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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Regional surveillance of emergency-department visits for outpatient adverse drug events

A. Capuano · A. Irpino · M. Gallo · L. Ferrante · M. L. Illiano · B. Rinaldi · A. Filippelli · F. Rossi

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Abstract
Aims To determine the (1) incidence of adverse drug events (ADEs) in 10 emergency department (EDs) of general hospitals in the Regione Campania (southern Italy), (2) rate of ADE-related hospital admissions, (3) drug classes most frequently involved, and (4) the types of ADEs and their frequency.
Methods We performed a cohort study of all patients attending the EDs. This study was carried out in two observational periods of 10 days each in 10 EDs. Demographic, clinical, and pharmacological data about all patients admitted to EDs were collected by trained and qualified monitors. Records related to ADEs were analyzed and validated by a specific scientific committee.
Results Of 7,861 ED visits, 96 were ADE-related. The incidence of hospitalization was higher in patients who had taken medication than in patients with a negative drug history (24.9 vs. 16.4%). ADEs were significantly more frequent in women. Patients aged between 60 and 69 years and between 30 and 39 years were significantly more likely to experience an ADE. Serious ADEs were identified in 20 ED visits (20.8% of total sample). Antibiotics, NSAIDs, and agents acting on the renin-angiotensin system were the drugs most often involved in ADEs. In multivariate analyses, the adjusted odds ratio was 3.4 (95% CI: 1.07–2.84) for patients taking NSAIDs, 4.78 (95% CI: 2.26–10.12) for those taking β_2-adrenergic-receptor agonists, and 6.20 (95%CI: 2.74–14.06) for those taking β-lactam antibiotics.
Conclusion This study shows that ADEs are an important problem in industrialized countries. Moreover, it shows that ADEs affect hospital admission rates and reinforces the importance of drug-induced disease as a public health problem.

Keywords Adverse drug event · Emergency room · Antibiotics · NSAIDs · Renin-angiotensin system agents

A. Capuano (✉) · M. Gallo · L. Ferrante · M. L. Illiano · B. Rinaldi · A. Filippelli · F. Rossi
Department of Experimental Medicine,
Section of Pharmacology Leonardo Donatelli,
Center of Pharmacosurveillance and Pharmacoepidemiology,
Faculty of Medicine and Surgery, Second University of Naples,
Naples, Italy
e-mail: annalisa.capuano@unina2.it

A. Irpino
Department of European and Mediterranean Studies,
Faculty of Political Studies and Higher European
Education Jean Monnet, Second University of Naples,
Naples, Italy

Introduction

Adverse drug events (ADEs) are a remarkable health-care cost problem, and a major cause of morbidity and mortality [1–4]. It has been estimated that ADEs account for 0.2–24% of all hospital admissions [5–7] and for 0.86–5.9% of hospital emergency-department visits [8–15]. This wide range of incidences may reflect the various types of hospitals included in the studies or methodological differences (i.e., retrospective data collection in most studies, variability in the definition of ADE among studies, and use of non–drug experts in determination of ADEs, which has been reported to lead to underestimations of ADEs by up to 50%). Thus far, studies have focused on inpatient populations, and little is known about ADE-related emergency department (ED) visits. In fact, many studies have approached the drug-related problem by observing hospital admissions, and only a few studies have estimated the drug-

related problems in emergency departments [9, 14, 16–18]. Moreover, most of these studies were conducted in university or tertiary hospitals, rather than in general hospitals. Evaluation of this issue from the ED perspective could contribute to a better understanding of drug-related problems that arise from general practitioner' prescriptions.

Previous studies showed that ED patients are at a high risk of adverse drug interactions and that drug-related illness is not uncommon in the emergency department [19, 20]. Moreover, recent findings have reported that one-third are likely preventable [21] and that about half could be avoided with greater prescription care [22].

In light of these findings, the primary aim of our study was to determine the incidence of ADEs in 10 EDs of general hospitals in the Regione Campania (southern Italy). Secondary endpoints were to estimate the rate of ADE-related hospital admissions, the drug classes most frequently involved in ADEs, the types of ADEs and their frequency, and to identify risk factors for ADEs requiring an ED visit.

