Exploratory Research in Clinical and Social Pharmacy 3 (2021) 100056

Contents lists available at ScienceDirect

Exploratory Research in Clinical and Social Pharmacy

journal homepage: www.elsevier.com/locate/rcsop

Potential drug interactions in adults living in the Brazilian Amazon: A population-based case-control study, 2019

Tayanny Margarida Menezes Almeida Biase [a], Marcus Tolentino Silva [b], Tais Freire Galvao [c,*]

[a] Graduate Program of Pharmaceutical Sciences, Federal University of Amazonas, Manaus,Amazonas, Brazil
[b] Graduate Program of Pharmaceutical Sciences, University of Sorocaba, Sorocaba, Sao Paulo, Brazil
[c] School of Pharmaceutical Sciences, State University of Campinas, Campinas, Sao Paulo, Brazil

ARTICLE INFO

Article history:
Received 8 April 2021
Received in revised form 21 July 2021
Accepted 3 August 2021

Keywords:
Drug utilization
Drug interactions
Contraindications
Drug
Drug therapy
Combination

ABSTRACT

Background: Drug interactions are important causes of adverse events. Assessments of pharmacological interactions outside healthcare services settings are scarce.
Objective: To assess the frequency and factors associated with these potential interactions in adults living in Manaus, Amazonas, Brazil.
Methods: We conducted a case-control study in 2019 with residents who had taken two or more medicines two weeks before the interview. The cases involved people with potential drug interaction, according to Micromedex™, and adults without drug interactions formed the control group. The factors associated with interaction were identified by multivariate logistic regression.
Results: 752 adults out of 2321 interviewed were using two or more medicines and were included. The prevalence of potential drug interactions was 30.2% (95% CI: 26.9; 33.5%). We identified 457 drug interactions, more frequently one interaction per person (49.7%), of major severity (61.9%), and with fair documentation (61.7%); three individuals were using contraindicated associations. Individuals aged 45–59 years (OR 1.88, 95% CI 1.03–3.42), using 3 or more drugs simultaneously (p-value < 0.001), had higher chance of drug interactions.
Conclusion: Drug interaction was common in among adults living in Manaus, mostly of major severity. The odds of interaction increased with age and number of concomitantly medicines.

1. Introduction

Drug therapy is the main tool in clinical practice to treat diseases.[1] The prescription of multiple drugs can favor the occurrence of pharmacological interactions, especially in tertiary healthcare.[2] In such context, the frequency of interactions increases with age, number of drugs and comorbidities.[2,3] These combinations put people at risk and can lead to hospitalizations, the worsening of clinical conditions, longer hospital stay, and higher health costs.[4]

Investigations of drug interactions usually refer to it as the theoretical possibility of one drug interacting with another when administered simultaneously.[5] These interactions are generally assessed through a series of prescriptions recorded in medical records, using database sources as a reference for identification.[6,7] In this context, pharmacological interactions appear to have limited clinical importance,[8,9] but they are a proxy indicator of potentially dangerous therapeutic combinations that should be avoided to prevent harms to patients.[4]

Drug-drug interaction investigations – regardless of the country or region – are mainly focused on hospitalized patients, with serious illnesses, older age, and under chronic therapeutic regimens.[10,11] Representativeness is also limited by restriction to a single health setting or reduced number of participants, being concentrated on drugs prescribed by physicians – thus excluding self-medication, for example – or for institutionalized individuals.[11–13]

Evidence of the frequency and relevance of drug interactions in the general population is scarce. Individuals living in the community analyzed here are generally healthier and younger, but they cannot rely on timely help from health professionals. In fact, each environment requires a specific analysis of possible strategies to support patients and to avoid the adverse consequences of drug interactions.[14] This scenario represents a partially neglected area of research, and population-based studies can enlighten the debate.

