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REVIEW ARTICLE

PATIENT SAFETY: DRUG INTERACTIONS IN ADULTED PATIENTS

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ABSTRACT

Objective: to investigate evidence in the literature about interactions arising from drug prescriptions of hospitalized adult patients. **Method:** this is an integrative literature review carried out through six steps. Data collection took place in July 2020, in the BDENF, LILACS via BVS, CINAHL, SCOPUS, Web of Science via Capes Periodicals Portal and SciELO databases, using the descriptors drug interactions, drug prescriptions and patient safety. Eighteen productions were selected in the time frame from 2008 to 2020. **Results:** of the articles selected, ten were national and eight international studies. Intensive care and emergency units were the most investigated scenarios. The results were categorized into three thematic axes: prescriptions and drug interactions; scheduling and drug interactions; interventions and drug interactions. **Conclusion:** drug interactions occur at high rates, mainly in cases of drug prescriptions associated with polypharmacy and in critical units. Interventions with software to support clinical decision and the presence of a clinical pharmacist brought significant and positive results.

Keywords: Drug interactions. Drug prescriptions. Patientsafety. Hospitals.

INTRODUCTION

Today, patient safety (PS) has occupied a prominent place in national and international discussions about the quality of care provided to health users. Results and estimates of incipient research were sufficient to demonstrate, on a global scale, the importance of PS when the World Health Organization (WHO) launched the World Alliance for Patient Safety with the purpose of improving the quality and safety of health services, to which Brazil was a signatory country[1].

The implementation of the National Patient Safety Program (NPSP)[2] was formally approved in Brazil by the Ministry of Health Ordinance number 529. This fact highlights the need for organizations and health professionals to converge on safer care.

Accordingly, WHO proposed six international goals for patient safety, the third related to safety in the prescription, use and administration of drugs. In 2017, the Third Global Patient Safety Challenge was launched with the theme medication without harm. This is a global initiative to reduce severe, avoidable medication-related harm by 50% in all countries in the next five years[1].

Research on PS is ongoing, especially with regard to medication systems, which range from prescription to monitoring the therapeutic effect of drugs. These steps require a multidisciplinary and coordinated work, in which nurses participate with direct and exclusive responsibility in several stages[3]. Among these, the scheduling stage stands out, which is conceptualized as the act of assigning times when medications will be administered by the nursing team according to the dosage indicated in the prescription[4].

Drug interactions (DI) are clinical events in which the effects of a drug are changed by concomitant administration with a food, beverage, supplement, or another drug or any environmental chemical agent. Scheduling can favor DI when simultaneous administration is planned[5].

When two drugs are administered

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simultaneously to a patient, they can act independently or interact with each other with possible synergism (increased desirable effects in the proposed therapy), antagonism (decreased undesirable effects) and neutralization (ineffective effects or toxicity). Since the number of medications prescribed to the same patient has increased, the chances of coinciding times increase, favoring undesirable DI[5].

In this context, this study aimed to investigate evidence in the literature on DI in hospitalized adult patients.

METHODOLOGY

This is an integrative literature review carried out in six steps[6]. The first was the definition of the research question using the PICo strategy, an acronym for the words: "Population, phenomenon of Interest and Context". Therefore, the guiding question was: what is the evidence in the literature about DI in hospitalized adult patients?

The next step was the search and selection of articles. The following controlled descriptors were defined according to the Health Science Descriptors (DeCS): interações de medicamentos, prescrições de medicamentos, and segurança do paciente. In the English databases, the following Medical Subjects Headings (MeSH) were used: drug interactions, drug prescriptions and patient safety.

The databases consulted were the Nursing Database (BDENF) and Latin American and Caribbean Health Sciences Literature (LILACS) via the Virtual Health Library (VHL), Cummulative Index to Nursing and Allied Health Literature (CINAHL), SCOPUS, Web of Science via Capes Periodicals Portal, and Scientific Electronic Library Online (SciELO).

Data were collected during the month of July 2020 independently by two peer reviewers. The Boolean term "and" was applied, resulting in 272 potential articles.

