Adverse Drug Events Detected by Clinical Pharmacists in an Emergency Department : A Prospective Monocentric Observational Study

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Objectives: Adverse drug events (ADEs) are a major public health issue in hospitals. They are difficult to detect because of incomplete or unavailable medication history. In this study, we aimed to assess the rate and characteristics of ADEs identified by pharmacists in an emergency department (ED) to identify factors associated with ADEs.

Methods: In this prospective observational study, we included consecutive adult patients presenting to the ED of a French 2600-bed tertiary care university hospital from November 2011 to April 2015. Clinical pharmacists conducted structured interviews and collected the medication history to detect ADEs (i.e., injuries resulting directly or indirectly from adverse drug reactions and noncompliance to medication prescriptions). Unsure ADE cases were reviewed by an expert committee. Relations between patient characteristics, type of ED visit, and ADE risk were analyzed using logistic regression.

Results: Among the 8275 included patients, 1299 (15.7%) presented to the ED with an ADE. The major ADE symptoms were bleeding, endocrine problems, and neurologic disorders. Moreover, ADEs led to the ED visit, hospitalization, and death in 87%, 49.3%, and 2.2% of cases, respectively. Adverse drug event risk was independently associated with male sex, ED visit for neurological symptoms, visit to the ED critical care unit, or ED short stay hospitalization unit, use of blood, anti-infective, antineoplastic, and immunomodulating drugs.

Conclusions: This study improves the knowledge about ADE characteristics and on the patients at risk of ADE. This could help ED teams to better identify and manage ADEs and to improve treatment quality and safety.

Key Words: emergency department, adverse drug event, clinical pharmacist, medication history

The Institute of Medicine defined an adverse drug event (ADE) has “any injury resulting from medical intervention related to a drug.” This definition includes harm caused by the drug and harm from the use of the drug.[1] Adverse drug events occur in 2% to 22% of inpatients[2] and in 5% to 35% of outpatients.[3] Moreover, between 10% and 19% of visits to an emergency department (ED) are related to an ADE.[4–6] Adverse drug events are major public health issues in hospitals because of their high morbidity/mortality and economic costs.[7,8] For instance, a study on the injectable medication error burden in the United States showed that half of ADEs are preventable because these are caused by medication errors and that ADEs affect more than 7 million patients, cause 7000 deaths, and cost more than U.S. $21 billion in

direct medical costs annually. [9] In the general population and in specific categories, such as elderly people, causes of drug-related hospital admissions/ED visits include polypharmacy, polyphysicians, noncompliance, medication errors, and inappropriate prescriptions.[10–12]

Adverse drug event detection, documentation, and reporting are essential for adequate medical care and to improve the knowledge on the risk/benefit profiles of medications throughout their lifecycle. However, in the clinical practice, ADE underreporting is a generalized and widespread problem,[13,14] with up to 93% of identified ADEs without relevant internal occurrence report.[15] The main reasons for underreporting are difficulties in determining the ADE cause, lack of time, poor integration of ADE-reporting systems, uncertainty about the reporting procedures, and lack of immediate clinical interest by the clinicians.[13,16]

Rapid ADE detection is also crucial because its successful treatment depends on the ability of physicians to attribute the symptoms to a medication. However, ADE detection by ED physicians is often suboptimal,[17,18] particularly because of the unavailability or poor accuracy of the patients' medication history.[19] Indeed, up to two third of medication histories contain at least one error.[20] Several studies suggest that among healthcare providers, pharmacists and student pharmacists might be better suited to obtain detailed medication history[21–23] and to perform medication reconciliation, including in EDs.[24,25]

Therefore, a pharmacist team is routinely deployed in the ED of our hospital since November 2011 to help the ED team detect ADEs, particularly by collecting the patients' medication history. The primary objective of our study was to assess the rate and characteristics of ADEs identified by the pharmacist team in our ED. The secondary objective was to identify risk factors associated with ADEs and particularly with severe ADEs in ED patients. Indeed, a more detailed knowledge of ADE characteristics and risk factors may improve their detection by ED physicians.

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The authors disclose no conflict of interest. MV, IG, MS, and CB conceived and designed the study. ML, VG, OV, DP, VP, LL, IG, MV, AJ, ACN, MS, and CB performed all data collection. CB,MF, VM, and GM conducted data analysis. CB, VM, and MF drafted the article, and all authors contributed substantially to its revision. CB takes responsibility for the article as a whole.

METHODS

Design

This prospective observational study was conducted in the ED of our University Hospital, France (a 2600-bed tertiary care center). All patients included in the study received standard clinical care. Briefly, on the basis of their FRench Emergency Nurses Classification in Hospital (FRENCH) triage scale[26] level (used for care prioritization), patients presenting at our ED are directed toward the observation emergency unit or the emergency critical care

unit. Patients who require longer surveillance are addressed to the short stay emergency hospitalization unit. Our study was performed according to the World Medical Association Declaration of Helsinki and was approved by the hospital institutional reviewboard. Oral consent was obtained from all participants or from a member of their family. This study was registered on ClinicalTrials.gov (NCT03442010). Only the authors involved in the patients' management had access to their nonanonymized medical data. Patient data were then anonymized by removing any identifying information before the analysis.