In Brazil, the studies in this area are restricted to the elderly, and are held in more developed regions of the country.[15,16] From 1990 to 2016,

* Corresponding author at: School of Pharmaceutical Sciences, State University of Campinas, R. Candido Portinari, 200 - Cidade Universitária Zeferino Vaz, CEP: 13083-871 Campinas, Sao Paulo, Brazil.
E-mail address: taisgalvao@gmail.com (T.F. Galvao).

http://dx.doi.org/10.1016/j.rcsop.2021.100056

life expectancy of Brazilians has increased from 68 to 75 years, with a decrease in mortality and disability in the period.[17] Ischemic heart disease and violence are the main burden of diseases in Brazil.[17] The Brazilian Amazon, one of the most impoverished areas of the country, is poorly investigated in this aspect. In 2019, a population-based survey was conducted in Manaus, the capital of Amazonas, the biggest state of the region, representing an opportunity to estimate the occurrence and risk factors to potential drug interactions in the adult population.[18] The aim of this study was to assess the prevalence and factors associated with potential drug interactions in adults living in Manaus, as well as to describe the severity, therapeutic classes, and other characteristics of the drug interactions that occurred in this general population.

2. Methods

2.1. Participants and variables

This research is a case-control study nested in a population-based survey carried out in the city of Manaus from April to June 2019.[18] The main research employed a probabilistic sampling in three stages (census track, household, and individual) used to interview adults aged ≥18 years in their household and those who had taken at least two medicines in the last 15 days. Self-reported use of medicines is the main assessment of the topic in Brazil, as shown in a previous systematic review.[19]

The sample size of the original study was 2300 participants, based on the adult population living in Manaus (2,106,355), absolute precision of 2%, design effect of 1.5, and 20% of use of health services as primary outcome – not restricted to individuals who had taken at least two medicines.[18] The statistical power for our analysis was estimated *post-hoc* using OpenEpi power for unmatched case-control studies (http://www.openepi.com/Power/PowerCC.htm).

We defined the cases as participants taking two or more medicines and who had potential drug interactions. Participants taking two or more medicines that did not have potential drug interactions composed the control group, since they were originally from the same population. For simplicity, herein we used drug interactions as a synonym of potential drug-drug interactions.

The independent variables analyzed as exposure to drug interaction were sex (men, women), age (in years, categorized as 18–24, 25–34, 35–44, 45–59, ≥60), economic classification (A/B, C, D/E, where A refers to the richest and E to the poorest strata, according to the 2018 Brazilian economic classification criteria),[20] education (higher education or more, high school, elementary school, less than elementary school), self-reported health status (good, fair, poor), number of chronic diseases (0, 1, ≥2), use of healthcare services in the previous 15 days (yes, no), and number of medicines used in the previous 15 days (2, 3–4, ≥5).

2.2. Data sources and measurement

All variables were based on the self-report of participants, collected from face-to-face interviews carried out at the participants' house by experienced interviewers. Use of medicines was assessed by the question "*In the previous 15 days (two weeks) did you take any medicine?*", with possible answers being "yes" or "no." The name of the medicine was recorded as informed by the participant (if available, the prescription or the medicine was photographed) and was further coded according to the Brazilian Common Denomination and then by the Anatomical Therapeutic Classification (ATC) system of the World Health Organization.[21]

One researcher searched all medicines taken by the participants who used two or more medicines at Micromedex™ database, a frequently used source to guide pharmacists' decision-making, as well as studies on drug interactions. If an interaction was detected, the combination of medicines was recorded and categorized based on the severity level (contraindicated, major, moderate, minor) and on the documented evidence level (excellent, good, fair), according to the database classification.[22] The interaction mechanism, potential outcome, and suggested management were also recorded as available at the database.[22] When more than one interaction was observed per participant, the drugs involved and classifications in each interaction were recorded separately.

2.3. Statistical methods

The participants were described statistically according to independent variables and differences in the distribution; cases and controls were assessed by Pearson's Chi-squared test at the significance level of $p < 0.05$. The characteristics of potential drug interactions were also described according to number of interactions, severity, documentation, potential outcome, and suggested management (the 10 most frequent categories were described, and the remaining were grouped under "others").

