ClinicoEconomics and Outcomes Research

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ORIGINAL RESEARCH

Seriousness, preventability, and burden impact of reported adverse drug reactions in Lombardy emergency departments: a retrospective 2-year characterization

This article was published in the following Dove Press journal:
ClinicoEconomics and Outcomes Research
3 December 2014
Number of times this article has been viewed

Valentina Perrone[1,*]
Valentino Conti[2,*]
Mauro Venegoni[2]
Stefania Scotto[2]
Luca Degli Esposti[3]
Diego Sangiorgi[3]
Lucia Prestini[4]
Sonia Radice[1]
Emilio Clementi[5,6]
Giuseppe Vighi[2,4]

[1]Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, University Hospital Luigi Sacco, Università di Milano, Milan, Italy; [2]Regional Centre for Pharmacovigilance, Lombardy, Milan, Italy; [3]CliCon Srl, Health, Economics and Outcomes Research, Ravenna, Italy; [4]Unit of Clinical Pharmacology and Pharmacovigilance, Niguarda Ca'Granda Hospital, Milan, Italy; [5]Unit of Clinical Pharmacology, CNR Institute of Neuroscience, Department of Biomedical and Clinical Sciences, University Hospital Luigi Sacco, Università di Milano, Milan, Italy; [6]Scientific Institute, IRCCS Eugenio Medea, Lecco, Italy

*These authors contributed equally to the work

Objective: The purpose of this study was to determine the prevalence of adverse drug reactions (ADRs) reported in emergency departments (EDs) and carry out a thorough characterization of these to assess preventability, seriousness that required hospitalization, subsequent 30-day mortality, and economic burden.

Methods: This was a retrospective cohort study of data from an active pharmacovigilance project at 32 EDs in the Lombardy region collected between January 1, 2010 and December 31, 2011. Demographic, clinical, and pharmacological data on patients admitted to EDs were collected by trained and qualified monitors, and deterministic record linkage was performed to estimate hospitalizations. Pharmacoeconomic analyses were based on Diagnosis-Related Group reimbursement.

Results: 8,862 ADRs collected with an overall prevalence rate of 3.5 per 1,000 visits. Of all ADRs, 42% were probably/definitely preventable and 46.4% were serious, 15% required hospitalization, and 1.5% resulted in death. The System Organ Classes most frequently associated with ADRs were: skin and subcutaneous tissue, gastrointestinal, respiratory thoracic and mediastinal, and nervous system disorders. The most common Anatomical Therapeutic Chemical classes involved in admissions were J (anti-infectives and immunomodulating agents), B (blood and blood-forming organs), and N (nervous system). Older age, yellow and red triage, higher number of concomitantly taken drugs, and previous attendance in ED for the same ADR were significantly associated with an increased risk of hospitalization. The total cost associated with ADR management was €5,184,270, with a mean cost per patient of €585. Fifty-eight percent of the economic burden was defined as probably/definitely preventable.

Conclusion: ADRs are a serious health/economic issue in EDs. This assessment provides a thorough estimation of their seriousness, preventability, and burden impact in a large population from a representative European region.

Keywords: adverse drug reaction, preventability, economic impact, emergency department, pharmacovigilance

Introduction

Adverse drug reactions (ADRs) are a leading cause of mortality and morbidity in health care and a significant burden on health care resources.[1,2] Estimates of the prevalence of ADRs in the literature vary depending on the definition of ADR used, the study setting, and the study population.[3] In addition, the incidence of ADR-related admissions may be underestimated due to lack of documentation in patient medical notes,[4–6] on average being 0.1%–54% of all hospital admissions. ADRs are a significant cause of emergency

