Prevalence and characteristics of adverse drug events in Brazil

Prevalência e características dos eventos adversos a medicamentos no Brasil

Prevalencia y características de los eventos adversos con medicamentos en Brasil

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Abstract

The aim of this study was to describe the prevalence of adverse drug events (ADEs) and associated factors reported by users of medicines in Brazil. This was a cross-sectional population-based study conducted from September 2013 to February 2014 with data from the Brazilian National Survey on Access, Use, and Promotion of Rational Use of Medicines *(PNAUM). The study included all individuals that reported the use of medicines and identified, among them, all those reporting at least one problem with the medicine's use. A descriptive analysis was performed to estimate ADE prevalence and 95% confidence intervals (95%CI) among the target variables. Crude and adjusted prevalence ratios were calculated using Poisson regression to investigate factors associated with ADEs. Overall ADE prevalence in Brazil was 6.6% (95%CI: 5.89-7.41), and after multivariate analysis, higher prevalence was associated with female gender, residence in the Central and Northeast regions, consumption of more medicines, "bad" self-rated health, and self-medication. The drugs most frequently reported with ADEs were fluoxetine, diclofenac, and amitriptyline. The most frequent ADEs were somnolence, epigastric pain, and nausea. Most reported ADEs were mild, avoidable, and associated with medicines used frequently by the population. The study provided knowledge on the size of the problem with use of medicines in Brazil.*

Drug Utilization; Drug-Related Side Effects and Adverse Reactions; Pharmacovigilance; Health Surveys

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Introduction

Drugs play an essential role in the care of persons, whether for treatment, prevention, or diagnostic purposes; however, they also have the potential to cause unwanted events [1]. The World Health Organization (WHO) defines adverse drug event (ADE) as *"any negative or harmful occurrence that takes place during treatment, that may or may not be associated with a medicine"* [2] (p. 26).

ADEs are considered a serious public health problem, since they not only account for increased morbidity and mortality in patients, but also lead to unnecessary expenditures by health systems. They thus have negative clinical, human, and economic impacts [3,4].

Factors contributing to ADEs in users of medicines include age [3,4,5], female gender [4,5], comorbidities [3,5], previous history of ADEs [6], polypharmacy [3,5,6], drug dose [5], nutritional status, environmental factors, and social habits [6]. In addition to patient-related factors and factors inherent to the drug, resulting from its mechanism of action, lack of or insufficient treatment orientation, prescription of inappropriate medicines, lack of treatment adherence, and lack of treatment follow-up can lead to ADEs [4,6].

Numerous studies have investigated adverse events in the hospital setting [3,4,7]. Cano & Rosenfeld [7] conducted a systematic review on ADEs in hospital inpatients in 13 countries and found ADE rates ranging from 1.6% to 41.4%.

However, the data are still incipient on ADE prevalence in the community [6,8,9,10]. A population-based study in Cuba [8] found ADE prevalence of 22.6%. In Hong Kong (China) [9], ADE prevalence among persons that practiced self-medication was 6.4%, and in Italy, in the regions of Veneto [10] and Campania [11], interviews with pharmacists in community pharmacies found ADE prevalence rates of 9.4% and 10.8%, respectively.

A population-based study by Arrais [6] in Fortaleza, Ceará State, Brazil, found ADE prevalence of 8%. Prevalence was higher in women (9.7%), in the 50-64-year age bracket (14.9%), in individuals with chronic diseases (12%), among persons with lifetime report of ADEs (10%), and among those that rated their health as "bad", and increased according to the number of medicines used.

According to the Brazilian National Notification System for Sanitary Surveillance (NOTIVISA) of the Brazilian Health Regulatory Agency (Anvisa; http://www.anvisa.gov.br/hotsite/notivisa/rela torios/index.htm, accessed on 20/Mar/2016), 103,887 adverse events were reported in Brazil from 2006 to 2013, of which 38,730 were related to medicines.

ADEs in hospitals and the community compromise patient safety and have thus drawn increasing attention in the literature [12]. However, the shortage of community-based studies on this topic hinders information on the true extent of drug-related morbidity and mortality and the extent to which ADEs affect patient safety in the broad scenario of modern consumer society [3]. This lack of information hampers planning measures to implement a culture of patient safety among health professionals and to reduce the occurrence of ADEs [13].