To investigate the factors associated with potential drug interaction, the odds ratio (OR) and 95% confidence interval (CI) were calculated by logistic regression. In the bivariate analysis, the unadjusted OR of each independent variable was calculated, and those significant at $p < 0.20$ were included in the multivariable analysis to obtain the adjusted OR. Significance calculated by the Wald test and associations with $p < 0.05$ were considered statistically significant. We performed all analyses using Stata 14.2 (Stata Corporation, College Station, TX, United States).

2.4. Ethics

This study was approved by the Ethics Committee of the Federal University of Amazonas (Opinion No. 3,102,942), on December 28, 2018 (Certificate of Presentation for Ethical Appreciation 04728918.0.0000.502020). All participants signed an informed consent form.

3. Results

Out of the 2321 adults interviewed, 1569 were not taking two or more medicines in the 15 days before the interview – then 752 participants were included, 227 cases and 525 controls (Fig. 1). Prevalence of potential drug interaction was 30.2% (95% CI: 26.9; 33.5%).

Most participants were women (58.6%), aged between 45 and 59 years (27.3%), belonging to economic classification C (average middle class, 54.5%), with high school (49.2%), good health status (49.7%), had two or more chronic diseases (52.0%), had not used health services in the 15 days before the interview (52.1%), and had taken two medicines only (49.3%, Table 1). Cases and controls statistically differ in sex ($p = 0.013$), age ($p = 0.008$), economic classification ($p = 0.008$), self-reported health status ($p = 0.009$), number of chronic diseases ($p < 0.001$), and number of medicines ($p < 0.001$).

In total, we identified 457 drug interactions in 227 people, which ranged from 1 to 9 (Table 2). One interaction per person (49.7%; $n = 227$), major severity (61.9%; $n = 283$), and fair documentation (61.7%; $n = 282$) were more frequently observed. Three people were taking the following contraindicated drug associations: tranexamic acid-norethisterone acetate-ethinylestradiol ($n = 1$), simvastatin-gemfibrozil ($n = 1$) and dihydroergotamine-phenylephrine ($n = 1$). The main potential clinical consequence was increased risk of bleeding (32.3%), and the main suggested monitoring was periodic laboratory evaluation (14.8%).

The most frequent interactions observed was diclofenac / dipyrone ($n = 51$), followed by dipyrone / ibuprofen ($n = 42$), and diclofenac / ibuprofen ($n = 18$). The main mechanism of interaction was an additive effect on homeostasis, the more common clinical consequence was increased risk of bleeding, and main management recommendation was periodic laboratory evaluation (Supplementary Table 1).

In the multivariable analysis, a higher chance of interaction was observed in individuals aged 45–59 years (OR 1.88, 95% CI 1.03–3.42), who had taken 3 to 4 drugs (OR 2.66, 95% CI 1.86–3.81), and 5 or more drugs (OR 4.50, 95% CI 2.61–7.74) (Table 3). The statistical power for these analyses ranged from 99 to 100%.

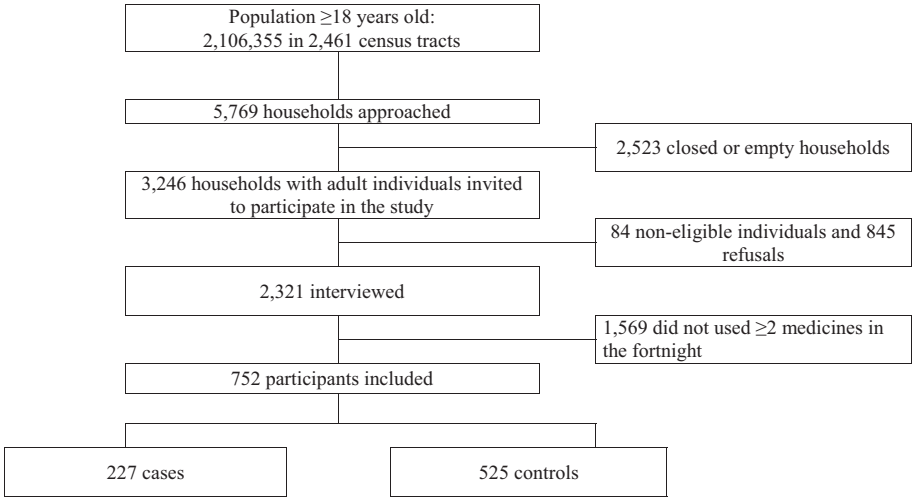

Fig. 1. Recruitment process and inclusion of participants in the research.

