Received: 16 November 2022 | Revised: 13 November 2023 | Accepted: 7 December 2023

DOI: 10.1002/pds.5743

ORIGINAL ARTICLE

WILEY

Descriptive analysis on disproportionate medication errors and associated patient characteristics in the Food and Drug Administration's Adverse Event Reporting System

Victor Pera[1] | Frauke van Vaerenbergh[1,2] | Jan A. Kors[1] | Erik M. van Mulligen[1] | Rowan Parry[1] | Marcel de Wilde[1] | Lies Lahousse[2,3] | Johan van der Lei[1] | Peter R. Rijnbeek[1] | Katia M. C. Verhamme[1,2]

[1]Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands

[2]Department of Bioanalysis, Ghent University, Ghent, Belgium

[3]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence
Victor Pera, Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands.
Email: v.pera@erasmusmc.nl

Funding information
European Health Data and Evidence Network (EHDEN) project; Innovative Medicines Initiative 2 Joint Undertaking (JU), Grant/Award Number: 806968

Abstract

Background: Medication errors (MEs) are a major public health concern which can cause harm and financial burden within the healthcare system. Characterizing MEs is crucial to develop strategies to mitigate MEs in the future.

Objectives: To characterize ME-associated reports, and investigate signals of disproportionate reporting (SDRs) on MEs in the Food and Drug Administration's Adverse Event Reporting System (FAERS).

Methods: FAERS data from 2004 to 2020 was used. ME reports were identified with the narrow Standardised Medical Dictionary for Regulatory Activities® (MedDRA®) Query (SMQ) for MEs. Drug names were converted to the Anatomical Therapeutic Chemical (ATC) classification. SDRs were investigated using the reporting odds ratio (ROR).

Results: In total 488 470 ME reports were identified, mostly (59%) submitted by consumers and mainly (55%) associated with females. Median age at time of ME was 57 years (interquartile range: 37–70 years). Approximately 1 out of 3 reports stated a serious health outcome. The most prevalent reported drug class was "antineoplastic and immunomodulating agents" (25%). The most common ME type was "incorrect dose administered" (9%). Of the 1659 SDRs obtained, adalimumab was the most common drug associated with MEs, noting a ROR of 1.22 (95% confidence interval: 1.21–1.24).

Conclusion: This study offers a first of its kind characterization of MEs as reported to FAERS. Reported MEs are frequent and may be associated with serious health outcomes. This FAERS data provides insights on ME prevention and offers possibilities for additional in-depth analyses.

KEYWORDS
disproportionality analysis, medication errors, pharmacovigilance, spontaneous reporting

Key Points

1. Medication errors are increasingly being reported throughout time.
2. One out of three reported medication errors are associated with serious health outcomes.
3. Medication errors among "antineoplastic and immunomodulating agents" are reported most frequently.
4. More than half of the medication error reports are submitted by consumers.
5. Medication error reports are not always complete and oppose challenges in future subanalyses.

Plain Language Summary

Medication errors (MEs) are a major public health concern which can cause harm and financial burden within the healthcare system. Characterizing MEs is crucial to develop strategies to prevent MEs in the future. The objective of this research was to characterize MEs reported more frequently than expected in the Food and Drug Administration's Adverse Event Reporting System (FAERS). The FAERS data from 2004 to 2020 was used. ME reports were identified based on 121 ME terms provided by the Medical Dictionary for Regulatory Activities® (MedDRA®). Drug names were converted and standardized. In total 488 470 ME reports were identified which mainly occurred in females (55%) and were mostly (57%) submitted by consumers. Median age of individuals with a ME was 57 years (interquartile range: 37–70 years). One in three reports stated a serious medical event associated with MEs. The most reported drugs related to MEs were anticancer drugs and drugs affecting the immune system (25%). The most common ME was "incorrect dose administered" (9%). Adalimumab was the most common drug associated with MEs, being reported roughly 1.2-fold more often than expected. In conclusion, this study offers a first of its kind characterization of MEs as reported to FAERS. Reported MEs are frequent and are reported to be harmful in some cases. This FAERS data provides insights on ME prevention and offers possibilities for additional in-depth analyses.

1 | INTRODUCTION

The National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) defines a medication error (ME) as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer."[1] This definition is also adopted by the Food and Drug Administration (FDA).[2] In addition, this definition excludes "the deliberate or intentional use (e.g., abuse, misuse, off label use) of a drug product in a manner that is inconsistent with FDA-required labeling."[3] The World Health Organization initiated the third Global Patient Safety Challenge in 2017 titled "Medication Without Harm" for the purpose of promoting solutions to address problems concerning safety of medication practices, which includes dealing with MEs.[4] In 2012 it has been estimated that the worldwide annual costs of avoidable MEs were 42 billion dollars.[5] A systematic review from 2018 showed that the prevalence of MEs ranged from 2% to 94% among adults in various study populations around the world.[6] Reported prevalence numbers of MEs vary greatly due to heterogeneity in studied populations and variations in ME definitions.[6,7] A recent 2020 study estimated that annually 237 million MEs occurred in England alone.[8] Of these MEs, the researchers estimated that 28% were potentially clinically significant. Furthermore, the same study estimated that the adverse drug events (ADEs) stemming from MEs have led to an additional annual consumption of 181 626 hospital-bed-days and contributed up to 1708 annual deaths. Another research estimated that annually 7150 ME-related deaths are preventable for inpatients in the United States of America (USA) with a life-expectancy greater than 3 months.[9] Besides the economic burden and the healthcare impact, MEs also contribute to a lack of trust in the healthcare system and to patient dissatisfaction.[10] Hence, it is of high importance to gain more insights into reported MEs in order to prevent MEs in the future.

Limited studies have been performed on MEs using data from the spontaneous reporting systems. Newbould et al. studied MEs within the European Medicines Agency (EMA's) EudraVigilance database and reported that between 2005 and 2015 a total of 147 824 case reports were related to MEs causing adverse drug reactions (ADRs), of which 41 355 occurred within the European Economic Area with a proportional increase of submitted reports over time.[11] The results of this paper mainly focused on trends over time, geographical origin of reports, and quantification of MEs and associated drugs, while there were limited results on patient characteristics, drug-ME combinations (DMEs), and no results on associated clinical event outcomes or on signals of disproportionate reporting (SDRs). Carnovale et al. found 468 677 case reports on MEs within the FDA's Adverse Event Reporting System (FAERS) between 2004 and 2017, showing more detailed results on DMEs in multiple age strata with emphasis on

SDRs.[12] However, this study provided limited information on patient characteristics and clinical outcomes of MEs. Furthermore, those studies did not touch upon the topic of data quality or completeness of the Individual Case Safety Reports (ICSRs), while research on the data quality within FAERS appears scarce.[13]

The objective of this paper was to provide an overview of ME reports from FAERS with emphasis on ME characteristics, associated patient characteristics, clinical outcomes, and SDRs of DMEs.