In this context, the household survey component of the *Brazilian National Survey on Access, Use, and Promotion of Rational Use of Medicines* (PNAUM) [14], by the Brazilian Ministry of Health, allows calculating ADE prevalence and inferring the potential effects, thereby contributing to user safety in the community.

The current study aimed to estimate the prevalence and characteristics of adverse events reported by users of medicines in Brazil, and to identify factors associated with their occurrence, comparing demographic and socioeconomic variables, self-rated health, number of medicines used, and self-medication.

Methods

This cross-sectional, population-based study of data from the PNAUM survey aimed to evaluate access to and rational use of medicines by the Brazilian population.

The PNAUM survey was conducted from September 2013 to February 2014 in a probabilistic sample of the Brazilian population, applying questionnaires. Household interviews were conducted by an outsourced company, trained by the PNAUM team, using tablets for the data collection. In the

case of persons under 15 years or with disabilities, the answers were given by their parents or guardians. Further details on the sampling plan and sample size are available in the article on methodological aspects of the PNAUM survey [14].

The questionnaire, consisting of 11 content sections and three forms with details on medicines, was developed and tested by the researchers involved in the PNAUM survey.

The target population for the current study included all persons who reported the use of at least one medicine, including drugs for continuous, occasional, or contraceptive use.

The "dependent" variable was defined as having consumed one or more medicines and having reported ADEs. Identification of users of medicines was based on the following questions:

For continuous-use medicines: "Have you used any medicine for (hypertension, diabetes, heart disease, high cholesterol, stroke, chronic lung disease, arthritis or rheumatism, depression, or another disease lasting more than six months)?" (yes, no). If yes, "Are you currently taking any of these medicines?" (yes, no);

For medicines with occasional use: in addition to the above-mentioned medicines, "Have you used any other medicine in the last 15 days, for (infection, problems sleeping or for nerves, stomach or intestinal problems, fever, pain, flu, cold, allergic rhinitis, nausea, or vomiting)?" (yes, no);

For contraceptive use: "Are you using any contraceptive pill to avoid becoming pregnant?" (yes, no). "Do you use some injection to avoid becoming pregnant?" (yes, no).

Presence of ADEs among users of medicines was investigated with the following questions:

Does this medicine bother you or cause any problem? (yes, no). If yes, why? (This same question was used for continuous and occasional-use medicines);

Does the contraceptive cause any health problem for you? If yes, what problem(s)?

All persons who reported at least one health problem with the use of these medicines were classified as having suffered an ADE.

The "independent" variables were demographic, socioeconomic, self-rated health, number of medicines, and self-medication, analyzed as follows:

(a) Demographic: sex (female, male); age (0-9 years, 10-19 years, 20-39 years, 40-59 years, ≥ 60 years ; region (North, Northeast, Central, South, and Southeast).

(b) Socioeconomic: schooling (0-8 years, 9-11 years, and ≥ 12 years; ABEP Economic Classification (A/B, C, D/E), according to the Brazilian Economic Classification Criterion of the Brazilian Association of Market Research Companies (ABEP; http://www.abep.org/).

(c) Health indicators: self-rated health status (very good, good, regular, bad, and very bad).

(d) Consumption of medicines: medicine(s) used; number of medicines (1, 2, 3-4, and 5 or more); form of consumption: self-medication (yes, no). Self-medication is defined here as the selection and use of medicines without supervision by a physician and/or dentist [15].

Medicines were listed and classified according to the Anatomical Therapeutic Chemical Classification System (ATC classification) [16]. Description of the medicines used the following ATC levels: first (organ or system where the medicine acts), second (therapeutic subgroup), and fifth (drug).

ADE was defined by the WHO criterion [2]. ADEs were classified according to the *Adverse Reaction Terminology* [17].

Statistical data analysis estimated the overall prevalence of ADEs in the study population and respective 95% confidence intervals (95%CI), according to the independent variables. The association between ADEs and target variables was investigated with the Pearson chi-square test, with significance set at 5% ($p < 0.05$). Poisson regression was used to estimate crude and adjusted prevalence ratios (PR) and 95%CI. Variables with $p < 0.20$ in the test of association were included in the multivariate model, with significance set at 5% for maintaining variables in the model, using backward selection of variables. The schooling variable entered the first stage of the multivariate adjustment (together with the other variables with $p < 20\%$ in the crude analysis). From that point on, as determined by the backward selection method, the non- significant variables were removed. The variables that were removed include schooling, which at some moment failed to show significance at 5% to remain in the final model. The analyses used a set of appropriate *svy* commands for analysis of complex samples, which guaranteed the necessary weighting of the sampling design.

