RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Paper

Open Access

# Potential drug interactions in adults and the older people in the hospital environment

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Submitted: 30-03-2023 Resubmitted: 18-05-2023 Accepted: 26-05-2023

Double blind peer review

## Abstract

**Objective**: to determine the prevalence of potentially serious and contraindicated drug interactions in adult and older people patients in public, mixed and private hospital settings. **Methods**: cross-sectional study with prescriptions for 27,088 patients over 18 years of age, divided into the "Adults" and "Older people" groups, from six public hospitals and five mixed and private hospitals in three regions of Brazil in February 2023. Data were collected from NoHarm platform, a tool used to organize the clinical pharmacist's work process, and analyzed potential serious and contraindicated drug interactions. **Results**: a total of 128,143 prescriptions were included in the study, 47.8% from the adults group and 52.2% from the older people group. The presence of at least one potential interaction in the prescription in the total population was 22.3%, being higher in the elderly population (24.5% *vs*. 19.9%, $P < 0.001$) in male patients (24.7% *vs*. 20.2%, $P < 0.001$), in prescriptions for patients in a 100% public hospital (27.8% *vs*. 16.1%, $P < 0.001$) and with a greater number of prescription items (18 *vs*. 3 items, $P < 0.001$). The total number of drug interactions found was 71,047, the most prevalent being among psychoactives and drugs that act on the gastrointestinal system, both in the adults group (32.9%) and in the older people group (22.4%). **Conclusion**: this study identified a high prevalence (22.3%) of drug interactions in hospitalized patients, more prevalent among older people and in public hospitals. The drug classes involved in the interactions varied between the adult and older people groups.

**Keywords**: drug interactions, inpatients, public hospitals, patient safety.

## Potenciais interações medicamentosas em adultos e idosos no ambiente hospitalar

## Resumo

**Objetivo**: determinar a prevalência de interações medicamentosas potencialmente graves em pacientes adultos e idosos no ambiente hospitalar público, misto e privado. **Métodos**: estudo transversal com prescrições de 27.088 pacientes maiores de 18 anos divididos entre os grupos "Adultos" e "Idosos", de seis hospitais públicos e cinco hospitais mistos e privados em três regiões do Brasil em fevereiro de 2023. Os dados foram coletados da plataforma NoHarm, ferramenta utilizada para organizar o processo de trabalho do farmacêutico clínico. Foram analisadas potenciais interações medicamentosas classificadas como graves ou contraindicadas. **Resultados**: um total de 128.143 prescrições foram incluídas no estudo, sendo 47,8% do grupo dos adultos e 52,2% do grupo dos idosos. A presença de, pelo menos, uma interação potencial no total de prescrições foi igual a 22,3%, sendo mais frequente na população idosa (24,5% *vs*. 19,9%, $P < 0.001$), do sexo masculino (24,7% *vs*. 20,2%, $P < 0,001$), internada em hospital público (27,8% *vs*. 16,1%, $P < 0,001$) e com maior quantidade de itens prescritos (18 *vs*. 3 itens, $P < 0,001$). O total de interações medicamentosas encontradas foi de 71.047, sendo mais prevalentes os medicamentos psicoativos e aqueles que atuam no sistema gastrointestinal, tanto no grupo dos adultos (32,9%), quanto no grupo dos idosos (22,4%). **Conclusão**: este estudo identificou alta prevalência (22,3%) de interações medicamentosas em pacientes hospitalizados, sobretudo entre os pacientes idosos e em hospitais públicos. As classes de medicamentos envolvidos nas interações variaram entre os grupos de adultos e idosos.

**Palavras chaves:** interações medicamentosas, pacientes internados, hospitais públicos, segurança do paciente.

## Introduction

The patient safety practice aims at reducing healthcare-related harms. Medication use is a crucial point of action and, in view of this, the last few years have been devoted to reducing serious and preventable harms through the global challenge called "Medication without Harms", promoted by the World Health Organization (WHO). The focus is on identifying risks and on developing and applying tools to prevent errors[1].

