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Brief Reports

ADVERSE DRUG EVENT NONRECOGNITION IN EMERGENCY DEPARTMENTS: AN EXPLORATORY STUDY ON FACTORS RELATED TO PATIENTS AND DRUGS

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Abstract—Background: Many adverse drug events (ADEs) are not identified by emergency physicians. Research has been done to study risk factors for ADEs and help emergency physicians diagnose ADEs. However, no research has specifically examined the causes underlying a lack of attribution of ADEs to medications in emergency department (ED) patients. **Objective:** We conducted an exploratory study in a medical ED to search for the factors associated with ADE nonrecognition that are related to ED patients and ADEs. **Methods:** We conducted an observational study in the medical ED of a French tertiary care hospital between January and December 2009. The study focused on all ADEs, whether or not they were related to the patient's chief complaint. ADEs were identified by an expert physician and pharmacist based on National Electronic Injury Surveillance System criteria. An ADE was considered "attributed" if any evidence of ADE suspicion, ADE diagnosis, or ADE management was documented on ED charts. Factors associated with ADE nonrecognition were identified using multiple logistic regression analysis. **Results:** Of the 465 included patients, 90 experienced an ADE at ED visit (19.4%; 95% confidence interval [CI] 15.9%–23.2%). Emergency physicians correctly recognized 36 of these cases (40.0%; 95% CI 29.8%–50.9%). On multivariate analysis, ADE nonrecognition was significantly associated with the following variables: nonrelation between the ADE and the patient's chief complaint; daily prescription of four drugs or more; and hospitalization ADE severity category. **Conclusions:** Our results

emphasize the importance of searching for ADEs in patients with daily polypharmacy or whose chief complaint does not seem to be drug related. © 2014 Elsevier Inc.

Keywords—emergency department; adverse drug event; pharmacoepidemiology; diagnosis

INTRODUCTION

Emergency departments (EDs) are an essential part of health care systems and serve as an interface between hospitals and communities. EDs are specialized to allow for the recognition and emergent care of any patient's chief complaint or condition severity, with complex decisions that often need to be made with very little information. This context makes the ED an ideal place to study adverse drug events (ADEs) (1,2).

ADEs are a significant cause of morbidity in many patients presenting to the ED with higher severity and substantially increased health services utilization and cost (1,3–9).

Successful treatment of ADEs first depends on the ability of emergency physicians to attribute ADEs to a medication-related problem and intervene when necessary, especially with drug regimen optimization or drug

discontinuation at ED, and communication with other care providers (10). Recent data suggest that emergency physicians are moderately successful in identifying ADEs in patients presenting to the ED, and are less able to identify ADEs that are not related to the patient's chief complaint (11–13).

Research was done to study how best to improve the emergency physician's skill in diagnosing ADEs. Risk factors for ADEs were highly studied in hospitalized patients and, to a lesser extent, in ED patients (1,6,8,12,14–17). Clinical decision rules were recently developed to identify ED patients at high risk for ADEs who require medication review by a medication specialist (18). However, to date, no research has specifically examined the causes underlying a lack of attribution of ADEs to medications in ED patients.

We conducted an exploratory study to contribute to the research on factors associated with ADE nonrecognition in ED patients. The study objective was to search for factors associated with ADE nonrecognition that are related to ED patients and ADEs.

METHODS

Study Design and Setting

This exploratory study was conducted in the medical ED of a French 3,000-bed tertiary care hospital with an annual ED census of 64,000 visits. The trauma, gynecologic, and psychiatric EDs are physically separated from the medical ED and were not included in this study.

At the time of the study, emergency medicine in France was a supra-specialty that was not recognized as a stand-alone specialty (19). At any time of day or week, every patient admitted to our medical ED was managed by a fellow physician who was supervised by a senior physician with a qualification in emergency medicine. Emergency physicians that intervened in our medical ED during the study were unaware of its specific objective, even if they were informed that a research project on ADEs in ED patients was being conducted there. The investigators reported any ADE that they could identify at the time of the care to the emergency physicians.

Institutional Review Board approval for noninterventional studies was obtained.

Selection of Participants

The selection process was designed as described previously (20). All adult patients presenting to the medical ED of the study hospital between January 2009 and December 2009 were eligible for enrollment. Of 261 weekdays during the study period, 85 were randomly selected, which allowed us to balance the number of time slots per weekday and per yearly quarter.