For the medicines, ADE frequencies were estimated according to organ or system (first ATC level), therapeutic subgroup (second ATC level), and drug (fifth ATC level), plus the respective 95%CI.

All the analyses used Stata, version 13.0 (StataCorp LP, College Station, USA).

The PNAUM research project was approved by the Brazilian National Commission on Research Ethics (case review n. 18947013.6.0000.0008) and by the Institutional Review Board of the Federal University of Rio Grande do Sul (UFRGS), where the survey is coordinated, under case review n. 19997.

Results

Of the 41,433 participants in the PNAUM survey, 50.7% reported consuming medicines.

ADE prevalence was 6.6% overall, and was higher in females (7.8%), in the 20-39-year age bracket (8.2%), in the Central region (8.4%), with "bad" self-rated health (14.8%), with consumption of 5 or more medicines (14.7%), and with self-medication (7.8%) (Table 1).

Bivariate analysis showed a positive and statistically significant association between ADEs and the following variables: female sex; age; Northeast, Southeast, and Central regions; "fair", "bad", and "very bad" self-rated health; use of 2 or more medicines; and self-medication. There was no significant association between ADE prevalence and socioeconomic status (ABEP) or schooling (Table 2).

However, the multivariate analysis showed that only female sex (PR = 1.34; 95%CI: 1.05-1.72); the Central (PR = 1.54; 95%CI: 1.16-2.02) and Northeast regions (PR = 1.36; 95%CI: 1.04-1.79); "bad" self-rated health (PR = 1.90; 95%CI: 1.22-2.98); use of 2 (PR = 2.15; 95%CI: 1.59-2.91), 3-4 (PR = 3.57; 95%CI: 2.54-5.01), and 5 or more medicines (PR = 6.30; 95%CI: 4.64-8.55); and self-medication (PR = 1.21; 95%CI: 1.02-1.44) continued to show a positive and statistically significant association with ADEs (Table 2).

Of the 57,424 medicines consumed by the interviewees, 2,447 (4.2%) were related to the reported ADEs. Table 3 shows the therapeutic groups and subgroups most related to ADEs.

The groups or systems with the highest frequencies of ADEs were related to antineoplastic and immune-modulating agents (19.2%), followed by medicines for the genitourinary system and sex hormones (8.6%), and systemic-use anti-infectious agents (8%). The therapeutic subgroups with the highest frequencies of ADEs were sex hormones and modulators of the genital system (8.2%), followed by antiepileptics (7.9%) and anti-inflammatory and antirheumatic drugs (7.3%). The drugs with the highest frequencies of ADEs were fluoxetine (9.3%), diclofenac (9%), and amitriptyline (8.5%) (Table 4).

The organs or systems affected by ADEs involved mainly the gastrointestinal system (36.9%), followed by psychiatric disorders (18.7%), general health status (13.1%), and the central and peripheral nervous systems (9%), with somnolence (12.5%), epigastric pain (10.5%), and nausea (6.8%) as the most frequently reported ADEs (Table 5).

Discussion

ADE prevalence in the overall Brazilian population was lower than in Cuba [8], Veneto [10] and Campania [11] in Italy, and Fortaleza [6] in Brazil, and was higher than in persons that practiced self-medication in Hong Kong [9].

Nationwide studies to identify ADEs reported by the population are quite incipient in the international literature, which hinders comparison between countries. The Cuban study [8] found an ADE prevalence rate approximately four times greater than in the current study (22.6%). This result is probably influenced by the fact that subjects in Cuba reported events any time in life.

In general, and considering that every adverse drug reaction is an adverse drug event, most studies have been conducted in the hospital setting, related to admission for ADEs in the emergency department or their occurrence during hospital stay [7,18,19]. In the case of ADEs that occur during hospital stay, studies are limited to the drugs used in this setting. In the community, however, the consumption of medicines reflects the products' wide availability on the pharmaceutical market, with countless pharmaceutical specialties, some of which have less than optimal intrinsic values and are even unnecessary or hazardous, which (associated with the pharmaceutical industry's marketing) can result in induction or encouragement for inadequate use of medicines [6,20].

