Incidence and Predictors of Adverse Drug Reactions Caused by Drug-Drug Interactions in Elderly Outpatients: A Prospective Cohort Study

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ABSTRACT - Purpose. The primary objective of this study was to investigate the incidence of drug-drug interactions (DDIs) related to adverse drug reactions (ADRs) in elderly outpatients who attended public primary healthcare units in a southeastern region of Brazil. The secondary objective was to investigate the possible predictors of DDI-related ADRs. **Methods.** A prospective cohort study was conducted between November 1, 2010, and November 31, 2011, in the primary public healthcare system in the Ourinhos micro-region in Brazil. Patients who were at least 60 years old, with at least one potential DDI, were eligible for inclusion in the study. Eligible patients were assessed by clinical pharmacists for DDI-related ADRs for 4 months. The causality of DDI-related ADRs was assessed independently by four clinicians using three decisional algorithms. The incidence of DDI-related ADRs during the study period was calculated. Logistic regression analysis was used to study DDI-related ADR predictors. **Results.** A total of 433 patients completed the study. The incidence of DDI-related ADRs was 6.5%. A multivariate analysis indicated that the adjusted odds ratios (ORs) rose from 0.91 (95% confidence interval [CI] = 0.75-1.12, $p = 0.06$) in patients aged 65-69 years to 4.40 (95% CI = 3.00-6.12, $p < 0.01$) in patients aged 80 years or older. Patients who presented two to three diagnosed diseases presented lower adjusted ORs (OR = 0.93 [95% CI = 0.68-1.18, $p = 0.08$]) than patients who presented six or more diseases (OR = 1.12 [95% CI = 1.02-2.01, $p < 0.01$]). Elderly patients who took five or more drugs had a significantly higher risk of DDI-related ADRs (OR = 2.72 [95% CI = 1.92-3.12, $p < 0.01$]) than patients who took three to four drugs (OR = 0.93 [95% CI = 0.74-1.11, $p = 0.06$]). No significant difference was found with regard to sex (OR = 1.08 [95% CI 0.48-2.02, $p = 0.44$]). **Conclusion.** The incidence of DDI-related ADRs in elderly outpatients was significant, and most of the events presented important clinical consequences. Because clinicians still have difficulty managing this problem, highlighting the factors that increase the risk of DDI-related ADRs is essential. Polypharmacy was found to be a significant predictor of DDI-related ADRs in our sample.

INTRODUCTION

Drug-drug interactions (DDIs) describe the ability of a drug to modify the action or effects of another drug administered successively or simultaneously (1). In several cases, the concomitant use of some drugs is intentional to obtain a specific pharmacological synergism.

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However, DDIs also present deleterious outcomes, such as DDI-related adverse drug reactions (ADRs), causing roughly 2.8% of all hospitalizations in older patients and representing an estimated healthcare cost of more than USD$1 billion per year (2-4).

The world-wide increase in the elderly population has raised new issues with regard to the burden of DDI-related ADRs. The prevalence of potential DDIs is elevated among elderly outpatients (range from 42.5% to 54.4%), and they present some characteristics (e.g., physiologic modifications attributable to the ageing processes, frailty, several co-morbidities, and polypharmacy) that could augment the risk of DDI-related ADRs (5-8). Such data indicate the need to develop preventive practices and policies to guarantee the safety of elderly outpatients with regard to DDI-related ADRs.

The knowledge of the incidence and predictors of DDI-related ADRs could aid in the development of preventive practices and policies. However, to the authors' knowledge, data on the incidence and risk factors for DDI-related ADRs in elderly outpatients is lacking. Previous studies performed in an outpatient setting focused on the prevalence and predictors of potential DDIs and did not evaluate when the potential event actually occurred (9-11). Many of the potential DDIs could have neutral effects in some cases, and studies that focus on DDIs that cause ADRs will provide a better understanding of the occurrence and risk factors for these events.

Therefore, the primary objective of this study was to investigate the incidence of DDI-related ADRs in elderly outpatients who attended a public primary healthcare system in a southeastern region in Brazil. The secondary objective was to investigate the possible predictors of DDI-related ADRs in elderly outpatients.

METHODS

Type of study and setting

This study was approved by the Research Ethics Committee of the State University of Maringa, Brazil. This was a prospective cohort study carried out from 1 November 2010 to 31 November 2011 in the primary public health system of the Ourinhos micro-region, Brazil. The Ourinhos micro-region has an estimated population of 280,000 individuals (28,929 older than 60 years), attended by 36 primary healthcare units (PHCUs). This study included 12 PHCUs, which are physical locations where primary public health care services are provided to the Brazilian population. PHCUs have medical consulting rooms, vaccine injection rooms, pharmacies, rooms for procedures such as dressing and inhalation, and administrative rooms to file the patients' medical records.

