Comorbidity Index Scores, Number of intake drugs, Serum Creatinine Concentration
Gnjidic, D *et al.*	Age and Continuous Comorbidity Score defined as the presence of self-reported medical conditions and depressive symptoms
Bourgeois, F. *et al.*	No description
Olivier, P. *et al.*	Number of Drugs being taken before admission, self-medication, severe renal insufficiency and exposure to drugs for acid-related disorders, antithrombotic agents, antibacterial for systemic use and neoplastic agents
Macedo, A F *et al.*	Gender
Laatikainen, O. *et al.*	No adjustment
Payne, Rupert A. *et al.*	Gender, Deprivation, Number of Clinical Conditions, Number of Prescription
Salvi, F. *et al.*	Age, Gender, Cognitive Impairment, Functional Impairment and Social Problems
Rausch, C. *et al.*	Marital Status, Charlson Comorbidity Index. Matched by: sex, age and residential area
Schottker, B. *et al.*	Age, Sex, Education, Smoking, Body Mass Index, Waist Circumference, Physical Activity, Comorbidity Index and Propensity Score
Marcum, Zachary A. *et al.*	Demographic, Health Status (including comorbidity) and access-to-care factors
Pedrós, C. *et al.*	No adjustment