Table 1

Prevalence of adverse drug events (ADEs) according to demographic and socioeconomic variables, self-rated health, use of medicines, and self-medication. *Brazilian National Survey on Access, Use, and Promotion of Rational Use of Medicines* (PNAUM), Brazil, 2014.

Variables	ADEs (%) *	95%CI	p-value **
Sex			0.000
Female	7.78	6.85-8.82	
Male	4.53	3.61-5.68	
Age (years)			0.000
0-9	3.31	2.34-4.64	
10-19	7.79	5.93-10.16	
20-39	8.17	7.07-9.42	
40-59	7.13	6.18-8.23	
≥ 60	4.88	3.95-6.01	
Region			0.007
North	4.44	3.53-5.57	
Northeast	7.15	6.11-8.35	
Southeast	6.88	5.55-8.51	
South	4.63	3.90-5.49	
Central	8.40	6.88-10.22	
ABEP classification ***			0.494
A/B	7.20	5.92-8.74	
C	6.51	5.61-7.54	
D/E	6.23	5.23-7.41	
Schooling (years)			0.164
0-8	6.19	5.45-7.02	
9-11	7.31	6.13-8.70	
≥ 12	6.94	5.33-8.99	
Self-rated health status			0.000
Very good	4.25	2.86-6.28	
Good	5.73	4.83-6.79	
Regular	9.60	8.32-10.98	
Bad	14.81	12.02-18.13	
Very bad	7.70	5.27-11.11	
Medicines used			0.000
1	2.76	2.19-3.49	
2	5.60	4.58-6.82	
3-4	9.32	7.45-11.61	
≥ 5	14.66	12.80-16.73	
Self-mediciation			0.003
Yes	7.79	6.72-9.02	
No	6.09	5.33-6.96	

* Percentages adjusted by sampling weights and post-stratification by age and sex;

** Chi-square statistic significant at 0.05;

*** Variable for economic classification according to the Brazilian Economic Classification Criterion of the Brazilian Association of Market Research Companies (ABEP; http://www.abep.org/).

As for ADE prevalence in females, the same was found by Alonso Carbonell et al. [8] in Cuba and by Arrais [6] in Fortaleza. The factors that may explain this phenomenon include pharmacokinetic, pharmacodynamic, and body-weight when compared to men, besides hormonal factors [6,21]. Women present more health problems, which are less serious on average, but they use health services more,

Table 2

Distribution of crude and adjusted prevalence ratios (PR) (Poisson regression) for adverse drug events (ADEs) and respective 95% confidence intervals (95%CI) according to study variables. *Brazilian National Survey on Access, Use, and Promotion of Rational Use of Medicines* (PNAUM), Brazil, 2014.

Variables	Crude PR (95%CI)	p-value *	Adjusted PR (95%CI)	p-value *
Sex		0.001		0.018
Female	1.72 (1.34-2.20)		1.34 (1.05-1.72)	
Male	1.00		1.00	
Age (years)		0.001		0.001
0-9	1.00		1.00	
10-19	2.36 (1.59-3.50)		1.34 (0.73-2.45)	
20-39	2.47 (1.74-3.49)		1.10 (0.61-1.99)	
40-59	2.16 (1.50-3.11)		0.66 (0.36-1.22)	
≥ 60	1.48 (1.01-2.14)		0.39 (0.20-0.72)	
Region		0.001		0.000
North	1.00		1.00	
Northeast	1.61 (1.22-2.12)		1.36 (1.04-1.79)	
Southeast	1.55 (1.13-2.12)		1.21 (0.90-1.63)	
South	1.04 (0.78-1.39)		0.82 (0.62-1.09)	
Central	1.89 (1.40-2.56)		1.54 (1.16-2.02)	
ABEP classification **		0.499		
A/B	1.16 (0.90-1.48)			
C	1.04 (0.85-1.29)			
D/E	1.00			
Schooling (years)		0.139		
0-8	1.00			
9-11	1.18 (0.99-1.41)			
≥ 12	1.12 (0.87-1.45)			
Self-rated health status		0.001		0.003
Very good	1.00		1.00	
Good	1.35 (0.90-2.01)		1.15 (0.79-1.68)	
Regular	2.26 (1.52-3.35)		1.47 (0.98-2.20)	
Bad	3.48 (2.23-5.44)		1.90 (1.22-2.98)	
Very bad	1.81 (1.03-3.17)		0.90 (0.50-1.62)	
Medicines used		0.001		0.001
1	1.00		1.00	
2	2.02 (1.51-2.70)		2.15 (1.59-2.91)	
3-4	3.37 (2.52-4.51)		3.57 (2.54-5.01)	
≥ 5	5.30 (4.15-6.80)		6.30 (4.64-8.55)	
Self-mediciation		0.003		0.006
Yes	1.28 (1.09-1.50)		1.21 (1.02-1.44)	
No	1.00		1.00	