The articles were submitted to the following inclusion criteria: articles available in full length, in Portuguese, Spanish and English, whose title and abstract were related to the object of study, conducted with patients aged 18 years or over, in the hospital context, and published in the last 12 years (2008 to June 2020). Articles with any of the following characteristics were excluded: duplicated in databases, with limited access, on neonatal/pediatric clients, and in the context of primary, home care, pharmacy and long-term care facilities. After reading the titles and abstracts, a total of 18 articles were selected, according to Box 1.

Box 1. Steps for selecting articles in the databases, Rio de Janeiro - RJ, 2020

Articles	SciELO	BDENF	LILACS	CINAHL	SCOPUS	Web of Science	Total
Found	7	4	36	107	107	11	272
Excluded	4	2	34	102	102	10	254
Selected	3	2	2	5	5	1	18

In the third step, the articles were read in full length and a form containing the following information was applied: title, authors, main objective, type of methodology, sample, subjects, main results and conclusions. After reading in full length, all the 18 studies selected were included in the review.

The fourth and fifth steps covered the evaluation and interpretation of results, for which the articles were organized and interpreted critically in comparison with the literature. In the analysis of the selected articles, three thematic axes contributed to the data discussion.

RESULTS AND DISCUSSION

Among the eighteen selected articles, ten were national and eight international studies. Eight articles were published between 2008 and 2013 and ten between 2014 and 2020. The authors of the studies were nurses, physicians and pharmacists, demonstrating the interest and multiprofessional involvement of the hospital medication system. Drug prescriptions were mainly made in adult intensive care units (ICU) (n = 6) and emergency care units (n = 4) and the DI were consulted, in addition to other sources, on MICROMEDEX® and on the website www.drugs.com®.

The selected articles were categorized through three thematic axes: prescriptions and

DI; scheduling and DI; and interventions and DI.

Prescriptions and drug interactions

In this thematic axis, ten articles were included. In Box 2, it can be seen that the ten studies identified high rates of DI present in drug prescriptions despite different methods to recognize DI.

Box 2. Distribution of articles included in the thematic axis prescriptions and drug interactions, Rio de Janeiro - RJ, 2020

Authors	Objective	Study site	Sampling	Frequencyof DI	Method of identification of DI
Antunes, 2015[7]	To identify the occurrence of potential DI in drug prescriptions for hospitalized elderly	Clinical emergency room of an Emergency Care Unit	101 drug prescriptions for the first 24 hours of hospitalization	7% serious interactions, 26.8% moderate interactions and 7% mild interactions were identified	Drugs.com®
Fonseca, 2008[8]	To characterize the profile of drugs and identify combinations arising from the co-administration of potentially interactive antimicrobials	Heart Institute of the Clinical Hospital, Faculty of Medicine, University of São Paulo	Seventy (70) drug prescriptions of patients undergoing bone marrow transplantation (BMT), all hospitalized	72.7% of the drugs presented interactive potential, with emphasis to precipitators (79.2%) and fluconazole (85.7%)	GUIAMED®, Micromedex® Martindale®.
Black, 2012[9]	To explore the application and safety of non-medical prescription in an accident and emergency and sexual health department	UK Department of Accidents and Emergencies and Sexual Health	Seven hundred and sixty four (764) nursing prescriptions were included 490 case notes that could not prescribe	Safe prescription practice was evident in 99% of cases, with lack of documentation (n = 2) and contraindicated prescription (n = 1)	-
Naught, 2012[10]	To assess the clinical suitability and safety of nurses and midwives in the practice of prescription	Ireland	One hundred and forty two (142) patient records and 208 medicines prescribed by 25 registered nursing prescribers	95-96% of the prescription drugs were indicated and effective. As for dosage, drug-drug DI and duplication of therapy were considered appropriate in 87-92% of the prescriptions	-
Okuno, 2013[11]	To identify the occurrence of potential drug interactions in medical prescriptions for adult inpatients	Emergency Service of São Paulo Hospital	200 prescriptions	526 potential drug interactions in 159 prescriptions (79.5%); among them, there were 109 serious interactions, 354 moderate interactions, 63 mild interactions, and in no interaction was seen in 41	Drugs.com®

To be continued...

