

# Prevalence and associated factors of severe proton pump inhibitors drug interactions in community pharmacy: a network analysis approach.

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## Abstract

**Objective:** The aim of this study is to identify the prevalence of severe drug interaction associated with proton pump inhibitors, associated factors and drugs involved. **Methods:** Cross-sectional study in 194 customers (> 18 years) of community pharmacies shortly after proton pump inhibitors acquisition (March 2019 to March 2020). Risk factors for drug interaction were assessed via multivariate logistic regression and relevance by network analysis. **Results:** The prevalence of drug interaction was 16.4% and was related to older age (OR=1.05; 95%CI 1.03 - 1.07) and female sex (OR=2.27; 95%CI 1, 15 - 4.47). The network analysis identified drug interaction involving omeprazole and pantoprazole as the most relevant and related to the prescription of levothyroxine, clopidogrel and cilostazol. **Conclusion:** The drug interaction among proton pump inhibitors users increase with age and are more common in women, especially those associated with levothyroxine, cilostazol and clopidogrel.

**Keywords:** Proton pump inhibitors; drug interactions; community pharmacy services; network analyses.

## Resumo

**Objetivo:** O objetivo deste estudo é identificar a prevalência de interação medicamentosa grave associada aos inibidores da bomba de prótons, fatores associados e medicamentos envolvidos. **Métodos:** Estudo transversal em 194 clientes (> 18 anos) de farmácias comunitárias, logo após aquisição de inibidores de bomba de prótons, no período de março de 2019 a março de 2020. Os fatores de risco para interação medicamentosa foram avaliados por meio de regressão logística multivariada e a relevância das interações por análise de rede. **Resultados:** A prevalência de interação medicamentosa foi de 16,4% e esteve relacionada à idade avançada (OR=1,05; IC95% 1,03 - 1,07) e sexo feminino (OR=2,27; IC95% 1, 15 - 4,47). A análise da rede identificou a interação medicamentosa envolvendo omeprazol e pantoprazol como a mais relevante e relacionada à prescrição de levotiroxina, clopidogrel e cilostazol. **Conclusão:** As interações medicamentosas entre usuários de inibidores de bomba de prótons aumentam com a idade e são mais comuns em mulheres, principalmente aquelas associadas à levotiroxina, cilostazol e clopidogrel. **Palavras-chave:** Inibidores da bomba de prótons; interações medicamentosas; serviços de farmácia comunitária; análises de rede.

## Introduction

Proton pump inhibitors (PPIs) are among the drugs most used by the general population,<sup>(1)</sup> especially among those with chronic diseases such as hypertension and diabetes.<sup>(2)</sup> Usually recommended for a few weeks for the treatment of diseases related to gastric hyperacidity,<sup>(3)</sup> the prolonged use of PPIs (6 months or more) has been increasing, mainly associated with self-medication.<sup>(3-5)</sup> Additionally, the presence of drug interactions in community pharmacy prescriptions is common,<sup>(6,7)</sup> which may represent a risk in cases of prolonged use of PPIs. PPIs are potent competitive inhibitors of enzymes of the CYP450 family, especially CYP2C19, a characteristic commonly related to potential serious interactions.<sup>(8-10)</sup>

Drug interaction is a topic widely explored in the literature in different scenarios. However, these studies commonly point out the frequency of interactions, but do not fully assess the intricate profile that these various interactions can present in a given group of patients. In this sense, drug interactions can be characterized more efficiently using network analysis. This computational approach allows processing a large volume of data in search of complex patterns, ranging from protein structure to the development of new drugs and their interaction mechanisms. (11, 12, 15) As far as we know, there are no studies that aim to characterize drug interactions using the network analysis approach.

Despite the minor clinical relevance in most cases, the number of possible drug interactions (DI) in a single prescription can be high. For example, probabilistically, a prescription with four drugs can result in six potential interactions. In these cases, methodological approaches that allow the identification of complex patterns relating relationships between drugs, frequency and intrinsic characteristics (severity of the interaction) would be adequate to measure the problem. Network analysis comprises an effective approach to identifying complex patterns in data obtained from patients, including drug interactions.<sup>(11, 12)</sup> As far as we know, there are no studies that analyze the profile of interactions associated with PPIs using network analysis tools.

