Prevalence of potential drug interactions of clinical importance in primary health care and its associated factors

Prevalência de potenciais interações medicamentosas de importância clínica na atenção primária à saúde e seus fatores associados

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ABSTRACT
Introduction: older patients usually had multiple diseases and so use many medicines. The elevated risks of pharmacotherapy in this population justified the development of ratings for unsafe medicines.
Objective: to estimate the prevalence of potential drug interactions of clinical importance in primary health care and its associated factors, improving prescription practices and increasing patient safety.
Methods: a cross-sectional study of dependent variable "number of potential drug-drug interactions of clinical importance", in all medicines and patients who accessed medicines via public primary health care, 2013. The independent variables were socio demographic, accessibility of health services and pharmacotherapy. Multivariate analyses were performed using the Statistical Learning Theory with Exaustive-CHAID algorithm, with test Pearson's chi-square adjusted by the Bonferroni method.
Results: a total of 4,037 patients were included in this study and the patient prevalence of at least one drug-drug interaction was 36.5% with severity moderate (66.2%) or major (28.5%). The most prevalent conduct for management of them were monitor the patient (59.0%), adjust the dosage of the medicines (21.9%) and monitoring signs and symptoms (16.7%). In the multivariate analysis by the Theory of Statistical Learning when we compared the "patients who had at least one drug interaction of clinical importance" with those who did not have them at the first hierarchical level of relevance, the variable "number of drugs in use" prevailed with a p value <0.0001. The analysis also proposed 7 different risk strata to explain the distinction between having at least one interaction of clinical importance, namely: 1, 2, 3, 4, 5, 6-7 and> 8 drugs. When comparing patients with 2 medications and those with 8 or more medications, the prevalence of drug interactions increases by about 80%. Using polypharmacy (5 or more drugs) as the cutoff point to make the same comparison, the increase is about 45%. Other variables with statistical relevance to explain having or not having hair were "multiple drug dispensations per month" ($p = 0.003$ and $p = 0.01$) and "being elderly" ($p = 0.003$). Having "multiple drug dispensations per month" reduced the prevalence of interactions by about 10% for both patients with 3 medications ($p = 0.003$) and those with 6 or 7 medications.
Conclusions: the drug-drug interactions showed be different in primary care of hospitals and other place for health care. And the number of medications in use by the patient seems to be the main marker for patient selection for this type of analysis, with polypharmacy being a relevant cutoff point, but above all the use of 8 or more medications indicates a prevalence of more than 90% patients of at least one interaction of clinical importance. There are few studies of potential drug-drug interactions in public primary health care, especially with analysis of the severity and management of them. We recommend more studies for clarify prevalence, types and associated factors.

Key words: drug-related side effects and adverse reactions, potentially inappropriate medication list, primary health care, polypharmacy.

ABSTRACT

Introdução: os pacientes mais velhos geralmente tinham várias doenças e por isso usam muitos medicamentos. Os elevados riscos da farmacoterapia nessa população justificaram o desenvolvimento de classificações para medicamentos inseguros.

Objetivo: estimar a prevalência de potenciais interações medicamentosas de importância clínica nos cuidados de saúde primários e seus fatores associados, melhorando as práticas de prescrição e aumentando a segurança do paciente.

Métodos: um estudo transversal da variável dependente "número de interações medicamentosas potenciais de importância clínica", em todos os medicamentos e pacientes que tiveram acesso a medicamentos através da atenção primária à saúde pública, 2013. As variáveis independentes foram socio demográficas, acessibilidade dos serviços de saúde e farmacoterapia. As análises multivariadas foram realizadas utilizando a Teoria de Aprendizagem Estatística com algoritmo Exaustivo-CHAID, com o teste Qui-quadrado de Pearson ajustado pelo método de Bonferroni.

