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# Potential drug-drug interactions in prescriptions of hospitalized patients with respiratory diseases in a university hospital during the amazonian winter

**Robert Candido PICANÇO[1], Vitor Souza LIMA[1], Cintia Pessoa SANTOS[2], Weilla Cordeiro SILVA[2], Bruno Quadro GOMES[2], Ademar Soares MELO[3], Alan Barroso GRISÓLIA[3]**

[1]Universidade Federal do Pará, Pará; [2]Hospital Universitário João de Barros Barreto, Pará;
[3]Hospital Universitário João de Barros Barreto, Pará, Unidade de Farmácia Clínica

Corresponding author: Grisólia AB, alangrisolia@gmail.com

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## Abstract

**Objective:** To identify and demonstrate the prevalence Potential drug-drug interactions (DDI) in hospitalized patients with respiratory diseases during the Amazonian winter, also seeking to classify DDI according to risk and clinical management. **Methods:** A descriptive, cross-sectional, retrospective study with a quantitative approach of patients admitted to the university hospital in Amazonian winter. 40 patients were selected and 120 prescriptions were answered, collecting data such as patient identification, diagnostic hypothesis, and medications used. The investigation of DDI occurred in the period of 24 hours, 7 and 14 days. The identification and classification of DDI risks are carried out by the LexicomP® support platform via the UpToDate® software. Descriptive statistics were performed on the data, which were compiled in a Microsoft Excel® spreadsheet. **Results:** 55% of patients were men, the mean age was 46 ± 22 years old, the mean length of stay was 41 ± 30 days, most patients had Pulmonary Tuberculosis, Unspecified Pneumonia and Pleural Effusion. In this population, the analysis of the risk classification DDI showed a total of 989, with approximately 8 DDI/prescription. A DDI prevalence of low risk (classes C and B). Among the drugs involved, omeprazole x dipyrone, dipyrone x captopril, these being risk B and C, respectively. Despite the majority of DDI being low risk, there were also high risk ones, not recommended (Class X), totaling 51 DDI, the most prevalent was omeprazole and rifampicin, which can induce gastrointestinal discomfort, and its management consists of replacing make omeprazole for pantoprazole. In addition, the second most frequent X-risk interaction was scopolamine plus ipratropium bromide, which could induce anticholinergic effects in patients. And a DDI was also detected between Promethazine x Bromopride with a risk of neuroleptic malignant syndrome or extrapyramidal reactions, these should be managed individually. **Conclusion:** A high occurrence of DDI was identified in the prescriptions of patients with respiratory diseases during the putative Amazonian winter period. Despite being mostly low risk, DDI classified as X were present and consequently demanding clinical management. On the other hand, for evaluate its clinical repercussions, more methodologically different studies are needed. Still, knowledge of DDI can help establish appropriate therapeutic strategies in this population.

**Key words:** respiratory diseases; Potential drug-drug interactions; Clinical pharmacology; rifampicin, Amazonian winter.

# Potenciais interações medicamentosas em prescrição de pacientes internados com doenças respiratórias em hospital universitário durante inverno amazônico

## Resumo

**Objetivo:** Identificar e descrever a prevalência potenciais interações medicamentosas (PIM) em pacientes internados com doenças respiratórias durante período de inverno amazônico, buscando também classificar PIM em função do risco e o manejo clínico. **Métodos:** Um estudo descritivo, tipo transversal, retrospectivo, com abordagem quantitativa de pacientes internado no hospital universitário durante inverno amazônico. Foram selecionados 40 pacientes e analisadas 120 prescrições, coletando dados como identificação do paciente, hipótese diagnóstico, medicamentos utilizados. A investigação de potenciais interações ocorreu no período de 24 horas, 7 dias e 14 dias. A identificação e as classificações quanto aos riscos das PIM formam realizadas pela plataforma de apoio LexicomP® via aplicativo *UpToDate*®. Foi feita estatística descritiva dos dados, os quais foram compilados em planilha do *Microsoft Excel*®. **Resultados:** Dos 40 pacientes, 55% eram homens, a média de idade foi de 46 ± 22 anos, o tempo médio de internação foi de 41 ± 30 dias, a maioria dos pacientes apresentaram Tuberculose Pulmonar, Pneumonias não especificadas e Derrame Pleural. Nessa população, análise da classificação de risco das PIMs, mostrou um total de 989 interações medicamentosas, com aproximadamente 8 PIM/prescrição. Um

