

ORIGINAL ARTICLE

Drug-induced hypersensitivity: A 5-year retrospective study in a hospital electronic health records database

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Summary

What is known and Objective: Hypersensitivity adverse drug reactions (HADR) are associated with considerable morbidity and mortality. The aim of this study was to identify cases of HADR within a hospital electronic health records (EHR) database.

Methods: Data were extracted from EHR through the Portuguese catalogue of allergies and other adverse reactions (CPARA). This registry allows the collection and sharing of information on HADR in a structured and harmonized way across the healthcare system. This module is used by healthcare professionals to record HADR within the EHR of each patient. It applies to patients admitted to hospital because of HADR and also to inpatients developing such reactions during hospitalization. Data recorded from 2013 to 2017 within the Centro Hospitalar de Entre o Douro e Vouga (CHEDV) hospital (397 beds; ~20 300 inpatients/year) were considered. The MedDRA[®] classification was used to codify HADR. The ATC classification system was used to codify drugs. The concept of individual case safety report (ICSR) was considered for performing analyses.

Results and discussion: The database contained 464 valid cases (severe, n = 330; 71.1%), corresponding to 380 patients and 559 HADR. Most patients were female (n = 254; 66.8%); the median age was 55 years. Approximately 0.1% local inhabitants and ~0.4% inpatients have experienced HADR over the study period. Most cases (n = 245; 52.8%) were associated with systemic antibacterials. Most HADR were skin and subcutaneous tissue disorders (n = 266; 47.6%) and immune system disorders (n = 231; 41.3%). The pattern of suspected drugs implicated in anaphylactic reactions was the same as those involved in other HADR.

What is new and conclusion: This registry contains HADR that are relevant for the pharmacovigilance system, but none was spontaneously reported. The responsible authorities should address this problem. The results also reinforce the association between systemic antibacterials and HADR.

KEYWORDS

drug hypersensitivity, drug-related side effects and adverse reactions, electronic health records, retrospective studies

1 | WHAT IS KNOWN AND OBJECTIVE

Adverse drug reactions (ADRs) are a leading cause of morbidity and mortality in the healthcare process, with deleterious consequences both for the individual patient and for public health. Two categories of ADRs encompass most cases occurring in clinical practice, namely type A and type B reactions.¹ While the first refers to relatively common, predictable and dose-dependent ADRs, which are usually explained by the mechanism of action of the drug, type B reactions—also called “idiosyncratic reactions”—are less frequent, almost unpredictable and associated with higher morbidity and mortality. Type B reactions are responsible for approximately 15% of all ADRs and include hypersensitivity reactions.^{2,3}

Depending on their genesis, hypersensitivity reactions are classified as either allergic reactions, when there is evidence of underlying immunological mechanism (ie drug-specific IgE or IgG antibodies or T cells), or nonimmunological/nonallergic hypersensitivity reactions.⁴ Furthermore, hypersensitivity reactions can be classified as immediate or nonimmediate, according to the onset timing of symptoms.⁴ Immediate reactions typically occur within 1–6 hours following the first administration of a drug; they are IgE or IgG mediated, and the most common clinical manifestations include urticaria, angioedema, bronchospasm, anaphylaxis or shock. Nonimmediate or delayed hypersensitivity reactions may occur at least 1 hour after drug treatment initiation, but usually after several hours or even days. They are induced by delayed IgG-mediated or T cell-dependent mechanism and may include benign rashes (eg urticaria, maculopapular eruptions) or more serious adverse reactions (eg acute generalized exanthematous pustulosis [AGEP], Stevens-Johnson syndrome [SJS], Lyell's syndrome, and drug reaction with eosinophilia and systemic symptoms [DRESS]).^{3–6}

Hypersensitivity ADRs represent a significant public health problem. They have been described to affect 10%–20% of hospitalized patients and up to 7% of the general population exposed to drugs.² The frequency of drug-induced anaphylaxis was estimated to range between 0.2% and 3.1% in Europe.^{7–9} The registration of these cases in electronic health records (EHRs) is an important contribution for patient safety.¹⁰ This practice allows the characterization of the safety profiles of marketed drugs and may help to prevent further ADRs in certain patients. The aim of this study was to identify and characterize cases of drug-induced hypersensitivity reported in a Portuguese hospital over 5 years.