Brazil's Sistema Único de Saúde (SUS) is a universal, publicly funded, rights-based public healthcare system. The SUS states that every citizen, regardless of economic and social condition, has access to all levels of healthcare (primary, secondary, and tertiary), including medicines (12,13). Primary care offered to outpatients in PHCUs involves health education, prevention, surveys of disease spread, and drug dispensation. Family physicians, general practitioners, and nurses provide primary healthcare interventions, including consultations, exams, education groups, and vaccinations, and pharmacies within PHCUs provide patients with the drugs prescribed by these professionals. The primary care level of SUS is the unique choice for access to healthcare for approximately 70% of the Brazilian population who do not have the financial resources to pay directly for private healthcare services or drugs.

Each patient who attended the PHCU that participated in the study had a personal medical record where family physicians, general practitioners, and nurses recorded general patient information (e.g., identification, date of birth, sex, disease diagnoses, and clinical and laboratory exam results) and the interventions performed (e.g., drug prescriptions, alterations in prescribed drugs, laboratory exam requests, and specialist referrals). The SUS does not use software to create electronic medical records or drug prescriptions. Medical records and drug prescriptions are hand-written by healthcare professionals.

Study subjects

The patients were eligible for inclusion in the study if they were ≥ 60 years of age, under treatment in a participating PHCU during the study period, and presented at least one potential DDI (prescribed both within and across prescriptions). The use of drug combinations that resulted in a potential DDI must have been initiated during the study period. Exclusion criteria included the presence of previous potential DDIs in the patients' drug therapy, previous signs and symptoms related to potential ADRs, potential DDIs in which the clinical consequence would be an exaggerated result of the intended therapeutic goal (e.g., the potential hypotensive effect of a combination of drugs prescribed for the treatment of hypertension), potential DDIs that might cause only vague subjective complaints (e.g., dizziness or vaguely described gastrointestinal complaints), and difficulty speaking that would interfere with their participation.

Eligible patients were identified by six clinical pharmacists using drug prescription records, medical records, and structured interviews. This process initiated with the employees of participating PHCU pharmacies (29 employees) who registered patient identification (i.e., name, date of birth, and sex) and complementary information (i.e., drug dispensation amount, dosage, and date) in the drug prescriptions dispensed and retained them. The clinical pharmacists collected these prescriptions daily and searched for patients ≥ 60 years old.

Elderly patients had their medical records analyzed and were interviewed by the clinical pharmacists to develop a complete current medical record and search for exclusion criteria. The interviews were performed by telephone or by visiting the patient at home. Patients who met none of the exclusion criteria and used two or more drugs had their current medical record entered into four DDI-checker programs (DrugDigest [Express Scripts, Saint Louis, USA], Drugs [Drugsite Trust, Auckland, New Zealand], Micromedex [Thomson Reuters, New York, USA], and Medscape [WebMD, New York, USA]) (14-17). Only potential DDIs rated as major or moderate by at least two of these four DDI-checker programs were included in the analysis. A total of 491 patients met the inclusion criteria and none of the exclusion criteria.

Study protocol

Eligible patients were contacted by telephone or face-to-face in the patients' homes to participate in the study. After written and verbal informed consent was obtained from the eligible patients, the previously mentioned clinical pharmacists were responsible for patient follow-up for 4 months. The follow-up process consisted of weekly face-to-face structured interview assessments of the patients in the PHCU. During this follow-up process, the clinical pharmacists searched for DDI-related ADRs using objective markers (e.g., laboratory results) and subjective markers (e.g., headache, nausea, and rash) identified through patient notes. The clinical pharmacist contacted one researcher physician to request laboratory exams to evaluate potential DDI-related ADRs (e.g., creatinophospokinase to assess myophaty, international normalized ratio to assess overanticoagulation, serum concentration of drugs) based on a clinical protocol previously developed by the authors (PON and RC). The patients were instructed to contact the clinical pharmacist responsible for his or her follow-up if any different symptoms occurred or if a new drug was initiated during these 4 months. All of the information collected by the clinical pharmacists was noted on a data collection form specifically developed by the researchers for the study.

The DDI-related ADRs identified had their causality evaluated. These analyses were performed independently by the clinical pharmacist responsible for the follow-up of the patients and by three physicians who specialized in ADR reporting. The clinical pharmacist performed the analysis prospectively during the follow-up period, and the physicians performed the analysis retrospectively using notes from the data collection form and patient's medical record.