Methods

We performed a cohort study of all patients attending the ED. This study was carried out in two periods of 10 consecutive days, namely, from February 28 to March 9, and from June 19 to June 28, 2005.

Ten EDs located in Campania participated in the study. Campania is a geographically and administratively well-defined Mediterranean area located on the west coast of southern Italy. In the month before the survey, monitors underwent an intensive course on theoretical and practical aspects of pharmacovigilance in ED. The monitors, who collected the data in each ED, were specialists in clinical pharmacology and were informed about the aims of the study. All ED visits were monitored, prospectively from 8:30 AM to 8:30 PM, and retrospectively, through review of ED records, during the night. All patients admitted to ED during the monitored period, regardless of their presenting complaints, were included in the study, and the monitors then tried to determine if these patients had potential ADEs on questioning.

The monitors followed each patient's progress up to diagnosis and therapy. If the patient was conscious, he/she was interviewed by the monitor after giving informed consent. If the patient was unconscious, the caregiver was interviewed after the patient had undergone a medical examination. If the patient was transferred to another department (surgery, orthopedics, etc.) for further investigation, the ED physician informed the monitor about the patient's status, and the patient's record card was updated accordingly. The following data were recorded for each individual patient on a custom-made form: sociodemographic factors (gender, age, education, ethnic group), any cigarette or alcohol use, diagnosis, drug history, type of ADE, clinical condition, and in the case of hospitalized patients, details of progress and outcome were also included [15].

Subjects were required to provide information regarding any medication taken (including over-the-counter drugs, vitamins, or herbal remedies) over the fortnight prior to the ED visit and were asked to give the drug name, dosage, method of administration, and length of therapy. All the forms were collected and recorded in the same database following each period of observation. A case-control study was nested within the prospective study to identify any possible risk factors in terms of adverse drug reactions. Case patients were defined as all patients with a probable ADE. Control patients were patients admitted to same unit (ED) as the case patients with the most similar characteristics except ADE. Thus, controls had the same level of care as the case patients.

Characteristics of hospitals involved in the study

The hospitals participating in the study are general hospitals serving different catchment areas. The hospitals are community hospitals and referral centers for the entire Campania population. At least 70% of admissions are patients whose general practitioners are located close to the hospital.

Outcome measures

According to Nebeker [23], "an adverse drug event is an injury resulting from the use of a drug. Under this definition, the term ADE includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions, discontinuations of drug therapy, unsuccessful therapy also caused by non-compliance)."

In this study we considered ADEs as opposed to adverse drug reactions as the study sample group was mainly composed of outpatients. Indeed, in contrast to ADEs, medication errors are not included in adverse drug reactions. It is difficult to exclude such errors in outpatients since there is insufficient clinical monitoring and very little documentation. Patients with a previous history of drug abuse were assessed by a medical committee who considered the relationship between the event and the drug.

We recognize as preventable ADEs the adverse effects related to inappropriate prescribing, monitoring, or compliance, such as injuries resulting from the prescription of a high dosage for the patient's age or disease state, or resulting from administration of a drug to a patient with a known hypersensitivity according to some published criteria

[24]. The findings of the physicians on the committee were reported to monitors who collected the data and reviewed the forms in order to establish the time between drug intake and the onset of symptoms, both the patient's impression and attending emergency physician's assessment of the link between the drug and its symptoms, and any previously published data on event-drug association. In the case of patients using more than one drug, the relationship with the event was assessed separately for each type of medication and drug-drug interactions were also considered.

The events were not considered ADEs when there was no temporal association between symptoms and drug treatment. Intentional drug abuses were identified but not included as ADEs. Patients were excluded from this study if a drug was administered for other than ordinary therapeutic or prophylactic purposes. Therefore, cases of suicide attempts and drug abuse were not considered.

We excluded from the study all the forms that were lacking information about gender, age, drug history, concurrent disease, outcome after ED visits, and the ADE-related drugs.