Participants

Participation in this study was proposed by clinical pharmacists to all adult patients (>18 y) admitted to the ED from November 2011 to April 2015 and who underwent a medication history interview (for medication reconciliation) with a member of the pharmacist team from 8:00 a.m to 6.00 p.m., Monday to Friday (Fig. 1, flow chart). Patients were prospectively and consecutively included and were followed until ED discharge. Patients were not included if they presented acute psychological troubles or if they (or a family member) refused to participate in the study or in the case of voluntary medication poisoning.

Interventions

The ED medical staff includes junior emergency physicians, a senior physician who supervises medical decisions, and a pharmacist team (one senior pharmacist, one resident, and four pharmacy students). The ED pharmacist team carries out as many medication history interviews as possible from 8:00 a.m. to 6:00 p.m. (Monday–Friday) according to the availability of the pharmacist team. Therefore, all the patients included in the study were interviewed during these working hours but could have arrived at the ED at any time. All pharmacist team members received specific training on ADE detection[27–29] and medication reconciliation, according to the High 5s project standard operating procedures.[30,31]

With each included patient, the pharmacist team carried out a structured interview to determine (a) the best possible medication history (BPMH), including self-medication and medication reconciliation and (b) the self-reported adherence as well as when and how they took their drug(s). The BPMH interview was conducted following the standard operating procedures recommended by the World Health Organization,[30] as previously described.[32] The BPMH was defined as the most comprehensive list of all medications taken by the patient, including prescription drugs and self-medication, and was obtained through the following: (a) the patient's interview (or family interview if the patient could not answer); (b) drug prescriptions, if available; (c) phone calls to community pharmacies, physicians, and/or nurses; and (d) electronic medical record. The BPMH was based on at least two sources of information.

The sociodemographic data, medical history, current clinical status, FRENCH triage scale level, and clinical out-come were also collected by the pharmacist team.

Outcomes and Measurements

The primary outcome was the ADE rate. Adverse drug event was defined as any harm caused by the use of a drug or the inappropriate use of a drug.1 This definition included injuries (signs, symptoms, or laboratory abnormalities) resulting from adverse drug reactions (ADRs) or noncompliance to medication prescriptions. Voluntary medication poisoning was excluded from the ADE definition. Adverse drug events were classified in two categories: “direct ADR” (when the medication was judged to be the only cause of the pathological condition) and “participating ADR” (when the medication was judged not to be the only cause of the pathological condition, but to have facilitated or aggravated it).[19]

Adverse drug events were attributed to a medication by the pharmacist and confirmed by the treating senior ED physician, in real time. The medication causality was based on the search for chronological, semiological (symptoms, contributing factors, complementary exam results...), and bibliographic objective criteria.[27,29] The ADE severity was assessed according to the Common Terminology Criteria for adverse events as spontaneous regression, regression after symptomatic treatment, hospitalization with no life-threat, life-threatening risk, and death. Severe ADEs were defined as ADEs that required hospitalization or led to the patient's death.[28] In the case of doubt about the diagnosis or category of an ADE, the case was reviewed by an expert committee that included two senior ED physicians, one senior and one junior clinical pharmacists, and one pharmacovigilance physician. The medication causality was confirmed by consensus among the five members. Cases of medication toxicity were notified to the regional pharmacovigilance center at the physicians and pharmacists' discretion.

For each ADE, the medication involved as well as the ADE category (direct ADR, participating ADR, noncompliance to medication prescription), and severity were recorded.

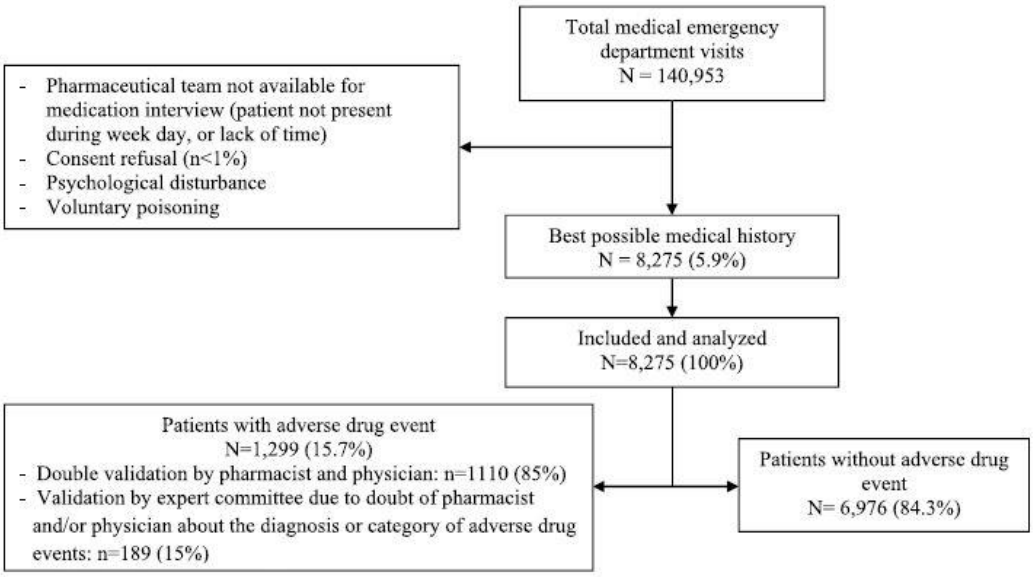

FIGURE 1. Flow chart of the study population.

