

**ORIGINAL ARTICLE**

# Fatal adverse drug reactions: A worldwide perspective in the World Health Organization pharmacovigilance database

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**Aims:** Adverse drug reactions (ADRs) are important causes of death. However, the main involved drugs are relatively unknown. The present study was performed to characterise death-related drugs recorded in a large pharmacovigilance database during the last 10 years.

**Methods:** A retrospective analysis of VigiBase, the World Health Organization pharmacovigilance database, was performed investigating fatal ADRs registered between 1 January 2010 and 31 December 2019 in male and female patients aged  $\geq 18$  years and reported by physicians. Analyses were descriptive investigating age, sex and *suspected* drugs. Differences in reporting according to sex, age and continents were investigated using disproportionality analysis with calculation of reporting odds ratio and its 95% confidence interval.

**Results:** Among the 23 millions ADRs recorded in VigiBase, 3 250 967 were included with 43 685 fatal. They were reported mainly in patients older than 75 years. The 3 most frequently involved drug classes were antineoplastic/immunomodulating drugs followed by nervous system and cardiac drugs. The top 3 individual drugs were denosumab, lenalidomide and thalidomide with marked differences according to age, sex, continents and countries. The risk of reporting fatal ADRs was higher in males, in the Americas and in patients  $\geq 65$  years.

**Conclusion:** Fatal ADRs registered in a large pharmacovigilance database during the last 10 years correspond to just over 1% of the total number of ADRs. They occurred more in males, after 65 years and with antineoplastic/immunomodulating drugs in general. Our study also highlighted, for the first time, important differences in fatal ADRs between continents and countries.

**KEYWORDS**

adverse drug reactions, death, drug safety, lethality, pharmacovigilance

The authors confirm that the PI for this paper is Prof. J.L. Montastruc. There is no direct clinical responsibility for patients since the work was performed in a pharmacovigilance database. As indicated in the text, "The database is freely available in our department. According to the French clinical research law, review by an ethics committee and patients' informed consent is not required for such pharmacovigilance studies."

## 1 | INTRODUCTION

Several studies have underlined the importance of adverse drug reactions (ADRs) in terms of public health. According to the main studies performed during the late 90s and the first years of the 21st century, ADRs are reported to be the most common cause of hospital admission and the fourth or sixth leading cause of death.<sup>1–5</sup> In addition to human health, ADRs also have a significant impact on healthcare costs.<sup>6</sup> However, relatively few studies have described the main characteristics of fatal ADRs.<sup>7–13</sup> The Global Burden of Disease Study only reported for “adverse effects of medical treatment”, prevalence (2 673 100 in 2017) and incidence (34 975 000 in 2017) values without describing the main drugs involved.<sup>14</sup>

Evolution of therapeutics with introduction of several new drugs during the last 10 years suggests the need to further evaluate these data. Thus, it was the aim of the present study to investigate the main drugs involved in fatal outcomes during the late 10 years (2010–2019), using data registered in the World Health Organization (WHO) pharmacovigilance database.

## 2 | METHODS

This study was performed in VigiBase, the WHO pharmacovigilance database, which includes >23 million reports of ADRs forwarded to the Uppsala Monitoring Centre by national pharmacovigilance systems from >130 countries.<sup>15,16</sup> The database is freely available in our department. According to the French clinical research law, review by an ethics committee and patients' informed consent is not required for such pharmacovigilance studies.

Among the deduplicated data registered in VigiBase, we selected ADRs reports registered as fatal between 1 January 2010 and 31 December 2019 in adults ( $\geq 18$  y). To define fatal ADRs, we selected in MedDRA, the Medical Dictionary for Regulatory Activities<sup>17</sup> the High Level Group Terms “death and sudden death” with the following Preferred Terms: “brain death, cardiac death, clinical death, death, sudden cardiac death, sudden death”, thus excluding “suicides, stillbirth, neonatal death, sudden infant death syndrome, unexplained death in epilepsy, accidental death, electrocution, maternal death during childbirth or affecting foetus, hanging, euthanasia and lithopaedion”. Only reports with known age, sex and origin were included. To improve the clinical validity of the study, we only included ADRs reported by physicians, excluding other reporters (other health professionals, patients etc.).