Correspondence: Emilio Clementi
Unit of Clinical Pharmacology, Luigi Sacco University Hospital, University of Milano, Via GB Grassi, 74 – 20157 Milan, Italy
Tel +39 02 5031 9643
Fax +39 02 5031 9646
Email emilio.clementi@unimi.it

department (ED) visits,[7,8] and many are preventable, eg, due to drug treatment, lack thereof, or therapies inconsistent with current best practice.[9,10] EDs are ideal places to study ADRs because they are an essential part of health care system, serve as an interface between hospitals and communities, and constitute the most important source of information about the incidence, seriousness, and costs of ADRs.[11–13]

Previous studies of ED visits associated with ADRs have been limited to one hospital setting,[14–16] a specific population,[17–21] specific classes of drug[22,23] or types of ADRs,[24,25] a retrospective study design,[26,27] short periods of observation,[13,28–32] or did not provide information on preventability.[33–35] More extensive studies of ED visits for outpatient ADRs are thus crucial and needed. We have determined the prevalence, preventability, seriousness requiring hospitalization, subsequent 30-day mortality, and economic impact of ADRs presenting to multiple EDs serving a large proportion of the Lombardy region over a 2-year period.

Materials and methods

Setting

This was a retrospective cohort analysis based on ADR charts collected between January 1, 2010 and December 31, 2011 as part of the prospective active pharmacovigilance project Monitoring of ADRs in ED (MEREAFaPS) that is collecting ADRs reported in EDs. The study involves 32 EDs in 16 general hospitals serving different catchment areas of Lombardy, the largest region in Italy with a population of almost 10 million, and altogether accounts for 37.9% of ED visits in the region in the study period. All ADRs reported from patients having at least one suspected ADR, except for those from vaccines, were included in the analysis. Patients who developed an ADR while in the ED for any other reason were included. The local institutional ethics committee of the coordinating center, Niguarda Ca' Granda Hospital, was informed of the study according to the legal requirements concerning observational studies.

Data source

For this study we used two sources of data, ie, ADRs in ED data collected prospectively as part of the MEREAFaPS project and hospitalization data from the hospital discharge database.

The physicians in each ED were informed about the aims of the MEREAFaPS study, and a monitor was assigned for each hospital. The monitors were medical doctors, pharmacists, and biologists, and underwent an intensive course on the theoretical and practical aspects of pharmacovigilance in an ED. For each ADR notified, the following information were recorded: demographic characteristics (age, gender, ethnic group, deduced from the place of birth if not otherwise indicated); patient clinical status on ED visits; triage code; ongoing therapy, (suspected and concomitant drugs, route, duration, and dosage) codified according to the Anatomical Therapeutic Chemical (ATC) classification system and therapeutic indication for the suspected drug; a description of the ADR according to diagnosis and symptoms, codified as detailed by the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and organized by System Organ Class (SOC)[15] and its degree of seriousness, classified according to the World Health Organization criteria as fatal, life-threatening, or requiring hospitalization of the patient, or causing serious/permanent disability;[36] history of previous presentation to an ED for the same ADR; and preventability. The diagnosis of ADR and investigation of the relationship between development of the ADR and the drug used were always done by the ED physicians in collaboration with the monitor.

The hospitalization database contains the following information: demographic characteristics (age, sex), 30-day mortality, and Diagnosis-Related Group (DRG) reimbursement rate. To estimate which of the ADRs observed at ED admission or during ED stay led to hospitalization, we performed a deterministic linkage between two data sources using the unique ID anonymous patient code existing in both databases.

Outcome measure

The primary outcome of the study was to determine the rate of ADRs presenting in ED, regardless of whether the ADR was a reason for the visit. In accordance with new European Medicine Agency legislation, diagnosis of an ADR is based on the following definition: a response to a medicinal product that is noxious and unintended, arising from use of a medicinal product within the terms of the marketing authorization as well as from use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors, and suspected adverse reactions associated with occupational exposure.[37] The causality assessment was done using the Naranjo algorithm.[38] Each ADR was characterized in terms of the SOC and ATC classes most frequently involved. We also assessed ADR preventability (defined as definitely or probably preventable, or not preventable), using the criteria devised by Schumock and Thornton.[39,40] We evaluated seriousness, estimated potential predictors of ADRs requiring hospitalization using a multivariate model, and analyzed 30-day mortality. In this group, only patients who died during

hospitalization or within the 30 days following hospital discharge were considered. Finally, we estimated the economic burden of ADR-related ED visits by calculating direct medical costs in two stages. Stage 1 included the average cost of an ED visit at each hospital, and stage 2 included costs related to patient hospitalization following an ADR, calculated from the DRG reimbursement present in the hospitalization data. Costs are reported in euros.