Resultados: um total de 4.037 pacientes foram incluídos neste estudo e a prevalência de pelo menos uma interação droga-droga foi de 36,5% com gravidade moderada (66,2%) ou maior (28,5%). A conduta mais prevalente para o manejo deles foi monitorar o paciente (59,0%), ajustar a dosagem dos medicamentos (21,9%) e monitorar sinais e sintomas (16,7%). Na análise multivariada pela Teoria da Aprendizagem Estatística quando comparamos os "pacientes que tinham pelo menos uma interação medicamentosa de importância clínica" com aqueles que não os tinham no primeiro nível hierárquico de relevância, a variável "número de medicamentos em uso" prevaleceu com um valor de p <0,0001. A análise também propôs 7 estratos de risco diferentes para explicar a distinção entre ter pelo menos uma interação de importância clínica, ou seja: 1, 2, 3, 4, 5, 6-7 e > 8 drogas. Ao comparar pacientes com 2 medicamentos e aqueles com 8 ou mais medicamentos, a prevalência de interações medicamentosas aumenta em cerca de 80%. Usando a polifarmácia (5 ou mais medicamentos) como ponto de corte para fazer a mesma comparação, o aumento é de cerca de 45%. Outras variáveis com relevância estatística para explicar ter ou não ter cabelo foram "doses múltiplas de medicamentos por mês" (p = 0,003 e p = 0,01) e "ser idoso" (p = 0,003). Ter "dispensas múltiplas de medicamentos por mês" reduziu a prevalência de interações em cerca de 10% tanto para pacientes com 3 medicamentos (p = 0,003) quanto para aqueles com 6 ou 7 medicamentos.

Conclusões: as interações medicamentosas mostraram ser diferentes nos cuidados primários dos hospitais e em outros locais de atendimento à saúde. E o número de medicamentos em uso pelo paciente parece ser o principal marcador para a seleção de pacientes para este tipo de análise, sendo a polifarmácia um ponto de corte relevante, mas acima de tudo o uso de 8 ou mais medicamentos indica uma prevalência de mais de 90% de pacientes com pelo menos uma interação de importância clínica. Existem poucos estudos sobre possíveis interações medicamentosas na atenção primária à saúde pública, especialmente com a análise da gravidade e do manejo das mesmas. Recomendamos mais estudos para esclarecer a prevalência, tipos e fatores associados.

Palavras-chave: efeitos colaterais e reações adversas relacionadas a drogas, lista de medicamentos potencialmente inapropriados, cuidados primários de saúde, polifarmácia.

1 INTRODUCTION

Drug-drug interactions are changes on responses pharmacological and clinical associated with simultaneous use of different medicines combinations, or even the combination of medicines with nutrients or environmental chemical.[1,2] Some combinations have great clinical importance, being considered beneficial for some therapeutic regimens to improve medicine efficacy, reduce toxicity or treat co-morbidities.[3,4]

Undesirable interactions are those that determine diminished effect or result, contrarily to expectations, increased incidence and range of adverse effects and the cost of the therapy.[5] The lack is of standardization in the health and communication system between professionals can contribute to an increase in the prevalence of potential drug-drug interactions.[6] In other way the knowledge of health professionals can contribute to the patient safety, minimizing the negative impacts through appropriate monitoring, when the combination of medicines are inevitable.[7]

The health care professionals can individualize pharmacotherapy or monitoring of patient by analysis of the risks, benefits, the therapeutic goal of every combination and recommendations of management of drug-drug interactions.[8,9] The drug-drug interactions can be classified according to severity: minor, where the effects are usually minor and its consequences may be bothersome or unnoticeable, moderate, where the effects may cause deterioration in a patient's clinical status and major, where the effects are potentially life-threatening or capable of causing permanent damage.[10,11] The recommendations for clinical management of patients are widely varied, but most frequently mentioned were: monitor patients, adjust the dosage of the medicines, monitor signs and symptoms and exchange of medicines.[12]

The incidence and prevalence of drug-drug interactions depends on several factors. The risk of drug-drug interactions is directly associated with increased number of medicines used, age, accessibility to health services, lack of communication between professionals and others.[13] The polypharmacy is the most important risk factor for the occurrence of potential drug-drug interactions and is directly related to older adult patients. However, in our study, the statistical learning theory indicated as additional stratifications for the number of drugs to use 6 and 7, as well as 8 or more drugs. The prevalence in these two additional extracts was significantly higher.

Aging increases incidence of chronic diseases and medicines use consequently chances for drug-drug interactions.[14] It is noteworthy that in our study this factor was at

the second hierarchical level of importance and only for one of the strata of number of drugs. Despite the importance of drug-drug interactions in clinical practice and their negative impact on the effectiveness and safety of treatments there are few epidemiological studies in primary care services.

The aim of this study is to estimate the prevalence of potential drug-drug interactions of clinical importance in primary health care and their associated factors, improving prescribing practices and increasing patient safety.

