Prevalence and Predictors of Potential Drug-Drug Interactions in the Elderly: A Cross-Sectional Study in the Brazilian Primary Public Health System

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ABSTRACT- Purpose. The primary objective of this study was to investigate the prevalence of clinically important potential drug-drug interactions (DDIs) in elderly patients attending the public primary health care system in Brazil. The secondary objective was to investigate possible predictors of potential DDIs. **Methods.** A cross-sectional study was carried out in 5 Brazilian cities located in the Ourinhos Micro-region, Sao Paulo State, between November 2010 and April 2011. The selected sample was divided according to the presence (exposed) or absence (unexposed) of one or more potential DDIs (defined as the presence of a minimum 5-day overlap in supply of an interacting drug pair). Data were collected from medical prescriptions and patients' medical records. Potential DDIs (rated major or moderate) were identified using 4 DDI-checker programs. Logistic regression analysis was used to study potential DDI predictors. **Results.** The prevalence of clinically important potential DDIs found during the study period was 47.4%. Female sex (OR = 2.49 [95% CI 2.29–2.75]), diagnosis of ≥ 3 diseases (OR = 6.43 [95% CI 3.25–12.44]), and diagnosis of hypertension (OR = 1.68 [95% CI 1.23–2.41]) were associated with potential DDIs. The adjusted OR increased from 0.90 [95% CI 0.82–1.03] in patients aged 60 – 64 years to 4.03 [95% CI 3.79 – 4.28] in those aged 75 years or older. Drug therapy regimens involving ≥ 2 prescribers (OR = 1.39 [95% CI 1.17–1.67]), ≥ 3 drugs (OR = 3.21 [95% CI 2.78–3.59]), ≥ 2 ATC codes (OR = 1.19 [95% CI 1.12–1.29]), ≥ 2 drugs acting on cytochrome P450 (OR = 2.24 [95% CI 2.07–2.46]), and ATC codes B (OR = 1.89 [95% CI 1.05–2.08]) and C (OR = 4.01 [95% CI 3.55–4.57]) were associated with potential DDIs. **Conclusion.** Special care should be taken with the prescription and therapeutic follow-up of patients who present characteristics identified as predictors. Knowledge of potential DDI predictors could aid in developing preventive practices and policies that allow public health services to better manage this situation.

INTRODUCTION

Earlier studies have reported that 54.4–80.0% of elderly Latin American outpatients presented with one or more potential drug-drug interactions (DDIs) (1,2), and the elderly population is increasing rapidly in Latin American countries (3). DDIs present deleterious outcomes, causing roughly 2.8% of all hospitalizations in older patients and representing an estimated cost of more than U$1 billion per year to health care systems (4-6). Several factors influence the occurrence of potential DDIs in elderly patients (7-9).

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Knowledge of predictors of potential DDIs could aid in developing preventive practices and policies (9). However, to the authors' knowledge, drug utilization studies analyzing these predictors in elderly patients at the primary health care level in Latin American countries are scarce.

A previous drug utilization study conducted in a tertiary hospital setting in Brazil, a Latin American country, indicated that patient characteristics, prescriber characteristics, and drug characteristics influenced the occurrence of potential DDIs (8), but these findings cannot be extrapolated to the primary health care level. Up to 70.0% of Latin American patients are attended at the primary care level, reinforcing the need to study potential DDI predictors in this setting.

The primary objective of this study was to investigate the prevalence of clinically important potential DDIs in elderly patients attending the public primary health care system in a south-eastern region of Brazil. The secondary objective was to investigate possible predictors of potential DDIs.

METHODS

Study design

This study was approved by the Research Ethical Committee of the State University of Maringa, Brazil (CAAE 0010-10). The research followed a cross-sectional study model, with the selected sample group divided between patients receiving drug therapies with one or more potential DDI (exposed) and those receiving drug therapies with no potential DDI (unexposed). The study was carried out between November 2010 and April 2011, using data from the public primary health care system in 5 Brazilian cities located in the Ourinhos Micro-region, Sao Paulo State. The Ourinhos Micro-region has an estimated population of 280,000 individuals (28,929 over the age of 60 years), attended by 36 Basic Health Units (BHUs). Twenty-seven BHUs participated in the study.