## Objective

Identify the prevalence and factors associated with the occurrence of severe drug interactions in users of community pharmacies using PPIs, in addition to identifying the most significant drugs in these interactions via network analysis.

## Methods

### Study design and population

This is a cross-sectional study based on interviews with community pharmacy users shortly after purchasing PPIs. Individuals of both sexes (>18 years old) who acquired PPIs for their own consumption were included and those who showed evident inability to answer the questionnaire (with hearing, cognitive and speech disorders) were excluded. Data were collected from March 2018 to March 2019.

All interviews were carried out in a chain of private pharmacies in the city of Natal - RN. The chain has twenty-two units distributed in the four health districts of the city (east district comprises 14.1% of the population and has 6 pharmacies, west: 27.1% of the population and 1 pharmacy; north: 38.3% of the population and 3 pharmacies, south: 20.5% of the population and 12 pharmacies). In order for the sample to approximately represent the population density of each area of the municipality, the number of interviews in each pharmacy was proportional to the number of residents per district divided by the number of establishments in the region.

This study was approved by the UFRN Research Ethics Committee, as determined by CNS Resolution n° 466/12 of the National Health Council, with opinion n° 2.446.211 and CAAE: 80257417.0.0000.5292. All individuals who agreed to participate in the research signed the consent form.

### Data collect

In participating pharmacies, individuals were consecutively approached about their interest in participating in the research soon after purchasing the PPI. After the description of the research, the consent form was signed and we employed a ques-

tionnaire for data collection purposes. The questionnaire used was developed in 3 blocks, the first refers to data for characterization of the sample (age, sex, income, education, smoking, alcohol consumption, weight and height), the second to self-reported diseases and the drugs used and the third, the purchased PPI (name, dosage, time of use and occurrence of self-medication). The questionnaire was previously tested in a pilot with 10 patients and the interviewers were previously trained.

Potential drug interactions (PDI) characterized as a clinical situation in which a drug can modify the action of another drug that was administered simultaneously or successively were identified. Drug interactions have three levels of severity: a) severe when interactions can be fatal and/or require medical intervention to minimize or prevent serious adverse events; b) moderate when interactions may result in exacerbation of the patient's condition and require a change in therapy and c) mild when interactions have a limited clinical effect.<sup>(13)</sup> Only severe PDI were considered in this study.

## Statistical analysis

The sample size was calculated at 200 participants. This number ensures, with a confidence of 95%, a maximum error of the estimates of  $\pm 7$  percentage points. For descriptive and inferential statistical analysis, Stata version 15 (Stata Corporation, College Station, TX, USA) was used. Data were presented as mean and standard deviation or relative and absolute frequencies when relevant. Prevalence was estimated by the occurrence of one or more severe PDI related to PPIs by the number of patients evaluated. To identify the factors associated with the occurrence of severe PDI involving PPI, univariate analysis by logistic regression was used. Variables with  $p > 0.10$  were excluded and a multivariate logistic regression model was used ( $p < 0.05$ ).

Potential IMP networks were analyzed using Gephi, an open source network analysis software program that allows visualization and quantitative analysis of network maps. To produce network maps between severe PDI pairs, the data were imported directly into Gephi where the connections (nodes) represent the drugs and the lines the interactions

between them. The final visualization of the PMI networks for this work was performed using the Yifan Hu<sup>14</sup> layout algorithm to present intuitive clusters, with nodes sized by betweenness centrality. Betweenness centrality is based on the flow of interaction between network elements. The nodes with high betweenness centrality are the ones with greater relevance in the system. Simplified versions of the networks were obtained by filtering. The entire network was exported for web viewing using Gephi's Sigmajs exporter plugin.

## Results

During the study period, 410 individuals were approached and 216 refused to participate citing lack of time. The characteristics of the population ( $n = 194$ ) are described in table 01, highlighting an average age of  $55.0 \pm 17.7$  years, a predominance of females 63.2% and 71.0% with income below 5 minimum wages. Regarding self-reported diseases, cardiovascular problems predominate (162; 45.1%) and the absence of other health problems (117; 32.6%).

