Review Article

PROFILE OF STUDIES OF POTENTIAL DRUG INTERACTIONS IN BRAZILIAN HOSPITALS: AN INTEGRATIVE REVIEW OF THE LITERATURE

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ABSTRACT

The risk of drug interaction (DI), especially in the hospital setting, increases along with the number of drugs used by the patient. Studies that evaluate drug interactions based on patient prescriptions are therefore useful to know this risk and guide strategies to improve drug use. The present study is aimed to identify studies that evaluated DI in patients of Brazilian hospitals. As of bibliographic search in several databases, we collected articles describing prescribing evaluations which focused on the analysis and identification of drug interactions in Brazilian hospitals. The search was conducted in 2017 and there was no restriction of publication time. Of a total of 273 articles retrieved, 23 were included for analysis. Most was published after 2010, and the predominant design was cross-sectional studies. The Micromedex® database was the most used to categorize the interactions, and midazolam and fentanyl was the most commonly reported potential DI in the studies. The results may guide futures research which should assess the real harm of IMP in patients and, then, promote the rational use of drugs,

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INTRODUCTION

Prescriptions with increasingly complex combinations result in difficulties for healthcare professionals involved in the use of medications – prescribing, dispensing and administration – to recognize potential drug interactions.[1,2] In 2006, Becker *et al* concluded that the use of two or more drugs increases the risk of potential drug interactions (PDI), leading to hospitalization due to worsening illness or even death.[3]

Therefore, the risk of drug interaction increases proportionally with the number of drugs prescribed to the patient and, if the patient is hospitalized, risks increase due to polypharmacy.[4,5] In this sense, in hospital clinical units, this topic deserves special focus, since polypharmacy, added to the severity and instability of the patients' clinical status, is an extremely relevant factor for their vulnerability.[6]

The estimates of the occurrence of PDI are between 3% and 5%, in patients who use two to nine drugs, and 20% among those who use 10 to 20 drugs, simultaneously.[4] Older data shows distinct results but corroborates with the premise that the risk of interaction increases with the number of drugs used.[5] Goldberg *et al* (1996) state that PDIs occur in 13% of patients taking two drugs and in 85% of patients taking more than six drugs.[7]

Hammes *et al.* cite data from the *Harvard Medical Practice Study* which revealed that complications related to drug use represent the most common type of adverse events in hospital admission (19% of patients), and 2% to 3% of hospitalized patients experience reactions specifically caused by PDI.[8]

In a study published in the year 2000, Meneses and Monteiro performed a study in intensive care units (ICU) in which the potential of drug interactions could occur from 44.3% to 95.0% of patients.[9]

In 2014, Gimenes *et al.* analyzed 289 prescriptions for patients in Intensive Care Units (ICUs), in a Brazilian hospital, in which 65.4% of the prescriptions exposed the patient to the risk of PDI, being classified, especially, as severe (50.2%) and moderate (42.3%). In this same study it was verified that the most common MP was that between midazolam and fentanyl, and, on the other hand, the drug most related to MP was amiodarone.[10]

In view of the high risk that hospitalized patients have of developing PDI, it is important to know the profile of the prescriptions that make PDI possible in Brazilian hospitals. To this end, drug prescription studies (EUM) can be used to build information that enables interventions to promote the rational use of medicines.[11] In this sense, literature review shows a strategy to identify this profile.

Thus, the objective of this study was to know the profile of the studies developed with the purpose of identifying the PDIs in patients hospitalized in Brazilian hospitals.

METHODOLOGY

An integrative review of studies on the use of drugs developed in hospitals in Brazil was carried out. The databases for searching the scientific articles were PubMed, *Scientific Electronic Library On Line* (Scielo) and Virtual Health Library (VHL).

The search for original articles considered the following descriptors and Boolean connectors: a) Scielo: Drug interactions and hospital, Brazil and study and prescription; *drug interactions and hospital*

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and Brazil and study and prescription. b) PubMed: *drug interactions and hospital and Brazil; drug interaction and hospital and observational study; drug interactions and hospital and Pharmacoepidemiology* c) VHL: Drug interaction and hospital and Brazil. Search strategies were executed distinctly due to the particularities of each database. Research was not limited only to articles, and academic documents could be inserted, if they were available in the databases consulted. There was no search in gray literature.

