RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Paper **Open Access**

Potential drug interactions and inappropriate medications prescribed for primary health care users

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Submitted: 17-04-2019 Resubmitted: 17-01-2020 Accepted: 08-05-2020

Peer review: blind reviewers

Abstract

Objectives: To analyze potential pharmacological interactions and drugs potentially inappropriate for the elderly in users of primary care of the Unified Health System. **Methods:** This is a cross-sectional study with individuals aged 18 years or over, who were approached at the health facilities of the city of Divinópolis, MG, at which time a home visit was scheduled. A structured questionnaire on drug use was applied and drug interactions were analyzed in Drugs.com® sources, Micromedex®, bulletin of the Brazilian Health Regulatory Agency (ANVISA). Only the frequencies of serious interactions were analyzed. Potentially inappropriate drugs for elderly people (MPI) were identified by the Beers Criterion (2015) and the Brazilian Consensus on Potentially Inappropriate Medications for the Elderly (2016). The Mann-Whitney test was performed to compare the medians of the analyzed variables. **Results:** Among the study participants, 55% were elderly. Comparing them with the adult population, it was observed that the number of medications and potential drug interactions were significantly higher ($p < 0.05$) among patients 60 years of age or older. Considering only the elderly, 77.3% used at least one MPI, according to the Beers Criterion. **Conclusion:** It was found that the vast majority of primary care users use at least one inappropriate drug and, when compared to adults, are more exposed to polypharmacy and potential drug interactions.

Keywords: drug interactions, pharmacoepidemiology, potentially inappropriate medication list, aged, primary health care.

Potenciais interações medicamentosas e medicamentos inapropriados prescritos para usuários da atenção primária à saúde

Resumo

Objetivo: Analisar as potenciais interações farmacológicas e os medicamentos potencialmente inapropriados para idosos em usuários da atenção primária do Sistema Único de Saúde. **Métodos:** Trata-se de um estudo transversal com indivíduos com idade igual ou superior a 18 anos, acompanhados em unidades de saúde do município de Divinópolis, Minas Gerais. Um questionário estruturado sobre uso de medicamentos foi aplicado durante visita domiciliar a uma amostra estratificada de usuários para investigação de interações medicamentosas potenciais e medicamentos potencialmente inapropriados para idosos (MPI), segundo Critério de Beers e Consenso Brasileiro de medicamentos potencialmente inapropriados para idosos. Foram utilizadas as fontes Drugs.com®, Micromedex® e bulário da Agência Nacional de Vigilância Sanitária (ANVISA) para análise das interações. **Resultados:** Dentre os participantes do estudo, 55% eram idosos. Comparando-os com a população adulta, observou-se que o número de medicamentos e de potenciais interações medicamentosas foi significativamente superior ($p<0,05$) entre pacientes com 60 anos ou mais. Considerando-se apenas os idosos, 77,3% utilizavam ao menos um MPI. **Conclusão:** A maioria dos idosos da atenção primária no município de Divinópolis faz uso de ao menos um medicamento inapropriado, e, quando comparados aos adultos, estão mais expostos a polifarmácia e potenciais interações medicamentosas.

Palavras-chave: interações medicamentosas, farmacoepidemiologia, lista de medicamentos potencialmente inapropriados, idoso, atenção primária à saúde.

Introduction

The use of drugs has become the most common form of therapy, which may be related to the increased availability and ease of access to drugs. But this use cannot always be associated with better health conditions or quality of life for the population[1]. Failures in prescription and dispensing, self-medication, and drug interactions can contribute to ineffective treatments, in addition to causing risks and harms to the health of the users[2].

The increasing trend in the use of drugs by the population favors the occurrence of drug interactions and serious adverse events[3]. A research study conducted by Obreli-Neto and collaborators[3], during 2010 and 2011, showed that 37.0% of the adverse drug reactions related to drug interactions culminated in hospitalization of older adults, all of which could have been avoided. In addition, potential drug interactions have been shown to be associated with the presence of polypharmacy[3].

According to the study by Dumbreck and collaborators[4], it is estimated that 6.5% of the unplanned hospitalizations in the UK are due to adverse drug events, and a proportion is caused by drug interactions.