Analysis

The patients' characteristics were described with percentages for categorical variables and means ± standard deviations for quantitative variables. The characteristics of patients with ADE and without ADE were compared with the Student t or the Mann-Whiney U test for continuous variables and with the $\chi 2$ or Fisher exact test for categorical variables. The variables considered as candidate ADE predictors included all data collected by the pharmacist team (e.g., patients' characteristics, demographic, reasons for ED visit, current medications…) and variables already reported in the literature as ADE risk factors (age,[33–38] sex,[33,39–43] number of treatments, and some drug types,37,44 such as antineoplastic compounds). The association between variables and ADE risk was analyzed using logistic regression.

The variables with P values lower than 0.15 in univariate models were considered for multivariable analyses. After stepwise selection, only the variables with P values lower than 0.05 in the multivariable model were considered significantly associated with ADE risk and were kept in the final multivariable model. All the variables analyzed in the univariate models

are represented in the tables that, however, only present the odds ratios of the variables included in the final multivariable model.

The risk factors of severe ADEs (hospitalization with no life threat, life-threatening risk, or death) versus spontaneous regression or regression after symptomatic treatment were also analyzed, using the same methodology. Missing data were not replaced. Statistical analyses were performed with SAS 9.1 (SAS Institute, France), and the statistical bilateral significance threshold was set at 5%.

RESULTS

Characteristics of the Study Population

Among the 140,953 patients who visited the ED from November 2011 to April 2015, 8275 patients (5.9%) were included in the study. The study population's baseline characteristics (at ED entry) are presented in Table 1. The mean ± SD age was 59.7 ± 22.9 years, and the sex ratio was close to 1; 68.8% of them arrived at the ED during working hours/days and 31.2% during the night or weekend.

Patients presented to the ED mainly for cardiovascular (23.8% of all included patients) and hepatogastrointestinal (22.1%) reasons. On average, they were taking 4.8 ± 4.2 drugs. In total, 3084 patients (38% of all included patients) were hospitalized after the passage at the ED, and 25 (0.3%) patients died at the ED. Moreover, 20.5% (633/3084) of hospitalizations and 52% (13/25) of deaths at the ED were related to an ADE. Adverse drug events were detected in 1299 patients (15.7% of the study population), with no difference between patients who entered the ED during working hours/days and during the night/weekend (15.8% versus 14.9%, P = 0.39). In comparison with the non-ADE population, the ADE population was older (65.8 ± 21.5 versus 58.5 ± 23.0 y), with a higher proportion of men (51.4% versus 47.7%), of patients living in institution (11.9% versus 7.5%), and number of taken drugs (6.3 ± 3.8 versus 4.5 ± 4.2) (Table 1). Moreover, the rates of death at the ED and hospitalization were higher in the ADE than in the non-ADE group (1% versus 0.2% and 49.3% versus 35.4%, respectively).

Description of ADEs Cases

The most frequent ADE-related symptoms were bleeding (24.7% of all ADEs), neurologic (17.0%), metabolic (14.5%), gastrointestinal (11.1%), and cardiovascular problems (8.9%). In total, 37.4% of ADEs were caused by direct medication effects (“direct ADR”), 23.6% by noncompliance with prescription (underuse or misuse), and 33.7% by the drug contribution to a multifactorial pathological condition (“participating ADR”) (Table 2). Among patients with ADE, the ADE was the direct cause of the ED visit in 86.7% of cases (n = 1126/1299), and it led to hospitalization in 48.8% (633/1299) and to death in 2.2% (29/1299) (1.0% in ED and 1.2% during the post-ED hospitalization). Medications targeting the nervous system (482 of the 1689 drugs taken by patients with ADE, 28.5%), blood and blood-forming organs (396/1,689, 23.4%), cardiovascular system (239/1689, 14.2%), and alimentary tract and metabolism (208/1689, 12.3%) were more often involved in the detected ADEs (Table 3). On the other hand, ADEs were more frequent in patients who took antineoplastic and immunomodulating agents (20.7% of all patients treated with these drugs), medications for blood and blood-forming organs (10.4% of all patients treated with these drugs), and anti-infective drugs for systemic use (9.3% of all patients treated with these drugs) (Table 3).

Adverse Drug Event Risk Factors

The multivariable analyses showed that overall, ADEs were associated with male sex, ED visit for neurologic problems, visit to the emergency critical care unit or to the short stay hospitalization unit, use of blood and blood-forming agents, anti-infective drugs for systemic use, and antineoplastic/immunomodulating agents (Table 4). Moreover, each ADE category was associated with different variables. Specifically, male sex, alcohol consumption, and visit to the short stay hospitalization unit were associated with participating and noncompliance ADRs, but not with direct ADRs. On the other hand, visit to the emergency critical care unit and antineoplastic/immunomodulating medications were associated with direct and participating ADRs, but not with noncompliance ADRs. A number of drugs higher than 5 was associated only with direct ADRs.