predomínio de PIM com risco baixo (classe C e B). Entre os medicamentos envolvidos o omeprazol x dipirona, dipirona x captopril, sendo essas de risco B e C, respectivamente. Apesar da maioria das PIM serem baixo risco, também ocorreram interações de risco elevado risco, não recomendadas (Classe X), totalizando 51 interações, sendo a mais prevalente e omeprazol e rifampicina, a qual pode induzir desconfortos gastrointestinais, e seu manejo consiste na substituição do omeprazol pelo pantoprazol. Além desse, segunda interação de risco X com maior ocorrência foi escopolamina mais brometo de Ipratrópio, a qual poderia induzir efeitos anticolinérgicos nos pacientes. E também foi detectado a PIM entre Prometazina x Bromoprida com risco de síndrome neuroléptica maligna ou reações extrapiramidais, esses devem ser manejados de maneira individualizada. **Conclusão:** Identificou-se uma elevada ocorrência de PIM nas prescrições de pacientes com doenças respiratorias durante o período putativo inverno amazônico. Apesar de na sua maioria ser de baixo risco, as PIM classificadas como X se mostraram presentes e consequentemente demandando manejo clínico. Por outro lado, para avaliar suas repercussões clínicas, mais estudos metodologicamente diferentes são necessários. Ainda assim, o conhecimento das PIM podem ajudar a estabelecer estratégias terapêuticas adequadas nessa população.

**Palavras-Chave:** doenças respiratórias; potenciais interações medicamentosas; Farmacologia clínica; rifampicina, inverno amazônico.

## Introduction

Respiratory conditions are diseases or infections that affect the upper and lower respiratory tracts and cause air passage obstructions both at the nasal and bronchiolar and pulmonary levels[1]. They can vary from acute infections, such as pneumonias and common colds, to more severe infections, such as tuberculosis[2]. The epidemiological pattern of these diseases in the populations may change depending on the region and on seasonalities[3], which shows the importance of studies aiming to evaluate the regional characteristics, risks and pharmacological management of these diseases.

They are responsible for a large part of ailments and deaths in adults and children and characterize the overload found in health care services[4]. Respiratory infections account for more than four million deaths per year and are the main cause of death in developing countries[5]. In Brazil, mortality due to the respiratory system diseases has been increasing during the years in all regions of the country: North, Northeast, South, Northeast, Southeast and Midwest[6]. In this context, the North region, the Amazon, stands out as the one with the greatest scarcity of studies in this field addressing the risks associated with these diseases, such as potential pharmacological interactions in hospitalized patients, especially in the so-called Amazonian winter (from January to August), when there is a seasonal increase in the incidence of respiratory diseases and hospitalizations[7].

In fact, some studies have shown that respiratory diseases represent a major challenge for health services, thus being the second leading reason for hospitalizations in Brazil, only behind cardiovascular diseases, accounting for a total of 5,926,023 hospitalizations from 2015 to 2019[8-9]. Therefore, given the high number of hospitalizations and the patients' weakened health status, polypharmacy use is common is these conditions, which is a factor associated with a risk for Potential Drug Interactions (PDIs) in these prescriptions. It is knows that PDIs are well-studied and associated in polypharmacy cases[10]. However, the topic is little explored and known in populations from the Amazon region, an endemic area for tuberculosis and for which little is known about the prevalence or types of PDIs.

In turn, PDIs are defined as a clinical event where the effects of a drug are altered due to another medication. Some drug interactions have the potential to cause harms and are responsible for the patients' clinical deterioration and increased hospitalization times, whereas other interactions are mild and do not require special measures. An estimated 35% to 60% of hospitalized patients are exposed to potential drug interactions, of which 5% to 10% progress to a severe adverse reaction, i.e., a harmful and unpleasant reaction resulting from the intervention related to using a medication[11]. This topic has already been known and explored in patients; however, few studies describe PDIs in hospitalized patients from the Amazon region, which has clinical, epidemiological and cultural singularities. In fact, the Amazonian winter (period with the highest rainfall rates) increases the incidence of and hospitalizations due to respiratory diseases in the region[12], showing the importance of conducting additional studies on the epidemiological and pharmacological characteristics during this period, so as to understand and characterize these aspects in the region.