The causality assessment was conducted using three decisional algorithms (Karch & Lasagna, Kramer and Naranjo) (18-20), with the level of "possible" causality considered the lower limit of acceptance of an adverse event, such as a DDI-related ADR (21). Only potential DDI-related ADRs rated inside the limit of acceptance in at least two algorithms by the majority of the evaluators were included in the study.

Data collection

For each patient, demographic, clinical, drug therapy, and DDI-related ADR data were collected from the data collection form and entered in an electronic database to facilitate the assessment of the information. The demographic data included patient age and sex. Diagnosed diseases and the number of diagnosed diseases were the clinical data. With regard to drug therapy data, we collected the international non-proprietary names of consumed drugs and number of drugs consumed per patient. DDI-related ADR data consisted of the occurrence of the event, the drugs involved, clinical consequences, and causality.

All of the drugs consumed were classified according to the first level of the Anatomical Therapeutic Chemical (ATC) classification system (22). In the ATC classification system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties (22).

Data analysis

The unit of analysis was the individual subjects. The individuals who had DDI-related ADRs were enumerated, counting each individual only once, regardless of the number of DDI-related ADRs they presented. These individuals comprised the exposed group. Patients without a DDI-related ADR during the study period comprised the non-exposed group. Descriptive statistical analysis of the collected data was performed for both the exposed and non-exposed groups. The data are presented as the absolute and relative frequency, mean, standard deviation (SD), and 95% confidence interval (CI) as appropriate. χ^2 tests were used for categorical variables, and independent-sample Student *t*-tests were used for quantitative variables. Values of $p < 0.05$ (two-tailed) were considered statistically significant.

Logistic regression analysis was used to study the factors that predisposed elderly outpatients to DDI-related ADRs. Exposure to a DDI-related ADR (Yes or No) was the dependent variable in the model. Each exposed individual was included in the logistic regression analysis only once, regardless of the number of DDI-related ADRs that the patient presented. Patient characteristics were incorporated into the model as independent variables, including age (categorical), sex (dichotomous), number of diagnosed diseases (discrete), and number of drugs consumed (discrete). The results are expressed as odds ratios (ORs) with a 95% CI. Values of $p < 0.05$ (two-tailed) were considered statistically significant. The analyses were performed using Statistica (StatSoft, Sao Caetano do Sul, SP, Brazil) version 8.0 and JMP (SAS, Cary, NC, USA) version 8.0.1 software.

RESULTS

General characteristics

A total of 433 patients completed the study (Fig. 1). DDI-related ADRs were verified in 6.5% of the sample (two patients presented two DDI-related ADRs, and 26 patients presented one DDI-related ADR). The statistical analyses indicated that some characteristics of the exposed group differed from the non-exposed group (Table 1).

Hypertension, diabetes, and dyslipidemia were the most common diagnosed diseases in the exposed and non-exposed groups. These patients received 87 different drugs. Captopril (42.9%) was the most frequently prescribed drug in the exposed group, followed by enalapril (39.3%), warfarin (39.3%), hydrochlorothiazide (35.7%), and amlodipine (28.6%). The five most prescribed drugs in the non-exposed group were hydrochlorothiazide (48.6%), captopril (26.9%), amlodipine (23.5%), metformin (23.2%), and atenolol (20.3%).

Drug-drug combinations verified

The drug combinations found in the exposed group are shown in Fig. 2A. A total of 21 drugs were involved in DDI-related ADRs, and warfarin was the most common of these, involved in 11 of the DDI-related ADRs, followed by acetylsalicylic acid (n = 5), digoxin (n = 5), and spironolactone (n = 5).

Gastrointestinal bleeding was the most frequent DDI-related ADR (n = 11 patients), followed by hyperkalemia (n = 5), myopathy (n = 4), arrhythmias (n = 3), vomiting (n = 2), overanticoagulation (n = 2), serotonin syndrome (n = 1), hypokalemia (n = 1), and Parkinson-like symptoms (n = 1).