A safe medication system includes paying attention to the most diverse stages of the medication process and, among them, medical prescriptions. Several drug-related problems that can occur in the prescription process, and drug interactions with potential risks to the patients are one of them[2].

Drug interactions take place when the pharmacological or clinical response of a medication is modified by the concomitant administration of a second one, which can generate synergistic or antagonistic effects. A drug interaction can reduce the effectiveness of a medication or also increase its toxicity, being harmful to the patient. There are interactions that can be beneficial and useful, which would justify the concomitant prescription of both medications[3].

As individuals age they tend to accumulate chronic medical conditions, becoming multimorbid (coexistence of two or more chronic medical conditions in a patient). Multimorbidity is associated with reduced functional status, high mortality, lower quality of life and increased health care use. There is a consistent cause-and-effect relationship between aging, multimorbidity and polypharmacy.[4]

Polypharmacy, namely the use of more than 5 medications, is increasing among patients with comorbidities[5], with a significant risk of inappropriate medication use, medication-specific adverse events and potential drug interactions[6-8]. Inappropriate polypharmacy (irrational prescription of many medications) should be reduced and appropriate polypharmacy (rational prescription of several medications based on the best available evidence and considering individual patient factors and context) should be ensured, when necessary. Therefore, appropriate polypharmacy should be considered at each point when a new treatment is initiated for the patient and when the patient passes through different care settings. The multiple negative outcomes of inappropriate polypharmacy include cognitive impairment/delirium, weight loss and malnutrition, falls leading to hip fractures, functional impairment and reduced mobility, hospitalization, reduced quality of life, death and increased costs to health care systems[9,10].

Studies on drug interactions have gained greater importance and attention in the medical field, as this situation is among the main causes of problems related to medication use[11]. Many of these interactions have clinical manifestations of slow onset and can be mistakenly interpreted as new diseases, hindering their proper management[12].

Hospitalized patients are more likely to be affected by drug interactions due to comorbidities, polypharmacy and frequent changes in their therapy[13,14]. According to the review by Yamagata *et al.*[15], most studies assess the prevalence of interactions in a hospital, with few multicenter studies[16], making it difficult to have a global view of the problem. The objective of this study was to determine the prevalence of potentially serious and harmful drug interactions in adult and aged patients in public, mixed and private hospital settings.

## Methods

This cross-sectional study was carried out with data from the NoHarm platform, a system that assists the evaluation process by clinical pharmacists, offering , in addition to other information, alerts to potential drug interactions.

The NoHarm platform is an open knowledge system (open source) that allows users to access data on Internet servers (Cloud Computing system), organizes patient information and generates alerts for clinical pharmacists, easing decision-making. Among the 65 hospitals served by NoHarm, their selection was at random, considering those with 100% public care (Unified Health System (*Sistema Único de Saúde*, [SUS]) and mixed/private care, located in three regions of the country (South, Southeast and North). Specialty hospitals (n=2), recently implemented ones (n=23) and those with impossibility to access the database (n=5) were excluded.

Potential serious and contraindicated drug interactions were analyzed, found in the prescriptions corresponding to February 2023 for patients over 18 years of age at the hospitals selected. Serious drug interactions were defined as those that could be life-threatening and/or require intervention to reduce or avoid serious adverse effects. The UpToDate, Micromedex and Drugs.com databases were consulted. Differences in severity were evaluated by consulting related scientific articles. Interactions with weak documentation or those considered positive and indicated in clinical protocols with proven scientific evidence were excluded. No specific sectors or services were filtered.

The dataset that served as the basis for the study was extracted from a PostgreSQL database. PostgreSQL is a relational database, that is, a type of database that organizes data into schemas with one or more tables that can present "relationships" based on a set of predefined rules. In this research, each schema represents data from a hospital and the tables represent subsets of data with similar characteristics, such as the prescriptions table, where there are relationships with the medication registration table, and another relationship with the patient registration table, for example. In this case, a prescription can have one or more medications and must have exactly one associated patient.