The Brazilian Public Health System provides free access to primary, secondary, and tertiary care to all inhabitants, including the supply of drugs by pharmacies located in health establishments. Primary care offered to outpatients in BHUs involves health education, prevention and surveys of disease spread, and drug dispensation. Family physicians, general practitioners, and nurses provide primary health care interventions (consultations, exams, education groups, and vaccinations), and pharmacies within BHUs provide patients with the drugs prescribed by these professionals.

Inclusion and exclusion criteria

According to the threshold set by the United Nations Programme on Ageing, patients aged over 60 years were considered elderly (10). The use of a cut-off of 60 years instead of 65 years augmented the sample size of the study. Patients $\geq$ 60 years of age with at least one prescription for 2 or more drugs (prescribed both within and across prescriptions) collected in participating BHU pharmacies were eligible for inclusion in the study.

The Brazilian public health system does not employ software to create electronic drug prescriptions. Drug prescriptions are hand-written by the physicians. According to Brazilian legislation, prescriptions must be signed and dated by the physician, legible, and written in ink, with no sign of tampering (e.g. different handwriting or written in different ink colours) or erasures (e.g. scribble and blots), to be considered valid (11). Exclusion criteria included signs of prescription tampering or erasure and illegibility.

Data collection

The Brazilian public primary health care system has no administrative prescription database. Thus, data collection was carried out by analyzing patients' drug prescriptions and medical records.

At the time of dispensing the medication, the employees of participating BHU pharmacies (51 employees) registered patient identification (name, date of birth, and sex) and complementary information (drug dispensation amount and date) in the prescriptions and retained them. Three researchers (NN, JV and GS) were responsible for weekly collection of these prescriptions and determination of those eligible for inclusion in the study. Information from eligible prescriptions (name, date of birth, sex, names of the drugs prescribed, amount of drug dispensed, prescribers' identification, date of prescription, and date of dispensation) was collected and entered into an electronic

database developed for the purpose of this study to rapidly access and assess this information. All prescriptions were classified according to the first level of the Anatomical Therapeutic Chemical (ATC) classification system, as recommended by the World Health Organization (12). In this system, active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties (12). The ATC codes (first level) are alimentary tract and metabolism (ATC code 'A'), blood and blood-forming organs (ATC code 'B'), cardiovascular system (ATC code 'C'), dermatologicals (ATC code 'D'), genito urinary system and sex hormones, excluding sex hormones and insulins (ATC code 'G'), antiinfectives for systemic use (ATC code 'J'), antineoplastic and immunomodulating agents (ATC code 'L'), musculo-skeletal system (ATC code 'M'), nervous system (ATC code 'N'), antiparasitic products, insecticides and repellents (ATC code 'P'), respiratory system (ATC code 'R'), sensory organs (ATC code 'S') and various (ATC code 'V').

Each patient attended in a BHU has a personal medical record file, where family physicians, general practitioners, and nurses register general patient information (identification, date of birth, sex, diseases diagnosed, clinical and laboratory exam results) and the interventions carried out (drug prescription, alterations in prescribed drugs, laboratory exam requests, and specialist referrals). This information was also entered into our electronic database. The same researchers were involved in the collection of patients' medical records and data collection from the prescriptions.

Four other researchers (EF, TM, CL and GB) accessed the electronic database to search for potential DDIs by listing the drugs prescribed in single prescriptions and across successive prescriptions for the same patient with the presence of a minimum 5-day overlap in days' supply for object and precipitant medications, based on prescription delivery dates irrespective of prescriber (13), in DDI-checker software. Potential DDIs were identified using 4 DDI-checker programs (DrugDigest®, Drugs®, Micromedex®, and Medscape®) (14-17) to promote greater sensitivity in the survey (18). These 4 DDI-checker programs have been widely used in previous published studies and represent the programs most used by Latin American pharmacists. The drug therapy regimen of each patient was typed and evaluated independently by the four researchers mentioned above using the 4 DDI-checker programs, to avoid possible mistakes in the typing and evaluation process. Only potential DDIs rated as major or moderate by at least 3 of the 4 DDI-checker programs utilised were included in the analysis.