* Level of significance (p < 0.05);

** Variable for economic classification according to the Brazilian Economic Classification Criterion of the Brazilian Association of Market Research Companies (ABEP; http://www.abep.org/).

have more appointments and tests, obtain more diagnoses and medical prescriptions, and thus consume more medicines, prescribed or not [15,22,23]. Another factor that may have contributed to this gender difference was the fact that ADEs were also reported by users of contraceptives in the study.

As for age bracket, we expected to find higher ADE prevalence at the extremes of age (children and elderly), since according to the literature these are the groups most predisposed to ADEs [24]. However,

Table 3

Frequency of adverse drug events (ADEs) and respective 95% confidence intervals (95%CI) according to the organ or system and therapeutic subgroup related to the drug reported as causing the problem. *Brazilian National Survey on Access, Use, and Promotion of Rational Use of Medicines* (PNAUM), Brazil, 2014.

Variables	% *	95%CI
Principal anatomical group		
Antineoplastic and immune-modulating agents	19.25	12.34-28.76
Genitourinary system and sex hormones	8.63	7.07-10.50
Anti-infectious agents for systemic use	8.05	5.82-1.03
Musculoskeletal system	7.09	5.84-8.60
Dermatological products	6.89	3.94-11.78
Blood and hematopoietic organs	6.65	4.10-10.59
Respiratory system	5.80	4.26-7.84
Anti-parasitic products, insecticides, and repellents	5.72	2.26-13.72
Nervous system	5.55	4.63-6.63
Systemic hormonal preparations except sex hormones and insulins	5.54	3.98-7.65
Herbal remedies, supplements, homeopathy, foods	5.15	3.80-6.95
Alimentary tract and metabolism	4.37	3.66-5.20
Cardiovascular system	4.02	3.28-4.93
Sense organs	3.66	1.95-6.77
Unknown	1.70	0.20-12.85
Various	0.79	0.10-5.83
Therapeutic subgroup		
G03 Sex hormones and modulators of the genital system	8.24	6.64-10.19
N03 Anti-epileptics	7.89	5.24-11.73
M01 Anti-inflammatory and Antirheumatic products	7.33	5.78-9.26
J01 Antibacterial drugs for systemic use	7.07	5.01-9.88
R01 Nasal preparations	7.06	3.92-12.41
N06 Psychoanaleptics	7.04	5.30-9.29
M03 Muscle relaxants	6.96	5.05-9.53
R06 Antihistamines for systemic use	6.95	3.92-12.04
H02 Corticosteroids for systemic use	6.81	4.41-10.36
R03 Drugs for obstructive airway diseases	6.78	4.38-10.34
C01 Cardiac therapy	6.47	3.76-10.93
N05 Psycholeptics	5.23	3.30-8.19
A02 Drugs for acid related disorders	5.15	3.98-6.64
A10 Drugs used in diabetes	4.98	3.77-6.56
N02 Analgesics	4.79	3.84-5.96
H03 Thyroid therapy	4.76	2.92-7.68
C03 Diuretics	4.56	3.32-6.24
C07 Beta blocking agents	4.47	2.83-7.01
R05 Cough and cold preparations	3.08	1.88-4.99
C10 Lipid modifying agents	2.92	2.08-4.10
A11 Vitamins	2.57	1.58-4.14
C08 Calcium channel blockers	2.41	1.54-3.76
A03 Drugs for functional gastrointestinal disorders	2.21	1.27-3.81

* Analyzed with weight and complex plan.

we observed the highest ADE prevalence in young people and young adults. This result may be explained in part by the ADEs reported by contraceptive users, or by difficulties by patients and/or caregivers in identifying ADEs; aggravated by lack of information, this may have influenced the result and contributed to minimizing ADE prevalence in children and the elderly [21,25].

Table 4

Frequency of adverse drug events (ADEs) and respective 95% confidence intervals (95%CI), according to drug reported as cause of problem. *Brazilian National Survey on Access, Use, and Promotion of Rational Use of Medicines* (PNAUM), Brazil, 2014.

