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ORIGINAL ARTICLE

Adverse drug reactions in Colombian patients, 2007-2013: Analysis of population databases

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Introduction: Recognizing adverse drug reactions (ADRs) is becoming more important in clinical practice.
Objective: To determine the frequency of adverse drug reactions and ADR suspicions among the population affiliated to the Colombian health system and to describe the drugs, reactions and associated variables.
Materials and methods: We revised ADRs and ADRs suspicion databases from drugs dispensed by Audifarma, S.A., both for inpatient and outpatient care from 2007 to 2013. Variables included ADR report date, city, drug, drug's Anatomical Therapeutic Classification (ATC), ADR severity, ADR type, ADR classification and ADR probability according to the World Health Organization's definitions.
Results: We obtained 5,342 reports for 468 different drugs. The ATC groups with the most reports were anti-infectives for systemic use (25.5%), nervous system agents (17.1%) and cardiovascular system drugs (15.0%). The drugs with the highest number of reports were metamizole (4.2%), enalapril (3.8%), clarithromycin (2.8%), warfarin (2.5%) and ciprofloxacin (2.4%). The most common ADR, classified following the World Health Organization adverse reaction terminology, were: skin and appendages disorders (35.3%), general disorders (14.2%) and gastrointestinal system disorders (11.8%). Overall, 49.4% of the ADRs were classified as "moderate" and 45.1% as "mild".
Conclusion: An increasing number of ADR reports were found coinciding with a worldwide tendency. Differences between inpatient and outpatient ADR reports were found when compared to scientific publications. The information on ADR reports, mainly gathered by the *Instituto Nacional de Vigilancia de Medicamentos y Alimentos – Invima*, should be made public for academic and institutional use.

Key words: Drug-related side effects and adverse reactions, adverse drug reaction reporting systems, pharmacovigilance, Colombia.

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Reacciones adversas a medicamentos en una población colombiana, 2007-2013: análisis de bases de datos

Introducción. La detección de las reacciones adversas a medicamentos es cada vez más importante en la práctica clínica.
Objetivo. Determinar la frecuencia de reacciones adversas a medicamentos y de los casos sospechosos de tales reacciones, en la población afiliada al Sistema General de Seguridad Social en Salud de Colombia.
Materiales y métodos. Se revisaron las bases de datos sistematizadas de reportes de sospecha de reacciones adversas a los medicamentos dispensados por la empresa Audifarma, S.A., para uso ambulatorio y hospitalario, entre 2007 y 2013. Las variables contempladas fueron: la fecha de radicación del reporte, la ciudad, el medicamento, la clasificación anatómica terapéutica del medicamento, la gravedad, el tipo de reacción adversa y su clasificación, así como la de su probabilidad de ocurrir, según las definiciones de la Organización Mundial de la Salud (OMS).
Resultados. Se obtuvieron 5.342 reportes de sospecha de reacción adversa a 468 medicamentos diferentes. Los grupos con más reportes fueron los fármacos antiinfecciosos de uso sistémico (25,5 %) y los medicamentos para el sistema nervioso (17,1 %) y para el sistema cardiovascular (15,0 %). Los medicamentos con más reportes fueron: el metamizol (dipirona) (4,2 %), el enalapril (3,8 %), la claritromicina (2,8 %), la warfarina (2,5 %) y la ciprofloxacina (2,4 %). Las reacciones adversas a medicamentos más frecuentes, según la clasificación de la terminología sobre reacciones

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Manuel José Londoño-Builes: data collection
Jorge Enrique Machado-Alba and Sergio Andrés Ochoa-Orozco: final text revision
All authors participated in the analysis of data and results and in their discussion.

adversas de la OMS, fueron los trastornos de la piel y anexos (35,3 %), los trastornos generales (14,2 %) y los trastornos del sistema gastrointestinal (11,8 %). El 49,4 % de las reacciones adversas a medicamentos se catalogaron como moderadas y, el 45,1 %, como leves.

Conclusiones. Se encontró un incremento de reportes de reacciones adversas a medicamentos en los últimos años, lo que concuerda con la tendencia mundial. Se evidenciaron diferencias entre los reportes hospitalarios y de consulta ambulatoria. La información sobre los reportes de reacciones adversas a medicamentos, sobre todo la recopilada por el Instituto Nacional de Vigilancia de Medicamentos y Alimentos (Invima), debería ser pública para su uso académico e institucional.