Authors	Objective	Study site	Sampling	Frequencyof DI	Method of identification of DI
Bhagavathula, 2014[12]	To determine the prevalence, clinical significance and associated potential drug interactions	Internal medicine ward at the university hospital in Gondar, Ethiopia	100 patients	413 potential drug interactions, 61.2% (n = 253) were moderate, 26% (n = 107) mild and 12.8% (n = 53) severe	Drugs.com®
Rodrigues, 2015[13]	To evaluate, quantify and qualify potential drug-drug DI	Adult ICU of a public hospital in Brazil	369 prescriptions	1844 potential drug-drug DI distributed in 405 paired combinations, 74% moderate and 9 contraindicated	Micromedex®
Siebe-nhuener, 2017[14]	To evaluate chronic pain therapy as to the potential for interaction in a sample of hospitalized patients with multiple chronic conditions	Department of Internal Medicine, Zurich University Hospital	1.039 patients	Almost 90% of patients were exposed to polypharmacotherapy. 3,186 potential drug interactions were identified, with 17% classified among analgesics	hospINDEX®
Kirilochev, 2019[15]	To conduct a frequency analysis of possible drug interactions in a psychiatric hospital	Psychiatric hospital	500 recordsofpsychiatricpatients	Potential drug interactions with moderate clinical significance occurred in more than 77% of hospitalized patients.	Drugs.com®
Cortes, 2019[16]	To estimate the prevalence of potential drug interactions related to high surveillance drugs	Intensive Care Center of a university hospital	244 prescriptions	846 potential drug interactions related to high surveillance drugs	Micromedex

Among the studies that used Drugs.com® as a tool to identify DI, a study[7] analyzed 101 drug prescriptions in the first 24 hours of hospitalization of elderly patients in the emergency room stands out, showing 7% of serious interactions , 26.8% moderate interactions, and 7% mild interactions. Another study[11] conducted in Brazil examined 200 prescriptions and found 526 potential drug interactions (PDI) in 159 prescriptions (79.5%), 109 of which were classified as serious also in the emergency.

In the international context, a study[12] conducted in Ethiopia found similar results, with 61.2% moderate DI in prescriptions of 100 nursing patients. Another study[15] found 500 records of psychiatric patients among which PDI was found in 77% of the hospitalized patients classified with moderate clinical significance.

Both foreign and national investigations find significant prevalence ratios that demonstrate the need to improve the interception of PDI in order to reduce them, as they can produce serious and fatal outcomes.

For the tool on the website drugs.com®, severe DI are combinations with high clinical significance, and association of drugs is not recommended, because the risk of the interaction exceeds the benefits. In moderate interactions, concomitant use is recommended only in special circumstances.

Regarding severity, the MICROMEDEX® tool classifies DI as contraindicated, when concomitant use is not recommended; as important when life is at risk; as moderate, when DI lead to a change in treatment; and as secondary, when the DI have limited clinical effects[4].

A study[13] that used the MICROMEDEX® tool found 1844 drug-drugPDI distributed in 405

paired combinations, among which 74% were moderate and 9% contraindicated in 369 prescriptions in a Brazilian ICU. This corroborates the results of another research[16] that used the same database in a highly complex environment, where 112 different PDI pairs related to high-surveillance drugs (HSD) were identified, with a prevalence of 96%.

Drug interactions are not desirable, especially in the intensive care environment in which patients have a more serious clinical status, and the potential harm to the patients may be irreversible, leading to death.

Among the studies that used other tools for identification of PDI, the study[14] carried out in Zurich used thehospINDEX® and identified 1,039 patients with 3,186 PDI. An investigation[8] with antimicrobials that associated four tools for the identification of PDI (GUIAMED® System, MICROMEDEX®, Martindale® and USP DI®) found even greater results. A frequency of 72.7% of PDI was identified in 70 drug prescriptions of patients undergoing bone marrow transplantation.

It is known that the frequency of DI can also be influenced by polypharmacy, which is directly proportional to the number of drugs prescribed and can vary according to the hospital unit due to the medication profile[17]. Most studies were notably concentrated in high complexity sectors and in specific populations, such as ICU and emergency units.