2 | METHODS

2.1 | Clinical registry

The Portuguese catalogue of allergies and other adverse reactions (CPARA) was developed to improve the process of collecting and sharing clinical information, particularly hypersensitivity reactions, in a structured and harmonized way across the Portuguese healthcare system. This module is used by physicians and nurses to

record hypersensitivity ADRs within the EHR of each patient. This registry applies to patients admitted to hospital because of ADRs and also to inpatients developing ADRs during hospitalization. However, this variable is not discriminated within the database. Furthermore, national legislation was put in force to impose the use of CPARA by healthcare professionals to record hypersensitivity reactions.^{11,12}

The CPARA registry is structured as follows: (a) source of information; (b) date of reaction; (c) classification of adverse reaction (ie identifies whether the reaction is related to food, drugs or other substances); (d) allergens and other substances (ie identifies the specific agent that caused the reaction); (e) adverse reaction (ie characterizes the adverse reaction, eg angioedema, eczema); (f) severity of the adverse reaction—severe or mild; (g) state (ie active [suspicion or confirmation of an allergy or adverse reaction, which should lead to the avoidance of an allergen], inactive [there is a suspicion of unconfirmed allergic disease, or there is an acquisition of tolerance], confirmed [the diagnosis is confirmed by an allergist/clinical immunologist through clinical or laboratory tests], or unconfirmed [the diagnosis is awaiting confirmation by an allergist/clinical immunologist]) (Figure 1).¹³

With the exception of drugs, all clinical information (including type of adverse reaction) is codified using the SNOMED CT[®] terminology. This terminology enables consistent representation of clinical content in EHRs.¹³ Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

2.2 | Setting and source of data

Data recorded with CPARA in the EHRs of patients between 2013 and 2017 within a hospital located at Santa Maria da Feira, District of Aveiro, Portugal (CHEDV—*Centro Hospitalar de Entre o Douro e Vouga*), were considered. This hospital provides health care to approximately 340 000 inhabitants from seven counties (*Santa Maria da Feira, Arouca, São João da Madeira, Oliveira de Azeméis, Vale de Cambra, Ovar and Castelo de Paiva*). The hospital has 397 beds and approximately 20 300 inpatients per year.¹⁴

2.3 | Selection and classification of suspected hypersensitivity ADR cases

Cases were identified and extracted from the hospital database using CPARA. This sample was first searched for duplicate cases, based on patients' initials and age, suspected drugs and reported hypersensitivity ADRs. All duplicates were excluded. The Medical Dictionary for Regulatory Activities (MedDRA[®]) classification system was used to codify ADRs. Noteworthy, the lowest level term (LLT) of the MedDRA[®] classification is the same as the term provided by the SNOMED CT[®] classification. The main reason for using MedDRA[®] classification was that it allows allocating terms into broader categories of ADRs, namely preferred term (PT) and system organ class (SOC), which eases the analysis and interpretation of aggregated data.