Another factor that contributes to obtaining unwanted health results is the use of Potentially Inappropriate drugs (PIMs) for older adults. These drugs are those whose possible benefits are fewer than their potential risks, coupled with the existence of a therapeutic alternative with greater safety[5]. According to a study by Baldoni and collaborators[6], the main factors associated with the use of PIMs are self-medication, the use of non-prescription drugs, psychotropic drugs, and polypharmacy. Silva and collaborators[7] also demonstrated this relation between polypharmacy and PIMs, by showing that approximately 90.0% of the older adults were submitted to polypharmacy and that 59.0% had at least one prescription of a PIM. The results of Nascimento and collaborators[8] associate the use of PIMs with mortality, pointing out that 56.0% of the older adults used PIMs and that the risk of death among PIM users was 44.0% higher than among those who did not use them.

In view of the above regarding the current medicalization scenario, the population aging process, and the scarcity of studies that explore in a comparative way the use of drugs in adults and older adults who are users of primary health care (PHC), the aim of the present study is to analyze the potential serious drug interactions and PIMs for the older adults prescribed to users of Primary health care of the Public Health System (*Sistema Único de Saúde*, SUS) in the municipality of Divinópolis, Minas Gerais.

Methods

Study locus and population

A cross-sectional study developed with users aged 18 years old or over, cared for in primary care units in the municipality of Divinópolis, in Minas Gerais. During the study period (September/2014-December/2016), the population was estimated at 230,848 thousand inhabitants[9] and the municipality had 12 health regions, with fourteen Conventional Health Centers (CHCs), 20 units of the Family Health Strategy (FHS), and five public pharmacies for dispensing the basic component of Pharmaceutical Service.

To guarantee sampling diversity, the units were drawn from each of the health regions of the municipality. The number of units drawn was proportional to the number of units in each of the health regions. Regions with only one health unit were included in the sample. Thus, the strategy to recruit the participants consisted in the following steps: a) selecting, by draw, the health units in the municipality of Divinópolis; b) inviting users of the units, at random, while they were waiting to be cared for, until the sample targets were reached.

For the purpose of sample calculation, the following parameters were considered: a) prevalence, a priori, of 50%, due to the variety of outcome variables; b) 5% accuracy; c) 95% confidence level, and d) 10% losses, totaling 423 individuals to be interviewed. The total number of interviews in each health unit was defined proportionally to the number of patients seen in the respective units, using the simple rule of three for this.

Selection of the participants and data collection

The individuals were invited to participate in the study when they were in their health units receiving care. Trained interviewers explained the objectives of the study and extended the invitation. Upon acceptance of the patient, a home visit was scheduled. Before the visit, the Free and Informed Consent Form (FICF) was read and signed by the researcher and the interviewed, in two copies. Patients who used only one medication or who withdrew from the study were excluded from the study.

Data collection instrument

Before applying the data collection instrument, it was analyzed by three judges (researchers in the field of pharmacoepidemiology), for possible changes and adjustments. After this phase, the instrument was tested in a pilot study with 10 users of the SUS, to analyze their understanding of the questions. The complete questionnaire addressed questions about the drugs in use by the patient at the time of the interview, storage location, expiration dates for the drugs, and adherence to the pharmacological treatment.

Potential drug interactions

The potential drug interactions were first identified with the aid of Drugs.com®[10] and, when the medication was not present in this database, the search was carried out in Micromedex®[11], and in the electronic form of the ANVISA[12], if necessary. Prior to the analysis, the drug interactions were classified by severity, according to Drugs.com®[10] or to Micromedex®[11] in the following categories: Minor: when the clinical risk was considered low, it is recommended to assess the risk, consider a therapeutic alternative, and insert a monitoring plan; Moderate: when the clinical risk was considered moderate, it is indicated to avoid the combination, using it only in special circumstances; Major: when the clinical risk was considered high, it is indicated to avoid the combination, as the risk exceeds the benefit[10].

The clinical impact and management of potential serious interactions have been proposed based on data from Drugs.com®[10] or Micromedex®[11]. For frequency analysis, only major interactions were considered, due to their clinical significance.

It should be noted that dipyrone was considered as a centrally acting analgesic, and not as a Non-Steroidal Anti-Inflammatory Drug (NSAID), as classified by Micromedex®[11].