Drugs	% *	95%CI
Fluoxetine	9.32	5.53-15.29
Diclofenac	9.05	5.12-15.50
Amitriptyline	8.54	5.45-13.13
Caffeine; carisoprodol; diclofenac; paracetamol	8.28	5.40-12.48
Prednisone	8.24	4.75-13.92
Nimesulide	8.04	4.60-13.70
Ethinylestradiol; levonorgestrel	7.60	5.68-10.10
Cyproterone; ethinylestradiol	7.29	4.25-12.24
Clonazepam	7.06	4.18-11.66
Amoxicillin	6.48	3.77-10.91
Metformin	6.41	4.74-8.62
Ibuprofen	6.27	4.16-9.34
Captopril	6.19	4.10-9.23
Dipyrone	5.26	3.85-7.15
Supplements	5.14	2.99-8.68
Omeprazole	4.99	3.61-6.85
Caffeine; dipyrone; orphenadrine	4.86	2.92-8.00
Levothyroxine	4.85	2.96-7.85
Hydrochlorothiazide	4.63	3.13-6.80
Enalapril	4.51	2.81-7.16
Caffeine; dipyrone; isometheptene	4.22	2.37-7.39
Ethinylestradiol; gestoden	3.89	2.15-6.92
Paracetamol	3.43	2.42-4.84
Atenolol	3.38	2.03-5.57
Acetyl salicylic acid	3.31	2.14-5.07
Simvastatin	2.60	1.76-3.83
Losartan	2.47	1.78-3.42
Amlodipine	2.26	1.30-3.90
Unknown	6.06	4.11-8.85

* Analyzed with weight and complex plan.

As for the higher association between consumption of medicines and ADEs in residents of the Northeast and Central regions of Brazil, the lack of similar studies prevents a more detailed explanation. However, this result may be influenced by difficulties in access to health services and the need to relieve minor symptoms with self-medication [15,22,26], which involves some of the most widely used medicines in this study [6,15,23,27]. Self-medication is practiced in all regions of Brazil. Self-medication rates in the North (17.8%), Northeast (23.5%), and Central (19.2%) were higher than the national rate (16.1%) [15].

Polypharmacy was significantly associated with ADEs, corroborating findings in the literature [6,24]. ADEs increase significantly with the number of drugs used by the patient and the treatment complexity, since polypharmacy appears as a potential risk factor for drug-drug interactions, medication errors, and inadequate use of medicines, potentially resulting in hospitalization, and in severe cases, death [28,29]. This risk can be minimized by greater control of polypharmacy by health professionals, adequate prescription, patient-adjusted doses, and effective pharmacotherapeutic follow-up [30].

As for self-rated health status, patients with "bad" self-rated health reported the most ADEs, similar to the study by Arrais [6]. This generally occurs because these patients are more likely to seek

Table 5

Characteristics of adverse drug events (ADEs) according to organ/system affected and reported events among interviewees that consumed medicines. *Brazilian National Survey on Access, Use, and Promotion of Rational Use of Medicines* (PNAUM), Brazil, 2014.

Variables	%	95%CI
Organ/System affected		
Disorders of the gastrointestinal system	36.9	32.6-41.3
Psychiatric disorders	18.7	14.6-23.7
Disorders of overall health status	13.1	10.6-16.1
Disorders of the central and peripheral nervous systems	9.0	6.8-11.8
Disorders of the urinary system	4.1	2.7-6.1
Disorders of the respiratory system	3.8	2.5-5.7
Disorders of cardiac rate and rhythm	3.5	2.3-5.3
Disorders of the cardiovascular system	1.4	0.7-2.7
Disorders of the female reproductive system	1.4	0.7-2.7
Disorders of the liver and gallbladder	1.3	0.7-2.5
Conditions of the skin and related disorders	1.1	0.6-2.1
Disorders of the sense organs	0.9	0.5-1.8
Other problems, not health	4.8	3.5-6.6
ADE reported		
Somnolence	12.5	9.6-16.0
Epigastric pain	10.5	8.3-13.3
Nausea	6.8	5.2-8.9
Gastric discomfort	4.6	3.1-6.7
Dizziness	4.4	2.8-6.7
Gastric hyperacidity	3.5	2.1-5.8
Tachycardia	3.2	2.0-5.0
Weight gain	3.4	2.3-5.0
Polyuria	3.4	2.1-5.3
Headache	3.1	1.9-4.8
Cough	3.0	2.0-4.5
Diarrhea	2.4	1.6-3.6
Weakness	2.3	1.2-4.2
Malaise	2.2	1.3-3.7
Dry mouth	1.5	0.7-3.3
Edema	1.2	0.6-2.3
Pain	1.0	0.5-1.9
Tremor	0.9	0.5-1.5
Vomiting	0.8	0.4-1.6
Decreased blood pressure	0.8	0.4-1.5
Insomnia	0.8	0.5-1.5
Not classified	2.6	1.8-3.9
Other *	25.2	21.6-29.2