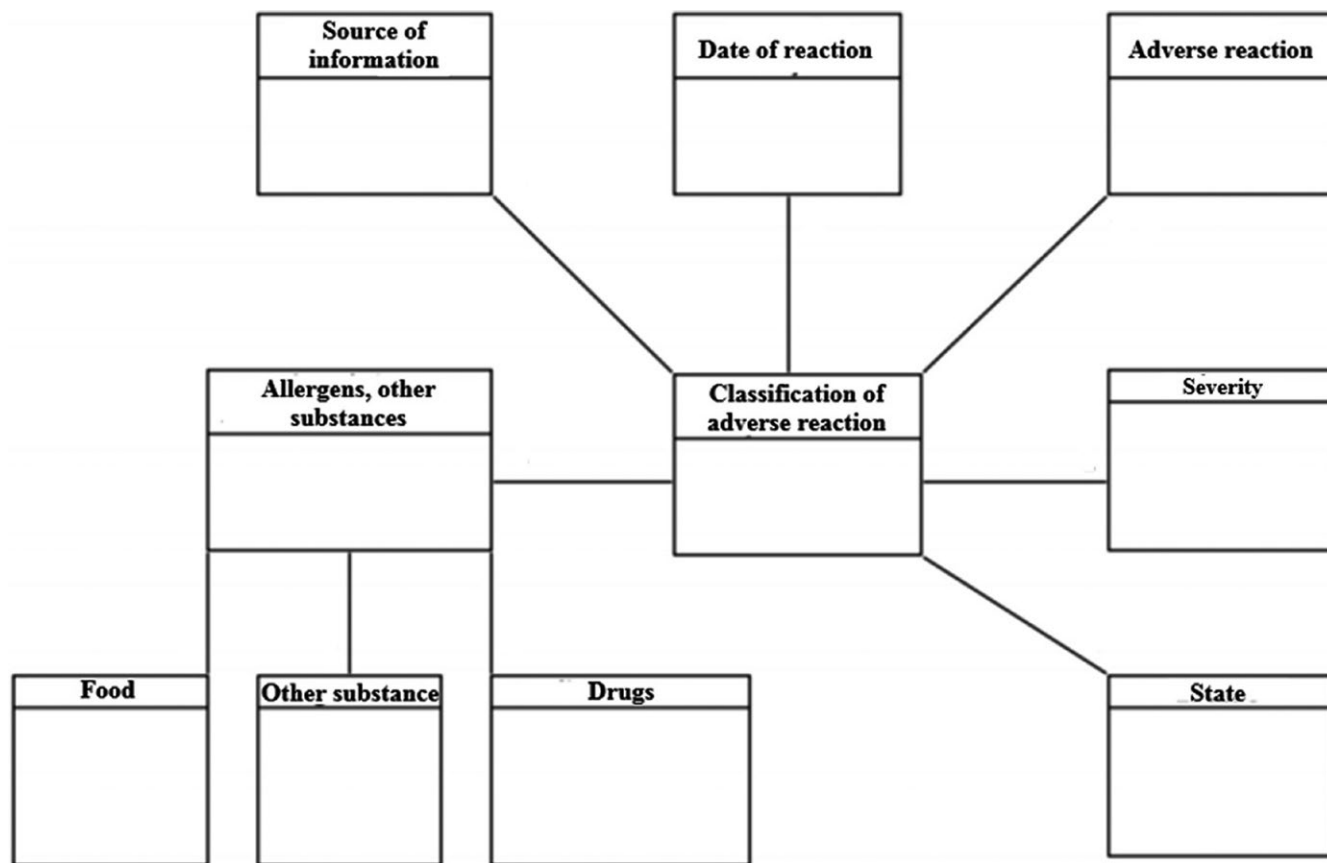


FIGURE 1 Diagram representation on the information model of CPARA. Adapted from Ref. [13]

As a single patient may experience more than one hypersensitivity ADR in association with a single suspected drug, the concept of individual case safety report (ICSR) was considered to carry out data analyses. An ICSR refers to “one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time”.¹⁵ Therefore, the number of suspected medicines equals the number of ICSRs. However, the number of patients can be lower than the number of ICSRs, because a patient may experience several cases of ADR in association with different suspected drugs at distinct points of time. Moreover, the number of suspected ADRs can be higher than the number of ICSRs, because a patient may experience more than one ADR in association with each suspected drug.

2.4 | Data analysis

Descriptive statistics were used to analyse data. The pattern of suspected drugs involved in anaphylactic reactions was compared with those associated with other hypersensitivity ADRs: odds ratio (OR) with 95% confidence interval (CI) was calculated whenever there were at least five cases of anaphylactic reactions associated with a particular class of suspected drugs (2nd level of ATC classification). Reporting rate of cases of hypersensitivity ADRs per million inhabitants per year was calculated. Five-year prevalence rates for patients with hypersensitivity ADRs were estimated using total numbers

of local inhabitants, and inpatients. Microsoft Office Excel® 2013 (Microsoft Corp., Redmond, WA, USA) was used.