4. Discussion

Over three in each 10 adults taking two or more medicines, sampled from the general population of Manaus, had potential drug interaction, and one third of them had more than one drug-drug interaction. More than half of the interactions had major severity and were mainly based on fair documentation. Middle-aged adults and higher number of medicines increased the odds of potential drug interactions in this population-based study.

Our results rely on the self-report of use of medicines and further designation as "drug interaction" based on theoretical information from one database. The interactions were not clinically confirmed in the participants and some may have caused negligible or irrelevant effects to them. Consequences such as adverse effects or hospitalizations were not assessed. These factors were highly considered in the interpretation of our findings, which may have been affected by information bias. On the other hand, the original

Table 1
Characteristics of participants and frequency of potential drug interaction, Manaus, 2019 (n = 752).

Variables	Total		Cases (n = 227)		Controls (n = 525)		p-value
	N	%	N	%	N	%	
Sex							**0.013**
Male	311	41.4	80	25.7	231	74.3	
Female	441	58.6	147	33.3	294	66.7	
Age (years)							**0.008**
18–24	108	14.3	23	21.3	85	78.7	
25–34	168	22.3	46	27.4	122	72.6	
35–44	147	19.6	46	31.3	101	68.7	
45–59	205	27.3	75	36.6	130	63.4	
≥60	124	16.5	37	29.8	87	70.2	
Economic classification							**0.008**
A/B	108	14.4	31	28.7	77	71.3	
C	410	54.5	110	26.8	300	73.2	
D/E	234	31.1	86	36.7	148	63.3	
Education							0.231
Higher education or above	60	8.0	21	35.0	39	65.0	
High school	370	49.2	104	28.1	266	71.9	
Elementary school	125	16.6	35	28.0	90	72.0	
Less than elementary school	197	26.2	67	34.0	130	66.0	
Health status							**0.009**
Good	374	49.7	99	26.5	275	73.5	
Fair	292	38.8	97	33.2	195	66.8	
Poor	86	11.5	31	36.0	55	64.0	
Number of chronic diseases							**<0.001**
0	179	23.8	39	21.8	140	78.2	
1	182	24.2	57	31.3	125	68.7	
≥2	391	52.0	131	33.5	260	66.5	
Seek for a healthcare service							0.823
No	392	52.1	121	30.9	271	69.1	
Yes	360	47.9	106	29.4	254	70.6	
Number of medicines							**<0.001**
2	371	49.3	70	18.9	301	81.1	
3–4	304	40.5	117	38.5	187	61.5	
≥5	77	10.2	40	52.0	37	48.0	

Bold values signifies differences between cases and controls in the variable.

Table 2
Main characteristics of potential drug interaction (n = 457).

Variables	N	%
Number of interactions per person		
1	227	49.7
2	83	18.2
3	63	13.8
≥4	84	18.4
Classification		
Major	283	61.9
Moderate	161	35.2
Minor	10	2.2
Contraindicated	3	0.7
Documentation		
Fair	282	61.7
Good	88	19.3
Excellent	87	19.0
Potential outcome		
Increased risk of bleeding	147	32.2
Increased risk of hypoglycemia	41	9.0
Renal dysfunction and increased blood pressure	41	9.0
Increased risk of gastrointestinal ulcer or bleeding	30	6.6
Decreased effectiveness of enalapril	14	3.1
Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia	13	2.8
Reduced diuretic effectiveness and possible nephrotoxicity	11	2.4
Reduction of blood pressure	11	2.4
Increased blood pressure	10	2.2
Reduced efficacy of low-dose salicylate	10	2.2
Others	129	28.2
Suggested management		
Perform laboratory evaluation periodically	68	14.9
Such concomitant use should be avoided	60	13.1
Monitor kidney function and antihypertensive efficacy	41	9.0
Monitor signs of bleeding	30	6.6
Conduct more frequent glucose monitoring	19	4.2
Monitor blood sugar carefully	16	3.5
Clinician should weigh the benefits against the risks	15	3.3
Consider the use of an NSAID that does not interfere with salicylate effects	13	2.8
Spaced administration	12	2.6
Decrease or discontinue the diuretic or increase salt intake	11	2.4
Others	172	37.6

NSAID: Nonsteroidal anti-inflammatory drugs.