Risk Factors of Severe ADEs

The results of the univariate and multivariable analyses for the risk of severe ADEs are presented in Table 5. In multivariable analyses, age, male sex, renal failure, visit to the emergency critical care unit or to the short stay hospitalization unit, and the use of blood and antineoplastic/immunomodulating medications and participating ADRs were associated with severe ADEs. Conversely, ED visit without immediate need of urgent care (FRENCH triage scale level 5) and ED visit for cardiovascular problems were associated with a lower risk of severe ADEs.

DISCUSSION

The rapid identification and treatment of ADEs are fundamental to improve the quality of care and therapeutic outcomes. In EDs, physicians need immediate and complete access to clinical and therapeutic information to diagnose ADEs and provide quality care. To this aim, physicians, pharmacists, and all healthcare professionals must work together to combine their respective expertise and resources. In our study, the clinical pharmacy team contributed to identify ADEs in 15.7% (1299/8275) of the patients who underwent a medication history interview during their visit to the ED. Moreover, our multivariable analysis highlighted some risk factors of ADE and severe ADE.

Previous studies have investigated ADE incidence and types in different healthcare settings, such as communities, community pharmacies, hospitals, and EDs.[45] However, comparisons are difficult because ADE definition differed among studies and sometimes overlapped with other terms, such as drug-related problems, drug related visit, or medication errors. Moreover, the methodologies used to assess ADE incidence often varied among works, which are either prospective studies including only a few hundreds of patients or retrospective cohort studies with several thousands of patients. Retrospective cohort studies are often based on National Health Service databases where ADEs are identified using a list of International Classification of Diseases codes.[46] The main limitation of such studies is that they can underestimate ADE rate because they rely on International Classification of Diseases codes[47] and because ADEs are frequently underreported.[14] Moreover, because of the variety of coding processes and of methods used to identify ADEs in administrative data, these analyses are much more difficult than the use of raw data.[46]

In our study, we included 5.9% of all patients who visited our ED. This rate is slightly higher than in comparable studies that included between 1.6% and 3.5% of patients presenting at the ED.[6,19,48,49]

TABLE 1. Characteristics of the Study Population

Characteristics	Missing Data	Total	No ADE	ADE
Patients, n (%)		8275	6976 (84.3)	1299 (15.7)
Age, y	0	59.7 ± 22.9	58.5 ± 23.0	65.8 ± 21.5
Sex, male	0	3993 (48.3)	3325 (47.7)	668 (51.4)
Time of ED entry	935	7340 (100)		
Working day/hours		5045 (68.8)	4290 (69.0)	755 (67.5)
Night or weekend		2295 (31.2)	1931 (31.0)	364 (32.5)
FRENCH triage scale	146	8129 (100)		
Level 1		126 (1.6)	86 (1.3)	40 (3.1)
Level 2		1003 (13.3)	832 (12.2)	171 (13.3)
Level 3		4400 (54.1)	3713 (54.3)	687 (53.4)
Level 4		1687 (20.8)	1431 (20.9)	256 (19.9)
Level 5		913 (11.2)	781 (11.4)	132 (10.3)
Type of ED unit	19	8256 (100)		
Emergency critical care unit		152	93 (1.3)	59 (4.6)
Observation emergency unit		8003	6806 (97.8)	1197 (92.5)
Short stay hospitalization unit		101	63 (0.9)	38 (2.9)
Lifestyle	1	8274 (100)		
At home		7589 (91.7)	6448 (92.4)	1141 (87.9)
In institution		679 (8.2)	524 (7.5)	155 (11.9)
Homeless		6 (0.1)	4 (0.06)	2 (0.2)
Main cause of ED visit	90	8185 (100)		
Cardiovascular		1945 (23.8)	1722 (24.7)	223 (17.5)
Hepatogastrointestinal		1807 (22.1)	1550 (22.4)	257 (20.2)
Genitourinary		639 (7.8)	571 (8.3)	68 (5.3)
Respiratory		949 (11.6)	813 (11.8)	136 (10.7)
Neurologic		543 (6.6)	389 (5.6)	154 (12.1)
Rheumatologic		384 (4.7)	351 (5.1)	33 (2.6)
Trauma		378 (4.6)	344 (5.0)	34 (2.7)
Skin		171 (2.1%)	102 (1.5)	69 (5.4)
Other		1369 (16.7)	1071 (15.5)	298 (30.5)
Patient interview	408	6473 (82.3)	5525 (83.7)	948 (74.8)
ED visit outcome	49	8226 (100)		
Discharge		5111 (62.1)	4467 (64.5)	644 (49.7)
Hospitalization		3084 (37.3)	2451 (35.4)	633 (48.7)
Death		25 (0.3)	12 (0.2)	13 (1.0)
Self-medication	0	3215 (38.8)	2877 (41.2)	338 (26.0)
Independent management of medications	1510	5043 (74.5)	4137 (75.3)	906 (71.3)
No. daily medications	0	4.8 ± 4.2	4.5 ± 4.2	6.3 ± 3.8

Data are presented as mean ± standard deviation or n (%). FRENCH triage scale level 1: immediately life-threatening; level 2: marked impairment of a vital organ, or imminently life-threatening, or functionally disabling traumatic lesion; level 3: functional impairment, or organic lesions likely to deteriorate within 24 h, or complex medical situation justifying the use of several hospital resources; level 4: stable, noncomplex functional impairment or organic lesions, but justifying the urgent use of at least one hospital resource; level 5: no functional impairment or organic lesion justifying the use of hospital resources.