3 | RESULTS

The database contained 484 ICSRs, of which 20 were found to be duplicates. Therefore, a total of 464 cases were valid for inclusion in the study. Of those, 330 (77.1%) were rated as severe. On average, there were 93 cases of hypersensitivity ADRs per year. The highest number of cases recorded in a single year was 115 in 2013, whereas the lowest was 60 in 2015. There were 223 active (48.1%), 126 inactive (27.2%), 61 unconfirmed (13.1%) and 54 confirmed (11.6%) cases. With respect to the source of information, cases were reported by healthcare professionals ($n = 369$; 79.5%), patients ($n = 93$; 20.1%) and specialists in immunological and allergic diseases ($n = 2$; 0.4%).

The 464 cases corresponded to a total of 380 patients and 559 hypersensitivity ADRs. Therefore, on average, each patient was exposed to approximately 1.2 suspected drugs and experienced nearly 1.5 hypersensitivity ADRs. The median age of patients was 55 years (range 2–98), and 254 (66.8%) were women.

More than half of cases ($n = 245$; 52.8%) were associated with the use of antibacterials for systemic use (Table 1), mainly beta-lactam antibacterials (Table 2). The majority of hypersensitivity ADRs were skin and subcutaneous tissue disorders ($n = 266$; 47.6%),

TABLE 1 Suspected drugs, classified according to the 2nd level of ATC classification

Suspected medicines ATC 2nd category	N	%
Antibacterials for systemic use	245	52.8
Anti-inflammatory and antirheumatic products	46	9.9
Analgesics	40	8.6
Stomatological preparations	21	4.5
Contrast media	17	3.7
Drugs for functional gastrointestinal disorders	14	3.0
Ophthalmologicals	14	3.0
Antiseptics and disinfectants	6	1.3
Cardiac therapy	5	1.1
Agents acting on the renin-angiotensin system	4	0.9
Cough and cold preparations	4	0.9
Other dermatological preparations	4	0.9
Antibiotics and chemotherapeutics for dermatological use	3	0.6
Antithrombotic agents	3	0.6
Calcium channel blockers	3	0.6
Drugs for obstructive airway diseases	3	0.6
Psychoanaleptics	3	0.6
Anaesthetics	2	0.4
Antianemic preparations	2	0.4
Corticosteroids, dermatological preparations	2	0.4
Drugs for acid-related disorders	2	0.4
Immunosuppressants	2	0.4
Muscle relaxants	2	0.4
Nasal preparations	2	0.4
Throat preparations	2	0.4
Urologicals	2	0.4
Antidiarrhoeals, intestinal anti-inflammatory/antiinfective agents	1	0.2
Antiemetics and antinauseants	1	0.2
Antiepileptics	1	0.2
Antifungals for dermatological use	1	0.2
Blood substitutes and perfusion solutions	1	0.2
Diuretics	1	0.2
Immune sera and immunoglobulins	1	0.2
Psycholeptics	1	0.2
Sex hormones and modulators of the genital system	1	0.2
Topical products for joint and muscular pain	1	0.2
Vitamins	1	0.2
Total	464	100.0

Sum total may not be 100.0% due to rounding.

TABLE 2 Suspected drugs associated with at least 10 cases of hypersensitivity ADRs, classified according to the 5th level of ATC classification

Suspected medicines ATC 5th category	N	%
Penicillins, combinations with other antibacterials	57	12.3
Benzylpenicillin	44	9.5
Penicillins with extended spectrum ^a	32	6.9
Acetylsalicylic acid	26	5.6
Amoxicillin and enzyme inhibitor	25	5.4
Amoxicillin	18	3.9
Combinations of penicillins	17	3.7
Paracetamol	15	3.2
Penicillamine	13	2.8
Ibuprofen	12	2.6
Tramadol	11	2.4
Diclofenac	10	2.2
Metoclopramide	10	2.2
Others	174	37.5
Total	464	100.0

^aPenicillins with extended spectrum is ATC 4th category, because 5th category was not available for these cases.

Sum total may not be 100.0% due to rounding.

such as urticaria (n = 106; 19.0%) and angioedema (n = 61; 10.9%), or immune system disorders (n = 231; 41.3%), namely anaphylactic reactions (n = 209; 37.4%) (Table 3). The pattern of suspected drugs implicated in anaphylactic reactions was the same as for the other hypersensitivity ADRs (Table 4).