The bibliographic survey was carried out in December 2017, including works published until this month. There was no restriction regarding the year of publication of the papers. The following inclusion criteria were considered: 1) studies carried out in Brazil; 2) observational studies; 3) articles describing a survey of prescriptions for the purpose of identifying and characterizing drug interactions; 4) studies performed in hospitals; 5) articles available in full.

Initially, duplicate articles were excluded. In the second stage, titles and abstracts were read and analyzed, and the all of the work done in other non-hospital health units, those carried out in other countries, articles of revision, or that had a non-observational design was excluded. All of the work that went through this scrutiny was reviewed in its entirety, excluding those who did not approach surveying drug interactions, even if they were kept in the previous stage.

The process of selecting papers for the present article was performed through peer review, independently. The divergences were discussed between the two authors until a consensus was reached on the articles that would, in fact, be selected and analyzed.

The following information was extracted from the studies included: authorship, year of publication, type of study, time of research (duration of data collection), sample (number of patients and prescriptions), age group, prevalence of PDI, source of information used to describe them, categorization of interactions according to the source consulted, more frequent PDI, whether the study was general or specific for a particular group of drugs, source for data collection and place of work execution.

For the purpose of categorizing PDI, those considered to be "serious" are those that are contraindicated or that represent a risk of death or require medical intervention in the patient. The sources of information commonly used to verify drug interactions bring this categorization. However, when the data of the original works was extracted, the classification used by the authors of each manuscript was respected.

It is also important to clarify that the studies analyzed in this review describe *potential drug interactions*, that is, that their potential was identified against the analysis of the prescriptions, but that because there was no follow-up of the patients, there was no confirmation of its occurrence.

Since this is a review of the literature, this study was not submitted to a Research Ethics Committee (REC).

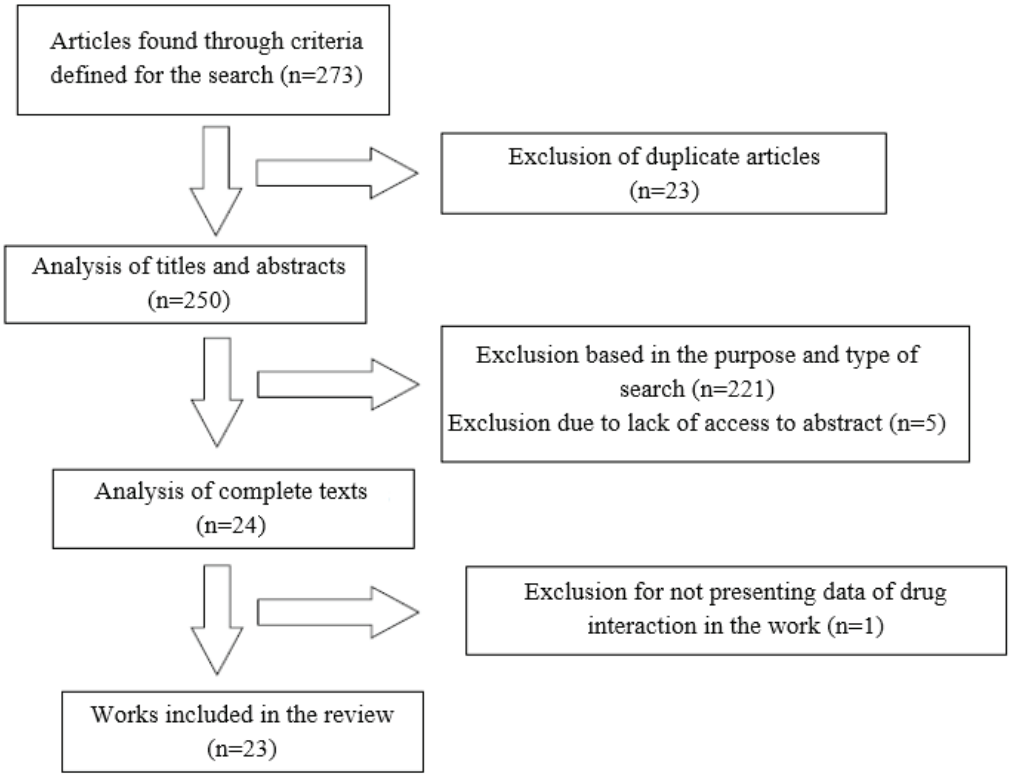
RESULTS AND DISCUSSION

In the search 273 articles were found, after the different stages, 23 papers were selected for this review, according to the flowchart shown in Figure 1.