In our analysis, we found that approximately 15% of ED visits were related to an ADE, in accordance with prospective studies reporting rates between 10% and 19%.4–6 The most common symptoms associated with ADEs were bleeding, endocrine, neurologic, and gastrointestinal problems, as previously reported.48 In agreement with various studies,[11,19] 20.5% of post-ED hospitalizations and 52.0% of deaths at ED were due to an ADE. The post-ED hospitalization rate was slightly higher, and mortality was fivefold higher (1% versus 0.2%) in the ADE than non- ADE group, similarly to the 3.5-fold death increase reported by Classen et al.[50]

TABLE 2. Characteristics of ADEs

	ADEs (n = 1299)
ADE symptoms	
Bleeding	321 (24.7%)
Gastrointestinal bleeding	113
Hematoma	69
Hematuria/hemoptysis/epistaxis	81
Others	58
Metabolic disorders	185 (14.5%)
Electrolyte disorders	64
Hyperglycemia/hypoglycemia	97
Others	24
Neurologic disorders	221 (17.0%)
Seizure	64
Altered consciousness/ confusion/discomfort	132
Other	3
Blood coagulation disorders	52 (4.0%)
Increase of blood INR values	37
Others	15
Fatigue/fall	37 (2.8%)
Pulmonary disorders	20 (1.5%)
Others	69 (5.3%)
ED visit caused by ADE	1126 (86.7%)
ADE categories	
Direct ADR	486 (37.4%)
Participating ADR	437 (33.7%)
Noncompliance to drug prescription	306 (23.6%)
Undetermined	70 (5.3%)
ADE severity	
Spontaneous regression	29 (2.2%)
Regression after symptomatic treatment	610 (47.0%)
Hospitalization with no life threat	562 (43.3%)
Hospitalization with life-threatening risk	71 (5.5%)

Others	25
Gastrointestinal disorders	144 (11.1%)
Abdominal pain/diarrhea	41
Gastroduodenal pain	23
Nausea/vomiting	35
Constipation	38
Others	7
Cardiovascular disorders	116 (8.9%)
Hypertension	17
Hypotension	28
Heart failure	20
Cardiac rhythm disorders	33
Others	18
Infections	81 (6.2%)
Pneumonia	19
Urinary tract infection	9
Infection syndromes	53
Skin diseases	53 (4.1%)
Allergic reactions	31
Urticaria	19
Other	3
Blood coagulation disorders	52 (4.0%)
Increase of blood INR values	37
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Hospitalization with life-threatening risk	71 (5.5%)
Death	29 (2.2%)
At the ED	13 (1.0%)
After hospitalization with life-threatening risk	16 (1.2%)
Unknown	14 (1.1%)

Data are presented as n (%).
Abbreviation: INR, international normalized ratio.

As previously described, the medications most involved in ADE (66% of cases) were nervous system, blood and blood forming organ, and cardiovascular system drugs.[11] In addition, during the medication history interview for medication reconciliation and BPMH, we recorded all the drugs taken by the patient, which allowed us to calculate ADE rate per class (Anatomical Therapeutic Classification [ATC] 1st level) and subclass (ATC 2nd level) of medications, which is usually not done in studies on ADEs. This is particularly important for the clinical practice. For example, antineoplastic and immunomodulating agents ranked fifth in terms of number of ADEs but were first in terms of occurrence. To our knowledge, this is the first time that a prospective study presents ADE incidence in function of the drug class and subclass in a cohort of more than 8000 patients with 42,511 medications.

Another originality of our study was to analyze risk factors for each ADE categories (direct ADRs, participating ADRs, and noncompliance) and for severe ADE. We found that

age was not independently associated with ADE risk (all categories), in agreement with most studies,[33–36] but not all.[37,38] Differences in ADE definition and in the patient populations may explain this heterogeneity among studies. On the other hand, age was an independent risk factor of participating ADR and severe ADEs. Medications for blood and blood-forming organs, antineoplastic and immunomodulating agents, and anti-infective drugs for systemic use were independent risk factors of all ADEs, as previously reported [37,44,51] and also of severe ADEs (except for anti-infective drugs). Moreover, ED visit to the emergency critical care and short stay hospitalization unit (i.e., the highest ED priority) were associated with ADEs and also severe ADEs. This information might contribute to improve the detection and management of patients with ADEs. In case of direct ADRs, a medication change or dosage adjustment may be proposed, whereas for noncompliance, a specific therapeutic education can be proposed. The most complex care management concerns patients with participating ADRs where the medication is not the only cause of the clinical event but also an aggravating factor. Accordingly, participating ADRs were associated with risk of severe ADE.