Statistical analysis

Descriptive statistics are shown as frequencies and percentages for categorical data and as means with standard deviations for continuous data. We used univariate and multivariate logistic regression to estimate the odds ratios (ORs) with 95% confidence intervals (CIs) of potential predictors of hospitalization among total ADRs. Economic estimates of cost are presented as means with standard deviations (SD).

All results were considered to be statistically significant at $P<0.05$. Data management and statistical analysis were carried out using SAS version 9.2 software (SAS Institute, Cary, NC, USA).

Results

In the 2-year study period, a total of 2,561,400 ED visits were made, of which 8,862 were ADR-related, with an overall prevalence rate of 3.5 per 1,000 ED visits (Figure 1). The characteristics of patients with ADRs are reported in Table 1. Patients with an ADR had a mean (± SD) age of 55.9±24.3 years, most are female and European, and more than half received two or more drugs at the time of their ED visit (Table 1). There were 4,111 serious ADRs (46.4%), and among these 1,332 (15% of total ADRs) led to hospitalization. The fatality rate for all ADRs reported in the ED was 1.5%.

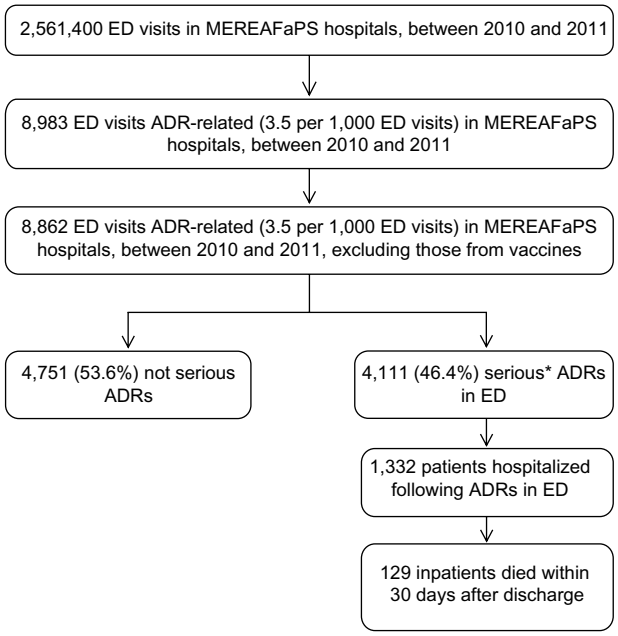

Figure 1 Flow chart of selection criteria of adverse drug reactions in emergency department and outcomes of interests, MEREAFaPS Hospitals, 2010–2011.
Note: *ADR that was fatal, life-threatening, required hospitalization of the patient, or caused serious/permanent disability.
Abbreviations: ADR, adverse drug reaction; ED, emergency department; MEREAFaPS, Monitoring of ADRs in ED.

Most patients with a serious ADR were taking more than one drug (64%) compared with overall ADR (54.3%); similarly, the amount of polypharmacy increased with the degree of seriousness, being 77.9% in patients hospitalized following ADR in ED and 82.2% in patients who died within 30 days of discharge.

Preventable ADRs, a definition which includes both the "definitely" and "probably" preventable ADRs, were in total 42%; of these 51.6% were serious, 59.6% were hospitalized, and 61.2% died.