Table 3
Factors associated with potential drug interactions in unadjusted and adjusted logistic regression, Manaus, 2019 (n = 752).

Variables	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	*p*-value
Sex		0.024		0.119
Male	1.00		1.00	
Female	1.44 (1.05–1.99)		1.31 (0.93–1.85)	
Age (years)		0.064		0.308
18–24	1.00		1.00	
25–34	1.39 (0.79–2.47)		1.46 (0.80–2.67)	
35–44	1.68 (0.94–3.00)		1.62 (0.87–3.01)	
45–59	2.13 (1.24–3.66)		1.88 (1.03–3.42)	
≥60	1.57 (0.86–2.86)		1.39 (0.71–2.71)	
Economic classification		0.031		0.109
A/B	1.00		1.00	
C	0.91 (0.57–1.46)		0.94 (0.58–1.54)	
D/E	1.44 (0.88–2.37)		1.38 (0.82–2.33)	
Education		0.386		
Higher education or above	1.00			
High school	0.73 (0.41–1.29)			
Elementary school	0.72 (0.37–1.40)			
Less than elementary school	0.96 (0.52–1.76)			
Health status		0.077		
Good	1.00		1.00	0.933
Fair	1.38 (0.99–1.93)		1.07 (0.74–1.55)	
Poor	1.57 (0.95–2,57)		1.01 (0.58–1.76)	
Number of chronic diseases		0.014		0.240
0	1.00		1.00	
1	1.64 (1.02–2.63)		1.47 (0.89–2.42)	
≥2	1.81 (1.20–2.73)		1.09 (0.66–1.80)	
Seek for a healthcare service		0.671		
No	1.00			
Yes	0.93 (0.68–1.28)			
Number of medicines		<0.001		<0.001
2	1.00		1.00	
3–4	2.69 (1.90–3.81)		2.66 (1.86–3.81)	
≥5	4.65 (2.77–7.80)		4.50 (2.61–7.74)	

OR: odds ratio; CI: confidence interval.

population-based survey[18] provided a fair opportunity to investigate potential drug interactions outside healthcare settings to enlighten the magnitude of the problem in this scenario.

The potential drug interactions were found in the Micromedex database, a frequently used source to guide pharmacists' decisions, as well as studies on interactions.[23] Other tools used to manage drug interactions include free access (Medscape, Drugs.com, WebMD) or subscription-based databases (Micromedex, Lexicomp, Stockley's Interactions Checker, and Facts & Comparisons). In previous studies, we observed no significant difference regarding the performance of these tools.[24,25]

The prevalence of potential drug interactions observed in this study was similar to that found in a study carried out with health services users who may have higher access to treatments. In China, researchers observed 30% of potential drug interactions in 2019, in 16,120 outpatient prescriptions, using Lexicomp UpToDate database and Stockley's drug interaction checker.[11] A national database analysis of prescribed drugs in Slovenia in 2015 identified 42% of potential drug interactions in almost 1,2 million outpatients, and estimated that 9% of the country's population was exposed to clinically relevant potential drug interactions using Lexicomp UpToDate database.[26]

More than half of the potential interactions had major severity, and three contraindicated drug associations were observed. Previous studies conducted in hospitals or emergency settings of low and middle income countries also detected higher frequency of severe drug interactions.[27–29] Brazilian studies that assessed outpatient population reported higher frequency of moderate potential interactions than severe ones.[30,31] Most of the potential interactions in our study were based on poor documentation, similarly to previous research in which half of potential drug interaction relied on fair documentation.[32,33] The higher frequency of major severity potential interactions in our population-based sample indicates the potential harms that they can cause to the community. Other frequent interactions in our study were symptomatic drugs and drugs used to treat chronic diseases, similarly to a previous assessment that found cardiovascular, gastrointestinal, nervous, and musculoskeletal system drugs.[11,26,28,30]