Clinical relevance was defined according to the criteria used by the DDI-checker software programs, which considered the 'potential' of DDIs for both adverse event risk and lack of efficacy. All DDIs was classified as of major, moderate, or minor clinical relevance on the basis of potential clinical outcomes and type, quality, and relevance of supporting clinical and pharmacological documentation. 'Major' DDIs were defined as drug combinations that should be usually avoided or may potentially lead to serious clinical consequences, such as severe adverse effects or no clinical effects, and required close monitoring; 'moderate' as drug combinations where the precipitant drug may modify the effect of the object drug, but the resulting effect can be controlled by adjustment of individual doses and/or drug plasma concentration; and 'minor' as drug combinations likely to have no clinical relevance or not completely assessed. For each potential DDI, the software also provided information on the mechanism responsible for the interaction (if available), the clinical or pharmacological effect of the interaction, and advice on measures to control or manage the risk of interaction.

Before beginning the study, agreement between the 4 DDI-checker programs was tested by entering 12 drug pairs described by Gagne *et al.* (9) as clinically important potential DDIs into each selected program. All the programs utilised identified all 12 pairs as major or moderate potential DDIs.

Predictor factors

Study of possible predictors of potential DDIs included patient characteristics and drug therapy characteristics. The following patient characteristics were analyzed: age, sex, number of diagnosed diseases, diagnosis of

hypertension, and diagnosis of diabetes. For each patient, the number of prescribers, number of drugs consumed, ATC code classification of the drug therapy, number of ATC codes per drug therapy, and number of drugs that act on cytochrome P450 (CYP450) per drug therapy of each patient were analyzed as drug therapy characteristics.

The list of substrates, inducers and inhibitors of CYP450 available in the appendix section of Lexi-Comp's Drug Information Handbook with International Trade Names Index 2010-2011 was used to identify drugs that act on CYP450 (19). The drug therapy regimen of each patient was checked independently by four researchers (EF, TM, CL and GB), to avoid possible mistakes in the process of searching for drugs acting on CYP450.

Before selecting the predictor factors, electronic searches of the published literature from 1990 to 2011 were conducted through EMBASE and MEDLINE databases to identify risk factors for potential DDIs verified in previous studies. The search strategy included the terms (alone and in combination) drug-drug interactions, elderly, pharmacoepidemiology, predictors, and risk.

Most selected predictor factors were chosen in accordance with the results of previous studies (2,7-9,20-23). Diabetes diagnosis was also included in the analysis because this disease was the second most prevalent disease in the sample.

STATISTICAL ANALYSIS

Data were presented as the absolute and relative frequency, mean, standard deviation (SD), and 95% confidence interval (CI), as appropriate. Chi-square tests were used for categorical variables, and independent sample Student t-tests were used for quantitative variables. Logistic regression analysis was used to study predictors of potential DDIs, with adjustment for age and sex. Exposure to a potential DDI (Yes / 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 potential DDIs to which he or she was exposed. Patient characteristics and drug therapy characteristics were incorporated into the model as independent variables. The results are shown as odds ratios (OR) with 95% CI. A P value < 0.05 was considered statistically significant. Analyses were performed using Statistica (StatSoft, Sao Caetano do Sul, SP, Brazil) version 8.0 and JMP software (SAS, Cary, NC, USA) version 8.0.1.

RESULTS

General characteristics

During the study period, 12,343 patients fulfilled the entrance criteria and met no exclusion criteria. The prevalence of clinically important potential DDIs found during the study period was 47.4%. Figure 1 illustrates the data collection flow throughout the study. Participants' general characteristics are shown in Table 1. Elderly patients received 51,042 drug prescriptions (28.8% of the overall 177,437 prescriptions). More than 80.0% of elderly patients were exposed to at least one drug utilised to treat a chronic disease.