The probability that a drug caused the visit was assessed using the classification of the WHO (certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessible/unclassifiable). We graded the severity of ADE according to the World Health Organization definition: ADEs that were fatal, life-threatening, required hospitalization of the patient, or caused serious/permanent disability were deemed "serious." The diagnosis of ED visits and any associated diseases were classified using the International Classification of Disease 9th revision (ICD-9) (World Health Organization's Ninth Revision, International Classification of Diseases), while drugs were classified using the Anatomical Therapeutical Chemical (ATC) system.

Statistical analysis

We used *t*-test statistics for the comparisons of means and the chi-square test for comparing distributions. The t-test and the chi-square test (significance level of $P \leq 0.05$) results were used when relevant in the evaluation of the results. A stepwise logistic regression analysis was carried out in order to assess any connection between potential risk factors and ADEs. All the determinants for the outcome were identified through univariate analysis, while those with a univariable significance of $P \leq 0.05$ were grouped together in a multivariate model. All analyses were carried out using STATA 7.0 (STATA, College Station, TX).

Results

A total of 8,073 patients were admitted to the 10 EDs during the two monitoring periods. Of these, 212 cases (6.3%) were excluded because of incomplete demographic data, drug history, or outcome after the ED visit. Table 1 shows the demographic and clinical characteristics of the 7,861 patients included in the study.

The mean age was 44.1±20.3 years, and 50.8% of patients were male. A total of 1,163 patients (14.8% of the total sample) had taken medication in the 2 weeks before the study. Their mean age was 52.7±20.7. Women were more likely to have taken at least one medication (57 vs. 41%; $P<0.0001$). For patient-administered medication, 96 patients with ADEs (1.2% of total ED visits and 8.2% of all subjects who took medication) were identified (Table 1). ADEs were more frequent in women (58.3 vs. 41.7%; $P<0.0001$). Patients aged between 60 and 69 years ($P<0.0001$) and between 30 and 39 years ($P<0.0001$) were significantly more likely to experience an ADE (Table 1). The incidence of hospitalization was significantly higher in patients who had recently taken medication than in patients with a negative drug history (24.9 vs. 16.4%; $P<0.0001$).

Serious ADEs were identified in 20 ED visits (20.8% of the total sample), and these patients were hospitalized. These included seven cases (35%) of life-threatening ADE (two cases of ropivacaine-induced angioedema, one case of beclomethasone-induced cardiogenic pulmonary edema, one case of amoxicillin-induced syncope, two cases of antidiabetic drugs-induced hypoglycemia, and one case of dexchlorpheniramine-induced anaphylactic shock). The systems/organs most frequently associated with ADEs were the skin (34.21%) and the gastrointestinal system (21.05%), followed by the peripheral/central nervous system (14.47%) and the cardiovascular system (11.84%) (Fig. 1). Table 2 lists the drugs implicated in causing ADEs. Antibiotics (18.1%), antiinflammatory agents (13.4%), and agents acting on the renin angiotensin system (11.4%) were most commonly implicated. The most frequent serious ADE-related symptom was abdominal pain (four events), which was associated with thiamazole, proton-pump inhibitors, ciprofloxacin, and gestodene + ethinylestradiol; followed by confusion (three events), which was mainly associated with antiinflammatory agents. We also observed tremors in two ADE visits, which were associated with β_2-adrenergic-receptor agonists and anticholinergic agents (Table 3). In the monitored period, there were no reported cases of gastrointestinal hemorrhage.