Drugs considered inappropriate for the older adults

For respondents aged 60 or over, the adequacy of the use of drugs was analyzed. The drugs were categorized as adequate and inadequate, according to the Brazilian Consensus on inappropriate drugs for the older adults (2016)[13] and to the Beers Criteria (2015)[5]. Regarding the Beers Criteria, Tables 2 (PIMs for use in older adults), 4 (PIMs that should be used with caution in older adults), and 7 (PIMs with deep anticholinergic properties) were considered. It were not considered: Tables 3 (due to lack of diagnosis), 5 (the drug interactions were analyzed using the sources already described), and 6 (due to lack of access to the patient's creatinine tests). The clinical impact and management of the use of drugs considered inappropriate for older adults were proposed based on the Beers Criteria (2015)[5] and in the narrative review carried out by Faria and collaborators[14].

Statistical analysis

Data was entered into Epi Info version 7.0 and analyzed using the Statistical Package for the Social Sciences (SPSS). The normality of the data was analyzed by the histogram, kurtosis value, and asymmetry value. Variables with non-normal distribution were considered if the histogram was non-asymmetric and if kurtosis >2 or asymmetry >7. For comparison between the medians of the adults and the older adults, the Mann-Whitney test was used, as these are two groups of unpaired samples with non-normal distribution. After the analysis, it was observed that the variables did not present a normal distribution and, therefore, the data were presented in median and interquartile range (P25 – P75).

Ethical aspects

This study was approved by the Research Ethics Committee of the Federal University of São João del-Rei (*Universidade Federal de São João del-Rei*, UFSJ) - Dona Lindu Midwest Campus (*Campus Centro Oeste*, CCO). Approval protocol: CAAE 30912314.0.0000.5545.

Results

During the recruitment period, 612 medication users were invited to participate in the research. Of these, 163 refused to participate, 26 withdrew from the study and 70 used only one medication. Thus, 353 individuals were included in the study, of which 55% (n=194) were older adults and 45% (n=159), adults. The number of drugs used by the participants ranged from 2 to 25. The medians of the number of drugs used by adults and older adults were 4 (3-6) and 5 (3-7), respectively, ($p < 0.05$).

The total amount of potential drug interactions (mild, moderate, and severe) varied from 0 to 48 per individual, and they were significantly more frequent in the older adults, when compared to the adults ($p < 0.05$). Considering only the 87 potential serious drug interactions found in both population groups, it was observed that the most frequent were between spironolactone and losartan, and between amlodipine and simvastatin (Table 1).

According to the Beers Criteria (2015)[5], 55 different drugs were identified as inappropriate (MPIs) or unsafe to be used in geriatrics. Whereas, considering the Brazilian Consensus of drugs potentially inappropriate for the older adults (2016)[13], that number dropped to 45 different types. The number of PIMs (Table 2) per individual varied from 0 to 7, according to the Beers Criteria (2015)[5], and from 0 to 6, according to the Brazilian Consensus of Inappropriate drugs for Older Adults (2016)[13]. Altogether, these drugs appeared 322 times, according to the Beers Criteria (2015)[5] and 222 times, according to the Brazilian Consensus (2016)[13], among the participating older adults. The proportion of older adult patients who used at least one PIM was 77.3%, according to the Beers Criteria (2015)[5] and, according to the Brazilian Consensus (2016)13, that figure dropped to 61.9%.

Table 1. Major serious interactions in adults and older adults who are users of primary care in Divinópolis-MG, 2014-2016 (n=353).

Drug combination	Effect	Clinical management	Frequency % (n)
Spironolactone and losartan	Risk of hyperkalemia	Monitor potassium levels and renal function	2.8 (10)
Amlodipine and simvastatin	Increases plasma concentrations of simvastatin, potentiating the risk of myopathy	Do not exceed 20 mg/day simvastatin or replace therapy with rosuvastatin, pravastatin, and fluvastatin	2.6 (8)
ASA and ketorolac	Potentiates adverse effects of NSAIDs	Avoid simultaneous use	0.6 (2)
ASA and nimesulide	Increases the risk of bleeding	Monitor for signs of bleeding. Take ASA two hours before the NSAID	0.6 (2)
Amitriptyline and cyclobenzaprine	Increases serotonin levels	Avoid concomitant use. Monitor serotonin syndrome symptoms	0.6 (2)
Amitriptyline and sertraline	Increases serotonin levels	Monitor signs and symptoms of serotonin syndrome and avoid association	0.6 (2)
Betamethasone and nimesulide	Increases the risk of gastrointestinal ulcers and bleeding	Monitor signs and symptoms when association is needed	0.6 (2)
Captopril and spironolactone	Risk of hyperkalemia	Monitor potassium levels	0.6 (2)
Cyclobenzaprine and sertraline	Risk of serotonin syndrome	Monitor symptoms of serotonin syndrome	0.6 (2)
Clopidogrel and omeprazole	Inhibition of the effects of clopidogrel	Avoid simultaneous use. Choose pantoprazole/lansoprazole instead	0.6 (2)
Colchicine and simvastatin	Risk of myopathy	Monitor creatine kinase levels, although this does not prevent the occurrence of myopathy	0.6 (2)
Diclofenac and nimesulide	Increases the risk of bleeding, renal, cardiovascular and gastrointestinal impairment.	Avoid simultaneous use	0.6 (2)
Hydrochlorothiazide and nimesulide	Reduces diuretic effects and possible nephrotoxicity	Monitor renal function	0.6 (2)
Sertraline and tramadol	Risk of serotonin syndrome	Monitor symptoms of serotonin syndrome	0.6 (2)