2 | METHODOLOGY

2.1 | Data source

FAERS is a database that contains spontaneous reports related to medication or medical devices, submitted to the FDA on adverse events (AEs), product quality complaints resulting in AEs, and MEs.[14] Anyone can freely send in a report through FDAs MedWatch Online Voluntary Reporting Form.[15] The Medical Dictionary for Regulatory Activities® (MedDRA®) is used to code AEs and MEs. This study uses MedDRA® version 23.1. The Legacy Adverse Event Reporting System (LAERS) is the predecessor of FAERS and it embodies earlier data from January 2004 up to September 2012.[16,17] The database files from the newer FAERS database are published since October 2012. The publicly available database files from LAERS and FAERS were the primary data source for this study. In the remainder of the manuscript, we refer to the combined LAERS and FAERS database as "the FAERS database."

2.2 | Data extraction and processing

The Adverse Event Open Learning through Universal Standardization (AEOLUS) system developed by Banda et al. was the cornerstone for extraction and processing of FAERS data.[18] The main functions of AEOLUS include standardization of FAERS data, deduplication of case reports, and generating SDRs. AEOLUS is available as a GitHub repository.[19] For this research, a forked version was used.[20] The original structured query language (SQL) scripts from AEOLUS were adjusted in such a way that all data files up to the end of 2020 could be downloaded. AIOLI, a drug mapping tool developed within the Medical Informatics department,[21] allowed conversion of drug names to Anatomical Therapeutic Chemical (ATC) classification. Various age units encountered in the data were converted to years. Ages between 0 and 120 years were considered valid. The age variable was considered unknown in case of missing age, missing time format, or negative age.

2.3 | ME case identification and characterization

ICSRs of MEs within FAERS were identified by using the preferred terms (PTs) from the narrow standardised MedDRA® Query (SMQ) for the key topic on MEs.[22,23] (See Table S1 for a complete list of PTs.) Characterization was performed on variables such as age, sex, drug use, indications and procedures, reporter type, country of origin, and clinical health outcomes. The clinical health outcomes were reported as "death," "life-threatening," "hospitalization (initial or prolonged)," "disability," "congenital anomaly," "required intervention to prevent permanent impairment or damage," and "other serious (important medical events)." The health outcome "other serious (important medical events)" is suggested by the FDA to be used in case that "the event [medication error] does not fit the other outcomes [i.e., death, life-threatening, etc.], but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes [i.e., death, life-threatening, etc.]."[24]

TABLE 1 Contingency table representing the necessary counts needed to perform a disproportionality analysis.

	Report count for medication error	Report count for all other events
Report count for drug of interest	A	B
Report count for all other drugs	C	D

2.4 | Disproportionality analysis

To assess the association between reported drug use and MEs, a disproportionality analysis was performed. DME-counts were performed by AEOLUS and shown in Table 1.[18]

The reporting odds ratio (ROR) was calculated with the equation:

$$\mathrm{ROR} = \frac{A/C}{B/D} = \frac{A \times D}{C \times B}. \quad (1)$$

The respective 95% confidence intervals (CIs) were calculated with the equation:

$$95\%\mathrm{CI\ for\ ROR} = e^{\ln(\mathrm{ROR}) \pm 1.96 \sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}}. \quad (2)$$

Only drugs that were marked as primary suspects in the ICSRs were considered for analysis. Thresholds for displaying relevant SDRs were applied according to the EMA: a lower bound of the 95% CI >1 and number of individual cases ≥3.[25] Stratified disproportionality analyses were also performed based on sex and age.

3 | RESULTS

The selection and the processing of ICSRs is displayed in Figure 1. A total of 14 919 552 reports were retrieved of which 10 651 341 (71%) were from the latest FAERS system. The AEOLUS system found 2 475 303 (17%) duplicates, leaving 12 444 249 (83%) reports for

data processing. A total of 11 096 667 (89%) ICSRs had a valid ATC code for the primary suspect drugs. Using the narrow SMQ for MEs, 488 470 (4%) ICSRs were identified to be related to MEs. A total of 1659 distinct DMEs could be classified under the narrow ME SMQ. About 25% of the DMEs met the criteria for disproportionality to be considered a SDR. Figure 2 shows how the number of spontaneous reports received by FAERS increased over the years from 204 538 in 2004 up to 1 588 017 in 2020, with a slight decrease in 2018. The proportion of ME reports followed a trend in which the proportion of MEs declined from 3.9% in 2004 to 1.7% in 2013, but increased up to 7.5% in 2020.

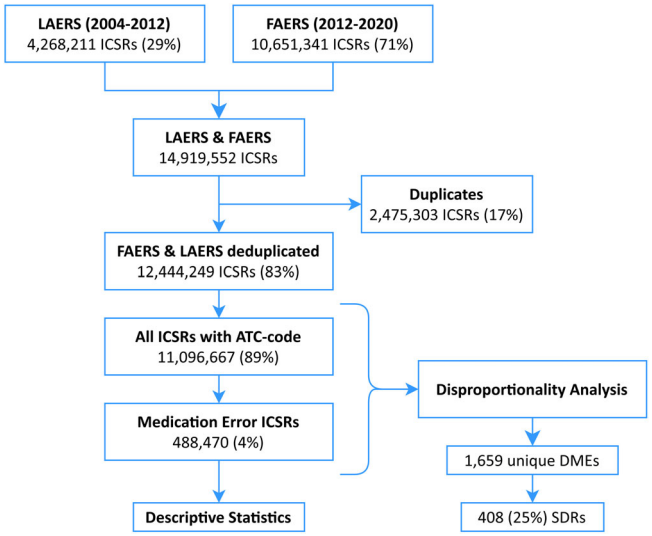

FIGURE 1 Flowchart for the selection and analysis of individual case safety reports (ICSRs). ATC, Anatomical Therapeutic Chemical classification; DME, Drug-medication error combination; FAERS, Food and Drug Administration's Adverse Event Reporting System; LAERS, Legacy Adverse Event Reporting System; SDR, Signal of Disproportionate Reporting.