SOCs most frequently associated with ADRs of significant severity were: skin and subcutaneous tissue, followed by gastrointestinal, respiratory thoracic and mediastinal, and nervous system disorders (Table 2). The ATC classes most commonly involved in admissions (Table 3) were J (anti-infectives for systemic use), B (blood and blood-forming organs), and N (nervous system). In terms of seriousness of ADRs, the ATC class most often involved was V (various), followed by A (alimentary tract and metabolism) and C (cardiovascular).

The most commonly involved drugs (see Table 4) were acetylsalicylic acid (34.5% being preventable), amoxicillin/clavulanic (32.1% preventable), and warfarin (48.6% preventable). The most frequent suspect drugs in serious ADRs and in inpatients who died within 30 days after discharge are reported in Table S1.

With regard to multivariate predictors of hospitalization, older age (OR 2.76, 95% CI 2.38–3.2), male sex (OR 1.2, 95% CI 1.06–1.37), yellow and red triage (OR 3.62, 95% CI 3.18–4.12), increasing number of concomitant drugs taken (from OR 1.81, 95% CI 1.54–2.13 in patients taking 2–4 drugs, to OR 5.5, 95% CI 3.65–8.29 in those taking ≥10 drugs) and previous attendance in ED for the same ADR (OR 2.04, 95% CI 1.45–2.88) were associated with a significantly increased risk of hospitalization (Table 5).

The total cost incurred by the National Health Service because of ADR-related ED visits and subsequent hospitalizations in MEREAFaPS hospitals for the 2010–2011 period was estimated to be €5,184,270, with an average cost of €585±2,149 per patient (Table 6). The average estimated

Table 1 Characteristics of patients with adverse drug reactions in emergency departments at MEREAFaPS hospitals, 2010–2011

Patient characteristics	ADRs in ED (n=8,862)	Serious ADRs* in ED (n=4,111)	Patients hospitalized following ADRs in ED (n=1,332)	Inpatients died within 30 days after discharge (n=129)
	n (%)	n (%)	n (%)	n (%)
Age, years				
<65	4,932 (55.7)	1,903 (46.3)	358 (26.9)	5 (3.9)
≥65	3,930 (44.3)	2,208 (53.7)	974 (73.1)	124 (96.1)
Mean ± SD age, years	55.9±24.3	62.0±21.6	70.7±(18.1)	81.8±9
Sex				
Female	4,936 (55.7)	2,265 (55.1)	678 (50.9)	64 (49.6)
Male	3,926 (44.3)	1,846 (44.9)	654 (49.1)	65 (50.4)
Ethnic group				
Others	420 (4.7)	134 (3.3)	22 (1.7)	0 (0)
European	8,442 (95.3)	3,977 (96.7)	1,310 (98.3)	129 (100)
Triage				
Missing	171 (1.9)	87 (2.1)	16 (1.2)	0 (0)
G + W	6,435 (72.6)	2,323 (56.5)	619 (46.5)	37 (28.7)
R + Y	2,256 (25.5)	1,701 (41.4)	697 (52.3)	92 (71.3)
Concomitant drugs (n)				
1	4,053 (45.7)	1,482 (36)	294 (22.1)	23 (17.8)
2–4	3,446 (38.9)	1,721 (41.9)	558 (41.9)	48 (37.2)
5–9	1,245 (14)	822 (20)	424 (31.8)	50 (38.8)
11+	118 (1.3)	86 (2.1)	56 (4.2)	8 (6.2)
Previous ED access for same ADR				
No	8,636 (97.4)	3,996 (97.2)	1,277 (95.9)	127 (98.4)
Yes	226 (2.6)	115 (2.8)	55 (4.1)	2 (1.6)
Preventability				
Not preventable	5,137 (58)	1,989 (48.4)	538 (40.4)	50 (38.8)
Probably/definitely preventable	3,725 (42)	2,122 (51.6)	794 (59.6)	79 (61.2)