2 METHODS

This was a population-based cross-sectional study that examined pharmacotherapy of patients who accessed medicines via public primary health care in a city with approximately 200,000 of the Minas Gerais that serves as a regional hub for health care for 55 cities. Minas Gerais is the second most populous Brazilian state, as well as being the third most economically important state. [15]

In this city, there is a high use of clonazepam[15,16] so in this study we selected for data collection all patients who accessed medicines in three months nonconsecutive: January, May and September of 2013. The information was collected from the Integrated Health System (SIS), a secondary database, which provides the patient demographic information, prescription medicines and the amount distributed to them. We collected the information of the last dispensation and of the 30 days before it, because public health system does make medicines delivery for 30 days period. If the patient has more than one dispensation in this period, maybe he has more than one prescription or prescriber, as well as some medicine in the prescription was missing in pharmacy at that time. Inclusion and exclusion criteria were being a resident in the city and have taken clonazepam on months in study (Figure 1).

The “patients with at least one potential drug-drug interactions” was the dependent variable. The identification of potential drug-drug interactions of clinical importance was carried out in accordance with the theoretical framework of Micromedex®[17] which evaluated the effects, mechanism probable, severity and clinical management. The potential drug-drug interactions recorded as "fair" were not included in this analysis.

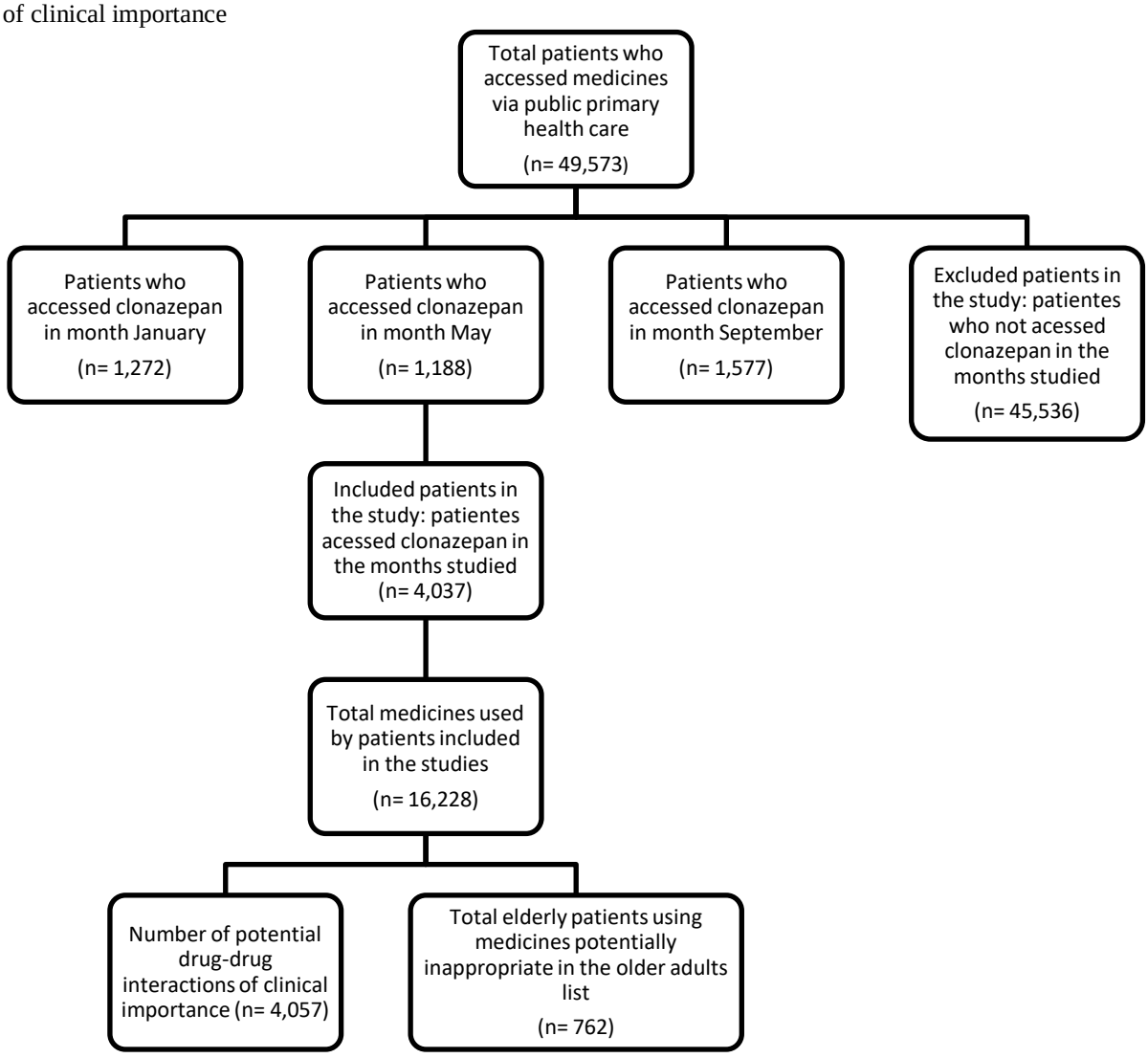
The existence of potentially inappropriate medications (PIM) in older adult was performed according to the Beers criteria.[18] We included in analyzes only the PIM in older adult and that medications to be used with caution by the older adults.[18] Because we used a secondary database, did not possible same analysis recommended in Beers