Table 2 provides an overview of the report, reporter, and database characteristics of the 488 470 ICSRs related to MEs. About 419 931 (86%) of the cases originated from the latest FAERS database. In 269 032 (55%) cases, the sex of the user of the primary drug suspect was registered as female, 162 445 (33%) were male, and 56 993 (12%) were not reported. The median reported age was 57 years with an interquartile range of 37–70 years as presented in Table 3. More detailed age distributions of both the ME population and the entire FAERS population, additionally stratified by sex, are provided in Figures S1–S6. Consumers accounted for 286 469 (59%) of submitted ICSRs, healthcare professionals (HCPs) for 117 788 (24%), lawyers for 2021 (<1%), and for 36 769 (8%) of ICSRs the reporter type was unknown. Most of the reports, being 387 656 (79%), originated from the USA and 29 640 (6%) were from unknown origin. The health outcome for most MEs was not reported, accounting for 338 744 (63%) reports. The most commonly reported health outcome was hospitalization in 65 369 (12%) reports. Health

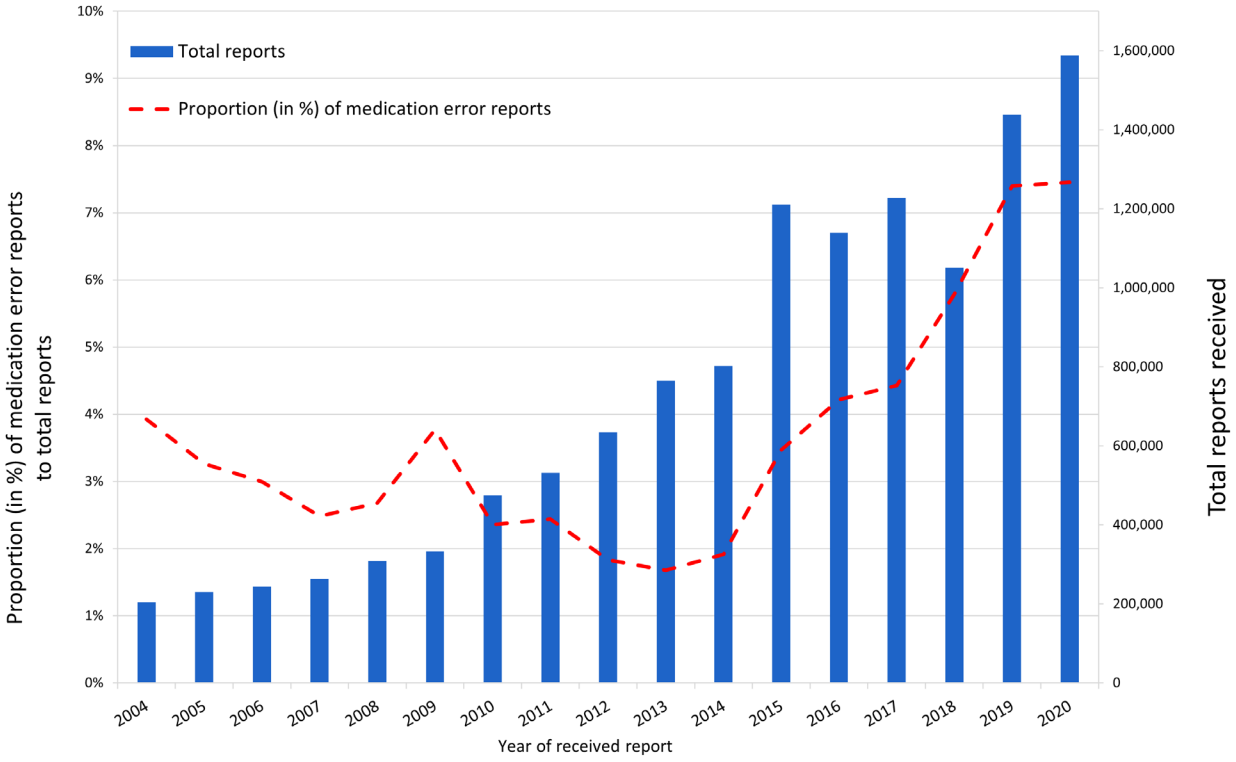

FIGURE 2 Proportion of medication error reports compared to the total number of reports received in FAERS between 2004 and 2020. FAERS, Food and Drug Administration's Adverse Event Reporting System.

TABLE 2 Patient, reporter and data characteristics of medication error related individual case safety reports.

	Reports (proportion)
Total medication error reports	488 470 (100%)
Database	
FAERS	419 931 (86%)
LAERS	68 539 (14%)
Sex	
Female	269 032 (55%)
Male	162 445 (33%)
Not reported	56 993 (12%)
Health outcomes	
Hospitalization (initial or prolonged)	65 369 (12%)
Death	19 891 (4%)
Life-threatening	9242 (2%)
Disability	5207 (1%)
Required Intervention to prevent permanent impairment/damage	1845 (<1%)
Congenital anomaly	156 (<1%)
Other serious (important medical event)	95 394 (18%)
Not reported	338 744 (63%)
Reporter	
Consumer	286 469 (59%)
Physician	81 365 (17%)
Pharmacist	36 423 (7%)
Other health-professional	45 423 (9%)
Lawyer	2021 (<1%)
Not reported	36 769 (8%)
Reporter country	
United States of America	387 656 (79%)
152 countries, each contributing <5%	71 174 (15%)
Not reported	29 640 (6%)
Unique drugs per report	
1	337 640 (69%)
2	56 900 (12%)
3	26 760 (5%)
4	16 434 (3%)
5	11 589 (2%)
6 or more	39 147 (8%)

Abbreviations: FAERS, Food and Drug Administration Adverse Event Reporting System; LAERS, Legacy Adverse Event Reporting System.

outcomes death, life-threatening, disability, congenital anomaly, and "required intervention to prevent permanent impairment or damage" were each reported in less than 5% of the cases. The majority of the ICSRs (337 640 reports; 69%) reported one drug per ICSR.

TABLE 3 Age characteristics of individuals from the medication error related individual case safety reports.

	Reports (proportion)
Reports with valid age	272 655 (55.8%)
Reports with invalid age	215 815 (44.2%)
Median age, in years (IQR)	57 (37–70)
Age groups	**Reports (proportion)**
Neonates (0–28 days)	1603 (<1%)
Infants (29 days–1 year)	2826 (1%)
Children (2–11 years)	13 685 (3%)
Adolescents (12–17 years)	11 147 (2%)
Adults (18–64 years)	161 190 (33%)
Elderly (≥65 years)	97 731 (20%)
Not reported	200 288 (41%)

Abbreviation: IQR, interquartile range.