Our study has many strengths. To our knowledge, this is the first prospective study that analyzed the rate, severity, and independent risk factors in different categories of ADEs detected by clinical pharmacists in a cohort of more than 8000 adult patients in an ED. Our ED population included all types of adult patients visiting an ED and was not limited to specific classes of medications. The rigorous prospective data collection performed by the pharmacist team included demographic, clinical, biological, and therapeutic data as well as information on the (correct or incorrect) use of treatments by the patient, self-medication, and medication adherence. This allowed us to assess ADE association with many variables related to the patients, their ED visit, and their treatment, in a more comprehensive manner than previously done.35 Finally, our study provides a robust estimate of ADE-related ED visits because f several methodological strengths. First, integrating the clinical pharmacist team in the ED for BPMH collection and medication reconciliation ensured a high level of ADE detection, particularly of participating ADRs. Second, an expert committee reviewed suspect cases, ensuring correct ADE diagnosis and classification.

TABLE 3. Distribution of Medications According to Presence of ADEs

Medication Involved (ATC 1st and 2nd Level)	Total	ADEs	Non ADEs
No. medications	**42,511**	**1689 (4.0%)**	**40,822 (96%)**
A. Alimentary tract and metabolism	**9072**	**208 (2.3%)**	**8864 (97.7%)**
A02. Drugs for acid-related disorders	3080	18 (0.6%)	3062 (99.4%)
A03. Drugs for functional gastrointestinal disorders	968	8 (0.8%)	960 (99.2%)
A06. Laxatives	930	5 (0.5%)	925 (99.5%)
A07. Antidiarrheal, intestinal anti-inflammatory/anti-infective agents	403	8 (2.0%)	395 (98.0%)
A10. Drugs used in diabetes	2165	163 (7.5%)	2002 (92.5%)
A11. Vitamins	489	0 (0.0%)	489 (100.0%)
Others	1037	6 (0.6%)	1031 (99.4%)
B. Blood and blood-forming organs	**3799**	**396 (10.4%)**	**3403 (89.6%)**
B01. Antithrombotic agents	3286	394 (12.0%)	2892 (88.0%)
Others	513	2 (0.4%)	511 (99.6%)
C. Cardiovascular system	**9816**	**239 (2.4%)**	**9577 (97.6%)**
C01. Cardiac therapy	1251	31 (2.5%)	1220 (97.5%)
C03. Diuretics	1556	62 (4.0%)	1,494 (96%)
C07. β-Blocking agents	1603	37 (2.3%)	1566 (97.7%)
C08. Calcium channel blockers	956	18 (1.9%)	938 (98.1%)
C09. Agents acting on the renin-angiotensin system	2302	77 (3.3%)	2225 (96.7%)
C10. Lipid-modifying agents	1812	9 (0.5%)	1803 (99.5%)
Others	336	5 (1.5%)	331 (98.5%)
D. Dermatologicals	**368**	**4 (1.1%)**	**364 (98.9%)**
G. Genitourinary system and sex hormones	**1108**	**18 (1.6%)**	**1090 (98.4%)**
G04. Urological drugs	810	12 (1.5%)	798 (98.5%)

Others	298	6 (2.0%)	292 (98.0%)
H. Systemic hormonal preparations	**1234**	**63 (5.1%)**	**1171 (94.9)**
H02. Corticosteroids for systemic use	481	51 (10.6%)	430 (89.4%)
H03. Thyroid therapy	719	12 (1.7%)	707 (98.3%)
Others	34	0 (0.0%)	34 (100.0%)
J. Anti-infective drugs for systemic use	**969**	**90 (9.3%)**	**879 (90.7%)**
J01. Antibacterial drugs for systemic use	807	73 (9.0%)	734 (91.0%)
Others	162	17 (10.5%)	145 (89.5%)
L. Antineoplastic and immunomodulating agents	**405**	**84 (20.7%)**	**321 (79.3%)**
L01. Antineoplastic agents	193	56 (29.0%)	137 (71%)
L04. Immunosuppressive agents	123	23 (18.7%)	100 (81.3%)
Others	89	5 (5.6%)	84 (94.4%)
M. Muscular-skeletal system	**1586**	**74 (4.7%)**	**1512 (95.3%)**
M01. Anti-inflammatory and antirheumatic products	988	60 (6.1%)	928 (93.9%)
M04. Antigout preparations	356	11 (3.1%)	345 (96.9%)
Others	242	3 (1.2%)	239 (98.8%)
N. Nervous system	**11,340**	**482 (4.3%)**	**10,858 (95.7%)**
N02. Analgesics	4588	118 (2.6%)	4470 (97.4%)
N03. Antiepileptic drugs	835	95 (11.4%)	740 (88.6%)
N04 Anti-Parkinson drugs	355	20 (5.6%)	335 (94.4%)
N05. Psycholeptics	3389	176 (5.2%)	3213 (94.8%)
N06. Psychoanaleptics	1918	54 (2.8%)	1864 (97.2%)
Others	255	19 (7.5%)	236 (92.5%)
R. Respiratory system	**2334**	**20 (0.9%)**	**2314 (99.1%)**
R03. Antiasthmatics	1442	14 (1.0%)	1428 (99.0%)
R06. Antihistamines for systemic use	486	6 (1.2%)	480 (98.8%)
Others	406	0 (0.0%)	406 (100.0%)
Others	480	11 (2.3%)	469 (97.7%)

Data are presented as n (%).