Thiazide diuretics (72.9%) were the most frequently prescribed drugs in patients exposed to clinically important potential DDIs, followed by angiotensin-converting enzyme inhibitors (ACEI) (63.0%), digitalis glycosides (44.3%), platelet aggregation inhibitors excluding heparin (44.0%), and loop diuretics (31.0%). The 5 most widely prescribed therapeutic groups in patients unexposed to clinically important potential DDIs were beta-lactam antibacterials (penicillins) (49.0%), biguanides (23.0%), dihydropyridine-derivate calcium channel blockers (19.0%), analgesics (anilides) (16.0%), and thiazide diuretics (16.0%).

Predictors of potential DDIs

Univariate and multivariate analyses of patient characteristics indicated female sex, diagnosis of 3 or more diseases and diagnosis of hypertension to be associated with increased risk of potential DDIs. Both univariate and multivariate analyses show age to be associated with an increasing risk of DDIs. The adjusted OR increased from 0.90 [95% CI 0.82–1.03] in patients aged 60 – 64 years to 4.03 [95% CI 3.79 – 4.28] in those aged 75 years or older. No statistical association was observed in the multivariate analysis with respect to a diagnosis of diabetes (Table 2).

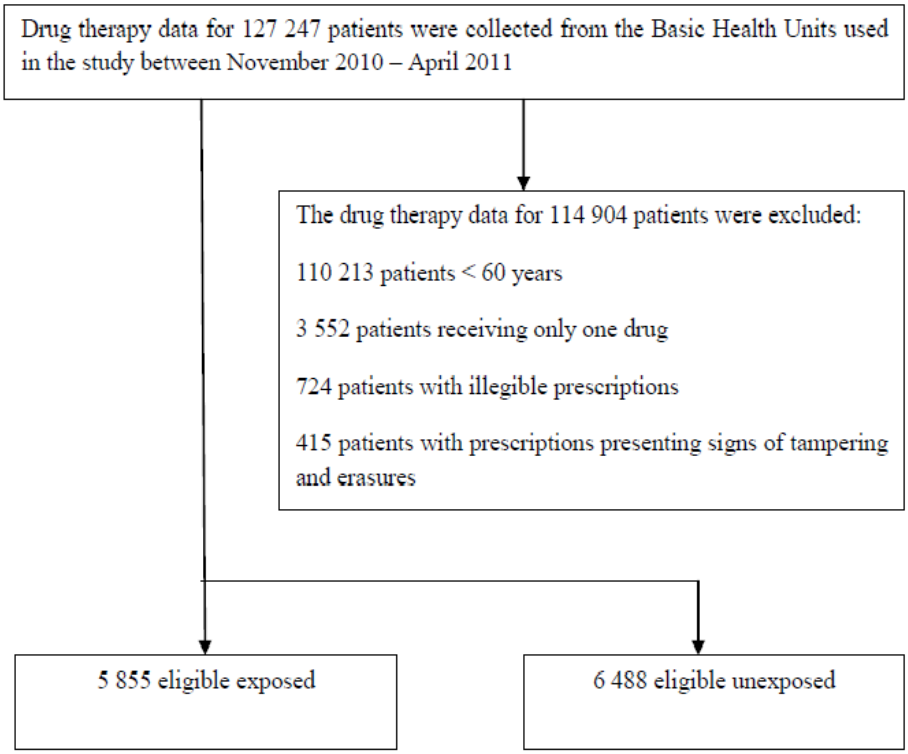

Figure 1. Flowchart of the data collection throughout the study.

Table 1. General characteristics according to exposure to clinically important potential drug-drug interactions.

