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

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1. Introduction

Drug therapy is the main tool in clinical practice to treat diseases. The prescription of multiple drugs can favor the occurrence of pharmacological interactions, especially in tertiary healthcare. In such context, the frequency of interactions increases with age, number of concomitant medicines, and higher health costs. Investigations of drug interactions usually refer to it as the theoretical possibility of one drug interacting with another when administered simultaneously. These interactions are generally assessed through a series of prescriptions recorded in medical records, using database sources as a reference for identification. In this context, pharmacological interactions appear to have limited clinical importance, but they are a proxy indicator of potentially dangerous therapeutic combinations that should be avoided to prevent harms to patients.

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. 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.

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. 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. From 1990 to 2016,
life expectancy of Brazilians has increased from 68 to 75 years, with a decrease in mortality and disability in the period.\textsuperscript{17} Ischemic heart disease and violence are the main burden of diseases in Brazil.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{18} 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.\textsuperscript{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),\textsuperscript{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.\textsuperscript{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.\textsuperscript{22} The interaction mechanism, potential outcome, and suggested management were also recorded as available at the database.\textsuperscript{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-ethinylo estradiol (\( n = 1\)), simvastatin- gemfibrozil (\( n = 1\)) and diltiazem-doxorubicin (\( n = 1\)). 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%.
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 (n=752) | Cases (n=227) | Controls (n=525) | p-value |
|-----------|--------------|---------------|------------------|---------|
| Sex       |              |               |                  |         |
| Male      | 311 (41.4)   | 80 (25.7)     | 231 (74.3)       | 0.013   |
| Female    | 441 (58.6)   | 147 (33.3)    | 294 (66.7)       |         |
| Age (years) |           |               |                  |         |
| 18-24     | 108 (14.3)   | 23 (21.3)     | 85 (78.7)        | 0.008   |
| 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)     | 205 (66.8)       |         |
| Poor      | 86 (11.5)    | 31 (36.0)     | 55 (64.0)        |         |
| Number of chronic diseases |       |               | 0                 | <0.001  |
| 0         | 179 (23.8)   | 38 (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)    | 50 (62.0)     | 27 (38.0)        |         |

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
Perfom 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.
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. 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). Previous studies, we observed no significant difference regarding the performance of these tools.

The work is in accordance with editorial standards and has no plagiarism.

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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.

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

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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.

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: Male/ Female          | 0.024/1.00             |         | 0.119/1.00           |         |
| Age (years): 18–24/ 25–34  | 0.064/1.00             |         | 0.308/1.00           |         |
| Number of chronic diseases: 0/1/2/≥ 2 | 0.014/1.00 | 0.240 | 1.00/1.00 | 0.933 |
| Number of medicines: <0/4 | <0.001/1.00            |         | <0.001/1.00          |         |
| Economic classification: A/B/C/D/E | 0.031/1.00 |        | 0.109/1.00 |         |
| Health status: Good/Fair/Poor | 0.077/1.00 |         | 1.00/1.00 | 0.88/0.32 |
| Sex: Male/ Female          | 0.024/1.00             |         | 0.119/1.00           |         |
| Age (years): 18–24/ 25–34  | 0.064/1.00             |         | 0.308/1.00           |         |
| Number of chronic diseases: 0/1/2/≥ 2 | 0.014/1.00 | 0.240 | 1.00/1.00 | 0.933 |
| Number of medicines: <0/4 | <0.001/1.00            |         | <0.001/1.00          |         |
| Economic classification: A/B/C/D/E | 0.031/1.00 |        | 0.109/1.00 |         |
| Health status: Good/Fair/Poor | 0.077/1.00 |         | 1.00/1.00 | 0.88/0.32 |

OR: odds ratio; CI: confidence interval.

population-based survey 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. 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). Previous studies, we observed no significant difference regarding the performance of these tools.

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. 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). Previous studies, we observed no significant difference regarding the performance of these tools.

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Use of inclusive language

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

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

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Appendix A. Supplementary data

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References

1. Dalton K, Byrne S. Role of the pharmacist in reducing healthcare cost: current insights. Integ 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. Ayersen W, Amawasam G, Isha 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 Ther 2017;6:118–124.
5. Morales-Rios O, Jasso-Gutiérrez L, Reyes-López A, Guaduño-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, Bazaar A, Huuzen N, Sahbar 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. Vamhan D, Spinewine A, Hantson P, Wittbole 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, Missal AO. 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 Ther 2020;42:1190–1196.
12. Hermann M, Cantrens N, Kringle 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 multitemer observational study. Eur J Clin Pharmacol 2020;76:1011–1019.
14. Burato S, Leonard 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;11:624868.