From the 488 470 ICSRs on MEs, there were 302 325 (62%) ICSRs which listed an indication for the primary drug suspect. The most frequent system organ classes (SOCs) corresponding with the indications of the primary drug suspect were "Musculoskeletal and connective tissue disorders" (46 129 reports; 15%), "Metabolism and nutrition disorders" (35 151 reports; 12%), "Nervous system disorders" (25 042 reports; 8%), "Skin and subcutaneous tissue disorders" (24 689 reports; 8%), and "Surgical and medical procedures" (23 062 reports; 8%), accounting for 51% of all SOCs. More details are provided in Figure S7.

A total of 512 933 DMEs were found among the 488 470 ME-related ICSRs as seen in Figure 3. About 70% of all DMEs were associated with "Antineoplastic and Immunomodulating agents" (129 588 DMEs; 25%), drugs from the "Nervous system" (90 090 DMEs; 18%), drugs involved in the "Alimentary tract and metabolism" (76 351 DMEs; 15%), and drugs for the "Respiratory system" (61 941 DMEs; 12%).

The most frequently reported PTs were "Incorrect dose administered" (90 903; 9%), "Wrong technique in product usage process" (84 642; 8%), and "Inappropriate schedule of product administration" (46 250; 5%) as seen in Table 4.

Disproportionality results are displayed in Table 5. Adalimumab (ATC: L04AB04) was the drug with most MEs reported, accounting for 25 678 ICSRs, and represented a ROR of 1.22 (95% CI: 1.21–1.24). The second most frequently reported drug with a stronger SDR was attributed to salbutamol, accounting for 17 175 ICSRs and a ROR of 14.77 (95% CI: 14.52–15.02). An almost equally frequent and strong SDR was shown for pegfilgrastim (ATC: 15089), accounting for 15 089 ICSRs and a ROR of 14.23 (95% CI: 13.98–14.49). Notably, the route of administration for most drugs displayed in Table 5 was parenteral.

Disproportionality results based on highest ROR are displayed in Table 6. Triprolidine (ATC: R01AX03) showed the strongest signal with a ROR of 48.08 (95% CI: 10.76–214.82), but the number of reports was three. Stratified results based on sex and age groups

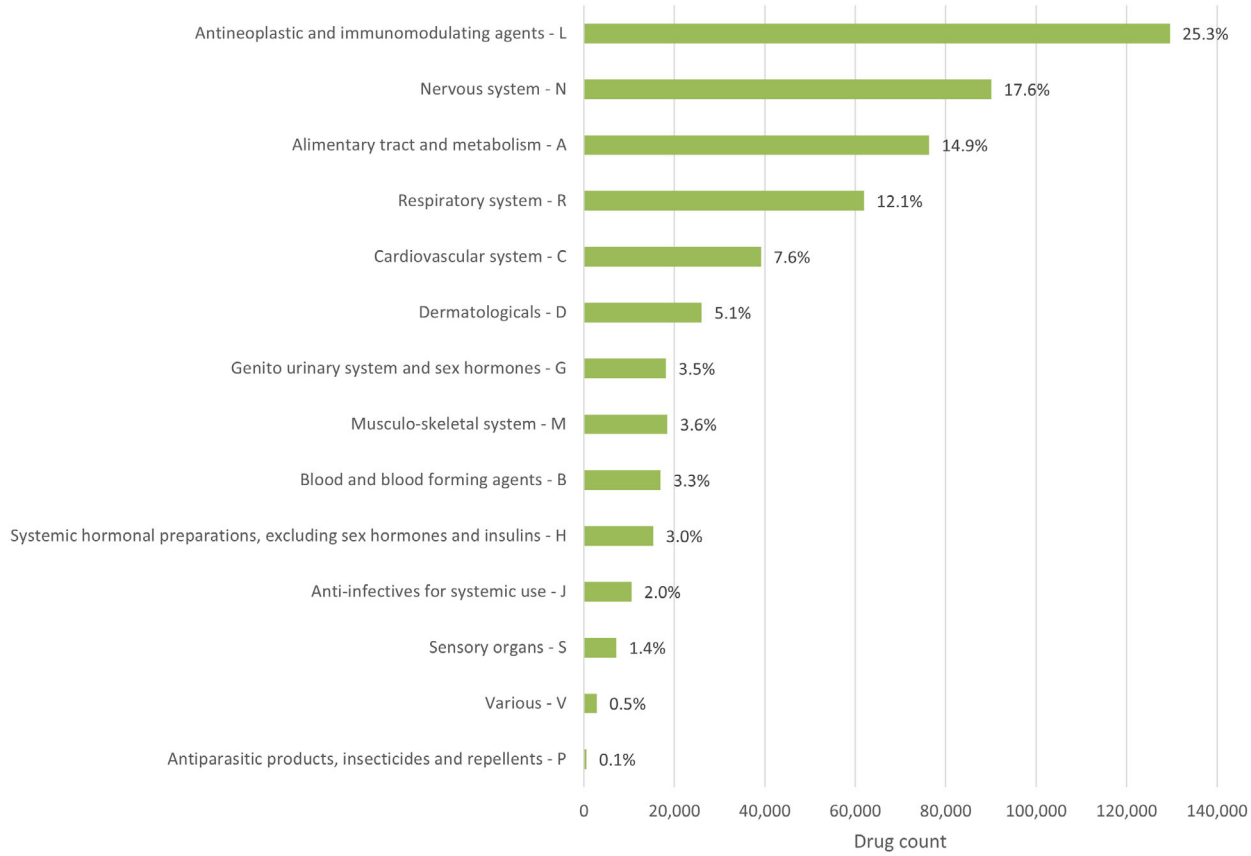

FIGURE 3 The drug count forthcoming from a total count of 512 933 drug-medication error combinations found in the 488 470 medication error-related individual case safety reports represented on level 1 of the Anatomical Therapeutic Chemical classification.

TABLE 4 Top 10 most common narrow medication errors reported.

	Occurrence (proportion)
Total drug-medication error combinations	512 933 (100%)
Reported type of medication error	
Incorrect dose administered	90 903 (9%)
Wrong technique in product usage process	84 642 (8%)
Inappropriate schedule of product administration	46 250 (5%)
Accidental exposure to product	31 922 (3%)
Medication error	30 910 (3%)
Accidental overdose	19 692 (2%)
Device use error	19 682 (2%)
Product storage error	19 337 (2%)
Expired product administered	17 443 (2%)
Wrong technique in device usage process	14 758 (1%)

showed some overlap, but overall there was a wide variety regarding the top 10 strongest SDRs. The stratified results are available in Tables S2–S9.