Note: *ADR that was fatal, life-threatening, requiring hospitalization of the patient, or that caused serious/permanent disability.
Abbreviations: ADR, adverse drug reaction; ED, emergency department; G + W, green and white triage; MEREAFaPS, Monitoring of ADRs in ED; R + Y, red and yellow triage; SD, standard deviation.

cost was €1,166±3,054 to treat patients with serious ADRs, €3,422±4,613 for ED visits leading to hospitalization, and €4,147±3,789 in ADRs that proved fatal. The proportion of preventable cases identified in this study indicates a potential

Table 2 Distribution of adverse drug reactions in emergency departments at MEREAFaPS hospitals, 2010–2011, according to first ten SOC classifications

SOC name	n (%[a])	Serious (%[b] per each SOC)
Skin and subcutaneous tissue disorders	3,241 (26.6)	35.8
Gastrointestinal disorders	1,899 (15.6)	53.0
Respiratory, thoracic and mediastinal disorders	1,245 (10.2)	42.3
Nervous system disorders	1,244 (10.2)	63.6
General disorders and administration site conditions	878 (7.2)	45.0
Metabolism and nutrition disorders	589 (4.8)	78.1
Vascular disorders	468 (3.8)	53.6
Psychiatric disorders	445 (3.6)	66.3
Cardiac disorders	319 (2.6)	59.6
Renal and urinary disorders	272 (2.2)	64.7
All others	1,595 (13.1)	–

Notes: [a]Column percentage; [b]row percentage.
Abbreviations: MEREAFaPS, Monitoring of ADRs in ED; SOC, System Organ Class.

Table 3 Distribution of adverse drug reactions in emergency departments at MEREAFaPS hospitals, 2010–2011, according to ATC level 1

Therapeutic category (level 1 ATC)	n (%[a])	Serious (%[b] per each ATC)
J. Anti-infectives for systemic use	2,333 (21.0)	36.1
B. Blood and blood-forming organs	2,028 (18.3)	52.4
N. Nervous system	1,943 (17.5)	53.8
C. Cardiovascular system	1,445 (13.0)	62.7
M. Musculoskeletal system	1,367 (12.3)	41.6
A. Alimentary tract and metabolism	986 (8.9)	67.7
R. Respiratory system	254 (2.3)	28.0
L. Antineoplastic and immunomodulating agents	177 (1.6)	59.3
G. Genitourinary system and sex hormones	146 (1.3)	31.5
H. Systemic hormonal preparations excluding sex hormones and insulins	142 (1.3)	45.8
S. Sensory organs	79 (0.7)	7.6
D. Dermatologicals	78 (0.7)	14.1
V. Various	76 (0.7)	68.4
P. Antiparasitic products insecticides and repellents	31 (0.3)	29.0

Notes: [a]Column percentage; [b]row percentage.
Abbreviations: ATC, Anatomical Therapeutic Chemical classification; MEREAFaPS, Monitoring of ADRs in ED.

Table 4 Ten most frequent suspect drugs for ADRs in ED and patients hospitalized following ADRs in EDs at MEREAFaPS hospitals, 2010–2011

	n	Probably/definitely preventable (%)
ADRs in ED (n=8,862)		
Acetylsalicylic acid	936	323 (34.5)
Amoxicillin-clavulanate	878	282 (32.1)
Warfarin	731	355 (48.6)
Amoxicillin	479	186 (38.8)
Insulins and analogs	377	250 (66.3)
Ketoprofen	353	153 (43.3)
Ibuprofen	245	95 (38.8)
Diclofenac	193	96 (49.7)
Acetaminophen	182	54 (29.7)
Levofloxacin	172	55 (32)
Patients hospitalized following ADRs in ED (n=1,332)		
Warfarin	263	150 (57)
Acetylsalicylic acid	215	118 (54.9)
Insulins and analogs	77	61 (79.2)
Acenocoumarol	51	26 (51)
Ticlopidine	51	37 (72.5)
Furosemide	47	33 (70.2)
Amoxicillin-clavulanate	40	15 (37.5)
Metformin	40	30 (75)
Digoxin	28	17 (60.7)
Enalapril	28	15 (53.6)

Abbreviations: ADR, adverse drug reaction; ED, emergency department; MEREAFaPS, Monitoring of ADRs in ED.

saving of €3,009,800 for the National Health Service, representing 58% of the total expenses incurred in the treatment of ADRs in the ED.