Adults aged between 45 and 59 years experienced higher occurrence of potential drug interaction, similarly to previous reports.[30,34,35] The elderly usually have higher risk of suffering drug interactions,[36–38] but this association was not significant in this study, possibly due to the low number of older participants. We did not observe associations between drug interactions and gender. A survey carried out in the Caribbean in 2017 also did not find associations between these factors.[29] Similar results were also observed in a study conducted in Brazil between 2014 and 2016, which included 283 hospitalized patients: 16% of individuals were exposed to potential drug interactions and in adjusted drug interactions they were not associated with sex.[39]

Use of three to four medicines doubled the chance of drug interactions and polypharmacy (five or more medicines) increased the chance of interaction by 6 times, in comparison to using two drugs after adjustment. Polypharmacy is a recognized risk factor for the occurrence of potential drug interactions.[40,41] A descriptive cross-sectional study conducted in six public hospitals in Jordan in 2019 included 801 patients on polypharmacy and identified that 96% of individuals on polypharmacy had at least one potential drug interaction.[42]

5. Conclusion

Potential drug interactions were common in adults living in Manaus, many of them being of major severity, based in low-quality evidence and more frequently for symptomatic drugs. People of older age who take three or more drugs were in higher risk and should be monitored to prevent adverse events from multiple medicines consumption. Further research could focus on clinically relevant drug interactions to investigate the real magnitude of this problem in this population.

Funding

This work was supported by the Brazilian National Council for Scientific and Technological Development (CNPq) [grant numbers 404990/2013-4, 448093/2014-6]; TFG receives a productivity scholarship from CNPq [grant number 310238/2020-0].

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics in publishing

The content of the publication is the sole responsibility of the authors. The work is in accordance with editorial standards and has no plagiarism.

Submission declaration and verification

The authors declare that article is original and has been submitted for publication in any other periodical, whether in part or in its entirety. We further declare that, once published, it will never be submitted by any of the authors to any periodical.

Use of inclusive language

The authors declare the use of inclusive language in the publication's content.

Role of the funding source

This work was supported by the National Council for Scientific and Technological Development (CNPq), Brazil (Grants No. 404990/2013–4 and 448093/2014–6). TFG receives a productivity scholarship from CNPq (Grant No. 3064482017–7).

Author contributions

Tayanny Biase: Conceptualization, Methodology, Research, Data curation, Writing - Original draft, Visualization. Tais Galvão: Conceptualization, Methodology, Validation, Formal Analysis, Writing - Review and Editing, Supervision, Project Management, Funding acquisition. Marcus Silva: Conceptualization, Methodology, Validation, Formal Analysis, Writing - Review and Editing, Supervision, Project Management.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rcsop.2021.100056.