Despite this scenario, a survey carried out in the United Kingdom analyzed the application and safety of 764 prescriptions by nurses in an emergency and sexual health service, showing that the safer prescription practice was present in 99% of the cases, with lack of documentation and contraindicated prescription being observed in only two cases[9].

This result corroborates another study[10] carried out in Ireland, which evaluated 208 drugs prescribed by 25 registered nursing prescribers regarding the clinical suitability and safety of the nurses and midwives in the prescription practice and found that 95-96% of the drugs prescribed were indicated and effective as to dosage and drug-drugs DI. Furthermore, duplication of therapy was considered appropriate in 87-92% of prescriptions.

It is worth mentioning that, in Brazil, according to the Nursing Professional Exercise Law 7498 of June 25, 1986, in its article 11, it is the nurse's responsibility, as member of the health team, to prescribe medications established in public health programs and within the routine approved by the health institution[18]. Except for these cases, nurses are not allowed to exercise this activity, unlike the reality of some countries such as Sweden, Australia, Canada, United States, United Kingdom, New Zealand, South Africa, Botswana, Ireland and Kenya, where the practice of prescription of medications iscarried out by nurses.

Scheduling and drug interactions

Four articles, addressing the scheduling profile and the classification of drug interactions were included in this thematic axis, as shown in Box 3.

No studies on drug interactions resulting from nursing scheduling were found in the international databases used in this study. It is conjectured that in foreign countries this stage is computerized, schedules are generated automatically when drugs are prescribed in an electronic system, without DI.

A study analyzed the scheduling of 135 medical prescriptions in an ICU and emergency unit in Rio de Janeiro as to the occurrence of PDI and found that prescriptions in which more than five drugs were combined (polypharmacy) had a 1.85 to 5.7-fold higher chance of causing serious interactions when compared to prescriptions without polypharmacy[19]. It is noteworthy that the fact that the scheduled medications are grouped into four predominant times prompts the appearance of DI.

Corroborating the above, a survey[20] methodologically similar to the previous study but with a broader scope to identify non-conformities in 362 prescriptions in a general ICU highlighted schedules with intervals not consistent with the prescription (80.5%), absence of the stamp of the scheduler (46%), and scheduling of suspended prescriptions and medical judgment (19%).

Such results demonstrate the need for more in-depth research on the subject, including sectors of less complexity, such as inpatient wards and outpatient clinics, where situations with non-conformities and polypharmacy are frequent.

A recent study[21] analyzed the sector of heart failure and transplantation and found 83.8% PDI prescriptions in 62 prescriptions; switch to alternative medication was advisable in 61 cases; concomitant administration was advisable in 52 cases; and most doses were scheduled for night time. Another similar study[22] showed that prescriptions with five or more medications are eight times more likely to present PDI.

In this context, as nurses are 24 hours at the patients' bedside, they are the professionals who supervise the process of preparing and administering medications and, therefore, are able to determine the best schedule for administration. Even the most computerized systems need updating because they do not consider the patient's clinical condition and are operated by people, who are liable to fail. Thus, patients must be evaluated by health professionals and there must be flexibility to make the necessary adjustments.

Box 3. Distribution of articles included in the thematic axis scheduling and drug interactions, Rio de Janeiro - RJ, 2020

Authors	Objective	Study site	Sampling	Frequencyof DI	Method of identification of DI
Silva, 2013[19]	To describe the profile of intravenous medication scheduling and analyze potential serious interactions resulting from scheduling	Sentinel hospital in the city of Rio de Janeiro	135 prescriptions with 1847 doses	Predominance of schedules during the night shift (57.11%); 43 serious interactions were found, with prevalence of 1.85 and 5.7 Odds Ratio, in prescriptions with more than five drugs	Micromedex®
Ribeiro 2018[20]	To identify non-conformities related to medication scheduling	General ICU of a university hospital in Rio de Janeiro	362 prescriptions	Similarity was identified in the scheduling between the people responsible for this task, concern with the use of odd hours, use of non-standard schedules in order to avoid drug interaction	-
Etelvino 2019[21]	To analyze the scheduling of medications by nurses with regard to the occurrence of potential drug interactions	Heart failure and heart transplant sector in Rio de Janeiro	62 prescriptions	83.8% of prescriptions presented potential drug interactions, 13.4% with high severity	Medscape Drug Interaction Checker
Sobrinho, 2020[22]	To identify and characterize potential serious drug interactions related to administration times	Cardiologywardof a hospital in Rio de Janeiro	99 prescriptions	22 pairs of drugs with serious interactions, most often at 6:00 pm and 6:00 am	Micromedex

Interventions and drug interactions

Four articles that proposed to analyze professional interventions or tools to prevent drug interactions were included in the last axis of the present study, as shown in Box 4.