Discussion

Our study is the first to contribute useful information on the clinical and economic impact of ADRs in Italy via a long-term survey of several EDs that included a substantial number of patients over a 2-year period. Ours is also one of the largest such studies. We present a clear picture, reporting on the prevalence, seriousness, and preventability of drug-related visits to the ED and their real economic impact over a long period in a large number of EDs. Previous studies addressing the issue of ADRs in the ED were limited to either single hospitals with small numbers of patients, or to short periods of observation or a specific population without insight into clinical or economic impact.[14,29,31,34,35,41] They also differ in the criteria used to identify ADR, collection periods, and study design.[28,42,43] Therefore, data from these studies cannot be extrapolated reliably to a general population.

In our study, the prevalence of ADR-related ED visits was less than 1%, as already reported for France.[44] However, this value is strikingly different from that observed in other studies.[14,26,42,43] The difference may be due in part to the different ADR inclusion criteria used in the various studies, ie, reported to EDs versus identified in ED or leading to ED visits, and/or due to the known dissimilarity in the incidence of medication-related ED visits between prospective and retrospective studies.[42,29,43]

Wiffen et al[45] observed that patients in their ADR group were prescribed more drugs on average than those in the non-ADR group, a situation known to be associated with an increased prevalence of ADRs.[43,46] In accordance with these data, our study shows a correlation between the risk of a serious ADR and the number of drugs being taken; regarding the effect of risk factors on the incidence of ADR-related hospitalization, multiple regression analysis showed a statistically significant association between use of a large number of medications and the risk of presenting with an ADR that would require hospitalization. Likewise, we add further information on the issue of polypharmacy as a cause of ADRs; previous studies were only in elderly people, where polypharmacy is common, and showed that polypharmacy is a reliable predictor of rehospitalization and a prolonged length of hospital stay during which at least one ADR occurred.[47]

Table 5 Factors associated with hospitalizations for patients with 8,862 adverse drug reactions in emergency department at MEREAFaPS hospitals, 2010–2011

	OR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
≥65 versus <65 years	4.21 (3.7–4.79)	<0.001	2.76 (2.38–3.2)	<0.001*
Male versus female	1.26 (1.12–1.41)	<0.001	1.2 (1.06–1.37)	0.002*
European ethnicity versus other	3.32 (2.15–5.12)	0.136	1.41 (0.9–2.22)	0.136
Triage yellow/red versus white/green	4.2 (3.72–4.75)	<0.001	3.62 (3.18–4.12)	<0.001*
Concomitant drugs (n) versus 1 as reference				
2–4	2.47 (2.13–2.87)	<0.001	1.81 (1.54–2.13)	<0.001*
5–9	6.6 (5.59–7.8)	<0.001	3.39 (2.81–4.09)	<0.001*
10+	11.55 (7.9–16.9)	<0.001	5.5 (3.65–8.29)	<0.001*
Previous ED access for same ADR	1.85 (1.36–2.53)	<0.001	2.04 (1.45–2.88)	<0.001*

Note: *Statistically significant in the multivariate model.
Abbreviations: ADR, adverse drug reaction; ED, emergency department; OR, odds ratio; CI, confidence interval; AOR, odds ratio adjusted for all variables in the table.