**Table 01.** Characteristics of population. Natal – Brazil, 2019.

Characteristics	Values	
Age in years (m, sd)	55.0 $\pm$ 17.7	
Female sex (n, %)	227	63.2
Income in minimum wage* (n, %)		
0 -5	252	71.0
6-10.	53	14.9
> 10	50	14.1
Education (n, %)		
Illiterate	15	4.2
High school	50	13.8
Elementary School	147	41.0
University education	147	41.0
Smoking (n, %)	17	4.8
Alcohol user (n, %)	46	12.8
Self-reported diseases (n, %)		
Cardiovascular diseases	162	45.1
No comorbidities	117	32.6
Bone diseases	22	6.1
Rheumatic diseases	7	2.0
Kidney disease	5	1.4
Musculoskeletal diseases	4	1.1
Liver diseases	1	0.3

m, sd: mean and standard deviation; n, %: absolute and relative frequency. \* Minimum wage in 2018 was R\$937.00, which was equivalent to US\$289 at the time.

In relation to medications in use (Table 02), when PPIs are excluded, individuals using antihypertensive drugs predominate (247; 35.0%), followed by hypoglycemic drugs (84; 11.9%) and lipid-lowering drugs (80; 11, 4%). Among PPIs, pantoprazole is the most used (154; 43% of respondents), followed by omeprazole (107; 29.9%) and esomeprazole (51; 14.2%). It is noteworthy that 41.2% of respondents reported the continuous use of inhibitors for more than 3 years and the prevalence of one or more severe PDI is 16.4%.

**Table 02.** Drug use profile and prevalence of potential drug interactions (PDI) related to proton pump inhibitors (PPI). Natal – Brazil, 2019.

Characteristics	n	%
Pharmacological classes (except PPIs)		
Antihypertensives	247	35.0
Antihyperglycemic	84	11.9
Lipid-lowering drugs	80	11.4
Supplements and vitamins	43	6.1
Antidepressants	37	5.3
Thyroid hormone	36	5.1
Anticoagulants	27	3.8
Sedatives and hypnotics	26	3.7
Non-steroidal anti-inflammatory drugs	21	3.0
Others	103	14.6
Total	704	100.0
Patients using PPIs		
Pantoprazole	154	43.0
Omeprazole	107	29.9
Esomeprazole	51	14.2
Dexlansoprazole	35	9.8
Lansoprazole	10	2.8
Rabeprazole	1	0.3
Continuous use of PPIs for more than		
3 years	148	41.2
Prevalence of PDI	59	16.4

n, %: absolute and relative frequency.

Multivariate analysis identified older age (OR=1.05 – 4.47; 95%CI 1.03 – 1.07; P>0.01) and female sex (OR=2.27; 95%CI 1.15 – 4, 47; P>0.02) as risk factors for a higher occurrence of severe PDI involving PPIs.

The network analysis (figure 01) indicated omeprazole and pantoprazole as the most relevant PPIs regarding the potential for drug interactions (centrality in the structure). Still in relation to omeprazole and pantoprazole, after filtering out the least relevant PDIs, PPIs associated with levothyroxine and, to a lesser extent, clopidogrel and cilostazol, stand out. Esomeprazole showed the same pattern of connections, however, with less centrality in the structure. It is noteworthy that all these interactions are classified as severe.