The choice for the month of February took into account that it was the one with complete data most recently closed before the analysis.

The prescriptions were divided, considering the patients' profiles, into the "Adults" group (between 18 and 59 years old) and the "Older Adults" group (at least 60 years old). The following variables were collected: type of service (public or non-public, mixed or private), sector, age, gender, number of items prescribed and presence and number of serious drug interactions, in addition to the medications and therapeutic classes involved in the interactions. All the medications prescribed, even those with "if necessary" dosages, were included in the analysis.

The descriptive analysis was performed by means of absolute and relative frequencies for the categorical variables (gender, presence of interactions, specific interactions) and medians and interquartile ranges were used for continuous variables without normal distribution (age, number of prescription items, number of interactions). Normality of the variables was assessed using the Kolmogorov-Smirnov test. The prevalence values were compared between groups using Pearson's chi-square test. The medians were compared using Mann-Whitney's U test, requiring a 50% sample to perform the test. Probability (*P*) values of 0.05 or less were considered statistically significant. The data analysis was performed in the SPSS software, version 21.0 (SPSS Inc., Chicago, IL).

The study was approved by the Research Ethics Committee of the Nossa Senhora da Conceição Hospital (Porto Alegre-RS, Brazil), with opinion number 4,763,390. As this is a data review, the Informed Consent Form was waived.

## Results

During the one-month period (February 2023), 128,143 prescriptions from 27,088 patients were analyzed, of which 47.8% are from the "Adults" group and 52.2% from the "Older Adults" group. In both groups, most of the population was female (64.8% in "Adults", 53.6% in "Older Adults"). The median age of the "Adults" group was 42 years old, whereas it was 72 in the "Older Adults" group. The data that describe the characteristics of each group and of the population in general are presented in Table 1.

The presence of at least one potential drug interaction in the total number of prescriptions was 22.3%, being higher in the aged population (24.5% vs. 19.9%, *P*<0.001), in prescriptions for male patients (24.7% vs. 20.2%, *P*<0.001), and in prescriptions from 100% public hospitals (27.8% vs. 16.1%, *P*<0.001).

The median of items per prescription for the entire population was seven (25$^{th}$ percentile of 2 and 75$^{th}$ percentile of 15), with a higher median in the aged population (8 vs. 6, *P*<0.001), in male patients (8 vs. 6, *P*<0.001), and in patients treated at a 100% public hospital (10 vs. 4, *P*<0.001). Prescriptions with at least one potential drug interaction presented a higher median of items prescribed than those without interactions (18 vs. 3 *P*<0.001).

**Table 1**. Characteristics of the population and in the "Adults" and "Older Adults" groups (2023).

| | "Adults" Group | "Older Adults" Group | Total |
|---|---|---|---|
| Patients (%row) | 15,929 (58.8%) | 11,159 (41.2%) | 27,088 |
| Prescriptions (%line) | 61,233(47.8%) | 66,910 (52.2%) | 128,143 |
| Items | | | |
| Median (25-75 Percentile) | 6 (2-14) | 8 (2-17) | 7(2-15) |
| Gender | | | |
| Male (%column) | 5,609 (35.2%) | 5,174 (46.4%) | 10,783 (39.8%) |
| Female (%column) | 10,318 (64.8%) | 5,984 (53.6%) | 16,302 (60.1%) |
| Age | | | |
| Median (25-75 Percentile) | 42 (30-52) | 72 (66-80) | 54 (35-69) |

The total number of drug interactions found was 71,047. The class most involved in drug interactions was psychoactive - psychoanaleptics and psycholeptics - (62.1% in the "Adults" group and 51.4% in the "Older Adults" group). The most frequent potential drug interaction was between psychoactive drugs and medications that act on the gastrointestinal system, both in the "Adults" group (32.9%) and in the "Older Adults" group (22.4%). The other more common interactions involve different classes in both groups under study.

In the "Adults" group, the second and third most prevalent classes in interactions were between psychoactive drugs (7.3%) and between psychoactive drugs and analgesics (6.7%). The most common interactions in the group of adult patients are presented in Table 2, showing the most common active ingredients in each class.