Table 2. Potentially inappropriate drugs for older adults who are users of primary care of Divinópolis-MG, 2014-2016 (n=194)

Medication n (%)	Brazilian Consensus on Potentially Inappropriate drugs for the Older Adults, 2016		Beers Criteria, 2015		
	Rational	Exception	Recommendation	Degree of recomm.	Quality of the evidence
Hydrochlorothiazide 61 (31.4)	Contraindication is dependent on clinical condition (gout)	None	Use with caution	Strong	Moderate
Omeprazole 42 (21.6)	Prolonged use can contribute to the development of osteoporosis, fracture, dementia, and renal failure	Dose reduction in the treatment of peptic ulcer, esophagitis, and gastroesophageal reflux disease. Discontinuation before eight weeks	Avoid use for > 8 weeks. Except in the treatment of erosive esophagitis, Barrett's esophagitis, and pathological hypersecretory condition	Strong	High
Clonazepam 21 (10.8)	Can induce delirium	Treatment of epileptic seizures, REM sleep disorders, benzodiazepine and ethanol withdrawal syndrome, severe generalized anxiety disorder, in perioperative anesthesia and palliative care	Avoid	Strong	Moderate
Furosemide 17 (8.8)	Safer and more effective alternatives available	None	Use with caution	Strong	Moderate
Spironolactone 14 (7.2)	Risk of hyperkalemia in patients with heart failure	None	Use with caution	Strong	Moderate
Diclofenac 12 (6.2)	May exacerbate the risk of gastrointestinal bleeding and peptic ulcer	If there are no other alternatives	Avoid chronic use	Strong	Moderate
Sertraline 11 (5.7)	Contraindication is dependent on clinical condition (history of falls/fractures and hyponatremia)	None	Use with caution	Strong	Moderate
Glibenclamide 10 (5.2)	Risk of prolonged hypoglycemia	None	Avoid	Strong	High
Chlorpheniramine 9 (4.6)	Risk of anticholinergic effects	In allergic reaction, use diphenhydramine	Avoid	Strong	Moderate
Nimesulide 9 (4.6)	Contraindication is dependent on clinical condition (kidney disease, history of peptic ulcer, and hypertension)	If peptic ulcer: concomitant use of agent for gastric protection	Avoid chronic use	Strong	Moderate

Source: Beers Criteria (2015)[5], Brazilian Consensus on potentially inappropriate drugs for the older adults (2016)[13]

Discussion

The exponential increase in chronic diseases and factors associated with aging contributes significantly to the difference between the pharmacoepidemiological profile of the older adults and of the adults. The greatest number of drugs used by the older adults is associated with sociodemographic, clinical, and pharmacotherapeutic factors[15].

Due to the high amount of drugs used by the population, impacts in the clinical and economic scope are generated, in addition to putting patient safety at risk, as this factor increases the chance of potential drug interactions[16]. The results obtained reinforce the need for greater attention when in a geriatric population, since there is a greater chance of occurrence of these interactions, which was evidenced by the medians of the number of drug interactions between adults and older adults: 1 (0-3) and 3 (1-5), respectively, with $p < 0.05$.

The significant discrepancy in the number of drug interactions between adults and older adults can be associated with the frequency of polypharmacy[17]. It can also be associated with some physiological conditions of aging, such as slower gastric emptying and reduced enzyme activity in the liver, which may also increase the impact of these drug interactions[18].