Therefore, this study aims at identifying, describing and classifying potential drug interactions in hospitalized patients with respiratory diseases during the Amazonian winter at a university hospital located in the region, in order to improve knowledge on the subject matter and contribute to the prevention and promotion of patients' health, as it is the first study seeking to identify PDIs in the study population during the aforementioned period.

## Methods

This study was previously submitted to *Plataforma Brasil* for the analysis by the Research Ethics Committee (*Comitê de Ética em Pesquisa*, CEP) and was approved through a Data Use Commitment Form (*Termo de Compromisso de Utilização de Dados*, TCUD) under number 4,951,726. All the project stages followed the criteria and requirements set forth in Resolution No. 466/12 of the National Health Council.

### Study design and research locus

This descriptive, cross-sectional, retrospective and quantitative study was conducted with patients hospitalized at the João de Barros Barreto University Hospital (*Hospital Universitário João de Barros Barreto*, HUJBB), a health, teaching and research center linked to the Federal University of Pará (*Universidade Federal do Pará*, UFPA), which is a reference institution in respiratory diseases in the region. The data were obtained by analyzing the pharmacological prescriptions and medical records from January to August 2021.

During this period, a survey showed a total of 48 hospitalized patients, of which 40 met the study inclusion criteria and were evaluated for all the medications prescribed.

### Participants and inclusion criteria

Patients of both genders and all ages were included. It is worth noting that age is not a predominant factor for the occurrence of PDIs, which is more associated with polypharmacy; in addition to that, the hospital has a pediatric unit where children younger than 14 years old are hospitalized. Thus, among these patients, the ones selected were those with at least 02 medications and hospitalized in the Respiratory and Pulmonary Diseases unit of the João Barros Barreto University Hospital from January to August 2021. The patients excluded were those with hospitalization times of less than 14 days and not hospitalized in the Respiratory and Pulmonary Diseases unit.

### Variables and data collection

Data collection was performed by analyzing the prescriptions found in the medical records of patients hospitalized in the Respiratory and Pulmonary Diseases unit. Variables related to identification of the patient, diagnosis and medications prescribed were collected. Data collection was based on the pharmacotherapy monitoring forms from the HUJBB Clinical Pharmacy unit.

The potential drug interactions were investigated at three different moments during hospitalization: Period 01 comprised the patients' first prescription, at 24 hours of hospitalization; Period 02 included the prescriptions made on the seventh hospitalization day; and Period 03 covered the medical prescriptions made after 14 hospitalization days. A total of 120 prescriptions and 55 medications were analyzed through the hospital's electronic prescription database. This total corresponds to the 3 analyses made in the electronic prescriptions of all 40 patients.

Therefore, based on the profile of the medications found in the prescriptions, the drug interactions were identified and classified in the LexicomP® support platform, which has evidence-based content reviewed developed based on sources usually employed in the health community. LexicomP® via *UpToDate*® classifies PDIs according to the risk level: X (contraindicated association), D (consider the possibility of changing the therapy), C (monitor the therapy) and B (no action required). Furthermore, in terms of severity, PDIs may be: MAJOR: the interaction can impose a risk to life and/or require medical intervention to minimize of prevent severe adverse effects; MODERATE: the interaction can result in intensification of the patient's condition and/or require a change in the therapy; MINOR: the interaction would limit the clinical effects. The manifestations can include an increase in the frequency or severity of side effects, but usually do not require major changes in the therapy. Subsequently, the frequency was analyzed and the clinically relevant interactions were described.

After classifying the interactions, emphasis was given to the five most prevalent ones corresponding to each risk. These five potential interactions were considered to account for approximately 80% of the PDIs with the highest risk, Risk X, which poses severe risk to the patients.

### Bias control and sample size

It is worth noting that the current study aimed at analyzing prescriptions, identifying PDIs and classifying them using the *UpToDate*® platform, without evaluating the clinical repercussion of these interactions in the patients, as there was no pharmacotherapy follow-up by any Clinical Pharmacy service during the period when the study was conducted, showing a limitation and a possible bias, which would be asserting the occurrence of events associated with the PDIs. Despite that, this is the first study conducted with patients from the Amazon region in order to identify PDIs, an important aspect to discover and identify eventual findings to support the multiprofessional team. From a universe of 48 patients, 40 met study the inclusion criteria during the period that comprised the Amazonian winter (from January to August 2021), when the occurrence of respiratory diseases increases in the region. This number indicates a 5% sampling error and 95% confidence interval, by sample calculation. However, the study was descriptive and without separation into groups.