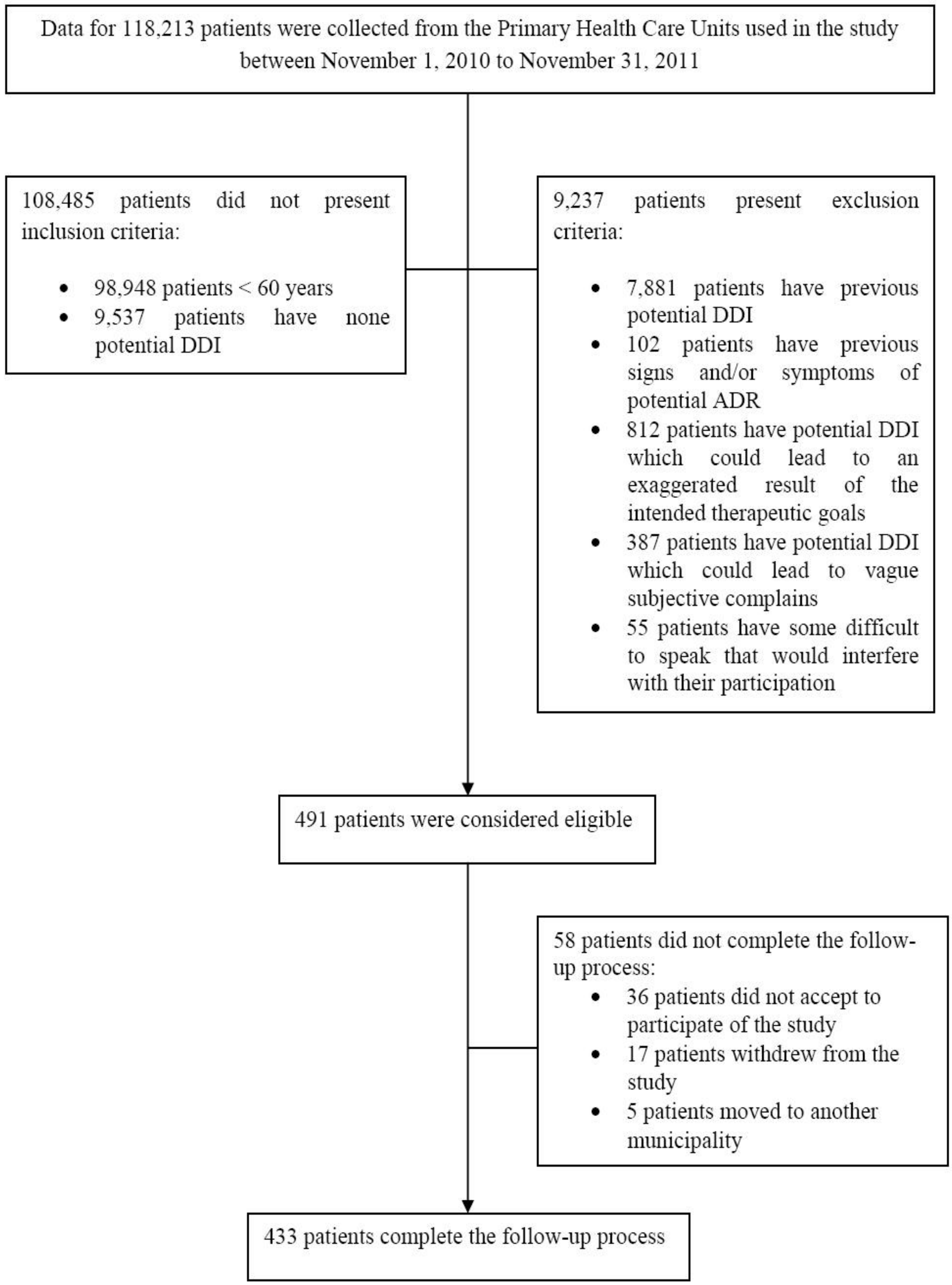

Figure 1. Flowchart of patients in the study.

Table 1. Patient characteristics according to exposure to adverse drug reactions related to drug-drug interactions.

Variable	**Exposed group n = 28 patients**	**Non-exposed group n = 405 patients**	***p* value[a]**
Demographic characteristics			
Age, mean (± SD)	80.3 (7.1)	65.9 (3.4)	< 0.01
Female gender, n (%)	24 (85.7)	322 (79.5)	0.43
Clinical characteristics			
Diagnosed diseases per patient, mean (± SD)	4.9 (1.4)	2.2 (0.7)	< 0.01
Most common diagnosed diseases			
Hypertension, n (%)	23 (82.1)	373 (92.1)	0.07
Diabetes, n (%)	12 (42.9)	176 (43.5)	0.95
Dyslipidemia, n (%)	9 (32.1)	138 (34.1)	0.83
Drug therapy characteristics			
Drugs consumed per patient, mean (± SD)	5.4 (1.6)	3.3 (1.0)	< 0.01
ATC codes of most consumed drugs			
Alimentary tract and metabolism (A), n (%)	14 (50.0)	190 (46.9)	0.75
Blood and blood-forming organs (B), n (%)	11 (39.3)	105 (25.9)	0.12
Cardiovascular system (C), n (%)	28 (100.0)	393 (97.0)	0.88
Antiinfectives for systemic use (J), n (%)	9 (32.1)	38 (9.4)	< 0.01
Musculoskeletal system (M), n (%)	7 (25.0)	73 (18.0)	0.36
Nervous system (N), n (%)	13 (46.4)	71 (17.5)	< 0.01

Abbreviation used: ATC, Anatomical Therapeutic Chemical classification system.
[a] χ^2 test and paired-sample *t*-test as appropriate.
Values of $p < 0.05$ were considered statistically significant.