In order to increase the surveillance of PDI, a recent study[26] analyzed the pharmacotherapeutic support of a tool to verify the adequacy of drug administration in a university hospital in Belgium. The system generated 39,481 alerts, the prevalent sector was the emergency unit, and the class of drugs most involved was anticoagulants. Support interventions by a pharmacist were accepted in 69% of the actions.

In Brazil, a study[23] investigated the role of the clinical pharmacist by analyzing 6,438 prescriptions, in which 933 pharmaceutical interventions were performed in highly complex sectors. Up to 14.6% of the prescriptions had problems with the medications, most frequently related to the dosage (46.73%). The positive effects of interventions of these professionals were also reported in other studies[27,28].

The clinical pharmacist is a new professional category in Brazil and aims to contribute to patient safety by preventing PDI, DI with food, and adverse reactions. These professionals also have the role of guiding physicians in

prescriptions and nursing professionals in the administration of medications[27].

Two other articles[24,25] evaluated the use of a computational tool to assist in clinical decision making. The study[24] that verified the effectiveness of INTERcheck, a computerized prescription support system, identified a significant reduction in PDI and minimized triggering of severe PDI.

A prospective cohort study in an ICU of a university hospital in Germany analyzed the intervention of a computerized support system for clinical decision with information on the risks of 9,453 drug combinations. The patient's chances of experiencing adverse events with at least one PDI decreased, confirming the hypothesis of the study ($p < 0.01$)[25].

In this sense, it is highlighted that health education and technologies play an essential role in preventing incidents and promoting safer practices[29,30], constituting a support resource but not a substitute for the clinical and laboratory evaluation and the consideration of basic human needs of users by professionals.

Box 4. Distribution of articles included in the thematic axis interventions and drug interactions, Rio de Janeiro - RJ, 2020

Authors	Objective	Study site	Sampling	Intervention	Frequency of DI	Method of identification of DI
Reis, 2013[23]	To analyze interventions performed by pharmacists during the review of medical prescriptions	Adult ICU, Cardiology and Clinical Cardiology ICU of a tertiary university hospital in Brazil	6,438 prescriptions were evaluated and 933 pharmaceutical interventions were performed	Daily analysis of prescriptions made by clinical pharmacists	The problems related to medications were the dosage, 46.73% (n = 436), then inappropriate/unnecessary drugs, 19.08% (n = 178), the most appropriate/available therapeutic alternative, 7.82% (n = 73), and interactions, 7.50% (n = 70). The acceptance of interventions was 76.32%	Drugdex®, UpToDate® e Medscape®
Ghibelli, 2013[24]	To evaluate the applicability and effectiveness of INTERcheck in reducing potentially inappropriate medication and severe DI	Acute geriatric ward in northern Italy	Elderly (aged 65 or over) hospitalized - Observational phase - 74 patients, intervention phase - 60 patients	INTERcheck is a Computerized Prescription Support System (CPSS) to optimize the prescription of drugs for elderly women with multimorbidities	The number of patients exposed to at least one potentially severe DI decreased from 45.0% to 33.3% [p 0.001]	Istituto Di Ricerchefarmacologiche Mario Negri
Bertsche, 2010[25]	To investigate the effect of written drug information for veteran clinicians on the incidence of DI and adverse events related to DI	ICU of a UH - Germany	265 patients (136 in the control group and 129 in the intervention group)	Computerized clinical decision support system containing information on risk and management of 9,453 drug combinations	The tool considerably decreased DI and adverse events related to DI	-
Quintens, 2019[26]	To describe the development of the Check of Medication Appropriateness (CMA) and evaluate its preliminary results	ICU of Leuven University Hospital – Belgium	39,481 clinical rule alerts were checked by pharmacists	Daily check of high risk prescriptions by a pharmacist	Of the 458 actions carried out, 69% were accepted by physicians	CMA

CONCLUSION

It is concluded that potential DI have a high prevalence in prescriptions, with emphasis on prescriptions with polypharmacy and in critical units. These findings demonstrate the need to investigate also sectors of low and medium complexity.