criteria[18] such as those in which it is necessary to know the patient's condition. Although Nitrazepam was not included in the Beers criteria, it was included as PIM in older adults in our study, because this a benzodiazepine used in Brazil and has a half-life exceeding 20 hours, with similar effects to the other present in the PIM in older adult list.[19,20]

During data analysis, a descriptive analysis was carried out firstly to measure the frequency of the variables studied. Bi and multivariate analysis was through dependent variable "patients with at least one potential drug-drug interaction" was performed using the Statistical Learning Theory [21]. This analysis ranks the independent variables by importance to explain the distinction of "having or not having patients with at least one potential drug-drug interaction" [gender, age, older adult (≥65 yeas); accessibility of health services (multiple dispensations in the month, number of medicines, multiple prescribers), number of medicines potentially inappropriate in the older adults list and polypharmacy (five or more medications)].[15] The algorithm used was Exhaustive Chi-squared Automatic Interaction Detector (Exhaustive CHAID), with test Pearson's chi-square adjusted by the Bonferroni method, with 10% of significance for inclusion on the model of 10% and 5.0% for the final model. The stopping criteria were: 100 cases in the parent node, 50 cases in child and a maximum of three hierarchical levels, with cross-validation for 10 subsamples.

The study was conducted following the Declaration of Helsinki guidelines and the provisions of the Brazilian National Health Committee; it was approved by Ethics Committee on Human Research of the Federal University of São João del Rei, with the number 714958 in 2014.

Figure 1: Flowchart: Total participants included in the study and number of potential drug-drug interactions of clinical importance



3 RESULTS

A total of 49,573 patients accessed medicines via public primary health care from them 4,037 patients were included in this study because they received clonazepam. Among the patients included, 16,228 medicines were used, with 124 different types, causing 4,057 drug-drug interactions of clinical importance. The numbers of patients using medicines potentially inappropriate in older adults list were about 19% of all the patients included. (Figure 1). Prevalence of patient with at least one potential drug-drug interactions was 36.5%. The recommendations for clinical management were monitor patient for 59%, adjust the dosage of the medicines for 21.9%, monitor signs and symptoms in 16.7% and finally exchange of the medicines for 2.4%. Analyzing the severity of the interactions most of them with severity moderate (66.2%), major (28.5%) and minor (5.3%).

The patient profile showed predominance of female (75.3%), with median age of 56.0 years old and 25.2% were older adult. Among these patients 29.5% had multiple dispensations in the month, 66.8 % had polypharmacy and 11.2% had multiple prescribers in month. Among patient's older adult with at least one drug-drug interactions, 19.7% used five or more medicines potentially inappropriate in the older adults list. Comparing those patients "who had" and "who had not" at least one potential drug-drug interactions all these independent variables were statistically significant (p value <0.01) (Table 1).

Considering the potential drug-drug interactions of clinical importance (n= 4057), carbamazepine and clonazepam was the most prevalent combination (7.6%) in our study with a severity "major". The recommendation for it management is monitor the patient for failure of clonazepam [6]. The second most prevalent combination was losartan and aspirin with prevalence of 4.6%, moderate risk and clinical control advised was monitor patient for decrease in antihypertensive effects and for increased risk of renal failure [22]. These drug-drug interactions were followed by aspirin and hydrochlorothiazide (4.3%), hydrochlorothiazide and captopril (3.5%) and by phenobarbital and clonazepam (3.1%). The 15 combinations listed in Table 2 constitute 44% of the prevalence of all potential drug-drug interactions detected.

Table 1: Socio demographic, accessibility of health services, prescription of medicines in potentially inappropriate medications in older adults list and comparison of between patients with or without potential drug-drug interactions.