4 | DISCUSSION

In this study, we investigated the frequency of MEs, it's characteristics, and signals of disproportionality. We observed an increase in reporting of MEs over time, almost half of the MEs were associated with serious health outcomes, and MEs among antineoplastic and immunomodulating agents were reported most frequently.

The observed increased reporting rate in FAERS can be related to increased healthcare access, utilization due to the Affordable Care Act enacted in 2010,[26–28] and the introduction of the reporting form FDA3500B, released in 2013, which aided consumers in voluntary reporting in addition to online reporting via MedWatch.[29] Also, public health campaigns on medication safety might have contributed to awareness on the necessity of reporting and therefore increased reporting.[30,31] The fact that FAERS ICSRs were mostly submitted by consumers rather than HCPs resonates with literature emphasizing many limiting factors for HCPs, such as lack of time, difficulties determining the cause of ADE, poor reporting systems and uncertainty about the reporting procedures.[32] Furthermore, other research reported that consumers were motivated to self-report if they were under the impression that HCPs did not (have the time to) report an ADR, did not take their ADR seriously, or if HCPs asked consumers to report themselves.[33] Also, we assume that MEs might not be

TABLE 5 The 10 most frequent drug-medication error combination resulting in a signal of disproportionate reporting.

ATC level 5 code	Generic drug name; route of administration	Reports	ROR	95% CI
L04AB04	Adalimumab; parenteral	25 678	1.22	1.21–1.24
R03AC02	Salbutamol; inhalant	17 175	14.77	14.52–15.02
L03AA13	Pegfilgrastim; parenteral	15 089	14.23	13.98–14.49
C10AX13	Evolocumab; parenteral	14 544	7.55	7.42–7.68
D10AD03	Adapalene; topical	11 812	2.32	2.28–2.37
N02CD01	Erenumab; parenteral	11 223	15.48	15.16–15.80
A10AE04	Insulin glargine; parenteral	11 172	4.59	4.50–4.68
A10AB04	Insulin lispro; parenteral	10 681	5.02	4.92–5.12
A10BJ01	Exenatide; parenteral	8721	2.46	2.41–2.51
N02BE01	Paracetamol; systemic, rectal	8719	4.55	4.46–4.66

Abbreviations: ATC, Anatomical Therapeutic Chemical classification; CI, confidence interval; ROR, reporting odds ratio.

TABLE 6 The 10 strongest signals of disproportionate reporting related to medication errors.

ATC level 5 code	Generic drug name; route of administration	Reports	ROR	95% CI
R01AX03	Triprolidine; oral	3	48.08	10.76–214.82
D08AX07	Sodium hypochlorite; topical	7	40.79	15.81–105.24
A10BJ04	Albiglutide; parenteral	7837	40.38	39.25–41.54
R06AX07	Phenylephrine; ophthalmic	3	38.46	9.19–160.95
S01GA05	Potassium acetate; parenteral	7	22.44	9.49–53.06
L03AA13	"Zoster, live attenuated; systemic"	50	19.79	14.41–27.17
A06AD15	Sodium acetate; parenteral	12	19.72	10.33–37.67
R01AX06	Tetracaine; topical	4	18.32	6.03–55.64
N02BA51	Ipratropium bromide; nasal	3	16.03	4.52–56.79
R03BX	Erenumab; parenteral	11 223	15.48	15.16–15.80

Abbreviations: ATC, Anatomical Therapeutic Chemical classification; CI, confidence interval; ROR, reporting odds ratio.

recognized or considered as AEs by the HCP, because the patient never mentions them or does not seek HCP guidance. Interestingly, the proportion and the amount of ME-related ICSRs also increased over time. Possible causes might be due to an increase in (i) dispensed prescriptions,[34] (ii) aging population,[35,36] (iii) novel drug approvals, (iv) healthcare complexity,[36] and (v) polypharmacy.[37–39]

Most described demographic attributes correspond with what is observed among the general population of health consumers. Most subjects in ME ICSRs were women, who receive more drug prescriptions and have a higher healthcare consumption than men.[40,41] Ageing coincides with an increased risk of disease development and thus increased drug use.[39] Despite lower amount of reports among the pediatric population in this study, the risk of MEs in children should not be underestimated; a systematic review reported that MEs occurred in up to 27% of treated children.[42] The observed ME health outcomes from this study as described in Table 2 show similarities with especially the moderate and severe health outcomes of MEs from a systematic review focusing on MEs among nursing home residents, mostly in the USA.[43] It seems that polypharmacy individuals were underrepresented in our study as less than one-third of the ICSRs reported individuals using 2 or more unique drugs at the time of the ME, while literature suggests that half of the medication users in the USA use 2 or more drugs concomitantly.[37]

Literature on MEs related to drug use is limited. Only a few recent studies that were performed outside of the USA emphasize the issue of frequent MEs among cancer patients.[44–46] The overall proportions of drugs on ATC level 1 related to MEs from the narrow SMQ in our study were largely similar to findings from Carnovale et al.[12] Findings by Newbould et al. based on EudraVigilance data showed that MEs were mainly reported for drugs belonging to the "nervous system" drug group, similar to our findings in FAERS.[11] Vaccines (ATC: J07) were most commonly reported in EudraVigilance, but rarely in FAERS data, as vaccine-related reports are primarily submitted to the Vaccine Adverse Event Reporting System (VAERS) in the USA. Findings from spontaneous reporting systems do not necessarily reflect findings from research focused on active identification of MEs,[47,48] which emphasizes the underreporting problem and thus the lack of a complete overview of MEs within a database with spontaneous reports on ADRs. The most frequently reported MEs by Carnovale et al. and Newbould et al.

correspond with our findings, although the exact frequencies or proportions were not provided in the paper of Carnovale et al.[11,12]

Not all of the most frequent and strongest SDRs observed in this study could be confirmed by literature. For instance, there is no focused literature on the association between adapalene use and the risk or causes of MEs. While there are studies published on adapalene adherence, there is no information regarding MEs.[49,50] Narratives of received ICSRs, provided by the FDA, show how patients have overdosed on over-the-counter (OTC) adapalene, without providing further background information on what was the root-cause of overdosing.

For the drug pegfilgrastim, MEs were mostly related to issues with (handling of) the device. Previous studies reported failure rates between 1.3% and 6.9%, in particular for the on-body injector formulation.[51–55] However, it is unclear whether this represents MEs or product quality issues. Received narratives from the FDA show a variety of circumstances under which pegfilgrastim-related MEs occurred, emphasizing the necessary caution when dealing with such drugs, especially in complex healthcare settings.