Palabras clave: efectos colaterales y reacciones adversas relacionados con medicamentos, sistemas de registro de reacción adversa a medicamentos, farmacovigilancia, Colombia.

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Adverse drug reactions (ADR) are events that may severely affect the health of people who consume drugs for therapeutic, diagnostic or prophylactic purposes (1). ADRs have been shown to be an important worldwide cause of hospitalization and death every year and are among the top ten causes of death in the United States (2-5). Besides compromising people's health, ADRs generate unexpected costs that affect the economy of health systems, which is why the early identification, prevention and resolution of ADRs are necessary (5-7). Several authors have calculated the percentage of preventable ADRs, demonstrating that a structured pharmacovigilance system could reduce human and economic repercussions generated by them (8,9).

In 2007, the World Health Organization (WHO) stated the importance of pharmacovigilance by releasing a resolution after the 27th Pan American Sanitary Conference urging member states to give priority to patient security by establishing and strengthening the scientific systems needed to improve security and attention quality (10).

The debate of active (search) and passive (spontaneous report) monitoring is open, contemplating costs and countries capacity in accordance with their own developmental level, with multiple considerations about experiences in different nations and the analysis of several classification and reporting systems (11-13).

Locally, the *Instituto Nacional de Vigilancia de Medicamentos y Alimentos – Invima*, the drug regulator entity in Colombia, constituted its national pharmacovigilance program in 1997, obtaining membership to the World Pharmacovigilance Program in 2004 with the recognition of a national initiative by the Uppsala Monitoring Center. Since then, ADR reports have been sent to the WHO collaborating center with regular feedback by the way of experts focused on standardizing the program. Trimestral bulletins with information on ADR reports, pharmacovigilance research and related news are published on its website (9,14). In 2006, the Colombian Health Minister established the Obligatory System of Health Attention Quality Guarantee by means of Decree No. 1011, making health institutions carry out an audit for the improvement of health attention quality by preventive actions and following-up drug dispensation and administration (15). This shows the importance of this topic in accordance to what has been discussed and adopted worldwide.

In 2011, a review of the literature published on research related to ADR detection in Colombian patients found 13 papers, including inpatient and outpatient populations monitored both passively and actively in institutions with different complexity levels. Nonetheless, these were small-scale studies with non-unified information (14). A survey carried out in 2002 among pharmacology teachers in the country showed that there was no pharmacoepidemiology or pharmacovigilance teaching culture in Colombia (16).

We aimed at determining the frequency of ADRs and ADR suspicion in the Colombian health system (SGSSS) population by means of the ADR notification system owned by Audifarma, S.A. (main drug dispenser in Colombia) from January 2007 to March 2013, and at describing associated variables.

Materials and methods

A retrospective cross-sectional study was conducted, revising ADRs and ADR suspicion report databases of the drugs dispensed by Audifarma, S.A., both for

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inpatient and outpatient populations, from January 1st, 2007 to March 1st, 2013, when it began to be systematized information. Audifarma, S.A., is a drug dispensation logistic operator covering over 6.2 million users of the SGSSS, corresponding to 32.6% of the population affiliated to the pay system. The databases were completed by pharmaceutical chemists associated with the company who received the report of Negative Outcomes Associated with Medication (NOM) including ADR suspicions, and data were verified with the help of a pharmacoepidemiologist if necessary. Databases presented variations on yearly information, so pertinent variables were manually standardized to create specific compilations by periods and a general compilation from 2007 to 2013 with all cases included. As this is a database used by several professionals across the country, information was carefully checked and terms were standardized.

The general database included: ADR report date, city, drug's generic name, drug's Anatomical Therapeutic Classification System (ATC) (code letter and first two digits), ADR severity (mild, moderate, serious), ADR type according to Edwards and Aronson (A, B, C, D, E, F) and ADR causality category according to WHO-UMC (Certain, Likely, Possible, Unlikely, Conditional, Unassessable). ADRs were standardized in accordance with WHO Adverse Drug Reaction Terminology (WHO-ART). The 15 drugs with the highest number of reports were classified and a list was created with the ADRs reported for them. The first 15 ATC subgroups (code letter and first two digits) were also extracted.

The study data were stored, processed, and analyzed using IBM SPSS®, Statistics, version 21.0 (SPSS Inc., an IBM company, Chicago, Illinois, United States); frequencies, percentages and means were employed. The study protocol was reviewed and approved by the bioethics committee of the *Universidad Tecnológica de Pereira*, Colombia.