### Statistical method

The descriptive statistical data analysis was performed to synthesize and summarize values, so as to allow for an overall view of the data from the study population during the aforementioned period, which were compiled into *Microsoft Excel*® spreadsheets. The data referring to sociodemographic variables, comorbidities, pharmacotherapeutic information and the PDIs identified and classified were represented in tables with reference values, proportions and absolute numbers, and the "age" and "hospitalization time" variables were expressed as mean and standard deviation.

## Results

### Participants and characteristics of the study population

As a first step, it was sought to assess all the information regarding the clinical and epidemiological characteristics that were described in Table 1. In the description, it is observed that 22 (55%) were men and 18 (45%) were women. The mean age was 46±22 years old, with a 47.8% coefficient of variation and 14 and 106 years old as the youngest and oldest ages. Most of the men were young and almost 60% of the women were aged. The mean hospitalization time was 41±30 days, with a 73.1% coefficient of variation and 15 and 136 days as the minimum and maximum values. When analyzing the diagnoses, it can be seen that Pulmonary Tuberculosis (Pulmonary TB) is the most prevalent disease among hospitalized patients, accounting for 19% of the diagnoses and followed by unspecified pneumonias and pleural effusion (Table 1).

### Main results regarding identification and classification of the potential drug interactions

Consequently, it was sought to identify the PDIs, as well as their risk and severity level classifications (Table 2). Among all the 989 interactions identified, there was predominance of PDIs with risk levels C and B. According to the *UpToDate*® support system, for these risk classifications the data show that the medications involved do not interact in a clinically significant manner, requiring a risk monitoring plan and individualized management according to each patient's clinical condition.

However, other interactions with different risk classifications were also identified. Once the PDIs had been classified, the medications

involved in the 5 more frequent interactions were grouped into each risk classification (Table 3). In general, it was identified that the most frequent PDI was omeprazole x dipyrone, accounting for 42.2% of the risk B interactions, followed by dipyrone x captopril, which accounts for 24.1% of the risk C interactions. It is worth noting that risk B and C PDIs predominate among those identified and classified.

As it is known that some PDIs pose greater risks and may require interventions, it was sought to evaluate them and, consequently, a table was created with the frequency distribution of drug interactions, a description of their mechanisms, risk levels and effects (Table 4). It is interesting to note that the most frequent Risk X interaction involved the most frequent pair of medications (omeprazole and rifampicin), which was detected 18 times (35%), followed by scopolamine x ipratropium bromide (16%) and by promethazine x bromopride (14%), therefore identifying their pharmacological mechanisms and pharmacotherapeutic management.

**Table 1.** Clinical and epidemiological characteristics of the patients

| **Age** | |
|---|---|
| Years old | 40 |
| Mean ± Standard Deviation | 46 ± 22 |
| Minimum | 14 |
| Maximum | 106 |
| Gender | |
| Female | 45% |
| Male | 55% |
| Hospitalization | |
| Time (days); Mean ± Standard Deviation | 41 ± 30 |
| Coefficient of Variation | 73,1% |
| Minimum Time | 15 dias |
| Maximum Time | 136 dias |
| Diagnoses | |
| Pulmonary TB | 19% |
| Unspecified Pneumonias | 10,6% |
| Pleural Effusion | 10,6% |
| COPD | 8,5% |
| Pulmonary Fibrosis | 8,5% |
| Bronchiectasis | 6% |
| Multidrug-resistant TB | 6% |
| Lung Neoplasm | 6% |
| Pleural TB | 6% |
| Disseminated TB | 2% |
| Pulmonary Emphysema | 2% |
| Cystic Fibrosis | 2% |
| Pulmonary Abscess | 2% |
| Atypical Pneumonia | 2% |
| Tracheobronchitis | 2% |
| Comorbidities | |
| Arterial Hypertension | 40% |
| Diabetes | 20% |
| Lupus | 10% |
| Neurological Disease | 10% |
| Kidney Disease | 10% |
| Hormonal Disease | 10% |

Profile of the patients hospitalized in the Respiratory Diseases unit. *COPD=Chronic Obstructive Pulmonary Disease; Pn=Number of patients; %=Percentages; SD=Standard Deviation; CV=Coefficient of Variation; TB=Tuberculosis.