## Discussion

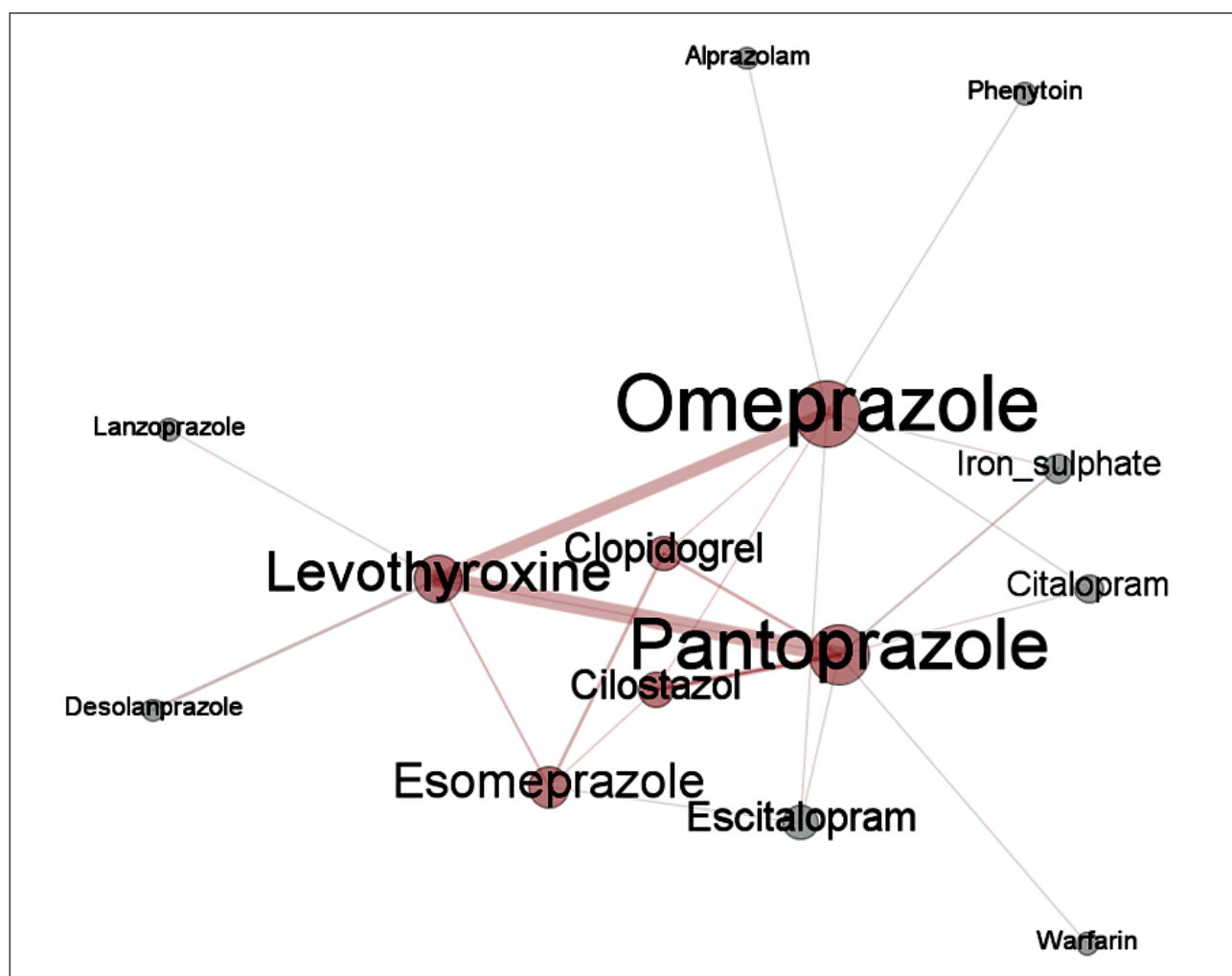
Through the execution of a prospective population-based study, we identified that 16.4% of community pharmacy users have some potential severe drug interaction related to PPIs, especially in older individuals and women. The pattern of interactions via network analysis highlighted pantoprazole, omeprazole and esomeprazole as the most relevant PPIs, especially interacting with levothyroxine and antiplatelet agents.

With lower prevalence in relation to our findings, other authors investigated the occurrence of PDI associated with PPI in customers of community pharmacies. Two Croatian studies from 153<sup>(6)</sup> 6 and 225 prescriptions<sup>(7)</sup> identified a prevalence of 11.1% and 12.4% respectively. A Brazilian study detected a much lower value (4.3%), however the data were collected from 350 prescriptions from public pharmacies in primary care. A common aspect in these works is the retrospective collection from medical prescriptions, disregarding the occurrence of self-medication or other prescribed drugs. Unlike our data, obtained through interviews and with the possibility of viewing the drugs actually purchased for use. These methodological characteristics would explain the higher prevalence observed in our study (16.4%).

**Table 03.** Multivariate logistic regression model for factors related to potential drug interactions (PDI) in proton pump inhibitors (PPI). Natal – Brazil, 2019.

Characteristics	Univariate			p	Multivariate			p
	OR	IC95%			OR	IC95%		
Age in years	1.051	1.031	1.071	>0.001	1.050	1.030	1.070	>0.001
Women	2.326	1.205	4.049	0.012	2.270	1.152	4.475	0.018
Income greater than 6 MW	1.608	0.895	2.089	0.112	-	-	-	-
Higher education	1.073	0.609	1.888	0.808	-	-	-	-
Smoker	1.094	0.304	3.934	0.890	-	-	-	-
Alcohol user	0.447	0.154	1.297	0.139	-	-	-	-
Self-reported illnesses					-	-	-	-
Cardiovascular diseases	3.370	1.849	6.141	>0.001	-	-	-	-
Bone diseases	3.204	1.279	8.027	0.013	-	-	-	-
Rheumatic diseases	2.070	0.392	10.93	0.391	-	-	-	-
PPIs for more than 3 years	1.596	0.911	2.795	0.102	-	-	-	-

OR: odds ratio; IC95%: 95% confidence interval and MW: minimum wage.