	Participating ADRs		Noncompliance	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
	1.02 (1.02–1.03)	<0.0001	0.97 (0.96–0.98)	<0.0001
	1.43 (1.12–1.83)	0.005	1.75 (1.29–2.37)	0.0003
	1.93 (1.27–2.93)	0.002	1.73 (1.13–2.64)	0.011
	0.59 (0.42–0.84)	0.003		
	1.58 (1.17–2.13)	0.003	0.23 (0.13–0.42)	<0.0001
			0.34 (0.15–0.78)	0.011
			2.36 (1.60–3.49)	<0.0001
	2.45 (1.36–4.39)	0.003		
	2.13 (0.98–4.64)	0.057	4.29 (1.98–9.26)	0.0002
	2.51 (1.86–3.38)	<0.0001		
	2.65 (1.75–4.03)	<0.0001		
			0.57 (0.33–0.99)	0.045

TABLE 4. Risk Factors of ADEs: Multivariable Analyses

	Total ADEs		Total ADEs		Direct ADRs	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (for 1 unit)						
Male sex	1.29 (1.07–1.54)	0.007	1.29 (1.07–1.54)	0.007		
Body mass index ≥ 30 kg/m^2 (versus <30 kg/m^2)						
In institution (yes versus no)						
Comorbidities						
Renal failure (GFR <60 mL/min/1.73 m) (yes versus no)						
Hepatic failure (yes versus no)						
Psychiatric disease (yes versus no)						
Dementia (yes versus no)						
Alcohol consumption (yes versus no)						
Tobacco use (yes versus no)					0.58 (0.43–0.77)	0.0002
Nonindependent management of medication						
FRENCH triage scale level 5 (versus other levels)						
Cause of ED visit						
Cardiovascular (versus other causes of ED visit)						
Hepatogastrointestinal (versus other causes of ED visit)						
Genitourinary (versus other causes of ED visit)					0.51 (0.31–0.85)	0.009
Neurologic (versus other causes of ED visit)	1.86 (1.35–2.57)	0.0002	1.86 (1.35–2.57)	0.0002	1.54 (1.12–2.12)	0.008
Respiratory (versus other causes of ED visit)						
ED unit visit						
Emergency critical care unit (versus observation emergency unit)	2.67 (1.49–4.77)	0.0009	2.67 (1.49–4.77)	0.0009	3.33 (2.16–5.13)	<0.0001
Short stay hospitalization unit (versus observation emergency unit)	2.78 (1.45–5.34)	0.002	2.78 (1.45–5.34)	0.002	2.36 (1.32–4.22)	0.004
No. drugs > 5 (versus ≤ 5)					1.29 (1.06–1.57)	0.009
Medications (ATC 1st level)						
B. Blood and blood-forming organs (versus other medication types)	1.50 (1.25–1.80)	<0.0001	1.50 (1.25–1.80)	<0.0001		
L. Antineoplastic and immunomodulating agents (versus other medication types)	2.07 (1.47–2.92)	<0.0001	2.07 (1.47–2.92)	<0.0001	2.57 (1.84–3.59)	<0.0001
J. Anti-infective drugs for systemic use (versus other medication types)	1.39 (1.08–1.80)	0.012	1.39 (1.08–1.80)	0.012	2.17 (1.70–2.76)	<0.0001

Abbreviations: FRENCH,[26] level 1: immediately life-threatening; level 2: marked impairment of a vital organ, or imminently life-threatening, or functionally disabling traumatic lesion; level 3: functional impairment, or organic lesions likely to deteriorate within 24 h, or complex medical situation justifying the use of several hospital resources; level 4: stable, noncomplex functional impairment, or organic lesions, but justifying the urgent use of at least one hospital

resource; level 5: no functional impairment or organic lesion justifying the use of hospital resources; GFR, glomerular filtration rate. Abbreviation: GFR, glomerular filtration rate.

Our study also has some limitations. Its monocentric design and our recruitment method may limit the generalization of our results, because of selection bias. First, pharmacists were present only during working days/hours and only 5.9% of patients who visited ED were included. However, patients visiting the ED during night or weekend and who were still present during working hours/days could be included (31.2% of our sample). Second, according to the French regulation, we included only patients who gave their consent for the study. However, only few patients refused (<1%), because the pharmacist's intervention is a routine practice in our ED. Because of the very small number of refusals, we did not record them, but the risk of recruitment bias seems negligible. Noninclusions due to psychological disturbance or voluntary poisoning not only were recorded but also represented a very small number of patients.

Another limitation comes from the decision to analyze only patients with outmissing data rather than using a multiple imputation method to replace missing data. This could result in a possible bias in the regression coefficients. However, because of the large number of patients and the small number of missing data for most variables, a multiple imputation approach was not included in our methodology. Lastly, our study highlighted the helpful role played by a pharmaceutical team integrated in an ED, as already described in endocrinology32 and surgery departments.52 Nevertheless, our observational design, without any control arm, does not allow to conclude about the specific role of pharmacists to improve the quality of care.