Results

The 5,342 ADRs and ADR suspicion reports were obtained from 55 cities, including 21 of the 32 departments in the country. The ten municipalities with the most reports (Bogotá, Barranquilla, Cali, Pereira, Medellín, Barrancabermeja, Bello, Manizales, Ibagué and Cartagena) accounted for 85.0% of the total. The number of reports per year was: 2007: 198 reports, 2008: 205 reports, 2009: 383 reports, 2010: 661 reports, 2011: 1,397 reports, 2012: 2,099 reports, and January-February 2013: 399 reports. The mean number of monthly reports was 71. Altogether, 468 different drugs received at least one notification; table 1 shows the ATC group distribution for these.

ATC groups with the highest report numbers were: Anti-infectives for systemic use (J) (n=1360, 25.5%), nervous system agents (N) (n=916, 17.1%), cardiovascular drugs (C) (n=802, 15.0%), alimentary tract and metabolism drugs (A) (n=592, 11.1%), and antineoplastic and immunomodulating agents (L) (n=530, 9.9%) (figure 1). Table 2 shows the top 15 ATC subgroups (code letter and first two digits).

The ATC group with the highest number of reports was "Anti-infectives for systemic use" with 17.7 reports for each of the group's drugs included in the database, while "Dermatologicals" obtained the lowest proportion, with 2.3 reports per drug.

The drugs with the highest number of reports were metamizole (4.2%), enalapril (3.8%), clarithromycin (2.8%), warfarin (2.5%) and ciprofloxacin (2.4%). In the list of the 15 drugs with the highest number of reports, there were four antibiotics (clarithromycin, ampicillin/sulbactam, ciprofloxacin and vancomycin), three antihypertensive drugs (losartan, nifedipine and enalapril), three analgesics/antipyretics (metamizole, diclofenac and tramadol), two monoclonal antibodies (infliximab and rituximab), one anticoagulant (warfarin), one antiemetic (metoclopramide) and one anti-ulcer drug (ranitidine) (table 3).

Table 1. Groups of drugs involved in adverse drug reactions among Colombian patients according to the Anatomical and Therapeutic Classification (ATC), 2007-2013

ATC group	Frequency	%
Nervous system (N)	77	16.5
Anti-infectives for systemic use (J)	73	15.6
Alimentary tract and metabolism (A)	59	12.6
Antineoplastic and immunomodulating agents (L)	56	12.0
Cardiovascular system (C)	54	11.5
Blood and blood forming organs (B)	24	5.1
Musculoskeletal system (M)	23	4.9
Respiratory system (R)	23	4.9
Genitourinary system and sex hormones (G)	22	4.7
Systemic hormonal preparations (H)	18	3.8
Dermatologicals (D)	14	3.0
Antiparasitic products, insecticides and repellents (P)	13	2.8
Sensory organs (S)	8	1.7
Various (V)	4	0.9
Total	468	100.0