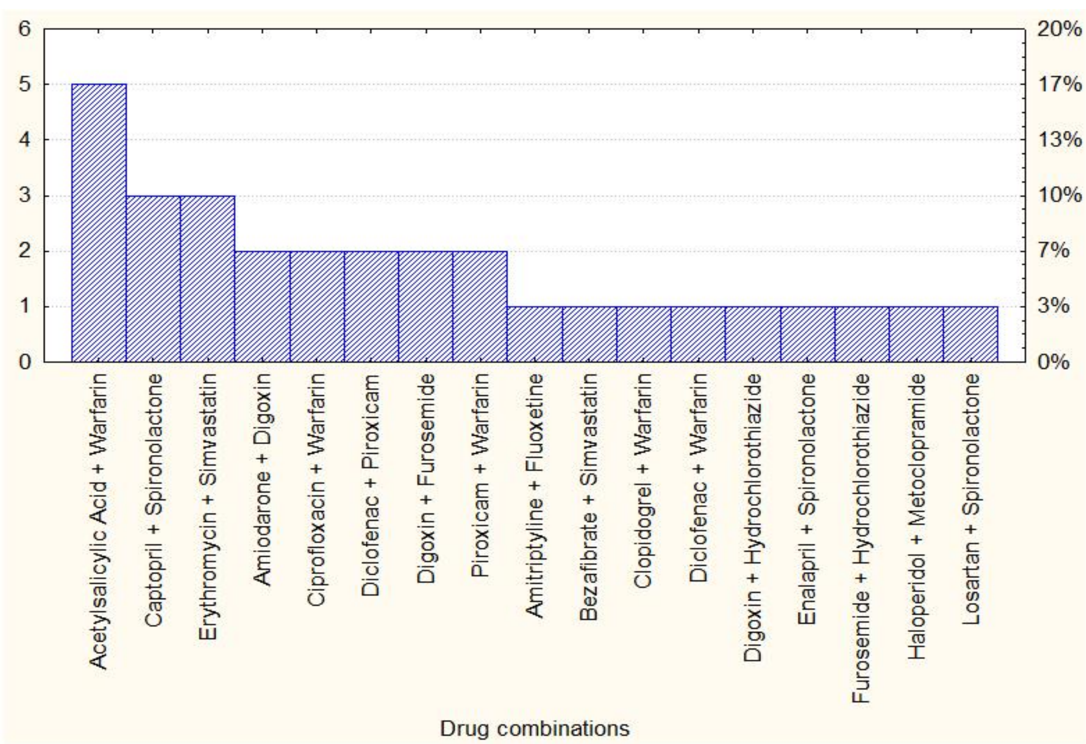

Figure 2. (A) Drug-drug combinations found in exposed group.