For triprolidine, which had the strongest SDR (but with low number of reports), there was no literature confirming this association. Limited literature was available on the second strongest SDR forthcoming from sodium hypochlorite in relation to MEs.[56–59] Albiglutide was overall found to be a relatively frequent and strong signal in terms of narrow PTs within FAERS, however, scientific literature on albiglutide was limited,[60] and the drug has been discontinued for commercial grounds since 2018.[61] The inhalation medication salbutamol produced a strong SDR, backed with a high frequency of ME occurrence. It is a commonly used drug among patients with a respiratory disease and it is known that MEs occur frequently among patients using inhaler devices, while sometimes HCPs can be also at fault for inhaler related MEs.[62–65]

4.1 | Strengths and limitations

As for all observational studies, our study has strengths and limitations. Despite the increased reporting of MEs over time, findings in literature suggest that barriers remain in healthcare practices for reporting MEs which lead to (i) underreporting as well as selective reporting.[66,67] It is already known that FAERS in general has an underreporting problem similar to all other spontaneous reporting systems.[68] (ii) Vaccine-related-ADRs are not included in the database (as these are not part of FAERS) and unmapped RxNorm names could not be included in the disproportionality analysis, which might bias the results and also make the results less comparable with findings from other spontaneous reporting systems.[11,12] (iii) MedDRA® PTs are by itself debatable in the sense that some describe similar concepts or seem generally too vague to interpret. On top of that, MedDRA® PTs might not have been properly chosen for ICSRs which indeed has already been described in practice.[69] (iv) Despite all efforts of the code-developers for the deduplication of the FAERS data, there might be some duplicate cases present in the data. (v) Missing data in FAERS limits the interpretability of some results and might prohibit stratified analyses. (vi) Finally, the disproportionality analysis only emphasizes the disproportionality of a given DME rather than true causality. Further causality analysis is necessary for an in-depth interpretation of a SDR. The strengths of our study are that we provided details on ICSRs for MEs in terms of patient characteristics, health outcomes, and reporter details. Also, this study provides more information on unreported data within the ME population which is important to consider when conducting subsequent research on MEs. Finally, this study contributes to the body of knowledge on reported MEs, providing insights on which MEs were commonly reported and what future focus areas should be for prevention of MEs.

5 | CONCLUSION

This study offers a first of its kind characterization of MEs as reported to FAERS. MEs were increasingly being reported, mostly by consumers. Most reported MEs were associated with adults and females. About 1 out of 3 of the reported MEs resulted in a serious health outcome. A wide variety of DMEs were found, some not or rarely reported in literature, most often involving parenteral drugs. This FAERS data provides insights on ME prevention and offers possibilities for additional in-depth analyses.

ACKNOWLEDGEMENTS

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work has received support from the European Health Data and Evidence Network (EHDEN) project. EHDEN has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No. 806968.

CONFLICT OF INTEREST STATEMENT

The research group from the Department of Medical Informatics receives/received unconditional research grants from Chiesi, GlaxoSmithKline (GSK), UCB, and Amgen, Johnson and Johnson, and the European Medicines Agency, none of which relate to the content of this manuscript. Outside this submitted work, the institution of LL received fees for lectures (IPSA vzw) and external expert consultation (AstraZeneca).

ORCID

Victor Pera https://orcid.org/0000-0002-0786-4712
Frauke van Vaerenbergh https://orcid.org/0000-0002-7709-7651
Jan A. Kors https://orcid.org/0000-0002-4929-026X
Erik M. van Mulligen https://orcid.org/0000-0003-1377-9386
Lies Lahousse https://orcid.org/0000-0002-3494-4363
Johan van der Lei https://orcid.org/0000-0002-9203-3410
Peter R. Rijnbeek https://orcid.org/0000-0003-0621-1979
Katia M. C. Verhamme https://orcid.org/0000-0001-8162-4904

REFERENCES

1. rxr@usp.org. About Medication Errors. NCC MERP. Published July 18, 2014. Accessed January 18, 2021. https://www.nccmerp.org/about-medication-errors