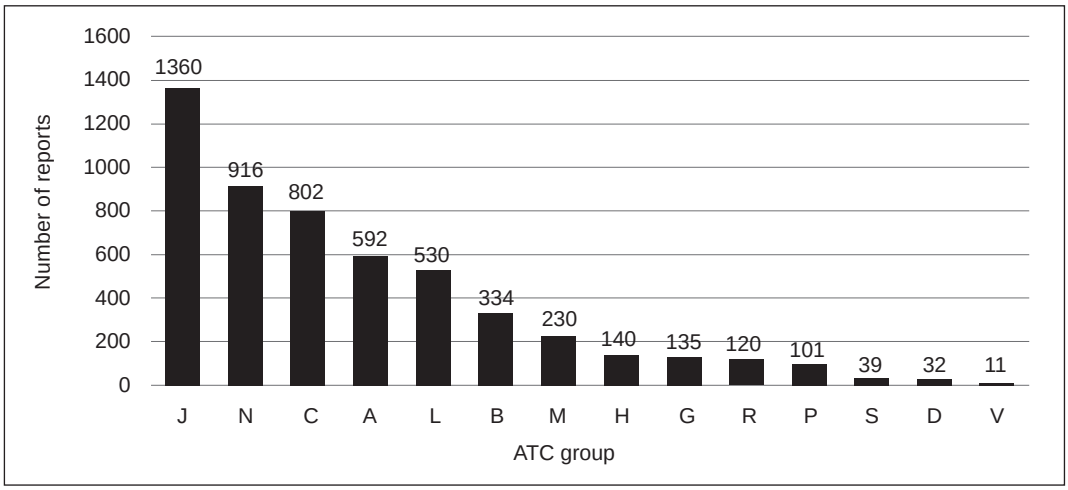

Figure 1. Total reports of adverse drug reactions in Colombia according to the Anatomical and Therapeutic Classification (ATC), 2007-2013. A) Alimentary tract and metabolism, (B) blood and blood forming organs, (C) cardiovascular system, (D) dermatologicals, (G) genito-urinary system and sex hormones, (H) systemic hormonal preparations, (J) anti-infectives for systemic use, (L) antineoplastic and immunomodulating agents (M), musculoskeletal system, (N) nervous system, (P) antiparasitic products, insecticides and repellents, (R) respiratory system, (S) sensory organs, (V) various.

Table 2. Reporting of adverse drug reactions attributed to the top 15 drug subgroups among Colombian patients according to the Anatomical and Therapeutic Classification (ATC), 2007-2013

ATC	Sub-group description	Reports	Percentage
J01C	Beta-lactam antibacterials, penicillins	330	6.2
L04A	Immunosuppressants	306	5.7
J01D	Other beta-lactam antibacterials	300	5.6
N02B	Other analgesics and antipyretics	292	5.5
J01F	Macrolides, lincosamides and streptogramins	237	4.4
C09A	Agents acting on the renin-angiotensin system	230	4.3
B01A	Antithrombotic agents	208	3.9
N02A	Opioids	178	3.3
J01X	Other antibacterials	164	3.1
N03A	Antiepileptics	164	3.1
M01A	Antiinflammatory and antirheumatic products, non-steroids	157	2.9
C10A	Lipid modifying agents, plain	139	2.6
J01M	Quinolone antibacterials	137	2.6
A02B	Drugs for peptic ulcer and gastroesophageal reflux disease	127	2.4
L01X	Other antineoplastic agents	115	2.2

The most common ADRs, classified following the World Health Organization Adverse Reaction Terminology (WHO-ART), were: Skin and appendages disorders, general disorders and gastrointestinal system disorders (table 4).

Table 5 specifically shows the most commonly reported ADRs for the 15 drugs with the highest number of reports.

For 3,292 reports (61.6% of the total), the severity of the notified ADR was indicated. Most were classified as “moderate” (n=1,626, 49.4%), followed by “mild” (n=1486, 45.1%), while “severe” ADRs were less common (n=176, 5.3%), even though there were 3 (0.1%) lethal reactions. Data for ADR type were obtained for 3,233 (60.5%) of the reports, which showed that type B (dose-independent) were the most frequent (n=2,366, 73.2%), and just 782 (24.2%) were type A (dose-dependent). There were also some notifications for type C (chronic) ADRs (n=64, 2.0%), type F (failure of therapy) (n=9, 0.3%) and type D or delayed (n=6, 0.2%).

Finally, 1,799 ADRs were classified as possible (45.0%), followed by likely (n=1,479, 37.0%), conditional (n=181, 4.5%), unlikely (n=170, 4.3%) and definitive (n=166, 4.2%). A total of 198 ADRs (5.0%) were unassessable.

Table 3. List of the 15 drugs with the highest number of adverse drug reactions in hospitals and ambulatory reports among Colombian patients, 2007-2013

ATC	Drug	Number of reports	Incidence x 1,000,000 inhabitants/year	Number of hospital reports n (%)	Number of ambulatory reports n (%)
N02BB02	Metamizole	225	0.73	175 (7.6)	50 (1.5)
C09AA02	Enalapril	203	0.65	40 (1.7)	163 (4.9)
J01FA09	Clarithromycin	147	0.47	113 (4.9)	34 (1.1)
B01AA03	Warfarin	150	0.42	81 (3.5)	69 (2.1)
J01MA02	Ciprofloxacin	130	0.42	81 (3.5)	49 (1.5)
N02AX02	Tramadol	104	0.34	65 (2.8)	39 (1.2)
J01CR01	Ampicillin/sulbactam	101	0.33	86 (3.8)	15 (0.4)
C09CA01	Losartan	124	0.32	17 (0.7)	107 (3.3)
L04AB02	Infliximab	95	0.31	13 (0.6)	82 (2.5)
J01XA01	Vancomycin	91	0.29	72 (3.1)	19 (0.5)
A03FA01	Metoclopramide	88	0.28	52 (2.3)	36 (1.0)
C08CA01	Amlodipine	78	0.25	7 (0.3)	71 (2.2)
A02BA02	Ranitidine	77	0.25	60 (2.6)	17 (0.5)
M01AB05	Diclofenac	72	0.23	44 (1.9)	28 (0.8)
L01XC02	Rituximab	72	0.23	11 (0.5)	61 (1.9)