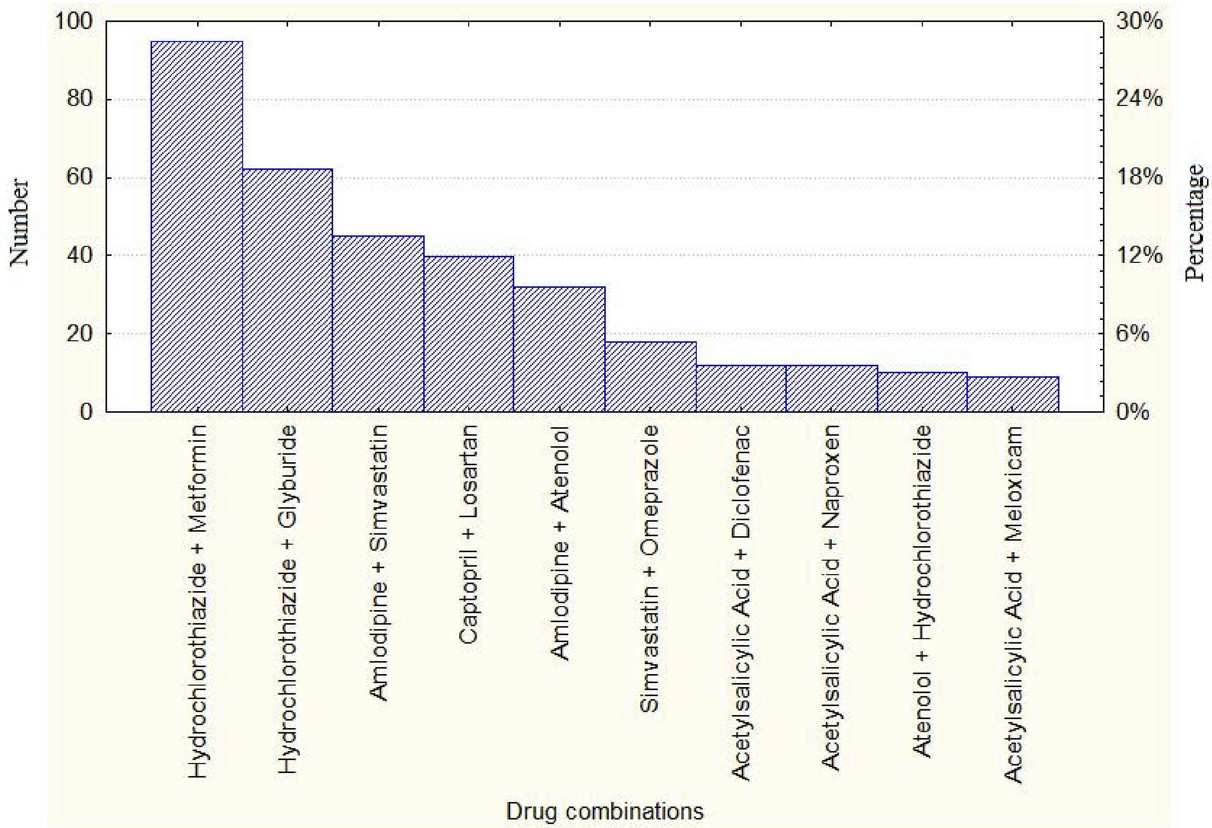

Figure 2. (B) Drug-drug combinations most frequently found in non-exposed group.

Hospital admission was necessary in 36.7% of the DDI-related ADRs. The discontinuation of drug therapy was necessary in 56.7% of the DDI-related ADRs, and no action was necessary in 6.6% of the DDI-related ADRs.

In the non-exposed group, a total of 48 drugs were involved in potential DDIs. Eight different drug combinations with potential clinical consequences were found. Hydrochlorothiazide (involved in 37.1% of DDI-related ADRs), metformin (20.2%), amlodipine (19.7%), simvastatin (16.3%), and glyburide (13.2%) were involved in the majority of potential DDIs (Fig. 2B).

Predictors of adverse drug reactions related to drug-drug interactions

Multivariate logistic regression showed that age, the number of diagnosed diseases, and the number of drugs consumed were associated with an increased risk of DDI-related ADRs. The adjusted ORs increased from 0.91 (95% CI = 0.75-1.12, p = 0.06) in patients aged 65-69 years to 4.40 (95% CI = 3.00-6.12, $p < 0.01$) in patients aged 80 years or older. Patients who presented two to three diagnosed diseases presented a lower adjusted OR (OR = 0.93 [95% CI = 0.68-1.18, p = 0.08]) than patients who presented six or more diseases (OR = 1.12 [95% CI = 1.02-2.01, $p < 0.01$]). Furthermore, the elderly who took five or more drugs had a significantly higher risk of DDI-related ADRs (OR = 2.72 [95% CI = 1.92-3.12, $p < 0.01$]) than those who took three to four drugs (OR = 0.93 [95% CI = 0.74-1.11, p = 0.06]). No significant differences were observed with regard to sex (Table 2).

DISCUSSION

To our knowledge, this is the first prospective cohort study conducted in outpatient settings that assessed the incidence and predictors of DDI-related ADRs in elderly patients. Most of the risk attributable to DDIs can be managed by healthcare professionals with appropriate prescriptions, monitoring, and patient education (23).

Table 2. Multivariate logistic regression analysis of patient characteristics associated with adverse drug reactions related to drug-drug interactions.

Variable	Odds ratio	95% CI	p[a]
Age, years			
60 – 64	-	-	-
65 – 69	0.91	0.75 – 1.12	0.06
70 – 74	1.06	0.85 – 1.69	0.09
75 – 79	1.23	0.98 – 2.41	0.03
≥ 80	4.40	3.00 – 6.12	< 0.01
Sex			
Male	-	-	-
Female	1.08	0.48 – 2.02	0.44
Number of diagnosed diseases per patient			
1	-	-	-
2 – 3	0.93	0.68 – 1.18	0.08
4 – 5	1.03	0.86 – 1.23	0.05
≥ 6	1.12	1.02 – 2.01	< 0.01
Number of drugs consumed per patient			
2	-	-	-
3 – 4	0.93	0.74 – 1.11	0.06
≥ 5	2.72	1.92 – 3.12	< 0.01

[a] Values of $p < 0.05$ were considered statistically significant.