Characteristic	**Exposed N = 5,855**	**Unexposed N = 6,488**	**P value**
Mean age (±SD) years	63.31 (3.47)	61.42 (2.25)	<0.001
Female sex, n (%)	4854 (82.9)	4163 (64.2)	<0.001
Mean number of prescribers (±SD)	1.05 (0.24)	1.03 (0.19)	<0.001
Mean number of drugs consumed (±SD)	2.94 (0.84)	2.25 (0.52)	<0.001
Mean number of ATC codes consumed (±SD)	1.72 (0.65)	1.56 (0.53)	<0.001
ATC code 'A' (alimentary tract and metabolism)	3116 (53.2)	1664 (25.6)	<0.001
ATC code 'B' (blood and blood-forming organs)	2541 (43.4)	1082 (16.7)	<0.001
ATC code 'C' (cardiovascular system)	5641 (96.3)	2953 (45.5)	<0.001
ATC code 'H' (systemic hormonal preparations, excluding sex hormones and insulin)	44 (0.7)	8 (0.1)	<0.001
ATC code 'J' (antiinfectives for systemic use)	2834 (48.4)	3278 (50.5)	0.019
ATC code 'M' (musculo-skeletal system)	1529 (26.1)	1843 (28.4)	0.005
ATC code 'N' (nervous system)	1393 (23.8)	1540 (23.7)	0.965
ATC code 'R' (respiratory system)	754 (12.9)	886 (13.7)	0.204
Mean number of drugs acting on CYP450 (±SD)	2.12 (0.94)	1.63 (0.98)	<0.001
Mean number of diagnosed diseases (±SD)	1.61 (0.58)	1.55 (0.50)	<0.001
Hypertension, n (%)	5357 (91.5)	3468 (53.4)	<0.001
Diabetes, n (%)	3289 (56.2)	1454 (22.4)	<0.001

The chi-square test and the independent sample Student's t-test were used as appropriate. P values < 0.05 were considered statistically significant.

The number of prescribers, drugs consumed, ATC codes, and drugs that act on CYP450 presented positive associations with potential DDIs in univariate and multivariate analyses of drug therapy characteristics. ATC codes B and C were also predictors of potential DDIs. The univariate analysis further indicated ATC codes A and H and potential DDIs rated as major and moderate to be associated with increased risk of potential DDIs, but multivariate analysis did not confirm these associations. ATC codes J, N, M, and R presented no statistical association in either univariate or multivariate analysis (Table 3).

Table 2. Patient characteristics associated with potential drug-drug interactions.

Predictor factor	Univariate analysis OR [95% CI]	Multivariate analysis OR [95% CI][a]	P value
Female sex	2.71 [2.49–2.95]	2.49 [2.29–2.75]	<0.001
Age (years)			
60 – 64	0.96 [0.85–1.04]	0.90 [0.82–1.03]	0.141
65 - 69	2.02 [1.88 – 2.19]	1.66 [1.49 – 1.80]	<0.001
70 - 74	3.12 [3.00 – 3.31]	3.00 [2.85 – 3.10]	<0.001
≥ 75	4.21 [4.02 – 4.41]	4.03 [3.79 – 4.28]	<0.001
Number of diagnosed diseases ≥ 3	26.38 [13.65–57.54]	6.43 [3.25–12.44]	<0.001
Diagnosis of hypertension	9.37 [8.44–10.39]	1.68 [1.23–2.41]	<0.001
Diagnosis of diabetes	4.44 [4.11–4.80]	1.04 [0.88–1.14]	0.153

[a]Adjusted for age and sex.
P values < 0.05 were considered statistically significant.

Table 3. Drug therapy characteristics associated with potential drug-drug interactions.

Predictor factor	Univariate analysis OR [95% CI]	Multivariate analysis OR [95% CI][a]	P value
Number of prescribers ≥ 2	1.41 [1.18–1.70]	1.39 [1.17–1.67]	<0.001
Number of drugs consumed ≥ 3	6.40 [5.90–6.94]	3.21 [2.78–3.59]	<0.001
Number of ATC codes ≥ 2	1.50 [1.40–1.61]	1.19 [1.12–1.29]	<0.001
ATC code 'A' (alimentary tract and metabolism)	3.30 [3.06–3.56]	1.07 [0.89–1.20]	0.005
ATC code 'B' (blood and blood-forming organs)	3.83 [3.53–4.16]	1.89 [1.05–2.08]	<0.001
ATC code 'C' (cardiovascular system)	31.56 [27.30–36.48]	4.01 [3.55–4.57]	<0.001
ATC code 'H' (systemic hormonal preparations, excluding sex hormones and insulin)	6.13 [2.99–13.94]	1.01 [0.91–1.18]	0.667
ATC code 'J' (antiinfectives for systemic use)	0.92 [0.86–0.99]	0.91 [0.85–0.99]	0.148
ATC code 'M' (musculo-skeletal system)	0.89 [0.82–0.97]	0.83 [0.80–0.98]	0.051
ATC code 'N' (nervous system)	1.00 [0.92–1.09]	0.91 [0.86–1.01]	0.149
ATC code 'R' (respiratory system)	0.93 [0.84–1.04]	0.91 [0.82–1.04]	0.149
Number of drugs acting on CYP450 ≥ 2	2.32 [2.12–2.53]	2.24 [2.07–2.46]	<0.001

[a]Adjusted for age, sex, number of chronic conditions, and number of drugs consumed.
P values < 0.05 were considered statistically significant.