2. Research C for DE and. Working to Reduce Medication Errors. FDA. Published online August 23, 2019. Accessed September 17, 2021. https://www.fda.gov/drugs/information-consumers-and-patients-drugs/working-reduce-medication-errors
3. Research C for DE and. Medication Errors Related to CDER-Regulated Drug Products. FDA. Published August 25, 2023. Accessed November 10, 2023. https://www.fda.gov/drugs/drug-safety-and-availability/medication-errors-related-cder-regulated-drug-products
4. WHO | Medication Without Harm. Published 2022. Accessed January 13, 2021. https://www.who.int/initiatives/medication-without-harm
5. Aitken M, Gorokhovich L. Advancing the responsible use of medicines: applying levers for change. *Social Sci Res Netw*. 2012. doi:10.2139/ssrn.2222541
6. Assiri GA, Shebl NA, Mahmoud MA, et al. What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature. *BMJ Open*. 2018;8(5):e019101. doi:10.1136/bmjopen-2017-019101
7. Lisby M. Department of Quality Improvement and Patient Safety AUH Aarhus,Denmark, Department of Clinical Pharmacology AUH Aarhus,Denmark, et al. how are medication errors defined? A systematic literature review of definitions and characteristics. *International J Qual Health Care*. 2020;22(6):507-518. doi:10.1093/intqhc/mzq059
8. Elliott RA, Camacho E, Jankovic D, Sculpher MJ, Faria R. Economic analysis of the prevalence and clinical and economic burden of medication error in England. *BMJ Qual Saf*. 2021;30:96-105. doi:10.1136/bmjqs-2019-010206
9. Rodwin BA, Bilan VP, Merchant NB, et al. Rate of preventable mortality in hospitalized patients: a systematic review and meta-analysis. *J Gen Intern Med*. 2020;35(7):2099-2106. doi:10.1007/s11606-019-05592-5
10. Tariq RA, Vashisht R, Sinha A, Scherbak Y. Medication dispensing errors and prevention. *StatPearls*. StatPearls Publishing; 2020 Accessed January 13, 2021. http://www.ncbi.nlm.nih.gov/books/NBK519065/
11. Newbould V, Le Meur S, Goedecke T, Kurz X. Medication errors: a characterisation of spontaneously reported cases in EudraVigilance. *Drug Saf*. 2017;40(12):1241-1248. doi:10.1007/s40264-017-0569-3
12. Carnovale C, Mazhar F, Pozzi M, Gentili M, Clementi E, Radice S. A characterization and disproportionality analysis of medication error related adverse events reported to the FAERS database. *Expert Opin Drug Saf*. 2018;17(12):1161-1169. doi:10.1080/14740338.2018.1550069
13. Wong CK, Ho SS, Saini B, Hibbs DE, Fois RA. Standardisation of the FAERS database: a systematic approach to manually recoding drug name variants. *Pharmacoepidemiol Drug Saf*. 2015;24(7):731-737. doi:10.1002/pds.3805
14. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). FDA. Published May 22, 2019. Accessed July 9, 2021. https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers
15. MedWatch Online Voluntary Reporting Form. Published 2019. Accessed July 9, 2021. https://www.accessdata.fda.gov/scripts/medwatch/index.cfm
16. Food and Drug Administration. FAERS Quarterly Data Extract Files. Published 2021. Accessed July 9, 2021. https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html
17. FAIRsharing Team. FAIRsharing record for: FDA's Adverse Event Reporting System. Published online 2022 10.25504/FAIRSHARING.AB1BD6
18. Banda JM, Evans L, Vanguri RS, Tatonetti NP, Ryan PB, Shah NH. A curated and standardized adverse drug event resource to accelerate drug safety research. *Sci Data*. 2016;3(1):160026. doi:10.1038/sdata.2016.26
19. Itscomputingllc/faersdbstats. Published online February 24, 2021. Accessed July 7, 2021 https://github.com/Itscomputingllc/faersdbstats
20. Parry R. AEOLUS. https://github.com/mi-erasmusmc/faersdbstats. Published online 2021. Accessed July 26, 2022. https://github.com/mi-erasmusmc/faersdbstats
21. Parry R. AIOLI. https://github.com/mi-erasmusmc/aioli. Published online 2021. Accessed July 7, 2021. https://github.com/mi-erasmusmc/aioli
22. List of SMQ topics. Published online September 2020. Accessed January 11, 2021. https://admin.new.meddra.org/sites/default/files/page/documents/List%20of%20SMQ%20topics%20September%202020.pdf
23. Standardised MedDRA Queries | MedDRA. Published 2021. Accessed January 11, 2021. https://www.meddra.org/standardised-meddra-queries
24. Office of the Commissioner. Reporting Serious Problems to FDA. FDA. Published September 9, 2020. Accessed March 25, 2022. https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda
25. European Medicines Agency. Screening for adverse reactions in EudraVigilance. Published online December 19, 2016. Accessed July 8, 2021. https://www.ema.europa.eu/en/documents/other/screening-adverse-reactions-eudravigilance_en.pdf
26. Affordable Care Act (ACA) – HealthCare.gov Glossary. HealthCare.gov. Published 2021. Accessed November 9, 2021. https://www.healthcare.gov/glossary/affordable-care-act/
27. Glied S, Ma S, Borja AA. Effect of the affordable care act on health care access. *Issue Brief Commonw Fund*. 2017;13:1-11.
28. Percent insured. Peterson-KFF Health System Tracker. Published 2021. Accessed November 9, 2021. https://www.healthsystemtracker.org/indicator/access-affordability/percent-insured/
29. Toki T, Ono S. Spontaneous reporting on adverse events by consumers in the United States: an analysis of the Food and Drug Administration adverse event reporting system database. *Drugs – Real World Outcomes*. 2018;5(2):117-128. doi:10.1007/s40801-018-0134-0
30. Recognize and Report It. Oncology Nursing News. Published October 12, 2018. Accessed November 9, 2021. https://www.oncnursingnews.com/view/recognize-and-report-it
31. Uppsala Monitoring Centre | #MedSafetyWeek. Published November 8, 2021. Accessed November 9, 2021. https://www.who-umc.org/global-pharmacovigilance/pharmacovigilance-communications/medsafetyweek/
32. Stergiopoulos S, Brown CA, Felix T, Grampp G, Getz KA. A survey of adverse event reporting practices among US healthcare professionals. *Drug Saf*. 2016;39(11):1117-1127. doi:10.1007/s40264-016-0455-4
33. Al Dweik R, Stacey D, Kohen D, Yaya S. Factors affecting patient reporting of adverse drug reactions: a systematic review. *Br J Clin Pharmacol*. 2017;83(4):875-883. doi:10.1111/bcp.13159
34. The Use of Medicines in the U.S. – Spending and usage trends and outlook. 2025 Published online May 2021. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-use-of-medicines-in-the-us/iqi-the-use-of-medicines-in-the-us-05-21-forweb.pdf
35. Bureau UC. The U.S. Joins Other Countries With Large Aging Populations. Census.gov. Published October 2019. Accessed November 10, 2021. https://www.census.gov/library/stories/2018/03/graying-america.html
36. Smith M, Saunders R, Stuckhardt L, McGinnis JM, America C, on the LHCS in, Medicine I of. *Imperative: Managing Rapidly Increasing Complexity*. National Academies Press; 2013 Accessed November 10, 2021. https://www.ncbi.nlm.nih.gov/books/NBK207221/
37. Quinn KJ, Shah NH. A dataset quantifying polypharmacy in the United States. *Sci Data*. 2017;4:170167. doi:10.1038/sdata.2017.167
38. Oktora MP, Denig P, Bos JHJ, Schuiling-Veninga CCM, Hak E. Trends in polypharmacy and dispensed drugs among adults in The Netherlands as compared to the United States. *PLoS One*. 2019;14(3):e0214240. doi:10.1371/journal.pone.0214240

39. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999–2012. *JAMA*. 2015;314(17):1818-1831. doi:10.1001/jama.2015.13766
40. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. *J Womens Health*. 2014;23(2):112-119. doi:10.1089/jwh.2012.3972
41. Osika Friberg I, Krantz G, Määttä S, Järbrink K. Sex differences in health care consumption in Sweden: a register-based cross-sectional study. *Scand J Public Health*. 2016;44(3):264-273. doi:10.1177/1403494815618843
42. Rinke ML, Bundy DG, Velasquez CA, et al. Interventions to reduce pediatric medication errors: a systematic review. *Pediatrics*. 2014;134(2):338-360. doi:10.1542/peds.2013-3531
43. Ferrah N, Lovell JJ, Ibrahim JE. Systematic review of the prevalence of medication errors resulting in hospitalization and death of nursing home residents. *J Am Geriatr Soc*. 2017;65(2):433-442. doi:10.1111/jgs.14683
44. Suh Y, Ah YM, Lee E, Lee JY. Association of inappropriate polypharmacy with emergency department visits in older patients receiving anti-neoplastic therapy: a population-based study. *Support Care Cancer*. 2021;29(6):3025-3034. doi:10.1007/s00520-020-05759-5
45. Schlichtig K, Dürr P, Dörje F, Fromm MF. Medication errors during treatment with new Oral anticancer agents: consequences for clinical practice based on the AMBORA study. *Clin Pharmacol Ther*. 2021;110(4):1075-1086. doi:10.1002/cpt.2338
46. Dorothy A, Yadesa TM, Atukunda E. Prevalence of medication errors and the associated factors: a prospective observational study among cancer patients at Mbarara regional referral hospital. *Cancer Manag Res*. 2021;13:3739-3748. doi:10.2147/CMAR.S307001
47. Laatikainen O, Sneck S, Turpeinen M. The risks and outcomes resulting from medication errors reported in the Finnish tertiary care units. *Front Pharmacol*. 2020;10:1571. doi:10.3389/fphar.2019.01571
48. Berdot S, Sabatier B, Gillaizeau F, Caruba T, Prognon P, Durieux P. Evaluation of drug administration errors in a teaching hospital. *BMC Health Serv Res*. 2012;12:60. doi:10.1186/1472-6963-12-60
49. Tobiasz A, Nowicka D, Szepietowski JC. Acne vulgaris—novel treatment options and factors affecting therapy adherence: a narrative review. *J Clin Med*. 2022;11(24):7535. doi:10.3390/jcm11247535
50. Moradi Tuchayi S, Alexander TM, Nadkarni A, Feldman SR. Interventions to increase adherence to acne treatment. *Patient Prefer Adherence*. 2016;10:2091-2096. doi:10.2147/PPA.S117437
51. Mahler LJ. On-body injector: an administration device for pegfilgrastim. *Clin J Oncol Nurs*. 2017;21(1):121-122. doi:10.1188/17.CJON.121-122
52. Joshi RS, Egbuna OI, Cairns AS, et al. Performance of the pegfilgrastim on-body injector as studied with placebo buffer in healthy volunteers. *Curr Med Res Opin*. 2017;33(2):379-384. doi:10.1080/03007995.2016.1257980
53. Stuessy P, Sanchez FA, Schober M. Retrospective review of pegfilgrastim on-body injector delivery rates in a large health system. *J Clin Oncol*. 2017;35(15_suppl):e18273. doi:10.1200/JCO.2017.35.15_suppl.e18273
54. Nicole MMP. Comparing grade 4 neutropenia associated with pegfilgrastim administered via the onpro device versus manual injection with a prefilled syringe. Published Online September 18, 2018. Accessed May 26, 2023. https://jhoponline.com/issue-archive/2018-issues/jhop-september-2018-vol-8-no-3/17561-comparing-grade-4-neutropenia-associated-with-pegfilgrastim-administered-via-the-onpro-device-versus-manual-injection-with-a-prefilled-syringe
55. Maahs L, Tang A, Saheli ZA, Jacob B, Polasani R, Hwang C. Real-world effectiveness of the pegfilgrastim on-body injector in preventing severe neutropenia. *J Oncol Pharm Pract*. 2022;28(1):17-23. doi:10.1177/1078155220980517
56. Gursoy UK, Bostancı V, Kosger HH. Palatal mucosa necrosis because of accidental sodium hypochlorite injection instead of anaesthetic solution. *Int Endod J*. 2006;39(2):157-161. doi:10.1111/j.1365-2591.2006.01067.x
57. Marroni M, Menichetti F. Accidental intravenous infusion of sodium hypochlorite. *DICP Ann Pharmacother*. 1991;25(9):1008-1009. doi:10.1177/106002809102500919
58. Peck BW, Workeneh B, Kadikoy H, Abdellatif A. Sodium hypochlorite-induced acute kidney injury. *Saudi J Kidney Dis Transplant*. 2014;25(2):381-384. doi:10.4103/1319-2442.128553
59. Pontes F, Pontes H, Adachi P, Rodini C, Almeida D, Pinto D Jr. Gingival and bone necrosis caused by accidental sodium hypochlorite injection instead of anaesthetic solution. *Int Endod J*. 2008;41(3):267-270. doi:10.1111/j.1365-2591.2007.01340.x
60. Zhou AY, Trujillo JM. Comparison of usability, accuracy, preference, and satisfaction among three once-weekly GLP-1 receptor agonist pen devices. *Diabetes Spectr Publ Am Diabetes Assoc*. 2018;31(4):359-366. doi:10.2337/ds17-0048
61. Eperzan▼(albiglutide): global discontinuation of medicine. Published online September 9, 2017.
62. Usmani OS, Lavorini F, Marshall J, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. *Respir Res*. 2018;19:10. doi:10.1186/s12931-017-0710-y
63. Sulku J, Bröms K, Högman M, et al. Critical inhaler technique errors in Swedish patients with COPD: a cross-sectional study analysing video-recorded demonstrations. *NPJ Prim Care Respir Med*. 2021;31:5. doi:10.1038/s41533-021-00218-y
64. Plaza V, Giner J, Rodrigo GJ, Dolovich MB, Sanchis J. Errors in the use of inhalers by health care professionals: a systematic review. *J Allergy Clin Immunol Pract*. 2018;6(3):987-995. doi:10.1016/j.jaip.2017.12.032
65. Sanchis J, Gich I, Pedersen S. Systematic review of errors in inhaler use: has patient technique improved over time? *Chest*. 2016;150(2):394-406. doi:10.1016/j.chest.2016.03.041
66. Rutledge DN, Retrosi T, Ostrowski G. Barriers to medication error reporting among hospital nurses. *J Clin Nurs*. 2018;27(9–10):1941-1949. doi:10.1111/jocn.14335
67. Rishoej RM, Hallas J, Juel Kjeldsen L, Thybo Christesen H, Almarsdóttir AB. Likelihood of reporting medication errors in hospitalized children: a survey of nurses and physicians. *Ther Adv Drug Saf*. 2018;9(3):179-192. doi:10.1177/2042098617746053
68. Alatawi YM, Hansen RA. Empirical estimation of under-reporting in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). *Expert Opin Drug Saf*. 2017;16(7):761-767. doi:10.1080/14740338.2017.1323867
69. Schroll JB, Maund E, Gøtzsche PC. Challenges in coding adverse events in clinical trials: a systematic review. *PLoS One*. 2012;7(7):e41174. doi:10.1371/journal.pone.0041174

SUPPORTING INFORMATION

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

How to cite this article: Pera V, van Vaerenbergh F, Kors JA, et al. Descriptive analysis on disproportionate medication errors and associated patient characteristics in the Food and Drug Administration's Adverse Event Reporting System. *Pharmacoepidemiol Drug Saf*. 2023;1-10. doi:10.1002/pds.5743