* Events that occurred at rates less than 0.8%.

medical care and consume more medicines, prescribed or not, in the attempt to solve their health problems [6,31].

Patients in this study that self-medicated showed higher ADE prevalence, corroborating the studies by Lam et al. [9] in Hong Kong, Arrais [6] in Fortaleza, and Yu et al. [32] in Korea Republic.

Self-medication is common not only in Brazil [15], but worldwide, and it involves economic, political, and cultural factors [26]. Self-medication may or may not benefit the individual: when used rational-

ly, it can mean a savings for the patient due to ease in acquiring the medicine and possible resolution of the health problem, and for health services, due to the reduction in demand for care and hospital expenses. But if used irrationally, self-medication can delay the correct diagnosis of a disease, mask symptoms, increase antimicrobial resistance, and harm the individual's health through the appearance of ADEs such as medication errors, adverse reactions, and intoxication [33].

Education and awareness-raising for health professionals and the general population are thus necessary, focusing on the rational use of medicines, the development of public policies fostering improved access to health services, more intense regulation of abusive advertising and irregular sales of over-the-counter drugs [34], and especially effective action by pharmacists in community pharmacies to minimize harm to the population's health due to self-medication [35].

ADEs were proportionally more frequent with less consumed drugs, but with greater potential for adverse reactions or drug-drug interactions, as with fluoxetine and amitriptyline, which should thus be used under strict supervision [36]. But ADEs also appeared with drugs that are frequently used in Brazil, with or without prescriptions, such as diclofenac, fixed-dose caffeine + carisoprodol + diclofenac + paracetamol, prednisone, and nimesulide [6,15,23,27].

In the case of non-steroidal anti-inflammatory drugs (NSAIDs), there are important restrictions on use in the elderly, with the possibility of gastrointestinal, renal, and cardiovascular risks and interaction with other drugs frequently used in primary care (paracetamol, some anti-hypertensives, antidepressants, and selective serotonin reuptake inhibitors) [37].

Adverse events associated with oral contraceptives featured levonorgestrel associated with ethinylestradiol, and ciproterone+ethinylestradiol, the most widely consumed oral contraceptives on the Brazilian pharmaceutical market [38]. Risks associated with contraceptives have been reported in the literature and range from mild and common, like nausea, headache, breast pain, anxiety, and irritability, to rare and severe, like thromboembolism and stroke, as an important cause of treatment switch and dropout [39].

ADEs reported in the community are generally mild [6,8] and considered preventable, since they usually do not require specific treatment or suspension of the drug [24,40]. However, the fact that they are mild does not minimize their importance, since they can interfere in quality of life, cause discomfort and malaise, and reduce treatment adherence and patients' trust in their physicians [3]. They may also aggravate the patient's clinical status, causing new adverse events if the patient fails to use other medicines to minimize or relieve the discomfort generated by the offending drug, triggering the so-called cascade effect [6].

Analyzing the three most frequently reported ADEs (somnolence, epigastric pain, and nausea), in some treatments these are already expected and do not greatly compromise the individual's quality of life, thus rarely resulting in hospitalization, but causing patient discomfort and potentially leading to other consequences (cited above) such as treatment dropout.

The study's limitations include the population's lack of knowledge for identifying the association between use of the medicine and the adverse event, probably due to the difficulty in differentiating between the problem caused by the drug and complications or evolution of the disease itself; the recall period used to investigate use of the medicine and appearance of the ADE; failure to detect more serious events leading to the treatment's interruption; inclusion of contraceptives in the analysis, favoring the inclusion of more females than males; and the fact that the question on adverse effects was worded in the context of treatment adherence and not as an objective formulation for evaluation.