Table 4. The most common adverse drug reactions classified according to the World Health Organization Adverse Reaction Terminology (WHO-ART), Colombia, 2007-2013

System-organ class	Frequency	%
Skin and appendages disorders	1681	35.3
Body as a whole - general disorders	676	14.2
Gastrointestinal system disorders	562	11.8
Central & peripheral nervous system disorders	382	8.0
Application site disorders	302	6.3
Respiratory system disorders	295	6.2
Cardiovascular disorders, general	247	5.2
Platelet, bleeding & clotting disorders	114	2.4
Musculoskeletal system disorders	77	1.6
Autonomic nervous system disorders	60	1.3
Heart rate and rhythm disorders	56	1.2
Reproductive disorders, female	51	1.1
Psychiatric disorders	48	1.0
Vision disorders	46	1.0
White cell and reticuloendothelial system disorders	31	0.7
Urinary system disorders	30	0.6
Endocrine disorders	29	0.6
Special senses other, disorders	26	0.5
Liver and biliary system disorders	18	0.4
Vascular (extracardiac) disorders	11	0.2
Metabolic and nutritional disorders	11	0.2
Red blood cell disorders	3	0.1
Hearing and vestibular disorders	3	0.1
Reproductive disorders, male	2	0.0
Total	4,761	100

Discussion

An increasing number of yearly ADR reports were found, a fact that coincides with a worldwide tendency; differences between inpatient and outpatient ADR reports were evident when compared to scientific publications (17,18). No similar scientific papers had been published in the region which is a strength of this work.

Other studies in Colombia have used active pharmacovigilance in hospitalized patients and retrospective enquiries of medical attention due to ADRs, but this work included both in- and outpatient reports, and compared the frequency of adverse drug reactions in hospitals and ambulatory settings (14). A study in a hospital in Colombia found the same three ATC groups as those found with the highest number of reports in this case, but in the opposite order, probably as a result of only taking hospital ADR reports into account (19). Antibiotics, which are usually associated with ADRs, were the most common, but adverse reactions to insulin and heparin, which are common in other pharmacovigilance reports, were not frequently reported in this study (1,19,20). Biotechnologic drugs, such as infliximab and rituximab, also presented an important number of ADR reports. A press communiqué by Invima in 2013 reported the risk of serious dermatological ADRs and anaphylaxis due to rituximab and recommended the notification of any type of adverse reaction associated with this drug to the Institute (21).

Scientific literature usually exposes antibiotics as the drugs that are most commonly associated with ADR reports and, in this case, four of the top ten drugs with the highest number of reports were of that class, with ATC group J (anti-infectives for systemic use) being first in the ADR report list (19,20).

Table 5. The most commonly reported adverse drug reactions attributed to the first 15 drugs with the highest number of reports among Colombian patients, 2007-2013

Adverse reactions	Frequency	%
Dermatologic reaction	408	31.3
Phlebitis	138	10.6
Cough	101	7.7
Nausea/dizziness	78	6.0
Bleeding	68	5.2
Dyspnea	53	4.1
Leg edema	41	3.1
Headache	40	3.1
Emesis	37	2.8
Thoracic pain	33	2.5
Bleeding risk	21	1.6
Hot flush	20	1.5
Hypotension	18	1.4
Extrapyramidal symptoms	17	1.3
Presyncope	16	1.2
Epigastric pain	15	1.2
Tachycardia	15	1.2
Anxiety/excitement	14	1.1
Eyelid edema	10	0.8
Paresthesia	10	0.8

The most common ADRs in any context are usually hypersensitivity reactions which mainly present as dermatological allergic reactions and were the most common in this report (19). A study carried out in two health institutions in Pereira, Colombia, in 2005 showed that the most common ADRs were allergic urticarial, hypoglycemia and acute gastritis. The latter two were not reported in this case, showing the difference between ADRs that occur in hospital settings and those in the outpatient setting (1).