In view of the selected studies, it was observed that all of them describe studies that were performed in hospitals of medium or high complexity.

Table 1 summarizes the data for the articles included in this review.

Figure 1. Flowchart of search of articles in databases on drug interactions in Brazilian hospitals



Source: the authors themselves, 2018.

Table 1: General characteristics of the articles included in this integrative review on drug interactions in Brazilian hospitals.

Author		Miyasaka e Atallah (2003)	Riechelmann (2005)	Cruciol-Souza (2006)	Junior (2008)	Furini (2009)	Lima (2009)
Type of study		Retrospective, quantitative	Retrospective, quantitative	Retrospective, case-control	Descriptive, cross-sectional	Retrospective	Descriptive, exploratory and cross-sectional
Study time		49 months	6 months	4 months	11 months	32 days	12 months
Sample (number of patients)		7242	100	1,785	47	100	102
Sample (number of prescriptions)		Not informed	Not informed	Not informed	Not informed	100	Not informed
Age group		Not informed	20 to 94 years old	12 to 98 years old	Not informed	Over 15 years old	18 to 96 years old
Source used		Micromedex®	Drug Interaction Facts software	Micromedex®	Not informed	Drug Interaction Facts on Disc® and Vade-Mécum®	Micromedex®
Prevalence of PDI		Of 169 patients who received antidepressants, MI was observed in 36 (20.3%).	63% of patients with PDI.	49.7% of the prescriptions	Not informed.	Not informed	74 of the 102 patients analyzed (72.5%).
Most frequent PDI		Not informed.	Opioids + BZD(I),ISRS(II) +AINES(III) with HBPM(IV)	Digoxin + Hydrochlorothiazide (3.4%)	Dipyrone + Captopril (76.6%)	Cephalexin and Ketoprofen	Midazolam + Fentanyl (14.5%)
PDI* %	Mild	Not informed.	25.00% (V)	Not informed	Not informed	21.40%	Not informed
	Moderate	Not informed.	56.70% (V)	Not informed	Not informed	56.30%	Not informed
	Severe	Not informed.	18.30% (V)	Not informed	Not informed	21.40%	Not informed
Scope of clinical or general / specific patients		Specific	Specific	General	Specific	Specific	General
Instrument for information gathering		Medical record	Medical record	Medical record	Medical record and direct interview with the patient	Medical record	Medical record
Location		Sao Paulo	Sao Paulo	Londrina - Paraná	Paraíba	Mirassol - São Paulo	Ceará

*PDI according to authors' classification

To be continued.

To be continued.