The most prevalent serious interactions were between spironolactone and losartan and between amlodipine and simvastatin. The concomitant use of angiotensin II receptor blockers (losartan) and potassium-sparing diuretics (spironolactone) may increase the risk of hyperkalemia. This association can be fatal in patients with risk factors such as chronic kidney disease, diabetes, old age, and severe heart failure[10]. The administration of amlodipine can significantly increase plasma concentrations of simvastatin and its active metabolite, and also increase the risk of statin-induced myopathy[10].

Given this, the prescription is of great importance for patient safety, because problems related to the use of drugs can be avoided at that moment. And on the other hand, it is important to note that inappropriate prescriptions can lead to the use of drugs that have a high risk of adverse events when there are equal or more effective alternatives with lower risks[13].

As the older adults are more vulnerable to adverse situations resulting from the use of drugs, their prescriptions require strategies aimed at reducing the risk of clinical problems arising

from drug interactions[16]. The use of potentially inappropriate drugs for the older adults can trigger adverse effects and problems, most of the time, avoidable. Therefore, the study and identification of the inappropriate therapy for this audience can be used to develop strategies to ensure patient safety[7] .

When compared to another two Brazilian studies, the prevalence of PIMs found in the present study was higher than that found by Silva and collaborators[7] (59.0%), and lower than that found in the study by Ulbrich, Cusinato, and Guahyba[19] (93.5%). This high prevalence of the use of PIMs is a public health problem, since it can result in a greater risk of hospitalization and in factors which worsen the mortality rates[8]. Thus, the clinical conditions of the older adults, the drugs in use, lifestyle, and the scientific evidence should serve as a basis for assessing the clinical impact on the patient's life and providing guidance on the use of PIMs.

In relation to the limitations of the study, it is important to highlight that the research was carried out only with users of the Public Health System (*Sistema Único de Saúde*, SUS) of a Brazilian municipality, not allowing for the extrapolation of the results, although it is observed in the literature that the profile of medication use in primary health care is similar among the Brazilian municipalities, due to the fact that the Municipal Lists of Essential drugs (*Relações Municipais de Medicamentos Essenciais*, REMUME) are guided by protocols and clinical guidelines which are used throughout the national territory and by the National List of Essential drugs (*Relação Nacional de Medicamentos Essenciais*, RENAME). In addition, another possible limitation that needs to be highlighted is the potential selection bias that exists, since the invitation to include the participants in the research was extended according to the order of arrival and to the acceptance of the patients who were in the units awaiting care. This was done until the sample goals were reached in each health unit.

In order to reduce the gap between scientific research and the needs of the health services, the findings of the present study made it possible to prepare two pharmacotherapeutic bulletins, namely: "Pharmacotherapeutic bulletin 01/2017: Safety in the use of drugs by the older adults"[20] and "Pharmacotherapeutic Bulletin 02/2017: Drug interactions"[21] . As a return to the municipality, these bulletins were sent to the Municipal Health Secretariat of Divinópolis and posted in health units in order to alert the health team about the risks that the patients are exposed to.

Finally, it is important to highlight that it is extremely important for the health professionals to know these drug interactions and the profile of potentially dangerous drugs for the older adults, as well as their impact and clinical management in order to monitor their use, avoid them when possible, and act in a way to contribute to the rational use of drugs, providing an improvement in the effectiveness and safety in the use of drugs[3].

Conclusion

Most older adults who are primary care users use at least one medication that is inappropriate for them and, when compared to the adults, are more exposed to a high number of drugs and to potential drug interactions. Such an event may imply increased costs and overload for the health systems. Thus, the rationalization of the use of drugs is one of the significant public health challenges, since the presence of polypharmacy, the practice of self-medication, and potentially inappropriate prescriptions are still prevalent, especially among the older adults.

Funding sources

National Council for Scientific and Technological Development (CNPq). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) . Finance Code 001.

Collaborators

RSR, MRF, RFC, and AOB participated in the conception and design, and in data analysis and interpretation. RSR, LGRS and AOB contributed to the writing of the article and with the relevant critical review of the intellectual content. RSR, LGRS, MRF, RFC, and AOB approved the final version to be published and declare responsibility for all the information on the work, ensuring the accuracy and integrity of any its parts.

Acknowledgments

We thank the Federal University of São João Del-Rei (*Universidade Federal de São João Del-Rei*, UFSJ) for encouraging the research, and the Municipal Health Secretariat of Divinópolis (*Secretaria Municipal de Saúde de Divinópolis*, SEMUSA) for their support.

Conflict of interest statement

The authors declare that there are no conflicts of interest regarding this article.

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