**Table 2.** Risk and severity classification expressed in absolute values

| **Risk** | **Gravity** | **Interaction Count** |
|---|---|---|
| | MAJOR | 1 |
| B | MODERATE | 17 |
| | MINOR | 193 |
| | MAJOR | 36 |
| C | MODERATE | 583 |
| | MINOR | 10 |
| | MAJOR | 48 |
| D | MODERATE | 50 |
| | MINOR | 0 |
| | MAJOR | 21 |
| X | MODERATE | 29 |
| | MINOR | 1 |
| | Total | 989 |

Identification of the potential drug interactions according to risk: X (contraindicated association), D (consider the possibility of changing the therapy), C (monitor the therapy) and B (no action required). Severity: MAJOR: the interaction can impose a risk to life and/or require medical intervention to minimize of prevent severe adverse effects; MODERATE: the interaction can result in intensification of the patient's condition and/or require a change in the therapy; MINOR: the interaction would limit the clinical effects. The manifestations can include an increase in the frequency or severity of side effects, but usually do not require major changes in the therapy. Count of interactions: the absolute number of times that each PDI was detected, out of a total of 989 potential drug interactions.

**Table 3.** Most frequent potential drug interactions according to risk level

| **Risk Classification** | **Severity** | **No.** | **%** |
|---|---|---|---|
| Risk X (N° 51) | | | |
| Omeprazole x Rifampicin | Moderate | 18 | 45% |
| Scopolamine x Ipratropium bromide | Moderate | 8 | 20% |
| Promethazine x Bromopride | Major | 7 | 17,5% |
| Linezolid x Metamizole | Major | 4 | 10% |
| Metamizole x Ketoprofen | Major | 3 | 7,5% |
| Risk D (N° 98) | | | |
| Enoxaparin x metamizole | Moderate | 21 | 34,5% |
| Tramadol x Scopolamine | Major | 16 | 26,2% |
| Captopril x Losartan | Moderate | 13 | 21,3% |
| Codeine and Paracetamol x Tramadol | Major | 5 | 8,2% |
| Metamizole x Furosemide | Moderate | 3 | 4,9% |
| Risk C (N° 629) | | | |
| Metamizole x Captopril | Moderate | 52 | 24,1% |
| Tramadol x Metamizole | Moderate | 49 | 22,7% |
| Tramadol x Bromopride | Moderate | 41 | 19% |
| Insulin x Tramadol | Moderate | 29 | 13,3% |
| Scopolamine x Bromopride | Moderate | 26 | 12,1% |
| Risk B (N° 211) | | | |
| Omeprazole x Metamizole | Minor | 71 | 42,2% |
| Insulin x Captopril | Minor | 36 | 22,9% |
| Tramadol x Captopril | Minor | 32 | 20,3% |
| Metamizole x Bromopride | Minor | 11 | 7,1% |
| Metamizole x Tramadol | Minor | 7 | 4,4% |

The five most prevalent potential drug interactions were identified, separated into groups according to risk: X (contraindicated association), D (consider the possibility of changing the therapy), C (monitor the therapy) and B (no action required); with values expressed in absolute and relative numbers within each group.

**Table 4.** Interactions classified as Risk X according to medications, risk level, frequency, mechanism of the interaction and effect.

| PDI | N (%) n=51 | Mechanism | Effect |
|---|---|---|---|
| Omeprazole X Rifampicin | 18 (35) | Induction of the CYP2C19 and CYP3A4 enzymes | Omeprazole can lose its therapeutic effect. With onset of gastrointestinal disorders. |
| Scopolamine X Ipratropium bromide | 8 (16) | Both are muscarinic antagonists | Ipratropium bromide can potentiate the anticholinergic effect of scopolamine. |
| Promethazine X Bromopride | 7 (14) | Inhibition of direct central dopaminergic activity | Bromopride can potentiate the toxic/adverse effect of promethazine. ↑Neuroleptic malignant syndrome or extrapyramidal reactions. |
| Linezolid X Dipyrone | 4 (8) | Unknown mechanism | Dipyrone can potentiate the adverse/toxic effects of the myelosuppression agents. ↑Agranulocytosis and pancytopenia. |
| Dipyrone X Ketoprofen | 3 (6) | COX-2 inhibition | Non-steroidal anti-inflammatory agents can increase the adverse/toxic effects of other non-steroidal anti-inflammatory agents. ↑Gastrointestinal toxicity. |

The five potential drug interactions classified as Risk X (contraindicated association) were identified, as well as their pharmacological mechanisms and probable pharmacological effects.