The first part of the study was descriptive reporting (i) the main characteristics of registered fatal ADRs: number, sex, age, origin of reports according to the patient's continent; and (ii) Individual drugs and Anatomical Therapeutic Chemical (ATC) classes of drugs defined as *interacting/suspected* according to the WHO causality assessment.<sup>18</sup> Since sex-specific differences in drug responses were previously described, with, for example, female sex described as a risk factor for developing ADRs,<sup>19</sup> stratified analyses were performed in

### What is already known about this subject

- Adverse drug reactions (ADRs) are the most common cause of hospital admission and the fourth or sixth leading cause of death, thus leading to significant impact on healthcare costs.
- However, relatively few studies have described the main drugs involved in these fatal ADRs.
- Introduction of new drugs in clinical practice during the last 10 years required a further evaluation of recent data on these fatal ADRs.

### What this study adds

- This study, performed in VigiBase, the World Health Organization pharmacovigilance database, provides crucial and new information on the drugs involved in fatal ADRs with major differences according to continents, countries and age.
- Fatal ADRs represent 1.34% of total ADRs. The most frequent Anatomical Therapeutic Chemical classes were antineoplastic/immunomodulating, neurological and cardiovascular drugs.
- Risk of reporting was higher in males, after 65 years and in the Americas.

males and then in females. For each criterion studied, the drugs were ranked according to the frequency of occurrence.

In the second part, we investigated the reporting risk of fatal reports using the case noncase method.<sup>20,21</sup> Disproportionality analyses were performed between reports of fatal ADRs in 1 continent (and in Europe in 1 country) vs. all other ones and according to sex and age. Cases were defined as fatal reports (as above) registered between 1 January 2010 and 31 December 2019 in patients  $\geq 18$  years. Noncases were all other reports registered in VigiBase during the same period. Unfortunately, the VigiBase structure does not precisely describe exact causes of death, which were thus not included in the present paper.

Results are presented, first, as a descriptive analysis of fatal reports (number, age, sex, geographical location, main *suspected* ATC classes and main individual *suspected* drugs) and second, as reporting odds ratios (ROR),<sup>20,21</sup> a ratio similar in concept to the odds ratio in case-control studies with their 95% confidence interval. Analysis of the database was made at the beginning end of October 2020 and statistical analysis performed using SAS 9.4 software.

### 3 | RESULTS

Among the 23 031 625 deduplicated reports registered in VigiBase, 3 250 967 (14.11%) were included according to the selection criteria. Among them, 43 685 (1.34%) were defined as fatal. More than 50% of reports concerned males. The most affected age group was >75 years in the total population and in females. In contrast, in males, most reports involved patients aged between 45 and 64 years. Most of them came from the Americas followed by Europe (Table 1). The percentages of fatal ADRs registered in VigiBase were stable (around 10–13% each year), except in 2010, 2012 and 2013 where lower values were observed (Supplemental data).

The 3 most frequently involved ATC drug classes in these fatal reports were antineoplastic/immunomodulating drugs (lenalidomide, thalidomide, bevacizumab) followed by nervous system drugs (clozapine, alprazolam, oxycodone) and cardiac drugs (bosentan, macitentan). Similar results were found in males and females (Table 1).

Table 2 describes the top 10 individual drugs involved in these fatal ADRs. In the total population, denosumab, lenalidomide

and thalidomide were the 3 first drugs. Analysis of rank order showed differences according to sex: in males, these 2 last drugs were in rank 1 and 2 and clozapine at the third place (denosumab seventh). In females, denosumab, bosentan and lenalidomide were the 3 first drugs and thalidomide ranked in sixth position.

Large differences in drugs *suspected/interacting* in these reported fatal ADRs were found according to the 5 continents (Table 3) and, in Europe, according to the 9 main countries (Table 4).

The risk of reporting fatal ADRs was higher in males than in females (ROR = 1.47 [1.44–1.50]) and in the Americas than in the other continents (ROR = 6.01 [5.89–6.13]). It was lower in Europe (ROR = 0.40 [0.39–0.41]), in Asia (ROR = 0.27 [0.26–0.28]), in Oceania (ROR = 0.07 [0.05–0.10]) and in Africa (ROR = 0.63 [0.57–0.70])—when each continent was compared to the 4 others). The risk of reporting fatal ADRs was higher in older ( $\geq 65$  y) patients (ROR = 13.45 [13.19–13.72]).

Table 5 shows that the 3 main drugs involved in fatal reports according to patients' age (before and after 65 y).