Overall, the reporting rate of cases of hypersensitivity ADRs was estimated at 273 cases per million inhabitants per year. Approximately 0.1% local inhabitants (380/340 000) and nearly 0.4% inpatients (380/101 500) had experienced hypersensitivity ADRs over the 5-year study period.

4 | DISCUSSION

In July 2012, CPARA was introduced in the Portuguese health system. Healthcare professionals use this tool to record cases of allergic reactions or intolerance to drugs, food or other agents/substances in the EHR of patients. This registry allows the identification of patients with a past history of allergic reactions, including suspected and/or confirmed ADRs, and therefore provides support to guide individual treatments.

The present results indicate that the database analysed in this study can be used to detect cases of hypersensitivity ADRs and therefore may play an important role for drug safety monitoring in clinical practice. Furthermore, most cases were severe (~71%), which highlights the importance of collecting and analysing such information within the national healthcare system. Nevertheless,

**TABLE 3** List of hypersensitivity ADRs, according to System Organ Class (SOC) and Preferred Term (PT) MedDRA Classification

Adverse drug reaction (SOC, PT)	N	%
Skin and subcutaneous tissue disorders	266	47.6
Angioedema	61	10.9
Dermatitis atopic	1	0.2
Dermatitis contact	14	2.5
Eczema	33	5.9
Erythema multiforme	2	0.4
Pruritus	46	8.2
Rash maculopapular	3	0.5
Urticaria	106	19.0
Immune system disorders	231	41.3
Anaphylactic reaction	209	37.4
Drug hypersensitivity	22	3.9
Respiratory, thoracic and mediastinal disorders	37	6.6
Asthma	2	0.4
Bronchospasm	2	0.4
Dyspnoea	27	4.8
Laryngeal oedema	6	1.1
Gastrointestinal disorders	20	3.6
Diarrhoea	2	0.4
Vomiting	18	3.2
General disorders and administration site conditions	3	0.5
Mucosal inflammation	3	0.5
Cardiac disorders	1	0.2
Cardiorespiratory arrest	1	0.2
Infections and infestations	1	0.2
Conjunctivitis	1	0.2
Total	559	100.0

A single patient may experience more than one case of ADR and more than one ADR per case. For example, a patient experienced eczema and dyspnoea after the administration of benzylpenicillin; other patient experienced three episodes of urticaria: one in association with nimesulide, other with paracetamol and a last one with dexibuprofen. Sum total may not be 100.0% due to rounding.

it should be noted that severity (severe or mild) is not synonymous with seriousness (serious or nonserious). Severity is used to describe the intensity of a given event, but not its clinical significance. Seriousness is defined based on patient's outcome, and it is used to guide regulatory reporting obligations in pharmacovigilance activities.¹⁶ As an example, dyspnoea can be severe during a limited period of time, but simultaneously nonserious if there are not clinically relevant consequences for the patient or medical intervention is not required to resolve it. Seriousness assessment is not performed within the CPARA registry.

The overall 5-year prevalence for patients with hypersensitivity ADRs among the general population (0.1%) and inpatients (0.4%) is

low as compared to previous studies in other settings.² It is important to recall that the present study was based on retrospective analysis and that the analysed data come from a single hospital. There is the possibility that some cases were not recorded in the database and that some individuals with hypersensitivity ADRs have been treated in other hospitals. Furthermore, under-reporting of ADRs is a known limitation of spontaneous reporting schemes.¹⁷ There is also the possibility that clinicians do not acknowledge a causal relationship between the exposure to drugs and the development of hypersensitivity reactions.¹⁸ Therefore, the real prevalence of these cases is probably higher than the estimations found here. A retrospective study using EHR data in Boston (USA) found that 0.3% of outpatients have hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) within 1 year of prescription.¹⁹