Although the questions on ADEs considered the time of use of the medicines, one cannot state for certain that the ADE actually occurred during this period, or that the problem was related to the reported drug, but at a different moment. In addition, since no investigation was performed to determine the correlation between use of the medicine and the appearance of ADEs, one cannot state with certainty whether the events are related to the drugs reported as causing the problems or that other factors are influencing the outcome.

Conclusion

The current study allowed identifying ADEs and their determinant factors in Brazil. The adverse events were mainly mild, avoidable, and associated with medicines frequently used by the population. This information will allow developing measures for the prevention and reduction of ADEs, thereby contributing to both patient safety and reduction in healthcare costs resulting from damage caused by the use of medicines, especially in primary care.

However, the scarcity of nationwide studies on this topic and the fact that Brazil is one of the world's 10 leading pharmaceutical markets [41] highlight the need to strengthen policies to promote the rational use of medicines.

Contributors

Acknowledgments

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Resumo

O presente trabalho tem como objetivo descrever a prevalência e fatores associados a eventos adversos a medicamentos (EAM) referidos por usuários de medicamentos no Brasil. Trata-se de um estudo transversal de base populacional, realizado no período de setembro de 2013 a fevereiro de 2014, com dados coletados na Pesquisa Nacional sobre Acesso, Utilização e Promoção do Uso Racional de Medicamentos (PNAUM). Foram consideradas todas as pessoas que referiram o uso de medicamentos; entre elas, foram identificadas as que referiram pelo menos um problema com o uso do medicamento. Realizou-se uma análise descritiva para estimar a prevalência e os intervalos de 95% de confiança (IC95%) de EAM entre as variáveis estudadas, e foram calculadas as razões de prevalência bruta e ajustada, pela regressão de Poisson, na investigação dos fatores associados aos EAM. A prevalência de EAM no Brasil foi de 6,6% (IC95%: 5,89-7,41), sendo maior e estatisticamente significante após a realização da análise multivariada, entre pessoas do sexo feminino; residentes nas regiões Centro-oeste e Nordeste; que consumiam maior número de medicamentos; que percebiam seu estado de saúde como "ruim"; e que se automedicavam. Os EAM foram mais relatados para os medicamentos fluoxetina, diclofenaco e amitriptilina. Os EAM mais referidos pelos entrevistados foram sonolência, dor epigástrica e náuseas. Os EAM mais referidos pelos entrevistados foram de natureza leve, considerados evitáveis e estiveram associados a medicamentos de uso frequente pela população. Em razão desse estudo, foi possível conhecer a dimensão do problema ocasionado pelo uso de medicamentos no Brasil.

Uso de Medicamentos; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Farmacovigilância; Inquéritos Epidemiológicos

Resumen

El presente trabajo tiene como objetivo describir la prevalencia y factores asociados a eventos adversos con medicamentos (EAM), informados por usuarios de medicamentos en Brasil. Se trata de un estudio transversal de base poblacional, realizado durante el período de septiembre de 2013 a febrero de 2014, con datos recogidos en la Encuesta Nacional sobre el Acceso, Utilización y Promoción del Uso Racional de Medicamentos en Brasil (PNAUM). Se consideraron a todas las personas que informaron del uso de medicamentos; entre ellas, se identificaron a las que informaron de por lo menos un problema con el uso del medicamento. Se realizó un análisis descriptivo para estimar la prevalencia y los intervalos de confianza a 95% (IC95%) de EAM entre las variables estudiadas, y se calcularon las razones de prevalencia bruta y ajustada, por la regresión de Poisson, en la investigación de los factores asociados a los EAM. La prevalencia de EAM en Brasil fue de un 6,6% (IC95%: 5,89-7,41), siendo mayor y estadísticamente significante tras la realización del análisis multivariado, entre personas del sexo femenino; residentes en las regiones Centro-Oeste y Nordeste; que consumían un mayor número de medicamentos; que percibían su estado de salud como "malo"; y que se automedicaban. Se informaron de más EAM en medicamentos como: fluoxetina, diclofenaco y amitriptilina. Los EAM más referidos por los entrevistados fueron somnolencia, dolor epigástrico y náuseas. Los EAM más referidos por los entrevistados fueron de naturaleza leve, considerados evitables y estuvieron asociados a medicamentos de uso frecuente por la población. Con motivo de este estudio, fue posible conocer la dimensión del problema ocasionado por el uso de medicamentos en Brasil.

Utilización de Medicamentos; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Farmacovigilancia; Encuestas Epidemiológicas