The drugs most frequently related to an ADE are shown in Table 4. Five drug types were associated with more than half of ADE visits. Antibiotics were the most frequent drug category (26% of total ADE), followed by NSAIDs (19%), agents acting on the renin-angiotensin system (16%), antiasthmatics (13%), and anticoagulants (9.6%). Other drugs associated with ADEs were drugs for acid-related disorders (6.7%), calcium-channel blockers, corticosteroids, and analgesics (4.8%). Among the drug categories involved

Table 1 Demographic and clinical characteristics of study sample and patients with an adverse drug event (ADE)

	Total sample (*n*)		Patients with positive drug history		Patients with an ADE	
	Number		Number	Percentage	Number	Percentage
No. of patients	7,861	100	1,163	14.8	96	1.2
Patients with a positive drug history				100		8.2
Age, years (mean±SD)	44.1±20.3		52.7±20.7		50.8±19.2	
Age groups (years)						
0–19	726	9.2	51	4.5	3	3.1
20–29	1,322	16.8	103	8.9	7	7.3
30–39	1,288	16.4	155	13.3	22	22.9
40–49	1,110	14.1	160	13.8	16	16.7
50–59	1,012	12.9	158	13.6	13	13.5
60–69	780	9.9	138	11.9	17	17.7
70–79	611	7.8	148	12.7	7	7.3
≥80	396	5.0	118	10.1	8	8.3
Missing	616	7.8	131	11.3	3	3.1
Gender						
Females	3,643	46.3	663	57.0	56	58.3
Males	3,991	50.8	477	41.0	40	41.7
Missing	227	2.9	23	2.0		
Outcomes						
Discharged	6,470	82.3	875	75.2	76	79.2
Admitted	1,385	17.6	288	24.8	20	20.8
Death	6	0.1				