References

1. Dalton K, Byrne S. Role of the pharmacist in reducing healthcare costs: current insights. Integr Pharm Res Pract 2017;6:37–46.
2. de Oliveira LM, Diel J, Nunes A, da Silva Dal Pizzol T. Prevalence of drug interactions in hospitalised elderly patients: a systematic review. Eur J Hosp Pharm 2021;28:4–9.
3. Ayenew W, Asmamaw G, Issa A. Prevalence of potential drug-drug interactions and associated factors among outpatients and inpatients in Ethiopian hospitals: a systematic review and meta-analysis of observational studies. BMC Pharmacol Toxicol 2020;21:63.
4. Greenblatt DJ. Mechanisms and consequences of drug-drug interactions. Clin Pharmacol Drug Dev 2017;6:118–124.
5. Morales-Ríos O, Jasso-Gutiérrez L, Reyes-López A, Garduño-Espinosa J, Muñoz-Hernández O. Potential drug-drug interactions and their risk factors in pediatric patients admitted to the emergency department of a tertiary care hospital in Mexico. PLoS One 2018;13, e0190882.
6. Wagh BR, Godbole DD, Deshmukh SS, Iyer S, Deshpande PR. Identification and assessment of potential drug-drug interactions in intensive care unit patients. Indian J Crit Care Med 2019;23:170–174.
7. Ali I, Bazzar A, Hussein N, Sahhar E. Potential drug-drug interactions in ICU patients: a retrospective study. Drug Metab Pers Ther 2020;35.
8. Das S, Behera SK, Xavier AS, Dharanipragada S, Selvarajan S. Are drug-drug interactions a real clinical concern? Perspect Clin Res 2019;10:62–66.
9. Vanham D, Spinewine A, Hantson P, Wittebole X, Wouters D, Sneyers B. Drug-drug interactions in the intensive care unit: do they really matter? J Crit Care 2017;38:97-103.
10. Castilho ECD, Reis AMM, Borges TL, Siqueira LDC, Miasso AI. Potential drug-drug interactions and polypharmacy in institutionalized elderly patients in a public hospital in Brazil. J Psychiatr Ment Health Nurs 2018;25:3-13.
11. Ren W, Liu Y, Zhang J, et al. Prevalence of potential drug-drug interactions in outpatients of a general hospital in China: a retrospective investigation. Int J Clin Pharmacol 2020;42:1190–1196.
12. Hermann M, Carstens N, Kvinge L, et al. Polypharmacy and potential drug-drug interactions in home-dwelling older people - a cross-sectional study. J Multidiscip Healthc 2021;14:589–597.
13. Pasina L, Novella A, Cortesi L, Nobili A, Tettamanti M, Ianes A. Drug prescriptions in nursing home residents: an Italian multicenter observational study. Eur J Clin Pharmacol 2020;76:1011–1019.
14. Burato S, Leonardi L, Antonazzo IC, et al. Comparing the prevalence of polypharmacy and potential drug-drug interactions in nursing homes and in the community dwelling elderly of Emilia Romagna region. Front Pharmacol 2020;11:624888.
15. Novaes PH, da Cruz DT, Lucchetti ALG, Leite ICG, Lucchetti G. The “iatrogenic triad”: polypharmacy, drug-drug interactions, and potentially inappropriate medications in older adults. Int J Clin Pharmacol 2017;39:818–825.
16. Santos TRA, Silveira EA, Pereira LV, Provin MP, Lima DM, Amaral RG. Potential drug-drug interactions in older adults: a population-based study. Geriatr Gerontol Int 2017;17:2336–2346.
17. Marinho F, de Azeredo Passos VM, Malta DC, et al. Burden of disease in Brazil, 1990–2016: a systematic subnational analysis for the global burden of disease study 2016. Lancet 2018;392:760–775.
18. Silva MT, Nunes BP, Galvao TF. Use of health services by adults in Manaus, 2019: protocol of a population-based survey. Medicine (Baltimore) 2019;98. e15769.
19. Gomes VP, Silva MT, Galvão TF. Prevalence of medicine use among Brazilian adults: a systematic review. Cien Saude Colet 2017;22:2615–2626.
20. Brazilian Association of Research Companies. *Brazil's Economic Classification Criteria 2018.* , vol. 2019São Paulo: ABEP. 2018.
21. WHO Collaborating Centre for Drug Statistics Methodology (WHOCC). *ATC/DDD Index. Vol 2019.* Oslo: Norwegian Institute of Public Health. 2019.
22. Micromedex. *Drug Interactions. Greenwood Village (CO).* Truven Health Analytics. 2020.