Characteristics	**Total (N= 4,037)**	**Patient with at least one potential drug-drug interactions**		**Value p**
		Yes (N= 1,474)	**No (N= 2,563)**	
Socio demographic				
Gender % (n)				
Female	72.9 (2,941)	75.3 (1,110)	71.4 (1,831)	<0.01[1]
Male	27.1 (1,096)	24.7 (364)	28.6 (732)	
Age (years) P_{50} (P_{25}; P_{75})	53.0 (44.0; 62.0)	56.0 (48.0; 65.0)	52.0 (43.0; 60.0)	<0.01[2]
Older adult % (n)	18.9 (762)	25.2 (372)	15.2 (390)	<0.01[1]
Accessibility of health services				
Multiple dispensations in the month % (n)				
Yes	19.9 (804)	29.5 (435)	14.4 (369)	<0.01[1]
No	80.1 (3,233)	70.5 (1,039)	85.6 (2,194)	
Number of medicines P_{50} (P_{25}; P_{75})	3.0 (2.0; 5.0)	6.0 (4.0; 8.0)	3.0 (2.0; 4.0)	<0.01[2]
Number % (n)				
One	13.1 (529)	1.0 (1.0)	20.6 (528)	<0.01[1]
Two	19.4 (783)	3.6 (53)	28.4 (730)	
Three	18.0 (728)	13.0 (191)	21.0 (537)	
Four	14.6 (589)	15.6 (230)	14.0 (359)	
Polypharmacy	34.9 (1,408)	66.8 (999)	16.0 (409)	
Multiple prescribers % (n)				
Yes	7.8 (3,719)	11.2 (165)	6.0 (153)	<0.01[1]

No	92.1 (318)	88.8 (1,309)	94.0 (2,410)	
Number of medicines potentially inappropriate in the older adults list[3]	**(n= 762)**	**(n= 372)**	**(n= 390)**	**Value p**
P_{50} (P_{25}; P_{75})	2.0 (2.0; 3.0)	3.0 (2.0; 4.0)	2.0 (1.0; 3.0)	<0.01[2]
Number % (n)				
One	23.0 (175)	7.0 (26)	38.2 (149)	<0.01[1]
Two	31.0 (236)	25.8 (96)	35.9 (140)	
Three	22.7 (173)	30.6 (114)	15.1 (59)	
Four	12.6 (96)	16.9 (63)	8.5 (33)	
Five or more	10.7 (82)	19.7 (73)	2.3 (9)	

[1] Pearson chi square. [2] Manm-Whitney. [3] Performed only for older adul

Table 2: Most prevalent potential drug-drug interactions in medium-sized municipality - Minas Gerais, Brazil in 2013.

Combination (MM1[1] and MM2[2])	Interaction effect[3]	Mechanism[3]	Gravity[3]	Conduct for the management[3]	Prevalence % n (N= 4,057)[4]	Prevalece relative % n (N=1,782)[5]
Carbamazepine Clonazepam	Reduced plasma levels of clonazepam	Induction of CYP3A4-mediated clonazepam metabolism by carbamazepine	Major	Monitor patient	7.6 (310)	17.4
Aspirin Losartan	Antihypertensive effects reduced and increased risk of kidney failure	Interference with the production of vasodilatory and natriuretic prostaglandins	Moderate	Monitor patient	4.6 (186)	10.4
Aspirin Hydrochlorothiazide	Concurrent use of nonsteroidal antiinflammatory agents and thiazide diuretics may result in decreased diuretic and antihypertensive efficacy	Decreased renal prostaglandin production	Moderate	Monitor patient	4.3 (173)	9.7
Hydrochlorothiazide Captopril	Concurrent use of angiotensin converting enzyme inhibitors and thiazide diuretics may result in postural hypotension (first dose)	Vasodilation and relative intra-vascular volume depletion	Moderate	Monitor patient	3.5 (142)	8.0
Fhenobarbital Clonazepam	Concurrent use of barbiturates and benzodiazepines may result in additive respiratory depression	CNS depression	Major	Adjusting dosage MM1 and MM2	3.1 (124)	7.0
Levothyroxine Simvastatin	Concurrent use of levothyroxine and simvastatin may result in decreased levothyroxine efficacy	Increased levothyroxine metabolism	Moderate	Adjusting dosage MM1	3.0 (120)	6.7
Levothyroxine Omeprazole	Concurrent use of levothyroxine and proton pump inhibitors may result in increased TSH levels	Unknown mechanism	Moderate	Monitor patient	2.7 (110)	6.2
Aspirin Captopril	Concurrent use of captopril and aspirin may result in decreased captopril effectiveness	Inhibition of prostaglandin synthesis	Moderate	Monitor patient	2.2 (88)	5.0
Aspirin Amlodipine	Concurrent use of calcium channel blockers and nonsteroidal antiinflammatory agents may result in an increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect	Additive effects of bleeding; decreased renal prostaglandin production	Moderate	Monitor patient (gastrointestinal bleeding)	2.0 (82)	4.6
Aspirin Furosemide	Concurrent use of loop diuretics and nonsteroidal antiinflammatory agents may result in decreased diuretic and antihypertensive efficacy	Decreased renal prostaglandin production	Moderate	Monitor patient	1.9 (76)	4.3
Fhenytoin Clonazepam	Concurrent use of clonazepam and phenytoin may result in altered concentrations of either drug	Altered hepatic metabolism of either drug	Minor	Monitor patient	1.7 (70)	3.9
Aspirin Fluoxetine	Concurrent use of nsaid and ssri may result in an increased risk of bleeding	Unknown mechanism	Major	Monitor patient	1.7 (68)	3.8