Clinically important potential DDIs

During the study, patients were exposed to 9,368 clinically important potential DDIs corresponding to 364 drug combinations. The mean number of DDIs per patient was 1.60 (range 1–4), with nearly 13.0% of cases having 2 or more DDIs. Most of potential DDIs identified were pharmacodynamic interactions (82.8%). Referent to clinical relevance, 33.4% of the potential DDIs identified were rated as major by at least 3 of the DDI-checker programs utilised.

The 12 most frequently observed DDIs (Table 4) were responsible for 5,361 (57.2%) of all potential DDIs. As expected, cardiovascular drugs (hydrochlorothiazide, captopril, furosemide, digoxin, spironolactone, simvastatin, losartan, verapamil, amiodarone, atenolol, bezafibrate, and diltiazem) and drugs affecting blood clotting (acetylsalicylic acid, ticlopidine, and warfarin) were the most frequently involved. Of the 413 active substances prescribed to exposed patients, 31.0% were responsible for potential DDIs.

The 9,368 clinical important potential DDIs corresponded to 364 drug combinations. However, the first 12 (Table 4) were responsible for 5,361 (57.2%) of all potential DDIs.

DISCUSSION

To the authors' knowledge, this investigation is the first cross-sectional study conducted in the public primary health care system of a Latin American country to assess the prevalence of clinically important potential DDIs and to investigate possible predictors of potential DDIs in elderly outpatients.

Knowledge of the prevalence and predictors of clinically important potential DDIs will help physicians and pharmacists identify patients at higher risk of DDI-related adverse drug reactions, who require more cautious pharmacotherapy management to avoid negative outcomes.

Table 4. Most common potential drug-drug interactions

Drug combination[a]	N (%)	Possible clinical consequences[a]	Clinical relevance[b]
Digoxin and Furosemide/ Hydrochlorothiazide	2533 (43.3)	Digitalis toxicity	Moderate
Captopril/Losartan and Spironolactone	1020 (17.4)	Hyperkalemia	Major
Acetylsalicylic acid and Ticlopidine	324 (5.5)	Bleeding and gastrointestinal lesions	Moderate
Amiodarone and Spironolactone	252 (4.3)	Ventricular arrhythmias	Moderate
Amitriptyline and Fluoxetine	203 (3.5)	Amitriptyline toxicity	Major
Acetylsalicylic acid and Warfarin	201 (3.4)	Bleeding and gastrointestinal lesions	Major
Verapamil and Atenolol	167 (2.8)	Bradycardia, sinus and atrioventricular depression	Major
Amitriptyline and Diazepam	150 (2.6)	Excessive or prolonged CNS[c] and respiratory depression	Moderate
Omeprazole and Simvastatin	148 (2.5)	Myopathy	Moderate
Amiodarone and Simvastatin	127 (2.2)	Myopathy and rhabdomyolysis	Major
Bezafibrate and Simvastatin	127 (2.2)	Myopathy and rhabdomyolysis	Major
Diltiazem and Simvastatin	109 (1.9)	Myopathy	Major

[a]DrugDigest®, Drugs®, Micromedex® and Medscape® were used to identify potential DDIs and their possible clinical consequences.
[b]Clinical relevance classified according to 3 or more DDI-checker programs utilised.
[c]CNS: central nervous system.

The patient characteristics such as female sex, more advanced age, diagnosis of hypertension, and greater number of diagnosed diseases were identified as predictors of potential DDIs. A large numbers of prescribers, drugs consumed, ATC codes, and drugs acting on CYP450 were verified as drug therapy-related predictors of potential DDIs. The present results further indicated that ATC codes B and C codes were predictors of potential DDIs.