23. Zheng WY, Richardson LC, Li L, Day RO, Westbrook JI, Baysari MT. Drug-drug interactions and their harmful effects in hospitalised patients: a systematic review and meta-analysis. Eur J Clin Pharmacol 2018;74:15–27.
24. Schjøtt J, Schjøtt P, Assmus J. Analysis of consensus among drug interaction databases with regard to combinations of psychotropics. Basic Clin Pharmacol Toxicol 2020;126:126–132.
25. Marcath LA, Xi J, Hoylman EK, Kidwell KM, Kraft SL, Hertz DL. Comparison of nine tools for screening drug-drug interactions of oral oncolytics. J Oncol Pract 2018;14:e368–e374.
26. Jazbar J, Locatelli I, Horvat N, Kos M. Clinically relevant potential drug–drug interactions among outpatients: a nationwide database study. Res Social Adm Pharm 2018;14:572–580.
27. Shafiekhani M, Moosavi N, Firouzabadi D, Namazi S. Impact of clinical pharmacist's interventions on potential drug-drug interactions in the cardiac care units of two university hospitals in shiraz, south of Iran. J Res Pharm Pract 2019;8:143–148.
28. Khan T, Muhammad K, Subhan F, Khan Z, Rehman NU. Frequency and nature of potential drug–drug interaction in medical wards: a cross-sectional study in a teaching hospital. Drugs & Therapy Perspect 2020;36:158–165.
29. Dookeeram D, Bidaisee S, Paul JF, et al. Polypharmacy and potential drug-drug interactions in emergency department patients in the Caribbean. Int J Clin Pharmacol 2017;39:1119–1127.
30. Santos JdS, Giordani F, MLG Rosa. Interações medicamentosas potenciais em adultos e idosos na atenção primária. Cien Saude Colet 2019;24:4335–4344.
31. WMD Santos, Secoli SR, SMDM Padoin. Potential drug interactions in patients given antiretroviral therapy. Rev Lat Am Enfermagem 2016;24.
32. Shakeel F, Aamir M, Khan AF, Khan TN, Khan S. Epidemiology of potential drug-drug interactions in elderly population admitted to critical care units of Peshawar, Pakistan. BMC Pharmacol Toxicol 2018;19:85.
33. Shakeel F, Khan JA, Aamir M, Hannan PA, Zehra S, Ullah I. Risk of potential drug-drug interactions in the cardiac intensive care units. A comparative analysis between 2 tertiary care hospitals. Saudi Med J 2018;39:1207–1212.
34. Olumuyiwa JF, Akinwumi AA, Ademola OA, Oluwole BA, Ibiene EO. Prevalence and pattern of potential drug-drug interactions among chronic kidney disease patients in South-Western Nigeria. Niger Postgrad Med J 2017;24:88–92.
35. Noor S, Ismail M, Khan F. Potential drug-drug interactions in patients with urinary tract infections: a contributing factor in patient and medication safety. Front Pharmacol 2019;10:1032.
36. Cavalcante MLSN, RKLD Alcântara, ICLD Oliveira, Aires SF, ALA Girão, REFLD Carvalho. Segurança medicamentosa em idosos institucionalizados: potenciais interações. Escola Anna Nery 2020;24.
37. Pagno AR, Gross CB, Gewehr DM, Colet CdF, Berlezi EM. A terapêutica medicamentosa, interações potenciais e iatrogenia como fatores relacionados à fragilidade em idosos. Revista Brasileira de Geriatria e Gerontol 2018;21:588–596.
38. Murtaza G, Khan MY, Azhar S, Khan SA, Khan TM. Assessment of potential drug-drug interactions and its associated factors in the hospitalized cardiac patients. Saudi Pharm J 2016;24:220–225.
39. Fernandes FM, da Silva Paulino AM, Sedda BC, da Silva EP, Martins RR, Oliveira AG. Assessment of the risk of QT-interval prolongation associated with potential drug-drug interactions in patients admitted to intensive care units. Saudi Pharm J 2019;27:229–234.
40. Sánchez-Fidalgo S, Guzmán-Ramos MI, Galván-Banqueri M, Bernabeu-Wittel M, Santos-Ramos B. Prevalence of drug interactions in elderly patients with multimorbidity in primary care. Int J Clin Pharmacol 2017;39:343–353.
41. Khandeparkar A, Rataboli PV. A study of harmful drug–drug interactions due to polypharmacy in hospitalized patients in Goa medical college. Perspect Clin Res 2017;8:180.
42. Nusair MB, Al-Azzam SI, Arabyat RM, Amawi HA, Alzoubi KH, Rabah AA. The prevalence and severity of potential drug-drug interactions among adult polypharmacy patients at outpatient clinics in Jordan. Saudi Pharm J 2020;28:155–160.