Skin and subcutaneous tissue disorders and immune system disorders comprised ~90% of all ADRs. This result was expected taking into account the main purpose of the CPARA registry. Although the spectrum of clinical manifestations is diverse, cases of anaphylactic reaction were considerably prevalent (~37%). Other frequently reported reactions included skin and subcutaneous manifestations, such as urticaria and angioedema, and also respiratory compromise, particularly dyspnoea. Similar findings were found in other studies.²⁰⁻²⁴ The pattern of hypersensitivity ADRs was relatively different in another study reviewing the allergy module of EHRs on 2.7 million US patients, with rash (14%) the most prevalent reaction, followed by hives (8.2%), gastrointestinal irritation (5.5%), pruritus (3.2%) and anaphylaxis (2.5%).¹⁰ Of note, acute onset of illness simultaneously involving skin and/or mucosal involvement (eg angioedema, pruritus) and either respiratory compromise (eg dyspnoea, bronchospasm) or blood pressure drop/end-organ dysfunction may assemble enough clinical criteria for the diagnosis of anaphylaxis.²⁵

Antibacterials for systemic use (~53%) and anti-inflammatory/antirheumatic products together with analgesics (~19%) were the most frequently reported suspected drugs in the database. These results are in line with findings from other investigations.²⁶⁻²⁹ Penicillins and NSAIDs (eg acetylsalicylic acid, ibuprofen and diclofenac) were particularly implicated, whereas tramadol and metoclopramide also deserve attention. A previous 4-year study, based on a nationwide notification system collecting cases of anaphylaxis from allergy specialists in Portugal, found that most cases of drug-induced anaphylaxis were caused by NSAIDs (~48%), including diclofenac, ibuprofen and naproxen.³⁰

From a regulatory perspective on drug safety surveillance, it is interesting to note that a single hospital recorded on average 93 cases of hypersensitivity ADRs per year, whereas the Pharmacovigilance Unit of the Centre Region of Portugal has received on average 332 cases of ADRs per year during the same period of time. Thus, this hospital alone has the potential to identify nearly one-third (~28%) of all drug safety problems that are currently identified by means of the spontaneous reporting scheme in the whole region, which covers approximately 1.7 million inhabitants. Moreover, the reporting rate was estimated at 273 cases of hypersensitivity ADRs per million inhabitants per year in the region covered by the CHEDV Hospital,

TABLE 4 Suspected drugs (2nd level of ATC classification) involved in anaphylactic reactions and other hypersensitivity ADRs

Type of hypersensitivity ADR	N	%
Anaphylactic reactions		
Antibacterials for systemic use	117	56.0
Anti-inflammatory and antirheumatic products	22	10.5
Analgesics	16	7.7
Stomatological preparations	11	5.3
Ophthalmologicals	7	3.3
Antiseptics and disinfectants	6	2.9
Drugs for functional gastrointestinal disorders	6	2.9
Cardiac therapy	3	1.4
Anaesthetics	2	1.0
Antianemic preparations	2	1.0
Contrast media	2	1.0
Cough and cold preparations	2	1.0
Drugs for obstructive airway diseases	2	1.0
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents	1	0.5
Antiemetics and antinauseants	1	0.5
Antithrombotic agents	1	0.5
Blood substitutes and perfusion solutions	1	0.5
Diuretics	1	0.5
Drugs for acid-related disorders	1	0.5
Other dermatological preparations	1	0.5
Sex hormones and modulators of the genital system	1	0.5
Topical products for joint and muscular pain	1	0.5
Urologicals	1	0.5
Vitamins	1	0.5
Total	209	100.0
Hypersensitivity ADRs, excluding anaphylactic reactions		
Antibacterials for systemic use	184	52.6
Anti-inflammatory and antirheumatic products	31	8.9
Analgesics	31	8.9
Contrast media	19	5.4
Ophthalmologicals	10	2.9
Stomatological preparations	10	2.9
Drugs for functional gastrointestinal disorders	8	2.3
Nasal preparations	5	1.4
Antiepileptics	4	1.1
Antithrombotic agents	4	1.1
Agents acting on the renin-angiotensin system	4	1.1
Calcium channel blockers	3	0.9
Psychoanaleptics	3	0.9
Other dermatological preparations	3	0.9
Antibiotics and chemotherapeutics for dermatological use	3	0.9

(Continues)

TABLE 4 (Continued)