In some situations, changing some drugs utilised by a patient is possible and can lead to safer drug therapy regimens. However, a huge number of clinically important potential DDI identified cannot be avoided in some situations. For example, congestive heart failure patients with atrial fibrillation receive drug therapy that includes ACEI, furosemide, spironolactone, and digoxin, despite the potential risk for DDIs. More cautious drug therapy management in this situation is extremely important to guarantee patient safety, especially in patients presenting other predictor of potential DDI.

Patient characteristic predictors

Consistent with the findings of previous drug utilization studies, older patients presented higher odds of exposure to potential DDIs in the present study. A study of outpatients in Thailand found that the risk of having at least one potential DDI increased with patient age (7). A significantly increased odds ratio was also reported by Cruciol-Souza *et al.* in patients ≥55 years in a Brazilian hospital (8). In studies of Italian outpatients, patients aged 65–74, 75–84, and ≥85 years showed increasing odds for exposure to potential DDIs (9), and the adjusted OR rose from 1.07 [CI95% 1.03–1.11] in patients aged 70–74 years to 1.52 [CI95% 1.46–1.60] in those aged ≥85 years (20). The prevalence of potential DDIs increased linearly with increasing age ($P < 0.001$) in a study of outpatients in Taiwan (24). A relationship between age and potential DDIs was also reported in a Danish outpatient population, with the risk of DDIs rising from 24.0% in individuals aged 60–79 years to 36.0% in those over 80 (25). These results can be attributed to the increased complexity of drug therapy regimens found in older adults, which result in a higher prevalence of potential DDIs (7).

The present results indicated that the female sex was associated with the occurence of potential DDIs. Published results concerning the influence of sex on potential DDI occurrence are variable. Cruciol-Souza *et al.* identified female sex as a predictor of potential DDIs in hospitalised Brazilian patients (8). Higher risks for potential DDIs in females were also reported by Costa *et al.* in a family practice centre in the USA (21). However, equal rates of potential DDIs in prescriptions for male and female outpatients were reported in the study conducted by Janchawee *et al.* in Thailand (7). Unlike the findings of our study, the results obtained by Johnell *et al.* showed a lower probability of potentially serious DDIs in female elderly Swedish outpatients (26). No statistically significant association was verified with respect to sex in studies conducted by Nobili *et al.* (20) Gagne *et al*. (9) with outpatients in Italy. This inconsistency in the results could stem from several factors, including differences in patient health status, study settings, sources used to identify potential DDIs, culture, and prescribing habits.

In the present study, the odds for potential DDI exposure were associated with a higher number of diagnosed diseases and diagnosis of hypertension. Costa *et al.* verified a higher relative risk in patients with a diagnosis of 3 or more diseases (21). Patients diagnosed with cardiovascular diseases were predictors for potential DDIs in a study conducted in family medicine clinics in Mexico (2).

Drug therapy predictors

Prescription of drug therapy regimens by 2 or more prescribers was associated with the occurrence of potential DDIs in the present study. This result was similar to that reported by Cruciol-Souza *et al.*, who found an association between multiple prescribers and potential DDI occurrence in a Brazilian hospital (8). This finding may be due to gaps in communication and coordination across multiple prescribers for the same patient (27).

The present results also support the findings of previous drug utilization studies demonstrating that a larger number of drugs consumed and ATC codes were associated with the occurrence of potential DDIs. Costa *et al.* verified the elevated relative risk for patients using more than 3 drugs in a family practice centre in the USA (21). Prescriptions containing more than 6 drugs and more than 2 ATC codes

were associated with the occurrence of potential DDIs in a Brazilian hospital (8). Doubova-Dubova *et al.* reported a significant association between drug therapy regimens of 5 or more drugs and having one or more potential DDIs (2). An association between the number of drugs prescribed and the occurrence of potential DDIs was also observed by Gagne *et al.* (9). The adjusted OR rose from 2.71 [95% CI 2.63–2.80] in patients using 3–5 drugs for chronic diseases to 5.59 [95% CI 5.39–5.80] in those using 6 or more drugs, in another study of outpatients in Italy (20). The mean number of drugs prescribed to Thai outpatients with potential DDIs was 5.8 ± 2.4, with a positive association between potential DDIs and increasing number of drugs consumed (24). A strong association between number of dispensed drugs and the probability of potential DDIs was also reported among outpatients in Sweden after adjustment for age and sex (26).