**Figure 1.** Network analysis of potential PPI buyers pairs in community pharmacy users. Natal – Brazil, 2019.

Age and female gender were identified as factors related to increased risk of severe PDI with PPIs. These two characteristics are strongly associated with greater use of medications, a determining factor for the occurrence of drug interactions. Polypharmacy is common in elderly patients,<sup>(16)</sup> with omeprazole being one of the most prescribed drugs for this segment.<sup>(4)</sup> While women are more likely to use medication, having a higher *per capita* consumption compared to men.<sup>(1, 4, 16, 17)</sup> Even regarding the use of PPIs, there is a higher prevalence of omeprazole prescription in female patients.<sup>(4, 18)</sup>

Among the interactions found in this study, the most relevant drugs were clopidogrel, cilostazol and levothyroxine. PPIs promote a significant decrease in the absorption of levothyroxine.<sup>(19, 20)</sup> Although limited, a study with 10 patients indicated an increase in THS values as a result of this interaction.<sup>(21)</sup> The interaction between PPIs and clopidogrel is based on competitive inhibition of the enzyme CYP2C19.<sup>(22)</sup> The Clopidogrel depends on hepatic metabolism to generate its active metabolite, so the metabolic inhibition action of omeprazole reduces its therapeutic efficacy.<sup>(23)</sup> In a large population-based study involving 13636 elderly people, a higher risk of recurrent myocardial infarction was identified (OR 1.27; 95%CI 1.03-1.57) in individuals using PPIs concomitantly with antiplatelet therapy with clopidogrel.<sup>(24)</sup>

The main metabolites of cilostazol, OPC-13015 and OPC-13213, responsible for about 50% of its pharmacological action, are generated mainly by CYP3A4 and CYP2C19 and PPIs are inhibitors of these enzymes.<sup>(25)</sup> From the pharmacokinetic evaluation of 20 healthy subjects, a decrease of approximately 50% in the serum values of the active metabolites of cilostazol was observed after a single dose of 40 mg of omeprazole.<sup>(26)</sup>

Considering the mechanisms of PDI described, there is the possibility of significant damage to the patient's health. For patients with hypothyroidism, erratic absorption of levothyroxine potentially related to PPI use can make it difficult to optimize the best dosage. However, the most worrisome would be the lower efficacy of antiplatelet treatment and the insidious risk of vascular accidents. We highlight that about two-fifths of our sample use PPIs continuously for three years or more, something already

observed in the literature,<sup>(27)</sup> investigation of the occurrence of these PDIs gains relevance.

This study had some limitations. Despite covering the entire metropolitan area of the city of Natal, it was restricted to a single chain of pharmacies which does not present a proportional distribution between the number of units and the total population of each health district. We did not have access to clinical history to confirm the self-reported diagnosis, as well as the presentation of the medical prescription at the time of purchase for self-medication evaluation, so there is a possibility of memory bias.

## Conclusion

It is concluded that among users of proton pump inhibitors purchased in community pharmacies, 16.4% of them have some severe drug interaction involving this pharmacological class. These interactions are more common in women and older people. Network analysis showed that the main drugs involved are omeprazole, pantoprazole and esomeprazole; the most relevant severe interactions being associated with levothyroxine, cilostazol and clopidogrel. Considering the characteristics of the mechanisms of interactions involved, in addition to the pattern of continuous use of these drugs, there is potential for relevant damage. Therefore, patients with hypothyroidism and using antiplatelet agents should be investigated regarding the possibility of interaction with PPIs.

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## Authors' contribution

The authors who contributed to the work described in this paper are as follows: AGO and RRM contributed to the study design. LMLA, JS, MVML and RSA conducted the study and collected data. RRM conducted to the data analysis. AGO, LMLA, JS and RRM were involved in interpretation of data. LMLA, JS and RRM wrote the first draft of the article. All authors reviewed the manuscript for important intellectual content and provided final approval of the version to be published.

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