Table 6 Cost of illness associated with ADRs in EDs at MEREAFaPS hospitals, 2010–2011

	Cost (mean ± SD)	Total cost
ADRs in ED (n=8,862)	585±2,149	5,184,270
Serious* ADRs in ED (n=4,111)	1,166±3,054	4,793,426
Patients hospitalized following ADRs in ED (n=1,332)	3,422±4,613	4,558,104
Inpatients died within 30 days after discharge (n=129)	4,147±3,789	534,963
Not preventable (n=5,137)	423±1,751	2,172,951
Probably/definitely preventable (n=3,725)	808±2,584	3,009,800

Notes: Data are shown as the mean, standard deviation, and total cost in Euros. *ADR that was fatal, life-threatening, requiring hospitalization of the patient, or that caused serious/permanent disability.
Abbreviations: ADR, adverse drug reaction; ED, emergency department; SD, standard deviation.

Consistent with previous work,[48–51] we found a high rate of preventability of ADRs requiring hospitalization and those resulting in death at 30 days. Reasons for such high rates may include errors in prescribing and/or monitoring, or poor compliance, underscoring the importance of developing strategies to improve the quality and safety of prescribing.

Among the various drug classes that are particularly worthy of attention in terms of preventable ADRs are the classical anticoagulants. We observed that most of the patients who died within 30 days of discharge had suffered from anticoagulant-associated ADRs, 40.3% of which were attributable to warfarin. This evidence is consistent with the findings of previous studies indicating that anticoagulants are among the drugs that need to be more closely monitored because of their propensity to lead to preventable hospitalizations.[4,11,52]

We found that several organ systems were affected by ADRs, with the highest frequency in the dermatological system, which is consistent with previous reports in the literature.[13,44] Likewise, our results in terms of therapeutic categories more frequently involved in ADR (antibiotics, anticoagulants, digoxin, diuretics, hypoglycemic agents, and nonsteroidal anti-inflammatory drugs) are not dissimilar from those in the literature.[53]

Another aspect of this study is the estimate of the economic impact associated with ADRs, information not yet available on ADRs observed in EDs and in such a large population.[54] Calculation of the impact of ADRs on costs is indeed complex.[55] ADRs may increase costs because of increased likelihood of hospitalization, prolongation of hospital stay, and the additional clinical investigations needed in more serious cases. Further, ADRs may trigger prescription cascade when new medications are prescribed for conditions that are a consequence of another medication, conditions which are often an unrecognized ADR.[56–58] This may explain in part why our analysis in an Italian setting estimated the costs for treatment of serious ADRs to be significantly higher than those observed in France, ie, €3,422 versus approximately €2,500, respectively.[59]

Studies carried out in general hospitals or specialist units suggest that the cost of an ADR depends on the nature of both the ADR and the culprit drug, and this has to be taken into account when designing programs to control costs and minimize ADRs.[10,16] Our economic analysis highlights two relevant issues. The first is that ATC class A is associated with a high number of serious ADRs, and about 20% of the drugs dispensed were to treat diabetes. Antidiabetic drugs (ATC code A10) typically require periodic monitoring, and our data strengthen previous evidence of a progressive and significant increase in health care costs for patients in whom diabetes is not properly monitored.[60] The second issue relates to preventability of ADRs. Our data show that 42% of reported ADRs were preventable, indicating a total cost-saving potential of €3 million, representing 58% of the total economic impact of ADRs. Likewise, a study in Germany showed the total cost of treating ADRs to be €434 million per year; considering the proportion of preventable cases (20.1%), this represented a potential cost saving of €87 million per year.[61] Certain strategies are known to reduce the impact of ADRs, such as improving adherence to therapeutic guidelines, educational programs, identification of risk groups, and associate therapeutic drug monitoring, whenever available, to the evaluation of reliable biomarkers of safety and efficacy.[16,62–64] The heavy burden of preventable ADRs may translate into potentially significant cost savings if these strategies can be implemented further. In this respect, cooperation should be encouraged between clinicians, clinical pharmacologists, and pharmacists, who may play a significant role in preventing and decreasing the burden of ADRs.[65]