**TABLE 1** Main characteristics of fatal adverse drug reactions registered in VigiBase between 1 January 2010 and 31 December 2019 in total population (both sexes), males and females (patients  $\geq 18$  y). Percentages (%) are given in relation to the total number of ADRs in each column. ATC classification = Anatomical Therapeutic and Chemical classification of drugs. ATC classification of drugs: 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 excluding sex hormones and insulin; 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

	Total	Males	Females
<b>Number (%)</b>	43 685 (100%)	22 445 (51.4%)	21 240 (48.6%)
<b>Patient age</b>			
18–44 y (%)	5280 (12.1%)	2826 (12.6%)	2454 (11.6%)
45–64 y (%)	13 601 (31.1%)	7201 (32.1%)	6400 (30.1%)
65–74 y (%)	10 262 (23.5%)	5538 (24.7%)	4724 (22.2%)
$\geq 75$ y (%)	14 542 (33.3%)	6880 (30.7%)	7662 (36.1%)
<b>Continent</b>			
Americas	29 123 (66.7%)	13 845 (61.7%)	15 278 (71.9%)
Europe	9090 (20.8%)	5289 (23.6%)	3801 (17.9%)
Asia	5076 (11.6%)	3111 (13.9%)	1965 (9.3%)
Africa	361 (0.8%)	181 (0.8%)	180 (0.8%)
Oceania	35 (0.1%)	19 (0.1%)	16 (0.1%)
<b>Drugs</b>			
<b>ATC classification</b>			
A	3302 (7.6%)	1798 (8.0%)	1504 (7.1%)
B	4207 (9.6%)	2148 (9.6%)	2059 (9.7%)
C	6873 (15.7%)	3070 (13.7%)	3803 (17.9%)
D	2297 (5.3%)	1229 (5.5%)	1068 (5.0%)
G	1286 (2.9%)	586 (2.6%)	700 (3.3%)
H	1195 (2.7%)	673 (3.0%)	522 (2.5%)
J	1617 (3.7%)	939 (4.2%)	678 (3.2%)
L	19 111 (43.7%)	10 836 (48.3%)	8275 (39.0%)
M	4438 (10.2%)	1237 (5.5%)	3201 (15.1%)
N	8659 (19.8%)	4575 (20.4%)	4084 (19.2%)
P	74 (0.2%)	38 (0.2%)	36 (0.2%)
R	2090 (4.8%)	1118 (5.0%)	972 (4.6%)
S	3718 (8.5%)	1935 (8.6%)	1783 (8.4%)
V	1986 (4.5%)	1065 (4.7%)	921 (4.3%)

## 4 | DISCUSSION

The present study was performed to describe the main pharmacological classes and individual drugs involved in fatal ADRs, an important cause of mortality.<sup>1–5</sup> We found that these fatal ADRs reported in adults by physicians represent just over 1% of total ADRs registered in VigiBase and occurred mainly in older patients (>75 y). The most frequent suspected ATC classes were antineoplastic/immunomodulators, neurological and cardiovascular drugs, whereas the top 3 individual drugs were denosumab, lenalidomide and thalidomide. Some differences were found according to sex, countries and age. Risk of reporting was higher in males, in older patients and in the Americas.

Although drugs are recognized as a major cause of mortality, there are, surprisingly, relatively few published data. Zoppi et al.<sup>7</sup> found a 0.05% incidence of fatal ADRs among 48 005 patients consecutively admitted to 3 Swiss internal medicine departments

**TABLE 2** Top 10 of suspected/interacting drugs registered in fatal adverse drugs reaction reports in VigiBase between 1 January 2010 and 31 December 2019 in patients ≥18 years

Total population (n = 43 685)	Males (n = 22 445)	Females (n = 21 240)
1-Denosumab: 2611 (5.4%)	1-Lenalidomide: 1211 (5.4%)	1-Denosumab: 2169 (10.2%)
2-Lenalidomide: 2083 (4.8%)	2-thalidomide: 1165 (5.2%)	2-Bosentan: 939 (4.4%)
3-thalidomide: 1869 (4.3%)	3-clozapine: 1150 (5.1%)	3-Lenalidomide: 872 (4.1%)
4-clozapine: 1761 (4.0%)	4-Imatinib: 651 (2.9%)	4-Macitentan: 829 (3.9%)
5-Bosentan: 1373 (3.1%)	5-bevacizumab: 572 (2.6%)	5-bevacizumab: 729 (3.4%)
6-bevacizumab: 1301 (3.0%)	6-Macitentan: 469 (2.1%)	6-thalidomide: 704 (3.3%)
7-Macitentan: 1298 (3.0%)	7-Denosumab: 442 (2.0%)	7-clozapine: 611 (2.9%)
8-Imatinib: 1060 (2.4%)	8-Bosentan: 434 (1.9%)	8-Imatinib: 409 (1.9%)
9-alprazolam: 752 (1.7%)	9-alprazolam: 362 (1.6%)	9-alprazolam: 390 (1.8%)
10-oxycodone: 606 (1.4%)	10-oxycodone: 292 (1.3%)	10-oxycodone: 314 (1.0%)