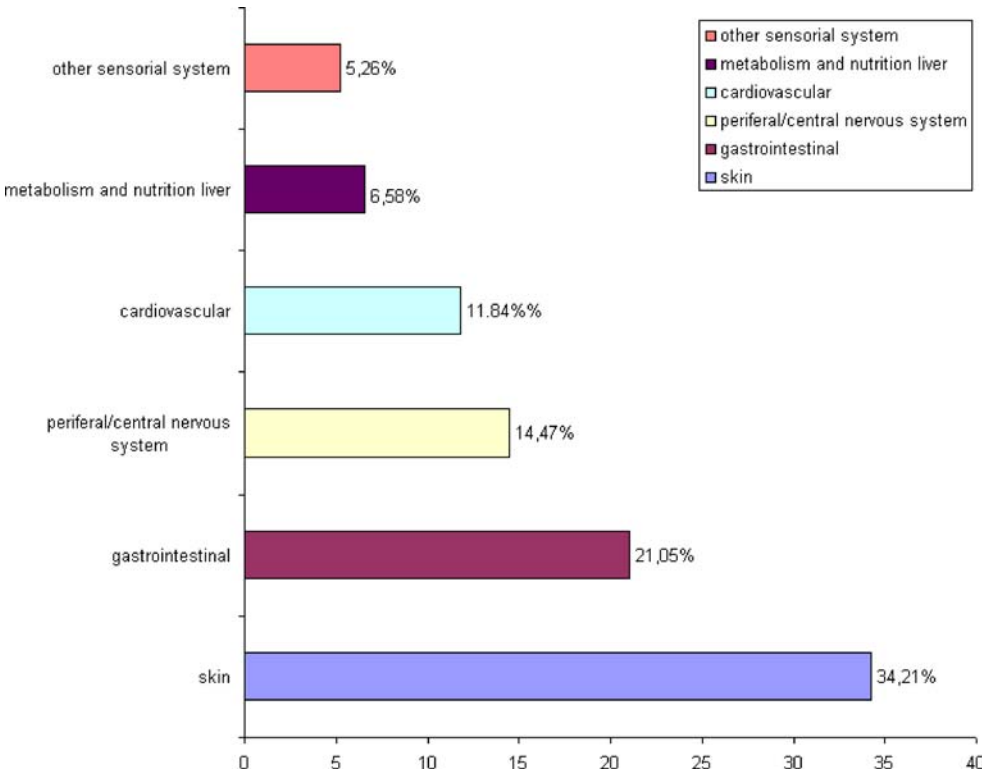

Fig. 1 Systems and organs most frequently associated with adverse drug effects

Table 2 Drugs associated with adverse drug events

Drug group	Number (%) of cases	Individual drugs[a] (*n*)	Adverse events
Antibacterials for systemic use	27 (18.12)	Amoxicillin + clavulanic acid (6), amoxicillin (6), ampicillin (4), cefazolin (3), cefixime (2), ceftriaxone (1), ciprofloxacin hydrochloride (2), lincomycin hydrochloride (1), sulfamethoxazole + trimethoprim (4)	Headache, confusion, diarrea, abdominal pain, epigastralgia, erythema multiforme, pharyngitis, urticaria, giant urticaria, giant pomphi, pruritus, cutaneous rash, allergic drug reaction, orticarioide reaction, syncope
Anti-inflammatory and antirheumatic products	20 (13.42)	Ibuprofen (10), ketoprofen (6), naproxen (4), nimesulide (8)	Pruritus, anemia, diarrhea, peripheral edema, erythema multiforme, cutaneous rash, giant pomphi, vertigo, vomiting
Agents acting on the renin-angiotensin system	17 (11.41)	Captopril + hydrochlorothiazide (4), enalapril + hydrochlorothiazide (5), fosinopril (6), fosinopril + hydrochlorothiazide (2), irbesartan (2), lisinopril (1), ramipril (2), zofenopril (2)	Confusion, dyspepsia, edema, peripheral edema, polyuria - head trauma, cough
Drugs for obstructive-airway diseaseas	14 (9.40)	Beclomethasone (4), fenoterol + ipratropium bromide (5), salbutamol (1), salbutamol + ipratropium bromide (2), salmeterol + fluticasone (4), theophylline (1)	Cardiogenic pulmonary edema, giant urticaria, palpitation, astenia and sweating, mental confusion, tremor
Antithrombotic agents	10 (6.71)	Acetylsalicylic acid (4), acenocoumarol (3), warfarin (4)	Confusion, dyspepsia, dispnea, gastralgia, atrial fibrillation, pomphi, cutaneous rash
Drugs for acid-related disorders	7 (4.70)	Esomeprazole (2), omeprazole (2), ranitidine (3), sodium alginate + potassium bicarbonate (3)	Abdominal colic, epigastralgia, headache, urticaria, pruritus, vertigo
Calcium-channel Blockers	5 (3.36)	Diltiazem (2), amlodipine (5)	Edema, hypoglycemia, hypoglycemic reaction, rash, vertigo
Corticosteroids for systemic use	5 (3.36)	Betamethasone (3), methylprednisolone (2)	Confusion, cutaneous rash, allergic reaction
Analgesics	5 (3.36)	Paracetamol (5), tramadol (1)	Erythema multiforme, vomiting
Beta-blocking agents	4 (2.68)	Bisoprolol (1), metoprolol (2), nebivolol (1)	Atrial fibrillation, syncope
Thyroid therapy	4 (2.68)	Levothyroxine (2), thiamazole (2)	Peripheral edema, abdominal pain
Drugs for functional gastrointestinal disorders	3 (2.01)	Domperidone (3), phloroglucinol (2)	Precordial pain, headache, spasms
Drugs used in diabetes	3 (2.01)	Human insulin (2), metformin (3)	Hypoglycemia
Antihypertensives	3 (2.01)	Doxazosin (3)	Dizziness, vertigo
Urologicals	3 (2.01)	Alfuzosin (2), tamsulosin (1)	Asthenia, precordial pain, atrial fibrillation
Psycholeptics	3 (2.01)	Alprazolam (2), levosulpiride (1), quetiapine (2)	Gastrointestinal disorders, spasms
Cough and cold preparation	3 (2.01)	Acetylcysteine (3), sobrerol (3)	Cardiogenic ulmonary edema, headache
Antipruritics including antihistamines, anesthetics	3 (2.01)	Dexchlorpheniramine (1), ropivacaine (2)	Anaphylactic shock, angioedema
Antianemic preparations	2 (1.34)	Sodium ferric gluconate (2)	Pharyngitis
Other hematological agents	2 (1.34)	Serrapeptase (2)	Pruritus
Cardiac therapy	2 (1.34)	Nitroglycerin (2)	Headache
Sex hormones and modulators of the genital system	2 (1.34)	Gestodene + ethinylestradiol (2)	Abdominal pain
Diuretics	1 (0.67)	Furosemide (1)	Cough
Antimycotics for systemic use	1 (0.67)	Fluconazole (1)	Erythema multiforme
Antiepileptics	1 (0.67)	Clonazepam (1)	Allergic drug reaction
Disulfiram	1 (0.67)	Disulfiram (1)	Vomiting
Total	100.00		