## Discussion

### Clinical and epidemiological characteristics of the patients

In the entire sample analyzed, there was predominance of male patients (55%) and most of the sample consisted of non-older adults (70%). On the other hand, there was higher prevalence of older adults among the female gender, approximately 60%. Differently from the data obtained in this research, which observed higher prevalence of females regarding aging, other studies concluded that it was the most prevalent gender, although it was conducted with a higher number of young individuals[13]. It is known that the aged female population is at a higher risk of developing toxicity due to medication use, which can be attributed to reduced metabolism and renal function loss. However, both genders can be subjected to PDIs[14].

In fact, several studies have indicated a higher risk for drug interactions related to age, a finding justified by the higher number of medications prescribed to the people with this profile[15-16]. Furthermore, other results showed that the proportion of PDIs is higher among hospitalized patients when compared to outpatients, also justified by the higher number of medications prescribed. This points to an increased risk for these interactions during the Amazonian winter, as there are more hospitalizations in this period[12]. However, more studies need to be conducted to prove this hypothesis.

Given this scenario of hospitalization, diagnoses gain relevance because they are mostly responsible for the patients to remain hospitalized. According to the results of this study, pulmonary tuberculosis (19%), unspecified pneumonias (10.6%) and pleural effusion (10.6%) were the most prevalent diseases diagnosed surveyed. In this context, it is interesting to note that tuberculosis is considered a major public health problem and is still one of the most transmissible diseases worldwide[17], standing out both in Brazil and in the Amazon region[18]. The country is among the 22 nations with a high tuberculosis burden[17-19]. This epidemiological profile may have a direct influence on the number and type of PDIs, as the diagnosis will determine the type of pharmacological treatment established for each patient. It is worth noting the importance of monitoring, as the pharmacological treatment for Pulmonary TB includes medications that act as strong enzyme inducers[20].

### Most relevant PDIs

Whether a drug interaction will take place or not cannot be foreseen with any certainty. However, patients with multiple diseases, kidney and liver dysfunctions, and those who make use of many medications, are more susceptible to this event[21]. In the population, many cases of drug interactions involve people who make use of several medications[22]. Within this context, it is interesting to highlight that identifying and evaluating PDIs contributes and exerts a direct impact on patients' health, by promoting effective and safe pharmacotherapy management, especially in regions with scarce information on this knowledge area.

Therefore, among the 120 prescriptions evaluated in this study, it was observed that only one did not have any PDI, showing the high presence of potential drug interactions. In these 120 prescriptions evaluated, a total of 989 drug interactions were found, with approximately 8 PDIs/prescription, and the most frequent interaction was omeprazole x dipyrone, which was detected 71 times. In relation to them, no action beyond the standard clinical care measures is required. Their mechanisms are probably related to induction of CYP2C19, the enzyme responsible for metabolizing omeprazole, with dipyrone accounting for that induction. Several pharmacokinetic studies with weak CYP2C19 inducers show that using dipyrone leads to a 66% reduction in omeprazole bioavailability[23]. In contrast, some studies show that omeprazole interferes with the pharmacokinetic processes of several medications[24]; therefore, it is always necessary to carefully evaluate and seek the real need for its use[25].

Another prevalent PDI identified in this study is dipyrone x captopril, detected 52 times (24.1%) in the risk C interactions. In this interaction, therapy monitoring is recommended because this combination can result in a significant decrease in renal function, potentiating the toxic or adverse effects of dipyrone, in addition to a possible reduction in the anti-hypertensive effect of captopril. The mechanism of this interaction seems to be related to the ability of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) to reduce synthesis of renal vasodilatory prostaglandins. This would affect vascular tone and fluid homeostasis[26]. This interaction is related to the comorbidity profile of the population under study, as arterial hypertension was the most prevalent comorbidity, detected in 40% of the patients in the current study.

**Prevalence and management of PDIs classified as Risk X**

The magnitude of the problems involving drug interactions increases significantly in certain populations, in parallel to the increase in the number of medications used[21]. Thus, some conditions impose on patients a high risk for drug interactions, with respiratory diseases among them[27].