between 1974 and 1993. Juntti-Patinen and Neuvonen,<sup>8</sup> investigating deaths in the Helsinki University Central Hospital in 2000, found that 5.0% of all deaths were drug-related (0.05% of hospital admissions). The most common ADRs were neutropenia caused by antineoplastic agents and gastrointestinal or intracranial haemorrhages due to anti-coagulants or nonsteroidal anti-inflammatory drugs. The Italian pharmacovigilance network, reporting its experience until 2006, found that around 1.7% of registered ADRs in the Italian spontaneous reporting database had a fatal outcome. Systemic anti-infective drugs have the highest percentage of fatal outcomes followed by antineoplastic/immunomodulating and nervous system drugs.<sup>9</sup> In a cross-sectional survey in adult inpatients at 4 hospitals in South Africa, Mouton's group<sup>10</sup> found that ADRs contributed to the death of 2.9% of medical admissions and that the most commonly involved drugs were tenofovir, rifampicin and co-trimoxazole. Several factors were independently associated with ADR-related death: HIV, antiretroviral therapy, exposure to >7 drugs and increasing comorbidity score.<sup>10</sup> Another cross-sectional study performed in southwest Ethiopia in 2015–2016 found that 1.5% of fatal ADRs were mainly from hepatic and renal origin: isoniazid, pyrazinamide, efavirenz and tenofovir were the commonly involved drugs.<sup>11</sup> Patel and Patel's meta-analysis (2000–2018) concluded that the mean prevalence of fatal ADRs was 0.2% and that warfarin, aspirin, renin-angiotensin system inhibitors and digoxin accounted for 60% of fatal ADRs.<sup>12</sup> Finally, a New Zealand study reported that opioids, antidepressants, antipsychotics and hypnotic-anxiolytics were the drugs causing most fatalities.<sup>13</sup> This short review shows that most of the papers on this topic were relatively old or came from only 1 country (or region) and thus did not include the most recently marketed drugs. It is for this reason that we have undertaken this study on a global scale.

Analysis of the present results allows 3 kinds of observations. First, we could discuss the drugs involved in these fatal ADRs. The first ATC group was antineoplastic/immunomodulators with 2 immunomodulatory drugs mainly used in multiple myeloma, lenalidomide and thalidomide, followed by the anti-VEGF antibody, bevacizumab, a drug prescribed in several kinds of cancers (colonic, ovarian, cervical cancers, glioblastoma etc.). Another widely used antineoplastic drug, a protein kinase inhibitor, imatinib, appeared in eighth position. The second group was nervous system drugs with first an atypical antipsychotic, clozapine, known for inducing agranulocytosis sometimes fatal, followed by an intermediate-acting anxiolytic benzodiazepine, alprazolam and an opiate analgesic, oxycodone, known as a major cause of

	Africa n = 361	Americas n = 29 123	Asia	Europe	Oceania
<b>Rank 1</b>	Imatinib 20.3%	Denosumab 8.6%	Imatinib 17.5%	Clozapine 11.8%	Clozapine 54.3%
<b>Rank 2</b>	Erythropoietin Human 13.0%	Lenalidomide 6.6%	Pembrolizumab 3.3%	Ranibizumab 3.0%	Octreotide 17.1%
<b>Rank 3</b>	Nivolumab 8.6%	Thalidomide 6.3%	Nilotinib 2.7%	Bevacizumab 2.1%	Pyrazinamide 8.6%

**TABLE 3** Top 3 of suspected/interacting drugs registered in fatal adverse drugs reaction reports in VigiBase between 1 January 2010 and 31 December 2019 in patients ≥18 years in the 5 continents

**TABLE 4** Top 3 of *suspected/interacting* drugs registered in fatal adverse drugs reaction reports in VigiBase between 1 January 2010 and 31 December 2019 in 9 European countries.