TABLE 5. Univariate and Multivariable Analyses of Variables Associated With ADE Severity (Hospitalization With No Life Threat, Life-Threatening Risk or Death Versus Spontaneous Regression or Regression After Symptomatic Treatment)

	Univariate Analysis		Multivariable Analysis	
	Odds Ratio (95% CI)	***P***	**Odds Ratio (95% CI)**	***P***
Age (for 1 unit)	1.03 (1.02–1.03)	<0.0001	1.02 (1.01–1.02)	<0.0001
Male sex	1.25 (1.01–1.6)	0.045	1.31 (1.02–1.70)	0.032
Body mass index ≥ 30 kg/m^2 (yes versus no)	1.25 (0.83–1.89)	0.28		
In institution (yes versus no)	1.12 (0.80–1.57)	0.50		
Comorbidities				
Renal failure (GFR <60 mL/min/1.73 m^2) (yes versus no)	2.23 (1.50–3.34)	<0.0001	1.55 (1.00–2.41)	0.049
Hepatic failure (yes versus no)	1.19 (0.61–2.34)	0.61		
Psychiatric disease (yes versus no)	1.10 (0.79–1.53)	0.56		
Dementia (yes versus no)	1.72 (1.22–2.41)	0.002		
Alcohol consumption (yes versus no)	0.83 (0.50–1.37)	0.47		
Tobacco use (yes versus no)	0.86 (0.36–0.66)	<0.0001		
Nonindependent management of medications	2.00 (1.52–2.65)	<0.0001		
Triage				

FRENCH triage scale level 5 (yes versus other levels)	0.45 (0.31–0.66)	<0.0001	0.51 (0.34–0.78)	0.002
Cause of ED visit				
Cardiovascular (versus other causes of ED visit)	0.63 (0.47–0.84)	0.002	0.60 (0.43–0.83)	0.002
Hepatogastrointestinal (versus other causes of ED visit)	1.02 (0.77–1.34)	0.91		
Genitourinary (versus other causes of ED visit)	1.05 (0.65–1.71)	0.84		
Neurologic (versus other causes of ED visit)	0.72 (0.51–1.01)	0.059		
Respiratory (versus other causes of ED visit)	1.33 (0.93–1.91)	0.12		
ED unit				
Emergency critical care unit (versus observation emergency unit)	3.82 (2.04–7.15)	<0.0001	3.29 (1.71–6.35)	0.0004
Short stay hospitalization unit (versus observation emergency unit)	2.65 (1.30–5.40)	0.007	2.34 (1.11–4.91)	0.025
No. drugs > 5 (versus ≤ 5)	1.86 (1.49–2.32)	<0.0001		
Medications (ATC 1st level)				
B. Blood and blood-forming organs (versus other medication types)	2.83 (2.26–3.55)	<0.0001	1.52 (1.14–2.02)	0.0041
L. Antineoplastic and immunomodulating agents (versus other medication types)	1.96 (1.28–3.00)	0.002	2.12 (1.32–3.41)	0.002
J. Anti-infective drugs for systemic use (versus other medication types)	0.75 (0.54–1.03)	0.008		
N. Nervous system (versus other medication types)	0.92 (0.72–1.17)	0.48		
C. Cardiovascular system (versus other medication types)	2.48 (1.96–3.13)	<0.0001		
A. Alimentary tract and metabolism (versus other medication types)	1.79 (1.43–2.25)	<0.0001		
ADE categories				
Direct ADRs (versus other ADE categories)	0.65 (0.52–0.82)	0.0002		
Participating ADRs (versus other ADE categories)	2.30 (1.81–2.92)	<0.0001	1.65 (1.26–2.17)	0.0003
Noncompliance (versus other ADE categories)	0.53 (0.41–0.69)	<0.0001		

Abbreviations: FRench Emergency Nurses Classification in Hospital scale (FRENCH)[26] level 1: immediately life-threatening; level 2: marked impairment f a vital organ, or imminently life-threatening, or functionally disabling traumatic lesion; level 3: functional impairment, or organic lesions likely to deteriorate within 24 h, or complex medical situation justifying the use of several hospital resources; level 4: stable, noncomplex functional impairment or organic lesions, but justifying the urgent use of at least one hospital resource; level 5: no functional impairment or organic lesion justifying the use of hospital resources; GFR, glomerular filtration rate.

CONCLUSIONS

In summary, 15.7% (n = 1299) of our large ED population (n = 8275) had ADEs detected by the pharmacist team and confirmed by the ED physician or expert committee. Most ADEs (71%) were related to a medication directly or indirectly, whereas 24% of ADEs were related to noncompliance with the prescription, and 5% had an undetermined cause. The most common ADE symptoms were bleeding, endocrine and neurologic problems, and were caused by anticoagulants, antibiotics, and antineoplastic/ immunomodulating agents. Finally, male sex, ED visit for neurologic problems, visit to the emergency critical care or to short stay hospitalization units, as well as blood, anti-infective, antineoplastic, and immunomodulating treatments were independent risk factors of ADE. Such risk factors may help primary care providers prioritize patients for medication reconciliation and detect rapidly ADE related ED visit, to reduce morbidity and mortality.

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