In the "Older Adults" group, the second and third classes present in the most prevalent interactions were between psychoactive and antithrombotic drugs, mainly between selective serotonin reuptake inhibitors and heparin (8.9%), and between psychoactive and analgesic medications (7.9%). The most common interactions in the group of aged patients are presented in Table 3, showing the most common active ingredients in each class.

Metoclopramide was the main active principle with potential drug interactions, both in the "Older Adults" group (19.9%) and in the "Adults" group (32.9%). The active principles most involved in potential drug interactions of the psychoactive class (psychoanaleptics and psycholeptics) in the "Adults" group were chlorpromazine (13.7%) and quetiapine (12.3%), while in the "Older Adults" group they were quetiapine (17.2%) and haloperidol (6.1%).

Among the potential drug interactions involving analgesics and psychoactive drugs in adult patients, the most prevalent active ingredient was tramadol, associated with amitriptyline (1.1%) and fluoxetine (1.0%). In the older adults, the most prevalent active ingredients were tramadol with amitriptyline (1.2%) and methadone with quetiapine (1.0%).

**Table 2**. Most frequent drug interactions in the group of adults and their classification in the databases (2023).

| Potential Drug Interactions | n | % |
|---|---|---|
| Psychoactive x Gastrointestinal | | |
| Chlorpromazine x Metoclopramide | 2,754 | 8.7% |
| Quetiapine x Metoclopramide | 2,585 | 8.2% |
| Haloperidol x Metoclopramide | 1,494 | 4.7% |
| Levomepromazine x Metoclopramide | 1,324 | 4.2% |
| Risperidone x Metoclopramide | 1,066 | 3.4% |
| Quetiapine x Bromopride | 400 | 1.3% |
| Psychoactive x Psychoactive | | |
| Chlorpromazine x Haloperidol | 885 | 2.8% |
| Quetiapine x Chlorpromazine | 246 | 0.8% |
| Psychoactive x Analgesic | | |
| Amitriptyline x Tramadol | 360 | 1.1% |
| Fluoxetine x Tramadol | 329 | 1.0% |
| Quetiapine x Methadone | 284 | 0.9% |
| Psychoactive x Antiepileptic | | |
| Diazepam x Phenytoin | 769 | 2.4% |
| Quetiapine x Carbamazepine | 272 | 0.9% |
| Chlorpromazine x Carbamazepine | 229 | 0.7% |
| Psychoactive x Antithrombotic | | |
| Sertraline x Enoxaparin | 379 | 1.2% |
| Fluoxetine x Heparin | 246 | 0.8% |
| Fluoxetine x Enoxaparin | 210 | 0.7% |
| Gastrointestinal x Antipruritic | | |
| Metoclopramide x Promethazine | 762 | 2.4% |
| Antilipemics x Antihypertensives | | |
| Simvastatin x Amlodipine | 680 | 2.1% |
| Antithrombotic x Anti-inflammatory | | |
| Enoxaparin x Ketorolac | 474 | 1.5% |
| Total | 31,657 | 100.0% |

Psychoanaleptics, ATC N06 (such as antidepressants, psychostimulants) and psycholeptics-ATC N05 (such as antipsychotics, anxiolytics, hypnotics and sedatives) were grouped in the Psychoactive class. The interactions representing more than 0.5% of the total interactions within the "Adults" Group are presented.