Carbamazepine Haloperidol	Concurrent use of carbamazepine and haloperidol may result in decreased haloperidol concentrations	Induction of CYP3A4-mediated haloperidol metabolism	Moderate	Adjusting dosage MM2	1.7 (68)	3.8
Amlodipine Simvastatin	Concurrent use of amlodipine and simvastatin may result in increased simvastatin exposure and increased risk of myopathy, including rhabdomyolysis	Unknown mechanism	Major	Adjusting dosage MM2	1.4 (57)	3.2
Aspirin Atenolol	Concurrent use of beta-adrenergic blockers and nonsteroidal antiinflammatory agents may result in decreased antihypertensive effect	Decreased production of vasodilating and renal prostaglandins	Moderate	Monitor patient and/or adjusting dosage MM2.	1.3 (54)	3.0
Aspirin Carvedilol	Concurrent use of beta-adrenergic blockers and nonsteroidal antiinflammatory agents may result in decreased antihypertensive effect	Decreased production of vasodilating and renal prostaglandins	Moderate	Monitor patient and/or adjusting dosage MM2	1.3 (54)	3.0

[1]MM1: Medicine 1. [2]MM2: Medicine 2. [3]Drug Interactions results - MICROMEDEX®. [4]We analyzed all medicines, but this table shows only 15 most prevalent. [5]Number considering only for 15 most prevalent combination

The Table 3 includes the medicines that most frequently appeared in potential drug-drug interactions: clonazepan (n= 4073), omeprazole (n= 813), hydrochlorothiazide (n= 697), simvastatin (n= 671) and losartan (n= 655). The fifteen most common medicines account for 66% of the total of all prescription medicines in this study (Table 3).