Author		Melo (2010)	Silva (2010)	Guastaldi (2011)	Moura. et al (2012)	Schimitt et al (2013)	Carvalho et al (2013)
Type of study		Retrospective, descriptive and observational.	Descriptive, cross-sectional	Cross-sectional, prospective	Cohort, retrospective	Retrospective, qualitative	Multicentric, cross-sectional and retrospective
Study time		6 months	3 months	7 months	12 months	2 years	12 months
Sample (number of patients)		647	36	70	1,487	202	1124
Sample (number of prescriptions)		5666	41	Not informed	Not informed	Not informed	Not informed
Age group of patients		Over 18 years old	18 to 50 years old	All ages	Over 18 years old	Over 18 years old	18 to 96 years old
Source used OPharmacêutico®, Micromedex®		Micromedex®	Website Drugs.com,	Drug Interactions Facts and Drug Inter. Handbook	Book Drug Interaction Facts	Not informed	Micromedex®
Prevalence of PDI		58% of prescriptions.	Not informed.	71.4% of the sample.	35% of patients.	MI with imidazole, 63 to 87%; with terbinafine, 31 to 36%. (VII)	70.6% in 24 hs; 72.5% m 120 hs
Most frequent PDI		Acetyl salicylic acid + Captopril (7.3%)	Metoclopramide + Tramadol (63.20%)	Fluconazole + Omeprazole (40.00%) Captopril + Spironolactone (10.6%),	Digoxin + Furosemide (11.40%) Amitriptyline, Propranolol, (+ imidazoles and terbirafine)	Fluoxetine, -38.60%	Fentanyl + Midazolam
PDI %	Mild		Not informed	7.70%	Not informed	Not informed	13.30%(VI)
	Moderate		Not informed	92.30%	Not informed	Not informed	50.10% (VI)
	Severe		Not informed	0.00%	Not informed	Not informed	36.50% (VI)
General/Specific		General	General	Specific	General	Specific	General
Instrument		Medical record	Medical record	Medical record	Medical record	Medical record	Medical record
Location		Sao Paulo	Campinas – São Paulo	Sao Paulo	Vitória da Conquista - Bahia	Curitiba, Paraná	Seven teaching hospitals (west, northeast and southeast of Brazil)

To be continued.

To be continued.

Author		Okuno et al (2013)	Cedraz e Junior (2014)	Reinert et al (2015)	Antunes et al (2015)	Furini (2015)
Type of study		Cross-sectional and descriptive	Quantitative, descriptive and cross-sectional	Cross-sectional	Cross-sectional	Retrospective
Study time		5 months	4 months	3 weeks	4 months	12 months
Sample (number of patients)		200	Not informed	56 patients	Not informed	40 patients
Sample (number of prescriptions)		Not informed	28	Not informed	101	Not informed
Age group of patients		Over 18 years old	Not informed (Average age: 48.54)	27 to 78 years old	> 60 years old	Not informed
Source used OPharmacêutico®, Micromedex®		Website Drugs.com	Micromedex®	UpToDate® and Medscape®	Website *Drugs.com*	Website *Drugs.com, Micromedex® e Medscape®*
Prevalence of PDI		79.5% of the prescriptions.	92.86% of the prescriptions.	19.5% of patients.	Informed separately, according to severity.	Not informed.
Most frequent PDI		Metoclopramide + Tramadol (30.40%) (11.11%); Dipyrone + Enoxaparin (11.11%)	Fentanyl + Midazolam	Antidepressants and antineoplastics	Enalapril + Spironolactone (6.4%)	Ritonavir + Tenofovir
PDI %	Mild	12.00%	5.05%	Not informed	7%	Not informed
	Moderate	67.00%	58.59%	Not informed	26.80%	Not informed
	Severe	21.00%	31.31%	8.9%	7%	8%
General/Specific		General	General	General	Specific	Specific
Instrument		Medical record	Medical record	Medical record and direct interview with the patient	Medical record	Medical record and direct interview
Location		Sao Paulo	Feira de Santana - Bahia	Porto Alegre - Rio Grande do Sul	São Paulo - São Paulo	São josé do Rio Preto - São Paulo

To be continued.

To be continued

Author		Oliveira Et al (2015)	Alvim et al (2015)	Guidoni et al (2016)	Moreira et al (2017)	Ferracini et al (2017)
Type of study		Descriptive and Retrospective	Cross-sectional	Cross-sectional	Retrospective	Cross-sectional
Study time		12 months	3 months	72 months	12 months	11 months
Sample (number of patients)		Not informed	82 patients	3048 patients	485 patients	58 patients
Sample (number of prescriptions)		725	656	42120	319	305
Age group		Not informed	18 to 89 years old	Not informed	Not informed	19 to 46 years old
Source used		Website *Drugs.com e Micromedex®*	*Micromedex®*	*Lexi-Interact®*	*Micromedex®*	*Micromedex®*
Prevalence of PDI		21% according to Micromedex; 36% as per Drugs.com	98 MI in 46% of patients evaluated.	48.7% of prescriptions with MI.	Not informed.	91% of prescriptions.
Most frequent PDI		Haloperidol + Promethazine (17.7%)	Fluconazole + Omeprazole	Warfarin + Enoxaparin	Midazolam + Fentanyl	Dipyrone + enoxaparin sodium
PDI %	Mild	Not informed	2%	Not informed	Not informed	71.60%
	Moderate	1%	16%	Not informed	Not informed	22.20%
	Severe	20%	50%	Not informed	Not informed	4.90%
General/Specific		Specific	Specific	Specific	Specific	Specific
Instrument		Medical record	Prescriptions	Prescriptions	Prescriptions	Prescriptions
Location		Uberlândia - Minas Gerais	Juiz de Fora - Minas Gerais	Ribeirão Preto - São Paulo	Rio de Janeiro - Rio de Janeiro	Campinas - São Paulo