[a] In some cases, several drugs were simultaneously reported

Table 3 Severe adverse drug events (ADEs) identified in visits to emergency departments and drugs involved

Type of severe ADE	Number	Drugs involved[a] (*n*)
Confusion	3	Fenoterol + ipratropium bromide (1), beclomethasone dipropionate (1), lisinopril (2), acetylsalicylic acid (2), ciprofloxacin (2), betamethasone (2)
Abdominal pain	4	Gestodene + ethinylestradiol (2), thiamazole (2), ciprofloxacin chlorhydrate (1), omeprazole (1), esomeprazole (1)
Headache	2	Nimesulide (2)
Vomiting	2	Paracetamol (2)
Tremors	2	Salbutamol (2), salbutamol + ipratropium bromide (2)
Angioedema	2	Ropivacaine (2)

[a] In some cases, several drugs were simultaneously reported

in ADEs, antiasthmatics were characterized by more severe ADEs. Although they accounted for only 13% of ADE visits, they were responsible for 42.9% of serious events.

As regard to single drugs, only two medications were associated with more than 10 ADE visits: nimesulide was the most frequent, accounting for 14 ADEs (13.4% of all ADE visits), and 3 of these were classified as serious. Amoxicillin/clavulanic acid was correlated with 10 events (9.6%), one of which was serious (data not shown).

Multivariate analyses of significant correlates of ADEs in the case-control study showed that sex was not associated with ADEs. In contrast, the 30–39 age group was an independent predictive factor of ADE with an odds ratio (OR) of 2.09 (95% CI: 1.25–3.47) as was comorbidity (age-adjusted OR: 5.21; 95%CI: 3.02–8.98). In multivariate analyses, the adjusted OR was 3.4 (95% CI: 1.07–2.84) for patients taking NSAIDs, 5.09 (95% CI: 2.68–9.69) for those taking penicillin, 4.78 (95% CI: 2.26–10.12) for those taking β_2-adrenergic-receptor agonists, and 6.20 (95%CI: 2.74–14.06) for those taking other β-lactam antibiotics.

Table 4 Number of adverse drug events (ADEs) and severe ADEs according to drug type

ATC code (III level)	Drug type[a]	Number of ADE visits (% of total)	Serious ADE visits (% of total)
J01	Antibiotics	27 (26)	4 (14.3)
M01	NSAIDs	20 (19)	3 (14.3)
C09	Agents acting on the renin-angiotensin system	17 (16)	2 (11.8)
R03	Antiasthmatics	14 (13)	6 (42.9)
B01	Anticoagulants	10 (9.6)	2 (18.2)
A02	Drugs for acid-related disorders	7 (6.7)	2 (28.6)
C08	Calcium-channel blockers	5 (4.8)	-
H02	Corticosteroids	5 (4.8)	2 (40)
N02	Analgesics	5 (4.8)	2 (40)
H03	Thyroid therapy	4 (3.8)	2 (50)

[a] We have considered only the 10 drug types most involved in ADE visits

Discussion

Our study, carried out in 10 EDs in Campania, showed an incidence of ADE visits of 1.2%, which compares with an incidence between 0.9 and 4.3% reported in other geographic areas [25]. However, it is difficult to compare results across studies because of differences in identification criteria of ADEs, data collection periods, and study design [26]. Two meta-analyses showed an incidence of ADE between 2.4 and 3.6% in Australia and an incidence of ADE between 3.1 and 6% in the United States [25, 27].