**Table 3**. Most frequent drug interactions in the "Older Adults" group and their classification in the databases (2023).

| Potential Drug Interactions | n | % |
|---|---|---|
| Psychoactive x Gastrointestinal | | |
| Quetiapine x Metoclopramide | 3,761 | 9.9% |
| Haloperidol x Metoclopramide | 1,758 | 4.7% |
| Quetiapine x Bromopride | 688 | 1.8% |
| Risperidone x Metoclopramide | 567 | 1.5% |
| Olanzapine x Metoclopramide | 349 | 0.9% |
| Chlorpromazine x Metoclopramide | 297 | 0.8% |
| Amitriptyline x Bromopride | 280 | 0.7% |
| Antithrombotic x Psychoactive | | |
| Enoxaparin x Sertraline | 503 | 1.3% |
| Enoxaparin x Escitalopram | 432 | 1.1% |
| Enoxaparin x Fluoxetine | 411 | 1.1% |
| Heparin x Fluoxetine | 346 | 0.9% |
| Enoxaparin x Citalopram | 195 | 0.5% |
| Psychoactive x Analgesic | | |
| Amitriptyline x Tramadol | 448 | 1.2% |
| Quetiapine x Methadone | 364 | 1.0% |
| Fluoxetine x Tramadol | 339 | 0.9% |
| Sertraline x Tramadol | 324 | 0.9% |
| Mirtazapine x Tramadol | 278 | 0.7% |
| Duloxetine x Tramadol | 238 | 0.6% |
| Antithrombotic x Analgesic | | |
| Clopidogrel x Morphine | 963 | 2.5% |
| Clopidogrel x Tramadol | 727 | 1.9% |
| Heparin x Acetylsalicylic Acid | 285 | 0.8% |
| Antilipemics x Antihypertensives | | |
| Amlodipine x Simvastatin | 2,137 | 5.7% |
| Antacids x Antipruritic | | |
| Omeprazole x Clopidogrel | 1,722 | 4.6% |
| Psychoactive x Psychoactive | | |
| Escitalopram x Quetiapine | 387 | 1.0% |
| Fluoxetine x Amitriptyline | 260 | 0.7% |
| Total | 37,804 | 100.0% |

Psychoanaleptics, ATC N06 (such as antidepressants, psychostimulants) and psycholeptics - ATC N05 (such as antipsychotics, anxiolytics, hypnotics and sedatives) are grouped in the psychoactive class. The interactions representing more than 0.5% of the total interactions within the "Older Adults" group are presented[1]. The acetylsalicylic acid interaction was only considered for presentations with more than 200 mg.

The most frequent active ingredient in potential drug interactions with metoclopramide in the "Older Adults" group was quetiapine. The active principles most involved in potential drug interactions between the class of psychoactive drugs (psychoanaleptics and psycholeptics) and antithrombotics in the "Older Adults" group were sertraline (1.3%), escitalopram (1.1%) or fluoxetine (1.1%), which have potential interactions with enoxaparin.

In the older adults, the most prevalent active ingredients were tramadol with amitriptyline (1.2%) and methadone with quetiapine (1.0%). In turn, for the potential drug interactions between the analgesic and psychoactive classes in the aged patients, the most prevalent active ingredients were tramadol with amitriptyline (1.2%) and methadone with quetiapine (1.0%).

## Discussion

In this study, an analysis of medical prescriptions for adult and aged patients from 11 general hospitals in three different Brazilian regions was performed, identifying 71,046 potential serious drug interactions.

The evaluation of drug interactions in adults and older adults is essential to certify safety and effectiveness of a treatment[15]. Carrying out a careful assessment of drug prescriptions, especially in older adults, who have multiple comorbidities and use different medications, is fundamental to minimize the risk of adverse events and ensure the benefits of the treatments. Potential drug interactions precede actual drug interactions, and reducing exposure to the concomitant administration of these medications is a strategy to minimize the risks associated with potentially harmful drug combinations[17].

There is a large number of studies on the prevalence of drug interactions in hospitals; however there is a significant difference in the way the results are presented and in the methodologies and databases used[16]. A review and meta-analysis showed that there is wide variation in the prevalence values reported by the studies: from 16.3 to 71.1%[16]. This research presented 22.3% presence of potential drug interactions, being significantly higher in prescriptions from the "Older Adults" group (24.5% vs. 19.9%, $P<0.001$), as this group also had a higher median of prescription items (8 vs. 6, $P<0.001$) when compared to the group of adults, in agreement with a previous study[18]. Due to aging, the elderly population ends up presenting more comorbidities, with the need to use more medications[4]. Polypharmacy is associated with greater presence of potential drug interactions[6-8].