Although further investigations are need to understand the phenomenon, the scheduling performed by nurses is already evidently associated with the potential of the occurrence of PDI, especially severe DI. Software-based interventions to support clinical decision making and the presence of a clinical pharmacist reviewing prescriptions are presented as strategies to minimize these problems.

In general, research on DI is incipient, but the results presented here allow us to conclude that DI are a relevant problem and that further investigations are needed to measure and carry out interventions in order to minimize the damage to hospitalized patients and promote safer practices.

Finally, this study had as a limitation the option of delimiting the survey of electronic articles available free of charge in some databases, which means that there may be articles on this theme that were not included in the present study.

SEGURANÇA DO PACIENTE: INTERAÇÕES MEDICAMENTOSAS EM PACIENTES ADULTOS INTERNADOS

RESUMO

Objetivo: investigar na literatura evidências sobre interações advindas de prescrições de medicamentos de pacientes adultos internados. **Método:** Trata-se de uma revisão integrativa da literatura, realizada por meio de seis etapas. A coleta de dados ocorreu em julho de 2020, nas bases de dados da BDENF, LILACS via BVS, CINAHL, SCOPUS, Web of Science via Portal Periódicos Capes e SciELO, com os descritores drug interactions, drug prescriptions e patient safety. Selecionaram-se 18 produções no recorte temporal de 2008 a 2020. **Resultados:** dos artigos selecionados, dez eram estudos nacionais e oito internacionais. As unidades de terapia intensiva e emergência foram os cenários mais investigados. Os resultados foram categorizados em três eixos temáticos: prescrições e interações medicamentosas; aprazamento e interações medicamentosas; intervenções e interações medicamentosas. **Conclusão:** as interações medicamentosas possuem altas taxas, principalmente nas prescrições medicamentosas com polifarmácia e em unidades críticas. As intervenções com software para apoio à decisão clínica e presença do farmacêutico clínico obtiveram resultados positivos e significativos.

Palavras-chave: Interações de Medicamento. Prescrições de Medicamentos. Segurança do Paciente. Hospitais.

SEGURIDAD DEL PACIENTE: INTERACCIONES MEDICAMENTOSAS EN PACIENTES ADULTOS HOSPITALIZADOS

RESUMEN

Objetivo: investigar en la literatura evidencias sobre interacciones provenientes de prescripciones de medicamentos de pacientes adultos hospitalizados. **Método**: se trata de una revisión integradora de la literatura, realizada através de seis etapas. La recolección de datos ocurrió en julio de 2020, en las bases de datos de la BDENF, LILACS vía BVS, CINAHL, SCOPUS, *Web of Science* vía Portal Periódicos Capes y SciELO, conlos descriptores *drug interactions, drug prescriptions* y *patient safety.* Fueron seleccionadas 18 producciones en el recorte espacio temporal de 2008 a 2020. **Resultados**: de los artículos seleccionados, diez eran estudios nacionales yocho internacionales. Las unidades de cuidados intensivos y urgencias fueron los escenarios más investigados. Los resultados fueron categorizados en tres ejes temáticos: prescripciones e interacciones medicamentosas; plazos e interacciones medicamentosas; intervenciones e interacciones medicamentosas. **Conclusión**: las interacciones medicamentosas poseen altas tasas, principalmente en las prescripciones medicamentosas con polifarmacia y en unidades críticas. Las intervenciones con *software* para el apoyo a la decisión clínica yla presencia del farmacéutico clínico obtuvieron resultados positivos y significativos.

Palabras clave: Interacciones de medicamento. Prescripciones de medicamentos. Seguridad del paciente. Hospitales.

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