Type of hypersensitivity ADR	N	%
Antiseptics and disinfectants	3	0.9
Immune sera and immunoglobulins	3	0.9
Urologicals	2	0.6
Cardiac therapy	2	0.6
Drugs for obstructive airway diseases	2	0.6
Muscle relaxants	2	0.6
Throat preparations	2	0.6
Anaesthetics	2	0.6
Immunosuppressants	2	0.6
Corticosteroids, dermatological preparations	2	0.6
Cough and cold preparations	2	0.6
Psycholeptics	1	0.3
Antifungals for dermatological use	1	0.3
Sex hormones and modulators of the genital system	1	0.3
Drugs for acid-related disorders	1	0.3
Total	350	100.0

OR (95% CI) for anaphylactic reaction vs. other hypersensitivity ADRs: antibacterials for systemic use, 1.15 (0.81-1.62); anti-inflammatory and antirheumatic products, 1.21 (0.68-2.15); analgesics, 0.85 (0.45-1.60); stomatological preparations, 1.89 (0.79-4.53); ophthalmologicals, 1.18 (0.44-3.14); antiseptics and disinfectants, 3.42 (0.85-13.82); drugs for functional gastrointestinal disorders, 1.26 (0.43-3.69).

which is higher than both the World Health Organization (WHO) goal for spontaneous reporting of suspected ADRs (250 cases/million inhabitants/year) and the result obtained by the Pharmacovigilance Unit of the Centre Region of Portugal in 2017 (267 cases/million inhabitants/year). Besides, the hospital database contains only cases of hypersensitivity reactions, excluding other types of ADRs. This fact also raises the question of whether adjustments on the existing computerized tools can allow recording other types of ADRs within patients' EHRs. This would improve the collection and widen the spectrum of the reported drug safety data. Furthermore, it is important to note that, for example, the healthcare professionals from this hospital have reported only one case of suspected ADR through spontaneous reporting to the PPS in 2017. Possibly, the current spontaneous reporting system is not as attractive or easy to use as EHRs. From the perspective of healthcare professionals, it is useful to have immediate access to information on patients' past drug allergy history through EHRs, while filling suspected ADRs' spontaneous reporting forms implies additional workload. Regulatory authorities and other stakeholders in the field of drug regulation should pay attention to these issues. The fact that the suspected ADRs identified during clinical practice are not reported to pharmacovigilance systems has implications for public health.

Nevertheless, there are some limitations within the CPARA that should be noted. Suspected drugs were not classified at the most specific level (ie name of the active substance—5th category

of ATC) in a considerable proportion of cases ($n = 95$; 20.5%). This is probably because the healthcare professionals who report the cases were not necessarily the prescribers of suspected drugs, which could make it difficult the access to that information. Other important missing information includes time of onset of hypersensitivity ADRs and the outcome of patients. In addition, the information recorded in patients' EHRs through the CPARA registry is limited if one needs to explore the influence of other risk factors for ADRs under evaluation. For example, the gender and age of patients, comorbidities (eg infections, underlying chronic diseases) and given gene polymorphisms, as well as nonreported concomitant drugs, may increase the risk of hypersensitivity reactions.³¹ Furthermore, hypersensitivity ADRs are sometimes overestimated because relying solely on history of clinical manifestations may be insufficient to determine a definite diagnose of drug allergy.³¹ In the present analysis, only 54 cases (~12%) had been confirmed with provocation tests by allergy specialists. A data linkage approach may be useful in future studies for connecting information provided by the CPARA registry with complementary clinical data registered with other tools, aiming at the improvement of the analyses.

5 | WHAT IS NEW AND CONCLUSION

Postmarketing drug safety evaluations should comprehend analyses of data obtained from multiple sources to assure evidence-based decisions. A passive pharmacovigilance approach, which relies mostly on spontaneous reports of suspected ADRs, was found to be insufficient. As noted in this study, cases of hypersensitivity ADRs registered in the EHRs of patients were not reported to the PPS. Responsible health authorities should promote more proactive ways of collecting clinical data to better identify and prevent ADRs, improve benefit-risk assessments, increase patient safety and protect public health. The results also reinforce the fact that antibacterials for systemic use and anti-inflammatory drugs deserve particular attention from clinicians because these therapies were found to be implicated in most cases of hypersensitivity ADRs.

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