(I) BZD (benzodiazepines)
(II) SSRIs (selective serotonin reuptake inhibitor)
(III) NSAIDs (non-steroidal anti-inflammatory drugs)
(IV) LMWH (low molecular weight heparin)
(V) PDI (potential drug interaction) of 63 patients detected as PDI
(VI) 24-hour data after hospitalization
(VII) Dependent on the amount of medication used by the patient

Analyzing the results of this integrative review, and considering that there was no restriction of the search period in the databases, it was observed that the retrieved articles are between the period of 2003 and 2017, with a predominance of those published from 2010 to here, that is, are relatively recent work. This indicates a positive aspect, which points to a greater interest in studying the prescriptions in hospitals and measuring their quality regarding drug interactions. These initiatives may be useful for detecting recurrent pharmacotherapy-related problems and targeting strategies to improve the prescribing pattern and thus the patient's health.

In 2007, Carvalho *et al* published a bibliographical review analyzing and identifying studies of drug use in Brazilian hospitals, in which it observed that the number of studies aimed at the use of drugs in hospitals has grown gradually since the 1980s.[34] This same tendency of increase was observed in the present research.

Regarding the study design of the articles described in Table 1, it can be observed that the studies are categorized by the authors more commonly as retrospective (cohorts) or cross-sectional studies. Although convenient and low-cost forms adopted in prescription analysis studies, once requiring only trained professionals and access to the patient's medical records (or any other document containing the medications used), they have important limitations. The main one is with regard to the possibility of non-reliability of the information collected or even loss of data.[35] In any case, they are useful for obtaining a picture of the use of medicines from a health service. In addition, this fact drives in that the interactions identified are always described as potential since, even if they occurred, there is no data recorded about it.

One of the most relevant aspects of a research is to delimit observation time. In this review, the work of Furini *et al* (2009),[16] who collected data for 32 days, and the work of Miyasaka and Atallah (2003),[12] whose collection occurred during 4 years and 1 month, showing a large variation in the temporal aspect. What can be argued regarding the time factor in prescription studies is that very short ones can be of low precision and long

ones can generate repetitive results.[36] However, the analysis of the studies included in this review does not allow us to presume an adequate time for the evaluation of PDI. Several factors may interfere with the accuracy of the results of a drug use study, and the sample is one of the most important. Calculation of the sample, in turn, depends on the research question, the type of study and also the population to be investigated, in this case often translated as the number of hospital beds in which the study is being conducted in addition to the frequency of the event that you want to measure,[35] having a relation with the error that will be tolerated. Therefore, in prescribing studies, sample calculation is minimally advisable and, in this case, search time will be derived from this sample.

Regarding the patient's age, this review did not intend to stratify this aspect; however, seven of the 23 included studies did not report the age of patients,[12,15,25,,28,29,31,32] one stated that it included all ages[20] and two exclusively covered prescriptions for pediatric patients.[14,16]

Analyzing Table 1, it can be seen that the sample size of each study varied greatly, in which there is no standard of study time in relation to the number of patients studied, i.e., the longer the observation time the greater the number of prescriptions included.

It was observed that, in general, Micromedex® was the most used query source, on account of the current low cost due to availability, because it is accessible to many researchers, reliable and contains a lot of information. This database is available on the Capes Portal, accessible to Brazilian universities,[37] and the Evidence Based Health Portal, available to all health professionals enrolled in their respective professional councils.[38] It should be noted that this availability has provided greater base access in recent years.