All patients who were physically present in the ED at the beginning of each time slot were screened for eligibility, regardless of entry date or illness severity. Patients were included if they (or their support person) agreed to participate, they did not visit the ED due to intentional drug poisoning, and it was their first visit to the ED during the study period. Readmissions were analyzed separately so as not to miss any ADE.

Data Collection and Processing

The investigators in this study were an emergency physician with special experience in internal medicine and a trained clinical pharmacist, neither intervened in the care of included patients. They are subsequently referred as “the investigator pair.”

Data were collected by 12 pregraduate pharmacists (5th-year graduate students) completing a training course in the ED on weekday mornings during their university hospital internship (21). The students became familiar with the data-collection process during a standardized 1-week pilot period. They were trained by the clinical pharmacist to review all available ED charts (eg, clinician records, nursing notes, emergency medical services logs, and discharge instructions) and interview the patients or their relatives when possible. Information was prospectively collected in real time after patient inclusion, at the time of the care, under daily supervision.

Data were collected in a standardized abstraction form (Sphinx 5 software, Sphinx Développement, Chavanod, France). The data collected included sociodemographic characteristics, medical history, current clinical status, and final diagnosis. Special attention was focused on drug exposure during the 2 weeks preceding the ED visit. If data collected during the ED visit were insufficient to identify an ADE with certainty, additional information was obtained from other medical contact, but not from the patients themselves.

Drugs were classified by pharmacy students on the basis of the Anatomical Therapeutic Chemical Classification Index (World Health Organization Collaborating Centre for Drug Statistics Methodology). ED diagnosis and injuries associated with ADEs were coded by the investigator pair according to the *International Classification of Diseases*, 10th revision (22). The Charlson Comorbidity Index, one of the most extensively studied comorbidity index for predicting mortality, was used to assess the burden of concomitant disease for each patient (23,24).

Methods of Measurement

ADEs were classified according to the definition used by the National Electronic Injury Surveillance System: Cooperative Adverse Drug Events Surveillance System

(NEISS-CADES) (2). The NEISS-CADES defines an ADE as an injury related to the patient's use of a drug and resulting from an allergic reaction (immunologically mediated effect), an adverse effect (undesirable pharmacologic effect at a recommended dose), an unintentional overdose (toxic effect linked to excess dose or impaired excretion), or a secondary effect (eg, falls and secondary infections). This definition excludes drug therapeutic failures, drug withdrawal, drug abuse, intentional drug poisonings, and ADEs that occurred as a result of ED medical treatment.

The investigator pair reviewed all cases together to identify ADEs. ADEs were identified on the basis of collected data using clinical knowledge and validated databases of known adverse drug reactions that were also accessible to the ED physicians. Contentious issues were resolved by consensus and, when required, by the expertise of a pharmacologist who was not involved in the research project. We studied ADEs that were either the cause for the patient's visit to the ED, or were unrelated to the patient's chief complaint.

ADE severity was assessed according to the five-stage Common Terminology Criteria for Adverse Events: A) spontaneous regression, B) regression after symptomatic treatment, C) hospitalization with no life threat, D) life-threatening risk, and E) death (25). Drug causality was assessed according to the four-stage Naranjo Probability Scale: "doubtful" (score 0), "possible" (score 1–4), "probable" (score 5–8), or "definite" (score ≥ 9) (26). When two or more drugs were assessed in a clinical scenario suspicious for an ADE, the drug with the highest probability score was considered for the attribution of a global causality level to the ADE case.

Finally, the investigator pair examined whether or not the identified ADEs were recognized by the ED physicians.

Outcome Measures

The primary outcome was the frequency of ADEs that were attributed to a medication-related problem by emergency physicians. An ADE was considered "attributed" if any evidence of ADE suspicion, ADE diagnosis, or ADE management (eg, drug regimen optimization, drug discontinuation, prescription of a symptomatic treatment, hospitalization for further investigation) was documented on ED charts. An ADE was labeled as "unattributed" when no evidence was found that the emergency physician suspected, recognized, or provided management of the ADE; conversely, an ADE could be labeled as attributed even though it was not explicitly documented in the ED charts (12).