Other studies have also shown that the incidence of adverse drug-related visits to hospital emergency departments can be considerably different depending on the definitions and methods applied [1–3, 6, 8, 9, 11, 12, 14]. Moreover, in our study, we also included drug-drug interactions, but excluded intentional overdose cases and the cases in which the causality, according to the WHO criteria, was not at least "probable/likely." This could be one explanation why our estimation of incidence of ADE visits to the ED is lower than in some other studies.

The ADE-related hospitalization rate in our study was 20.8%. This is lower than the 30.9% reported by Hafner et al. in the U.S. [14] and slightly higher than in one study conducted in EDs in Italy (19.1%) [15, 28].

Several studies suggested that old age and female gender might be risk factors for hospital admission caused by ADEs [29]. In our investigation, women and patients in the age groups of 30–39 and 60–69 years were significantly associated with ADEs. The association of ADEs with women may be partly attributable to the higher outpatient drug-prescription rate in women, as confirmed both in our and in other studies [3, 26, 30], whereas the association between patients in the 30–39 age group and ADE may be attributable to the higher proportion of self-medication-associated events (particularly NSAIDs intake). In fact, patients themselves can play a significant role in the occurrence of adverse drug reactions [31]. Patients should also reject the idea that there is a "pill for every ill" and avoid indiscriminate self-medication and doctor hopping [31].

Advanced age has been suggested to be a risk factor for ADEs [26]. We observed an incidence of ADEs higher in patients of 60–69 years. Probably in these patients the

increased number of comorbidities and regularly scheduled medications associated with advanced age may explain this effect. A few studies have assessed comorbidity or the number of current medical problems and found associations with ADEs [29, 32, 33]. However, it is difficult to explain the relatively low incidence of ADEs in patients over 70 years. It is possible that older people who suffer from more serious illness are more frequently hospitalized or referred to tertiary care units.

Our finding that ADE-related ED visits more frequently affected the skin (34.21% of total events) and the gastrointestinal system (21.05%) is in agreement with a previous report [21]. The drugs involved were antibiotics, NSAIDs, and agents acting on the renin-angiotensin system. In addition, the medications more frequently involved in serious ADEs were antiasthmatics drugs. Given the wide and frequently inappropriate use of antibiotic therapy [34], antibiotics were the drug category most associated with ADE visits in a previous study [34]. NSAIDs were the second drug category most frequently associated to ADE visits. This result could be because most NSAIDs are available over the counter in Italy and are widely used in self-medication [35]. Nimesulide was the NSAID most frequently associated with ADEs; this observation might be explained by the wide use of this drug in Italy. Although nimesulide was involved in 14 ADEs, its serious ADE rate was similar to that of other NSAIDs. Moreover, nimesulide was not associated with any hepatotoxic reaction in our study. According to the literature, the ADEs observed in our study are judged to be preventable.

Limitations of the study

Our study has some limitations. First, intra- and interrater agreement tests were not performed during the intensive course on theoretical and practical aspects of pharmacovigilance in emergency departments.

Another limitation was that the data were collected through a patient interview, so the patient's report may contain incorrect clinical attributions of symtoms to specific medicines. However, in our study, the diagnoses made by the ED physician were then verified by a medical committee through review of the ED forms in doubtful cases. Thus, we relied on the clinical experience and judgment of the clinical pharmacologist for classifying drug-related events.

In conclusion, our study shows that ADEs are an important public health problem in industrialized countries. Moreover, it shows that ADEs affect hospital admission rates and reinforces the significance of drug-induced disease as a public health problem. Efforts should be made to reduce ADEs through educational strategies aimed at improving awareness of the importance of pharmacovigilance among health professionals. In fact, according to Benichou [36] "a physician who cannot recognize an ADE represents a further risk factor."

Our study also confirms the validity of hospital EDs for surveys of ADEs. Using ED visits to study these events could lead to a better understanding of drug-related problems that arise from general practitioners' prescriptions. Therefore, further studies on large samples of patients are needed to better evaluate the incidence of ADEs in ED visits and to reduce and prevent drug-related injuries. This message should be communicated to relevant health-care policy-markers.

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