Country/drugs rank	1	2	3
<b>Germany</b> <i>n</i> = 2408	Bevacizumab 4.7%	Docetaxel 4.2%	Sunitinib 3.0%
<b>UK</b> <i>n</i> = 1869	Clozapine 51.8%	Ranibizumab 12.7%	Rituximab 1.7%
<b>France</b> <i>n</i> = 676	Methadone 9.0%	Sacubitril 4.9%	Buprenorphine 3.7%
<b>Netherlands</b> <i>n</i> = 614	Bosentan 7.7%	Denosumab 6.7%	Macitentan 5.7%
<b>Spain</b> <i>n</i> = 389	Ibrutinib 4.6%	Teriparatide 4.4%	Lenalidomide 3.3%
<b>Greece</b> <i>n</i> = 365	Erlotinib 8.7%	Erythropietin human 4.9%	Sacubitril 4.5%
<b>Norway</b> <i>n</i> = 253	Warfarin 30.8%	Acetylsalicylic acid 4.7%	Metformin 4.0%
<b>Italy</b> <i>n</i> = 250	Lenalidomide 12.8%	Influenzae vaccine 6.4%	Ribavirin* Bevacizumab* 2.4%
<b>Switzerland</b> <i>n</i> = 241	Calcium, magnesium, Icodextrin, sodium 7.1%	Ipilimumab 4.6%	Sorafenib 4.1%

\*equally placed: the 2 drugs had the same number of fatal reports

**TABLE 5** Top 3 of *suspected/interacting* drugs registered in fatal adverse drugs reaction reports in VigiBase between 1 January 2010 and 31 December 2019 in patients  $\geq 18$  years before and after 65 years

Drug rank/age group	18–64 y <i>n</i> = 18 881 53.1% males	$\geq 65$ y <i>n</i> = 24 804 50.1% males
1	Clozapine 6.6%	Denosumab 9.7%
2	Bevacizumab 4.4%	Lenalidomide 6.5%
3	Oxycodone 2.9%	Thalidomide 4.7%

death within the framework of the so-called opioid crisis, occurring mainly in USA.<sup>22</sup> In fact, 95% of oxycodone reports came from USA with mainly cardiorespiratory arrests as causes of deaths (when described). Cardiovascular drugs appeared in third position with 2 endothelin receptor antagonists, bosentan and macitentan. For these 2 drugs, one could suggest that death could be also, at least partly, related to disease progression in addition to a direct ADR (indication bias). Similar comments could be made for some antineoplastic/immunomodulators discussed above. Finally, one could underline that denosumab, the drug most frequently *suspected* in these drug-induced deaths does not belong to 1 of the first ATC groups but to the Musculoskeletal drug group, ranked fourth overall. Since

denosumab is prescribed not only in osteoporotic patients but also in cancer bone metastases, one can also discuss, at least partly, first an indication bias and, second, a sex bias (denosumab is more commonly prescribed in females than in males).

The second interesting point concerns the major differences from the previously published data since the most frequent *suspected* drugs were antineoplastic/immunomodulating ones and not anticoagulants, nonsteroidal anti-inflammatory drugs, anti-infective or psychotropic drugs, as in the previous studies discussed above.<sup>1–5</sup> These unexpected differences can be clearly explained by, first, inclusion of the whole world and, second, recent marketing of new drugs during the last 10 years. It should be emphasized that many of the suspected drugs are new: 6/10 received their marketing authorisation between 2000 and 2009, 2 before 2000 and 2 others since 2010. Thus, the present work allows the results to be generalized to the whole planet and not just to a single part of the world or a single country.

Third, we tried to approach some factors associated with fatal ADRs. As expected, the risk of reporting fatal ADRs was higher as the age of the patients rose. Moreover, we found that *suspected* drugs differed according to patients' age with 2 psychotropics (first clozapine and third oxycodone) before 65 years and the same 3 drugs (antineoplastics and immunomodulators) in older patients. As far as we know, such results were never described previously. Since differences in ADRs occurrence were previously described according to sex,<sup>23</sup> we also described *suspected* drugs in males and in females. We found that the risk of reporting fatal ADRs was higher in males. This is interesting because female sex is described as a risk factor for developing

ADRs.<sup>19</sup> We have seen a different risk related to sex for fatal ADRs. The drug rank was also different according to sex, with, for example in the first 2 ranks, 2 antineoplastic/immunomodulators in males vs. denosumab and an endothelin receptor antagonist in females. In contrast, alprazolam and oxycodone were in the same positions (eighth and ninth) in males and females.