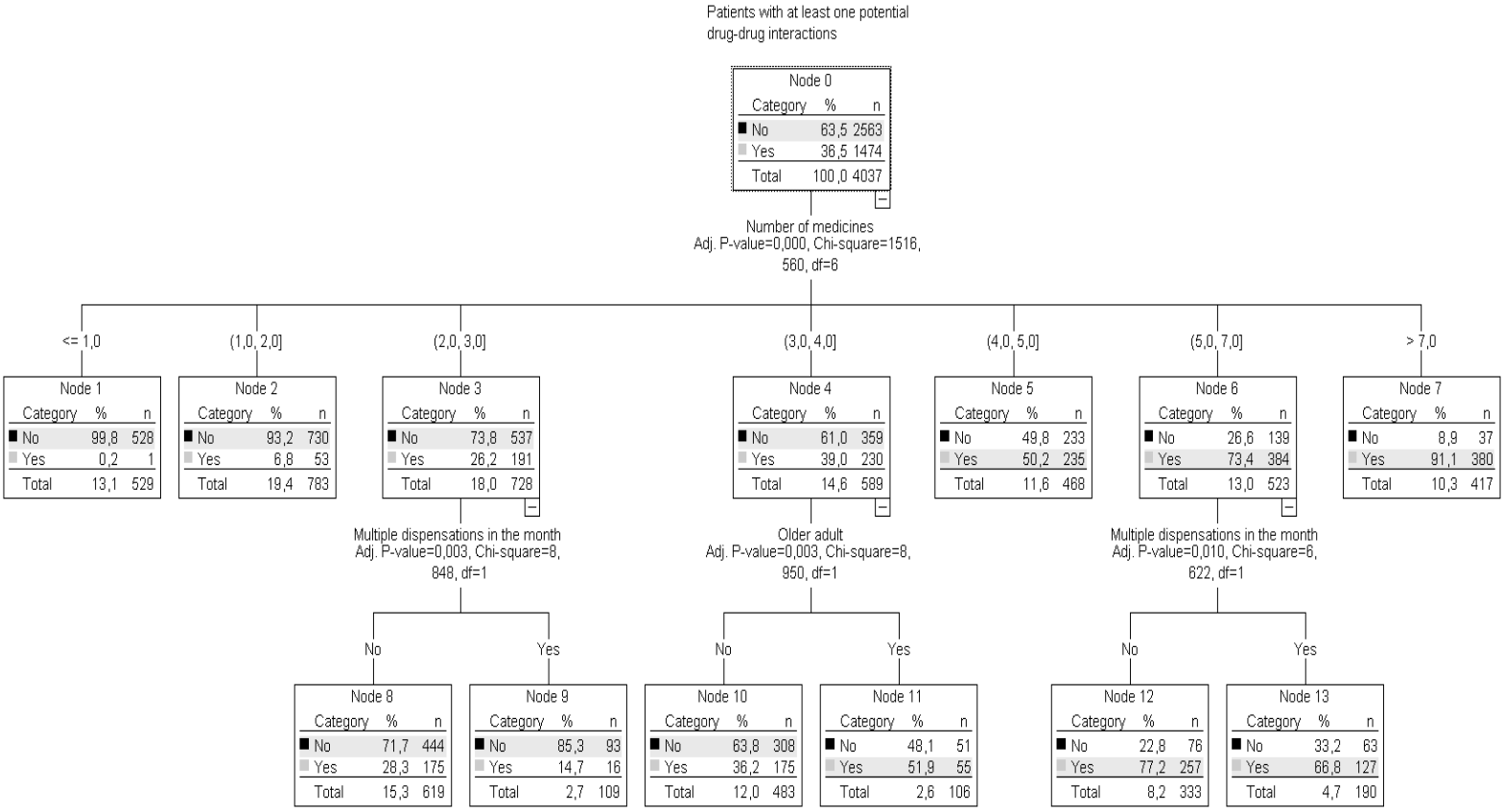
Table 3: Most prescribed potential drug-drug interactions in medium-sized city in Minas Gerais - Brazil.

More prescribed medicines	Total (N= 16,228)	Prescribed medicines of patients with drug interaction (N= 8,850)	Prescribed medicines of patients with drug interaction (N= 7,378)
	% (n)	% (n; position)	% (n; position)
Clonazepam	25.1 (4,073)	16.8 (1,490; 1)	35.0 (2,583; 1)
Omeprazole	5.0 (813)	5.3 (466; 3)	4.7 (347; 2)
Hydrochlorothiazide	4.3 (697)	5.4 (477; 2)	3.0 (220; 8)
Simvastatin	4.1 (671)	5.2 (460; 4)	2.9 (211; 9)
Losartan	4.0 (655)	4.6 (406; 5)	3.4 (249; 7)
Fluoxetine	3.4 (552)	2.8 (252; 10)	4.1 (300; 3)
Haloperidol	2.9 (474)	2.0 (180; 12)	4.0 (294; 4)
Amitriptyline	2.8 (455)	2.0 (178; 13)	3.8 (277; 5)
Levothyroxine	2.6 (429)	3.5 (314; 8)	1.6 (115; 16)
Aspirin	2.6 (424)	4.5 (400; 6)	0.3 (24; 40)
Biperiden	2.2 (361)	1.1 (96; 26)	3.6 (265; 6)
Carbamazepine	2.0 (332)	3.7 (329; 7)	0.0 (3; 76)
Captopril	1.9 (309)	2.9 (259; 9)	0,7 (53; 31)
Metformin	1.6 (254)	2.1 (186; 11)	0.9 (68; 22)
Chlorpromazine	1.5 (245)	1.0 (90; 28)	2.1 (155; 11)

In the multivariate analysis by the Theory of Statistical Learning when we compared the "patients who had at least one drug interaction of clinical importance" with those who did not have them at the first hierarchical level of relevance, the variable "number of drugs in use" was left with a p value <0.0001. The analysis also proposed 7 different risk strata to explain the distinction between having at least one interaction of clinical importance, namely: 1, 2, 3, 4, 5, 6-7 and> 8 drugs. When comparing patients with 2 medications and those with 8 or more medications, the prevalence of drug interactions increases by about 80%. Using polypharmacy (5 or more drugs) as the cutoff point to make the same comparison, the increase is about 45%.