In this sense, some studies corroborate the findings of the current research, which identified Pulmonary Tuberculosis as a highly prevalent chronic disease that requires a complex treatment[27]. Although antituberculosis drugs effectively fight against the microorganism, they can cause undesirable side effects, either due to the active principle itself or to its metabolites[28]. This leads to higher treatment abandonment rates, as they result in longer therapy times and in more hospitalizations[29]. Thus, there is the possibility that more medications are added to the patients' therapy. In this research, it was observed that the most prevalent Risk X PDI corresponded to omeprazole x rifampicin. Rifampicin, which is involved in this prevalent interaction, is one of the medications included in the treatment scheme for tuberculosis.

Some pharmacokinetic studies show that the omeprazole-rifampicin combination should be avoided, as rifampicin can reduce up to 87% the omeprazole plasma concentration, blocking the effect of the medication[30]. In fact, some studies point out that the most prevalent effects related to antituberculosis drugs are gastrointestinal disorders (40.3%)[28]. Therefore, due to the patients' complaints, changes in the therapeutic scheme are sometimes made because of these adverse effects, leading to the inclusion of one or more drugs, which may lead to new PDIs, such as those related to bromopride, a medication involved in the third more frequent PDI in this study[31]. However, more studies are required to confirm this observation, with another methodology that aims at performing a clinical assessment and a pharmacotherapy follow-up of these patients, which was not the objective of the current study.

On the other hand, the literature shows that the most feasible alternative to the PDI involving omeprazole x rifampicin would be replacing omeprazole by pantoprazole, as the latter is not metabolized by CYP2C19 or CYP3A4[32]. Despite being available in the hospital, this medication was not identified in the prescriptions evaluated, probably because it is considered a high-cost medication in the protocol of the aforementioned hospital. Therefore, it is important to conduct a cost-effectiveness study to support the substitution, as well promoting the professionals' awareness, as it is the most frequent Risk X interaction in our study population.

The second most prevalent Risk X interaction was scopolamine plus ipratropium bromide. Both drugs act as muscarinic receptor antagonists and can cause signs and symptoms related to cholinergic blockage[33]. However, as ipratropium is an inhalation medication, it is considered of topical use and, thus, poses low risk of systemic effects, although the patients should be instructed to perform mouth hygiene after using it. There is also the possibility for the emergence of some symptoms, such as urinary retention, dry mouth, dry eyes, constipation and tachycardia[34]. The patients should be under constant monitoring. This PDI can be related to the occurrence of COPD in the population under study, as it was the fourth most prevalent interaction among the patients hospitalized in the study period, and ipratropium is one of the drugs used in its treatment[35].

The third most prevalent Risk X PDI (promethazine x bromopride) can be directly related to gastrointestinal disorders, one of the main adverse reactions associated with the use of anti-tuberculosis medications[28], the most prevalent diagnosed disease among the patients hospitalized in the current study. This PDI should be evaluated individually, always considering the risk of developing severe neuroleptic malignant syndrome or extrapyramidal reactions. The other Risk X PDIs involved NSAIDs (dipyrone and ketoprofen) and can also cause gastric and/or renal complications, with the linezolid-dipyrone combination presenting myelosuppression risk. Together, these findings reinforce the importance of a duly certified professional monitoring the pharmacotherapy.

This scenario reinforces the need to learn about real and potential drug interactions, with the purpose of always working to prevent their occurrence or minimizing their role as triggering factors of preventable adverse events[38]. Therefore, there is an evident need to evaluate and monitor the prescriptions, in order to avoid the risk of potential interactions, especially Risk X ones, which mandatorily require guidance and clinical management.

## Conclusion

High occurrence of potential drug interactions was identified, approximately 8 PDIs/prescription, in hospitalized patients with respiratory diseases during the Amazonian winter. Although most interactions were of low risk, PDIs classified as Risk X were found, the most prevalent of which was rifampicin reducing the effect of omeprazole, probably because tuberculosis was the most commonly observed disease in these patients; and perhaps with gastrointestinal clinical consequences. However, additional studies with different methodologies involving clinical and pharmacotherapy follow-up are required to truly evaluate the clinical repercussions of these interactions, as it was not the objective of the current study. On the other hand, the knowledge generated by the findings on these PDIs herein described may help establish appropriate therapeutic strategies during the care process of Amazonian populations hospitalized due to respiratory diseases, especially during the Amazonian winter.

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**Declaration of conflicts of interest**

The authors declare that there are no conflicts of interests in relation to this article.

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