With respect to the influence of ATC codes in the occurrence of potential DDIs, no consensus is apparent among published results. In the present study, ATC codes B and C were associated with the occurrence of potential DDIs. Cruciol-Souza *et al.* also reported ATC codes B and C as predictors of potential DDIs (8). However, in contrast to the present results, they also found ATC codes S and J to be predictors of potential DDIs (8). This difference could be due to differences in health status between outpatients and hospitalised patients leading to different prescription characteristics.

In the present study, larger numbers of drugs that act on CYP450 were associated with the occurrence of potential DDIs. In another study conducted in Brazil, Cabrera *et al.* found that elderly outpatients used high levels of drugs that act on CYP450 (61.6%), thereby increasing the risk of potential DDIs in a group that is already vulnerable to adverse drug effects (28). This finding is of wide concern, because diseases frequently observed in elderly patients lead to hepatic metabolism changes, increasing the risk of negative outcomes associated with the use of these drugs (29,30).

The most frequently prescribed drugs affecting CYP450 were benzodiazepines, tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), anti-histamines, and selective serotonin reuptake inhibitors. These drugs are considered potentially inappropriate for the elderly due to their toxicity or low efficiency (31). Previous drug utilization studies have also verified the high prevalence for prescriptions of potentially inappropriate drugs for the elderly (32,33).

Cardiovascular drugs were predominant among potential DDIs in the present study. Cruciol-Souza *et al.* also identified cardiovascular drugs as the most frequently involved in potential DDIs (8). However, in a study conducted in Thailand, anti-infective drugs were involved in the majority of potential DDIs (34). Doubova-Dubova *et al.* reported NSAIDs as the most frequently involved drug in potential DDIs (2). This variation in published results may be due to several factors including differences in study setting, patient health status, assessment criteria for DDIs, sources for identifying potential DDIs, culture, and prescribing habits.

Limitations

The utilization of DDI-checker software provides only a 'potential' estimate of DDI occurrence. This approach cannot take into account whether the potential DDI produced an adverse event or negatively influenced the therapeutic effect of a drug. Furthermore, the definition of 'clinical relevance' according to the rating system of DDI-checker software does not take into account what intervention a clinician may use (dosage adjustment, laboratory or clinical monitoring) to avoid a potential adverse effect or to reduce DDI risk. However, despite these limitations, this approach is currently widely used to assess the clinical relevance and risk of exposure to potential DDIs (35).

The lack of consensus between various sources available to analyze potential DDIs, with different classifications of severity and clinical importance (36), also poses a challenge to potential DDI assessment studies. The present study utilised several sources to minimise this potential bias. The risk of interactions may be underestimated due to the limitations in the majority of instruments available for assessing the probability of DDIs, which consider only single pairs of drugs and do not account for interactions involving combinations of 3 or more drugs (37,38). Most of also do not account for the dosages or

duration of therapies or individual patient risk factors.

In addition, drugs prescribed to the sample group in other health settings were not included in the evaluation, which may underestimate the occurrence of potential DDIs. Furthermore, non-prescribed drugs including over-the-counter products, herbal remedies, and nutritional supplements were not considered, preventing us from assessing potential DDIs between these products and prescription drugs (39).

CONCLUSION

The results of this large population-based study indicated a significant prevalence of clinically important potential DDIs in elderly outpatients. Patient characteristics including female sex, increased age, diagnosis of multiple diseases, and diagnosis of hypertension were predictors of potential DDIs in the population studied. With respect to drug therapy regimens, larger numbers of prescribers, drugs prescribed, ATC codes, and drugs that act on CYP450 increased the risk for potential DDI occurrence. ATC codes B and C were also predictors for potential DDIs. By providing information on patient and drug therapy characteristics that increase the risk of potential DDIs in elderly patients in a primary care setting, these results could help in the development of prescribing and therapeutic follow-up guides.

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