Other variables with statistical relevance to explain having or not having hair were "multiple drug dispensations per month" (p = 0.003 and p = 0.01) and "being elderly" (p = 0.003). Having "multiple drug dispensations per month" reduced the prevalence of interactions by about 10% for both patients with 3 medications (p = 0.003) and those with 6 or 7 medications. (Figure 2).

Figure 2: Factors associated the occurrence of at least one potential drug-drug interactions in patients.



4 DISCUSSION

This study found a high prevalence of potential drug-drug interactions of clinical importance associated with increase of number of medicines, be an older adult and had multiple dispensations in the month, the last was protection. Patients profile had predominance of females and of older adult. The accessibility of health services showed great prevalence of multiple prescribers and multiple dispensations in the month, as well as polypharmacy. The prescription of medicine from the list potentially inappropriate medications in older adults also be frequent between adults and older adults.

Despite this were difficult compare results because there are few studies in primary health care settings analyzing drug-drug interactions [23] The higher number of potential drug-drug interactions in women and older adult may be associated with women's ability to seek more health care for taking care.[24] Already the older adult the higher prevalence of chronic diseases resulting of aging.[25]

Considering the types of drug-drug interactions, the carbamazepine and clonazepam was the most prevalent combination in this study, with severity major and

recommendation for patient monitoring. The mechanism for this drug-drug interactions is reduced plasma levels of clonazepam through the induction of CYP3A4-mediated clonazepam metabolism by carbamazepine.[19] In general, the severity assessment of potential drug-drug interactions in our study showed that most of the interactions were moderate, similar to found in another studies.[26,27]

Analyzing the pharmacotherapy profile most of medicines were taking by mouth and the most prescribed was clonazepam, omeprazole, and hydrochlorothiazide, respectively, consistent with primary health care settings. The explanation for this may be due to the severity of the clinical condition of patients that require a fast route of administration to obtain immediate clinical effects, besides allowing administer higher doses of medicines. The studies in different levels of health care have found similar route of administration (oral), but distinct medicines [28,29] Warfarin (42.5%), acenocumarol (9%), and allopurinol (8.5%) were most common in hospital patient in Italy.[29] Another study in pediatric patients showed acetaminophen (56.1%), fentanyl (48.9%), midazolam (47.4%), ranitidine (46.1%), heparin (44.4%) and morphine (43.8%) as most used medicines.[28]

Polypharmacy was directly associated with occurrence of potential drug-drug interactions findings similar to other studies.[30,31] The drug-drug interactions are also more frequent in older adults' patients who are in polypharmacy[28,30,31] which is consistent with the results of our study. One possible reason would that the older adult is more fragile and likely to have co-morbidities, therefore, increases the number of prescribed medicines and the probability of drug-drug interactions it can be confirmed by some studies.[2,8,31]

Multiple dispensations in a month had protective relationship with smaller higher incidence of potential drug-drug interactions. We did not find other studies that analysis these relations, so we suggest more efforts to clarify it. Despite this, there are directly influence of increase of the number of prescribers and increasing of interactions.[32,33]

The prevalence PIM in older adults list was similar another studies.[34] However lower than a study done in one Brazilian study with 42%.[35] In Brazil there are many medicines in the PIM in older adult list there are also considered essential medicine. So, their medicines are frequently prescribed and dispensed to older adult in public health system.[36] The review of National Essential Medicines List to include safer options for older adults is necessary.

The Brazilian public primary health care system has not a national electronic system for perform prescriptions, facilitate communication between professionals about

patient information. This can increase misinformation and the drug-drug interactions.[37] In this context is so much important simplify patient pharmacotherapy and reorganization of teamwork.[35] This is indicative of the relevance of use of the reference and counter-reference document, the hierarchic health care assistance and of inclusion of clinical pharmacist in the multi-professional team.[38] Pharmacists plays an important role in the patient follow-up doing medicines review, reconciliation or medication therapy management services improving of patient safety and of the clinical results.[39,40,41]

5 CONCLUSION

Despite high prevalence of potential drug-drug interactions of clinical importance in primary care health care, there are few studies in this setting. We recommend more studies to investigate their prevalence medicines involved consequences and associated factors in different age-groups in primary care. This can help comprehend groups under risk and patients to priorize for health care. Other aspects of drug-drug interactions to be assessed are relations with multiple dispensations in moth as well as adhesion and knowledge of health care professionals about their management.

DISCLOSURE OF INTEREST

The authors declare that they have no conflicts of interest concerning this article.

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