The information obtained in this work was from a spontaneous report system, because the data are conditioned to inter-individual factors and the motivation of doctors and pharmaceutical chemists that work with the affiliated population. Passive pharmacovigilance has shown an important under-reporting of the actual number of adverse events (5,10,22). Spontaneous reports of ADR might be useful for specific reactions or those with a temporal relationship linking them to a specific drug, but might be less helpful in other types of ADR such as cancer development (7,10).

The percentage of ADR notification, according to the 54 million drugs dispensed by Audifarma, S.A., in 2012, was 0.003%. Studies in Colombia showed an ADR frequency of 0.03% and 6.8% among hospitalized patients and 1.2% to 45% as a reason for consultation/hospitalization. Taking this into account, significant ADR underreporting occurred in this population (1,14).

A small percentage of ADRs were classified as “definitive”, which is in accordance with other reports and evidences the difficulty in determining the absolute relationship of a drug with an event (1,4,14). Failures in completing the on-line form were detected for some items that were not available for all cases. The WHO Pharmacovigilance Center in Uppsala has established criteria to guarantee the quality of ADR reports that should be met by Audifarma (10).

Pharmacovigilance systems constitute a permanent drug monitoring tool which can reduce the morbidity, mortality and cost for health systems (23). The number of ADR reports for a drug can increase if there are specific warnings about it, which allows health institutions to focus pharmacovigilance on certain drugs. In the past, this behavior has allowed the detection of drug security problems and has resulted in their withdrawal from the market (4). We considered 5.3% as a significant percentage of severe ADRs, as it is above reports in Spain (1.1%) and below those recorded in France and Canada (9.6% and 24%, respectively) (24-26). The differences may be due to the quality of reporting systems (25).

Segura, *et al*., calculated that the cost of health attention due to ADR in Colombia would reach approximately 29.4 to 88.9 million dollars in 2010, hence the pertinence of preventing their occurrence (2). Another study from Colombia showed that the average cost of care for each ADR case was US$ 78.1 (range: US$ 32 - US$ 259) (1). A study found that ADRs caused by anticoagulants, insulin and corticosteroids accounted for over 80% of global ADR attention cost, which shows the importance of certain drug groups even when they are not among those that are most commonly associated with drug reactions (19). To deepen the dilemma, national ADR information, collected by INVIMA, is not published on academic media as a tool that would allow improvements in decision making and procurement for patient security (27).

We concluded, then, that the drug groups most commonly related to ADRs in Colombia during the study period were anti-infectives for systemic use, cardiovascular drugs, nervous system agents, alimentary tract and metabolism drugs and anti-neoplastic and immunomodulating agents, the latter being a novelty in our country but in line with their growing use. Metamizole, enalapril and clarithromycin were the drugs with the highest number of reports, which is common in the case of

the analgesic, but has led to discussion regarding the frequency of the uncomfortable cough associated with the antihypertensive drug. It was also noteworthy that rituximab and infliximab, both biotechnological drugs, were among the 15 drugs with the highest ADR report number. Hypersensitivity reactions in skin, followed by phlebitis associated with intravenous antimicrobial use and cough, were the most common ADRs.

Among the limitations of this study we should mention that information was obtained from spontaneous ADR notification, and this renders a partial view of the events that could have happened. Also, the data correspond to a percentage of the Colombian population, so the results can only be extrapolated to persons with similar SGSSS affiliation characteristics.

The question could be asked about how much of the information on ADR reaches patients, a fact that seems to be underrated in most publications. The knowledge about the most common ADRs in the country could help patient communities to understand the risk to which they are exposed by using certain drugs (28). As there is little ADR notification and reports, and national pharmacovigilance programs in Colombia are deficient, we think our results can provide knowledge on the drug groups most commonly associated with ADRs in the country, as well as information on the events related to the administration of biotechnological drugs, which is a topic that the enquiry on this kind of undesired results must also focus upon. Work needs to be done on the design of digital systems to immediately record adverse reactions and give feedback to prescribing doctors in order to prevent related medication errors (29). In addition, due to the importance of ADR notification with regard to public health, the possibility of paying physicians for each report they fill in has been suggested with the aim of improving the quantity and quality of the information received (30). Finally, we should consider mandatory ADR reporting and have all health workers report each event. People responsible for health policies should create mechanisms to promote ADR reporting among physicians, and case investigation and timely notification among insurers and health care providers.

Conflicts of interest

One of the authors has a contractual relationship with both financial organizations (*Universidad Tecnológica de Pereira* and Audifarma, S.A.) without this affecting the content of the manuscript.

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