However, the study by Mountford *et al* (2010)[39] showed the use of other research platforms, such as Lexi-comp On line® and Clinical Pharmacology® that have superior quality and performance to Micromedex. This can be seen in another study, developed in Brazil, in which the authors found discrepancies between four information sources describing drug interactions, including Micromedex ®.[40]

Considering, therefore, the potential heterogeneity between the sources used in the studies described in this review, it is not possible to make a full comparative analysis between them. In addition, despite the method used in each analysis of potential drug interactions, it is recommended that at least two sources of information be used when this type of study is desired.

As a source of data collection, the patient's medical record was the basis for the research of all the works. The use of medical records is very convenient because they are generally easily accessible, they contain relevant information such as patient evolution and it is possible to relate the use of medications as well as adverse events related to medications and other health care. It is a tool widely used in retrospective studies; but when poorly filled or if it omits information, it ends up weakening the study, especially when these are retrospective, as previously discussed. The interview with the patient is essential, since it increases the veracity of the information contained in the medical record and provides more reliable information.

An overview of this review shows that most of the selected articles are concentrated in the Southeast region of the country, but studies have been carried out in all regions of the country, maintaining a trend already observed by Magarinos-Torres *et al.* (2007).[41].

Regarding the characterization of drug interactions in the studies that evaluated the intensity of PDI, it can be observed that the PDIs with moderate/severe classification are generally the most frequent. Interaction between midazolam and fentanyl was repeated in four studies, with captopril and spironolactone being cited in two studies and metoclopramide and tramadol in two articles, all considered severe or moderate, according to Micromedex® (2018).[37]

Considering the severity of these interactions and their high prevalence in prescriptions evaluated in different studies, it is possible to propose pharmacotherapeutic follow-up work specifically aimed at monitoring adverse events in patients using these drugs. According to Zheng et al. (2018), the prevalence of PDI does not predict the occurrence of drug interactions that will cause harm to the patient. The authors concluded this after a meta-analysis with a systematic review that found that 33% of hospitalized patients and 67% of those admitted to intensive care experience a potential drug interaction.[42]

Notwithstanding its relevance, this paper's main limitation is not to be a systematic review, which would result in a better level of evidence.[43] The scope of the survey was also compromised by involving only Brazilian hospitals and excluding those articles that were not available in full. In addition, the fact that only the most frequent PDI cited in each study has been highlighted may compromise the scenario of possible interactions in patients admitted to hospitals in Brazil. In addition, not including the gray literature also restricts the scope of this research.

In any case, it serves as a picture of the panorama of the way PDIs are being investigated in Brazil. Considering the most recent Global Patient Safety Challenge of the World Health Organization,[44] which aims to reduce the damages caused by medication errors, knowledge of the PDI profile can be guiding strategies for the development of actions to promote the safe and rational use of medications.

Final considerations

In this integrative review it was possible to observe the profile of prescription studies that evaluate drug interaction in Brazilian hospitals, adopting the research in medical records without contact with the patient or follow-up of the same. In addition, they use, in particular, Internet databases such as Micromedex®. In addition, they investigate a reduced number of patients/prescriptions which is generally related to the observation period. In this sense, the most used study drawings are retrospective (cohort) and cross-sectional; being performed predominantly in hospitals of medium/high complexity.

Regarding the PDIs profile, it was observed that they were not classified in all studies, but in those that were the most frequent was moderate, one of the most frequent being that involving midazolam and fentanyl.

Future studies are needed; however, they should seek the outcomes of the PDIs on the patient, involving those clinical, humanistic and economic. In addition, safe prescribing should be a strategy for all those involved in patient care, so the development of prevention strategies should be a priority in hospitals.

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Contributors

ATY and RMPCBJ carried out a review of the literature, systematization of information and writing of the manuscript. DG and MMMAM collaborated with the discussion of the results and performed a critical review of the manuscript. EVS was responsible for designing the project, guiding it in its execution, reviewing and writing the final manuscript.

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Conflict of interest

The authors have no conflict of interest with any company or entity related to the subject of the review.

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