In addition to age and gender, the type of care was also associated with greater presence of potential drug interactions. Patients treated at 100% SUS hospitals presented more potential drug interactions when compared to mixed and private hospitals (27.8% vs. 16.1, $P<0.001$). As there are differences in the methodologies and in the way the results are presented by the different studies on drug interactions[15,16], this comparison between the results of hospitals that offer different types of care (public, mixed and private) is impaired. In a multicenter study analyzed, this datum was not a collection variable, in addition to having been conducted only in an Intensive Care Unit[19]. Thus, we did not find this association between drug interactions and care at a public hospital in any other study, not even in a more recent review and meta-analysis[16]. This result may reveal that patients treated at a 100% public hospital have more comorbidities, as the number of items prescribed had a higher median (4 vs. 10). One of the hypotheses that could justify a higher percentage of drug interactions in the public hospitals studied may have been the lower availability of more expensive therapeutic alternatives, such as ondansetron, which ends up avoiding the most common interaction identified in the study: metoclopramide with antipsychotics. Another hypothesis would be the greater difficulty accessing public hospitals, causing patients with more comorbidities and more advanced diseases to be treated, as the number of prescription items was also higher[20].

The results obtained revealed that the classes of medications that most interacted with each other were psychoactive (psychoanaleptics and psycholeptics) and gastrointestinal, regardless of the studied group ("Adults" and "Older Adults"). This result can be justified by the facts that hospitals with mental health care were included in the population of this study and that there is a common practice of prescribing medications with gastrointestinal action in the hospital environment for the treatment of nausea and vomiting in Brazil[21].

Aging and the elderly population are particularly susceptible to cardiovascular diseases. Age is an independent risk factor for cardiovascular diseases and hypertension[22,23]. This justifies the greater use of antilipemic and antihypertensive drugs in the aged population and, therefore, the greater presence of interactions with simvastatin and amlodipine in this population.

The study did not consider poorly-based drug interactions and that the association is present in clinical protocols with proven scientific evidence to avoid trivializing the alerts on the platform, reducing attention to the interventions that are really necessary. When it comes to a decision-support platform, it is necessary to constantly update and analyze the alerts in order to avoid alert fatigue[24]. As stated by Yamagata *et al.* (2018)[15] in their review of drug interactions, it is recommended to use at least two information sources in drug interaction research. Using more databases for the evaluation of drug interactions is very important, as it allows for an even more reliable alert for better decision-making by health professionals. However, it is important to emphasize that precautions should be taken when interpreting drug interaction data provided by tertiary drug resources (databases and decision-support tools)[15]. Health professionals should be aware of the differences inherent in these resources[25] and trust in their clinical judgment to provide the best care possible to their patients.

One of the limitations of this study is due to the fact that the drug interactions identified were potential, that is, that their potential was identified through the analysis of the prescriptions; however, as there was no follow-up of the patients, their occurrence was not confirmed. Another limitation was that no assessment of the specificities of each sector, department or specialty of the prescriptions was carried out.

In future papers, it is planned to hold discussion forums on drug interactions among users of the platform researched.

## Conclusion

This study identified high prevalence of potential drug interactions (22.3%) in prescriptions for adult and aged patients in eleven Brazilian hospitals. Aged patients, male or treated at public hospitals had prescriptions with more items and with greater presence of potential drug interactions when compared to the private hospitals included in the study. It was also possible to identify that the classes involved in potential drug interactions are significantly different between adults and older adults.

### Funding sources

This paper was carried out with the support of the Artificial Intelligence in Health Institute.

### Collaborators

AHU, JDO, JCC, GXO, CSI: project design or data analysis and interpretation; AHU, JDO, JCC, GXO, CSI: writing of the article or critical review relevant to the intellectual content. All the authors approved the final version of the article, ensuring accuracy and integrity of the information expressed therein.

### Declaration of conflict of interests

The authors declare that there is no conflict of interest in relation to this article.

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