The early detection and recognition of clinically important DDIs by healthcare professionals are vital for monitoring the occurrence of DDI-related ADRs. Knowledge of the incidence and predictors of DDI-related ADRs will help physicians and pharmacists identify patients who are at higher risk for such events and require more cautious pharmacotherapy management to avoid negative outcomes.

The incidence of DDI-related ADRs in elderly outpatients in the present study was significant, and most of the events had important clinical consequences. These results are alarming because the drugs most frequently involved in DDI-related ADRs in our cohort were similar to the drug combinations that were most prevalent in previous reports of potential DDIs (9-11,24): cardiovascular, blood and blood-forming agents, antiinfectives for systemic use, and musculoskeletal agents. Digoxin, furosemide, hydrochlorothiazide, spironolactone, captopril, and losartan were the drugs most frequently involved in potential DDIs in elderly Brazilian outpatients (9). In a study developed by Nobili et al. with Italian outpatients, acetylsalicylic acid, digoxin, enalapril, hydrochlorothiazide, and amiloride were the drugs most frequently involved in potential DDIs (10). Another study conducted in Italy with outpatients of every age found that warfarin, non-steroidal antiinflammatory drugs, theophylline, aminophylline, and ciprofloxacin were the most involved in potential DDIs (11). In a study conducted in Thailand with patients of every age, isoniazid, rifampin, digitalis glycosides, and loop diuretics were involved in the majority of potential DDIs (24). These are drugs widely used in primary care, especially by elderly patients (7-10).

Consistent with the findings of previous reports of potential DDIs, older patients presented higher odds of exposure to DDI-related ADRs in the present study. Obreli-Neto et al. found an increase in the adjusted OR of exposure to potential DDIs in older patients (range of 0.90 [95% CI = 0.82-1.03] in patients aged 60-64 years to 4.03 [95% CI = 3.79-4.28] in patients aged 75 years or older) (9). In a study by Nobili et al., the adjusted ORs of exposure to potential DDIs rose from 1.07 (95% CI = 1.03-1.11) in patients aged 70-74 years to 1.52 (95% CI = 1.46-1.60) in patients aged 85 years or older (10). Outpatients aged 65-74, 75-84, and ≥ 85 years showed increasing odds of exposure to potential DDIs than younger patients in another Italian study (11). The odd of having at least one potential drug interaction was 1.8 (64.2%) when age increased by 20 years ($p < 0.01$) in Thai outpatients (24). The prevalence of potential DDIs increased linearly with increasing age ($p < 0.001$) in a study of Taiwanese outpatients (25). A relationship between age and potential DDIs was also reported in a Danish outpatient population, with the risk of DDIs increasing from 24% in individuals aged 60-79 years to 36% in individuals aged 80 years or older (26). These results suggest that more caution should be taken in the monitoring of potential DDIs as patients get older.

Despite some differences in co-morbidities, chronically used medication, hormone levels, and variations in the activity of cytochrome P450 isoenzymes between males and females (27), no influence of sex on the occurrence of DDI-related ADRs was verified in our cohort. No statistically significant association was found between sex and the occurrence of potential DDIs in a study conducted by Nobili et al. (OR = 1.02 [95% CI = 1.00-1.05]) (11) and Gagne et al. (OR = 0.77 [95% = CI 0.70-0.85]) with outpatients in Italy (10). Equal rates of potential DDIs in prescriptions for male and female outpatients were also reported in a study conducted by Janchawee et al. in Thailand (24). However, other studies found an association between sex and the occurrence of potential DDIs. Johnell et al. found a lower probability of potentially serious DDIs in elderly female Swedish outpatients (28). Obreli-Neto et al. found a higher adjusted OR of exposure to potential DDIs in elderly female Brazilian outpatients (OR = 2.49 [95% CI = 2.29-2.75]) (9). Higher risks for potential DDIs in females were also reported by Costa et al. in a family practice center in the United States (relative risk = 1.28 [0.65 < RR < 2.5]) (29). According to our results, the same process of monitoring DDI-related ADRs could be performed in male and female elderly outpatients.