Limits and strengths

This study was of a retrospective nature, so may have underestimated the prevalence of drug-related ED visits as a result of missing or inaccurately documented information. Indeed, retrospective studies cannot identify all reported ADR-related ED visits due to the limitations of the ICD codes used, which do not cover all illnesses potentially caused by ADRs. To address this limitation, we included only cases that were recognized and documented by emergency physicians as ADRs. Another limitation is that the ADRs in MEREAFaPS are the results of spontaneous reports of ADRs. The real prevalence

of ADRs is not known and a control group (with no ADRs) was not available; and this is also a limitation with regard to assessment of causality between ADRs and hospitalization. The DRG in Lombardy reflects reimbursement of hospitals by the National Health Service and not the actual costs incurred, although is designed to represent actual costs as far as possible. We could not extract from the DRG those costs associated with management of conditions not strictly related to the ADR.

This study has some important strengths. For example, we used computerized monitoring programs and trained professionals to detect ADRs, and physicians working in EDs to identify ADRs. In addition, this is the first retrospective analysis within a prospective study evaluating the reporting of ADRs in a large number of EDs over a long period. Further, the study recorded mortality occurring up to 30 days after discharge. This is recognized as a good patient outcome indicator,[66] although we cannot exclude as a confounding factor the possibility that mortality in some cases was due to other reasons. Moreover, this is the first study assessing hospitalization-related ADR costs in terms of seriousness and preventability, making it possible to estimate the potential cost savings in relation to the preventable cases observed.

Acknowledgment

The study was supported by grants from the Regional Pharmacovigilance Centre of Lombardy and the Italian Medicines Agency (AIFA).

Author contributions

VP and VC conceptualized and designed the study, interpreted the data, drafted the manuscript, and revised and approved the final manuscript as submitted. SS, DS, and LP participated in the design of the study and interpretation of the data, revised the manuscript, and approved it as submitted. LDE supervised data collection, analysis, and interpretation, revised the manuscript, and approved it as submitted. MV, SR, EC, and GV conceptualized and designed the study, participated in analysis and interpretation of the data, coordinated and supervised data collection, and finalized and approved the manuscript as submitted. All authors had full access to the data, including the statistical results and tables for this study, and take responsibility for the integrity of the data and the accuracy of the data analyses. GV is the study guarantor.

Disclosure

The authors declare that they have no competing interests in this work.

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Supplementary materials

Table S1 Ten most frequent suspect drugs in: serious* ADRs in ED at MEREAFaPS hospitals, 2010–2011 and in inpatients who died within 30 days after discharge

	n	Probably/definitely preventable (%)
Serious* ADRs in ED (n=4,111)		
Acetylsalicylic acid	437	190 (43.5)
Warfarin	420	234 (55.7)
Insulins and analogs	312	209 (67)
Amoxicillin-clavulanate	311	131 (42.1)
Amoxicillin	169	66 (39.1)
Ketoprofen	134	76 (56.7)
Ibuprofen	99	44 (44.4)
Furosemide	90	56 (62.2)
Ticlopidine	80	47 (58.8)
Diclofenac	75	48 (64)
Inpatients died within 30 days after discharge (n=129)		
Warfarin	52	31 (59.6)
Acetylsalicylic acid	18	13 (72.2)
Ticlopidine	11	8 (72.7)
Furosemide	7	4 (57.1)
Spironolactone	4	3 (75)
Acenocoumarol	3	2 (66.7)
Allopurinol	3	1 (33.3)
Amiloride hydrochlorothiazide	3	2 (66.7)
Clopidogrel	3	0 (0)
Ceftriaxone	3	2 (66.7)

Note: *ADR that was fatal, life-threatening, requiring hospitalization of the patient, or caused serious/permanent disability.

Abbreviations: ADR, adverse drug reaction; ED, emergency department; MEREAFaPS, Monitoring of ADRs in ED.