Primary Data Analysis

A Student's *t*-test was used to compare differences between the means for normally distributed variables, and a Wilcoxon rank sum test was used for the other variables. A comparison of groups for categorical variables was tested by a χ^2 test or a Fisher's exact test. The level of significance was set at 5%.

To explore the factors associated with ADE nonrecognition, the following variables of interest were studied after verifying that no data were missing: age, sex, Charlson Comorbidity score, priority at the ED visit (triage acuity score), number of daily medications, ADE diagnosis, drug categories causing ADEs, relation between ADE and the patient's chief complaint, ADE causality assessment, and ADE severity. The link between ADE nonrecognition and covariables was first tested by univariate logistic models. Only the variables with $p < 0.2$ were retained for multivariate analysis. After assessing for collinearity, variables were selected in multivariate logistic models with a manual backward procedure including clinical judgment. Only clinically relevant interactions were tested. The model fit was tested (Hosmer-Lemeshow test). All analyses were performed using SAS statistical software (SAS 9.1, SAS Institute, Cary, NC).

RESULTS

Of 472 patients who met inclusion criteria, 7 (1.5%) were excluded because the ED medical investigations were insufficient to identify an ADE with certainty (Figure 1). The baseline characteristics of the 465 patients considered for analysis are presented in Table 1.

We determined that 90 patients visited our medical ED with an ADE (19.4%; 95% confidence interval [CI] 15.9%–23.2%). Emergency physicians attributed 36 of these cases (40.0%; 95% CI 29.8%–50.9%) to a medication-related problem (Table 2). No ADE was identified in all three readmissions.

ADE diagnoses were most frequently bleeding (16.7%), secondary infectious disease (12.2%), water–electrolyte imbalance (11.1%), acute renal failure (11.1%), constipation (7.8%), and consciousness disorders (7.8%). Of the identified ADEs, 51 (56.7%) led to hospitalization (C–E gravity categories), and 6 of these were deemed to be serious and 2 were fatal (2 cases of intracerebral bleeding when on antithrombotic therapy, leading to 1 death in ED and 1 death after ED discharge to a medical department). Drug categories most commonly causing ADEs were antithrombotic agents (13.0%), agents acting on the renin–angiotensin system (12.3%), opioids (10.9%), diuretics (global: 9.4%; furosemide: 8.0%), and glucocorticoids (7.2%).

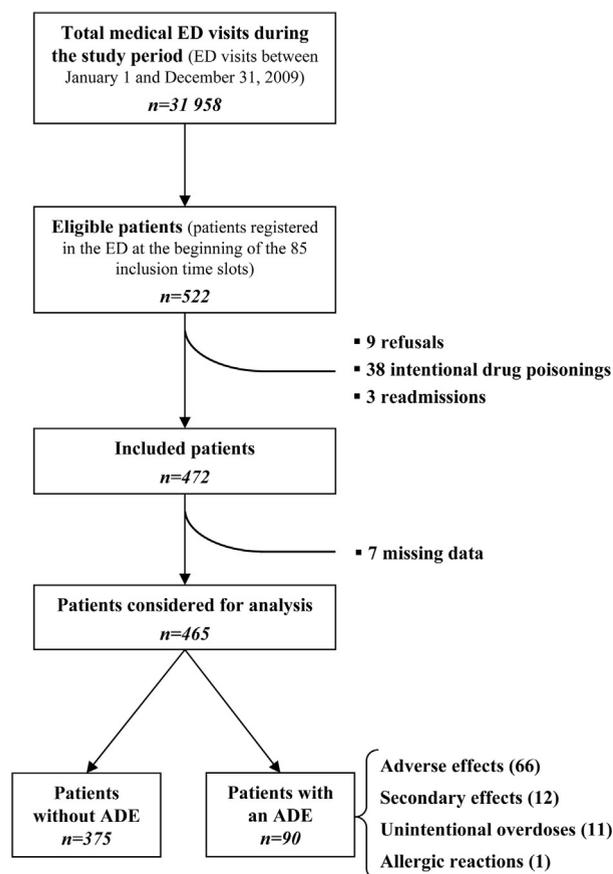


Figure 1. Patient flow. ADE = adverse drug event; ED = emergency department.

On univariate analysis, ADE nonrecognition was significantly associated with increasing age, increasing number of daily medications, the nonrelation between the ADE and the patient's chief complaint, a possible ADE causality category, and a hospitalization ADE severity category (Table 2). An ADE diagnosis of bleeding was more frequent in patients with an attributed ADE than in patients with an unattributed ADE (27.8 vs, 9.3%, respectively, $p = 0.021$).