Patients in our cohort who presented an elevated number of diagnosed diseases (i.e., four or more) were at an increased risk of the occurrence of DDI-related ADRs. Previous reports also verified an increase in the risk of the occurrence of potential DDIs in patients who presented a higher number of diagnosed diseases. The adjusted OR for exposure to potential DDIs in elderly outpatients who presented three or more diagnosed diseases was 6.43 (95% CI = 3.25-12.44) in a Brazilian study (9). The odds of exposure to potential DDIs in patients with Chronic Condition Drug Group (CCDG) scores of 2 or 3 were 1.96-fold higher (95% CI = 1.74-2.20) than in patients with CCDG scores of 0 or 1 in a study conducted with Italian outpatients of every age (11). Costa et al. verified a higher relative risk in elderly outpatients in the United States with a diagnosis of three or more diseases (relative risk 3.71 [2.09 < RR < 6.60]) (29). Based on these results and to guarantee patient safety, a more intensive approach in the monitoring of DDI-related ADRs should be performed in elderly patients who present an elevated number of diagnosed diseases.

Polypharmacy was found to be a significant predictor of DDI-related ADRs in our sample. These results are similar to previous reports of potential DDIs. Obreli-Neto et al. verified an adjusted OR of exposure to potential DDIs of 3.21 (95% CI = 2.78-3.59) in elderly Brazilian outpatients who consumed three or more drugs (9). Elderly Italian outpatients who took more than five drugs on a chronic basis had a significantly higher risk of potentially severe DDIs (OR = 5.59 [95% CI = 5.39-5.80) than those who took less than three (i.e., reference category) or three to five such drugs (OR = 2.71 [95% CI = 2.63-2.80]) (11). The odds of exposure to potential DDIs were positively associated with the number of drugs prescribed, with an OR of 1.39 (95% CI = 1.37-1.41) in a study conducted by Gagne et al. with Italian outpatients of every age (10). Logistic regression analysis of the rate and size of prescriptions showed that the OR was 2.831 (95% CI = 2.427-3.301, p = 0.000, $p = 1/[1 + e^{4.36)1.04\ \text{Prescription size}}]$) when the prescription size increased by one in Thai outpatients (24). A strong association was found between the number of dispensed drugs and probability of potential DDIs among outpatients in Sweden after adjusting for age and sex (28). Costa et al. also verified an increased risk of potential DDIs in patients who took more than three drugs (relative risk 3.61 [2.11 < RR < 6.20]) in a family practice center in the United States (29). These results suggest that a more cautious approach should be taken in the process of monitoring DDI-related ADRs in elderly outpatients who consume an elevated number of drugs.

Strengths and limitations

Our study combined a prescription database, patient interviews and medical records to assess drug use and the occurrence of DDI-related

ADRs. This study design reduced some bias such as recall bias due to lack of information in medical records (missing or inaccurately documented information), the patients forgetting about the use of certain drugs, lack of information about patient compliance to the drug regimen, and the incompleteness of pharmacy record files. Another strong point was the prospective design, which provided important information markers (objective and subjective) about DDI-related ADRs that the clinical pharmacists could assess in real time during follow-up. Further, the long duration of the study (13 months) excluded any potential seasonal bias in drug use.

Despite these advantages, our study does have some limitations, which must be acknowledged. The various sources available to analyze potential DDIs, with different classifications of severity and clinical importance (30,31), are not in consensus, and this poses a challenge to DDI assessment studies. We utilized several sources to minimize this potential bias.

The risk of DDIs may be have been underestimated: most instruments available for assessing DDIs consider only pairs of drugs and do not account for interactions involving combinations of 3 or more drugs (32). Further, most instruments also do not consider the dosages or duration of therapies or individual patient risk factors. Nonetheless, these instruments are widely used currently to assess the clinical relevance and risk of exposure to potential DDIs (33).

The causality assessment of DDI-related ADRs was conducted using decisional algorithms that have been developed with the claim that the scoring systems proposed are more explicit and therefore less susceptible to bias (18-20). However, none of the algorithms published have been universally accepted as a gold standard, with several disagreements between the obtained results when used to assess causality using the same ADR reports (21). In the present study, we used the consensus of 4 clinicians (3 physicians who were ADR specialists and 1 trained clinical pharmacist) and 3 decisional algorithms to minimize this potential bias.

Lastly, our study involved only 12 PHCUs, and there is likely to be variation among PHCUs because of differences in local population characteristics. Caution must therefore be exercised while generalizing our results. Nevertheless, the data presented here on DDI-related ADRs in elderly outpatients are important and will help in identifying medication risks.

CONCLUSION

The incidence of DDI-related ADRs in elderly outpatients was significant, and most of the events presented important clinical consequences. The rate of such events increased with the patient's age, number of diagnosed diseases, and number of drugs consumed. Polypharmacy was found to be a significant predictor of DDI-related ADRs in our sample.Because clinicians still have some difficulty managing this problem, highlighting the factors that increase the risk of DDI-related ADRs is essential.

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