The number of reports and risk of reporting were also higher in the Americas than in other continents. This could suggest differences in ADR reporting according to continents with a higher drug safety culture in the Americas than in other parts of world. More interesting, we found, for the first time, that drugs involved in fatal ADRs clearly differ according to continents with mainly anticancer drugs in Europe, Africa and Asia. It is interesting to underline that the protein kinase inhibitor, imatinib, was the first drug involved both in Africa and Asia. In Asia, 3 anticancer drugs were found with another protein kinase inhibitor, nilotinib, in rank 3 and pembrolizumab, a programmed cell death 1 inhibitor in rank 2. In Africa, 54 reports with fatal outcomes involving erythropoietin with no specific cause of death were registered. Oceania has a quite different profile with, first, clozapine followed by a somatostatin analogue, octreotide and an antimycobacterial drug, pyrazinamide. As expected, the top 3 drugs in America were the same as worldwide. More surprisingly, major differences were found in Europe according to the main countries. Anticancer drugs were found in most countries but some features were found in several countries: clozapine in the UK, 2 opiate drugs (methadone, buprenorphine) and sacubitril (a drug used in advanced heart failure) in France, warfarin, acetylsalicylic acid and metformin in Norway. For the UK, one can suggest that high reporting associated with clozapine is related to the need for all patients receiving clozapine to be registered with mandatory patient monitoring service. The antiangiogenic monoclonal antibody, ranibizumab, widely used in macular degeneration, was found in rank 2 in Europe and particularly in the UK. The fact that, first, the main causes of deaths with ranibizumab in VigiBase were myocardial infarction and cerebrovascular accidents (when defined) and that, second, >80% of deceased patients were older than 75 years could also suggest another indication bias, with deaths related, at least partly, to underlying disease in addition to the drug. These variations observed according to countries, age and sex may reflect important differences in prescribing patterns, ADR reporting and individual responses to drugs.

The present study suffers from some compulsory methodological drawbacks, in addition to the indication bias, as previously described above. Like every pharmacovigilance study dealing with spontaneous ADR reporting, the present work was not performed to evaluate the true prevalence of fatal ADRs due to several confounding factors such as underreporting or selective reporting of ADRs, differences in clinical and/or reporting practices or individual susceptibilities according to the countries.<sup>15,16</sup> Since pharmacovigilance systems are based on spontaneous ADR reports, analyses of pharmacovigilance databases cannot be used to measure prevalence but are useful to described main characteristics of ADR reports. However, consequences of underreporting on our results are low since underreporting does not differ between cases and noncases.<sup>20</sup> It was not possible to conclude

incidence of ADRs since data about drug consumption in the different parts of world were not included as they are not widely accessible. We minimized these biases using the disproportionality method for comparisons. Moreover, due to the structure of the database, it was not possible to largely describe the causes of deaths since most of them are not fully registered in VigiBase. The indication bias discussed above is another limit of the present work. In fact, this bias is usual and inevitable in this kind of study. Another study limitation is the exclusion of paediatric reports: they were excluded since the problems posed by paediatric drug prescriptions are totally different from those found in adults. Moreover, it was not the purpose of the study to investigate fatal ADRs in children.

In contrast, the present work has several important strengths. First, VigiBase is the largest pharmacovigilance database in the world offering unique opportunities to cover the whole global population with differences in medical and cultural habits and make comparisons between countries. The present paper is the largest study ever published with more than 43 000 reports of drug-related deaths. As far as we know, the method used is the only 1 validated today to analyse such characteristics of fatal ADRs. Another interesting point is that we only included reports from 2010 to 2019 in order to offer recent data.

## 5 | CONCLUSION

This work provides recent and updated data on the demographic features and drugs involved in fatal ADRs. Fatal ADRs reported in VigiBase by physicians in adults represent just over 1% of total ADRs. The most frequently involved drugs were those used in neoplastic diseases. Variations observed according to countries, age and sex reflect differences in prescribing patterns, ADR reporting and individual responses to drugs. Large pharmacovigilance databases are unique tools defining the main characteristics of fatal ADRs and to perform comparisons around the world. Further studies using other methods are necessary to confirm the present results.

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## COMPETING INTEREST

None.

## CONTRIBUTORS

All the authors designed the study. J.L.M. (principal investigator) extracted the data from the database and performed the statistical analysis. All the authors analysed and discussed the data. J.L.M. wrote the paper. All the authors reviewed the successive versions of the manuscript and approved the final version.

## DATA AVAILABILITY STATEMENT

Data are available on request from the main author (J.L.M.).

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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