All included patients were considered for multivariate analysis. After adjustment for confounders, ADE nonrecognition was significantly associated with the nonrelation between the ADE and the patient's chief complaint, a daily prescription of four drugs or more, and a hospitalization ADE severity category (Table 3). A good fit of our model was not rejected ($p = 0.80$).

DISCUSSION

The results of this study confirm that ADEs, although frequent among patients visiting our ED, are incompletely recognized by emergency physicians. On multivariate analysis, ADE nonrecognition was significantly associ-

Table 1. Baseline Characteristics of the Study Population

Characteristics	Included Patients (n = 465)
Age, y, mean (SD)	60.1 (22.2)
Female sex, n (%)	211 (45.4)
Charlson score, n (%)	
0	217 (46.7)
1–3	162 (34.8)
≥4	86 (18.5)
Triage acuity score, median (min–max)	2 (1–4)
ED outcome, n (%)	
Discharge	206 (44.3)
Hospitalization	258 (55.5)
Death in ED	1 (0.2)
Number of daily medications, n (%)	
0	72 (15.5)
1–3	127 (27.3)
≥4	266 (57.2)
Self-medication, n (%)	
Yes	283 (60.9)
No	39 (8.4)
Unknown	143 (30.7)

ED = emergency department; SD = standard deviation.

Emergency department triage acuity score included four stages of decreasing priority: 1) life-threatening situation; 2) situation with no life threat but rapid care is needed; 3) situation within emergency ability but care can be delayed; and 4) situation not within emergency ability but within ambulatory setting ability.

ated with the nonrelation between the ADE and the patient's chief complaint, a daily prescription of four drugs or more, and an ADE leading to hospitalization.

As previously substantiated, we observed that a significant proportion of ADEs are not correctly identified by emergency physicians (11,12). Focusing on four covariates defined a priori, Hohl et al. suggested an association between younger age and ADE attribution to a medication-related problem (11). We specifically examined the factors related to ADE nonrecognition by emergency physicians.

Our findings confirm that ADEs leading to an ED visit are recognized much more than the ADEs that are not related to the patient's chief complaint, a type of ADE whose diagnosis was expected to be more difficult (13). As a consequence of the ED organization with high workload and little time for extensive investigations, emergency physicians usually focus on the patient's chief complaint. In accordance with former hypotheses, we assume that emergency physicians can miss the opportunity to identify an ADE for this reason (11).

Our results also demonstrate that ADE nonrecognition is strongly associated with polypharmacy. If polypharmacy is a well-known risk factor for ADEs, it is also clear that effort and time required to monitor a prescription consistently increase with the number of medications (1,6,16–18). In addition, medication histories obtained from ED staff are often incomplete (27). Additional research should examine to what extent these factors

Table 2. Characteristics of Attributed and Unattributed Adverse Drug Events to a Medication-Related Problem

Characteristics	Attributed ADEs (n = 36)	Unattributed ADEs (n = 54)	p Value
Patients			
Age, y, mean (SD)	63.8 (20.0)	76.1 (13.8)	0.0030
Female sex, n (%)	15 (41.7)	31 (57.4)	0.14
Hospitalization after the ED visit, n (%)	20 (55.6)	38 (70.4)	0.20
No. of daily medications, mean (SD)	6.6 (3.0)	8.1 (3.7)	0.048
Charlson score, mean (SD)	1.9 (2.4)	2.2 (2.1)	0.22
Injuries			
Relation between ADE and patient's chief complaint, n (%)	33 (91.7)	35 (64.8)	0.0039
ADE classification, n (%)			
Adverse effects	23 (63.9)	43 (79.6)	0.098
Secondary effects*	5 (13.9)	7 (13.0)	0.90
Unintentional overdoses	7 (19.4)	4 (7.4)	0.089
Allergic reactions	1 (2.8)	0	NA
ADE causality assessment, n (%)			
Definite	1 (2.8)	1 (1.9)	NA
Probable	16 (44.4)	10 (18.5)	0.0070
Possible	19 (52.8)	43 (79.6)	0.0070
Doubtful	0	0	NA
ADE severity, n (%)			
Hospitalization (C–E severity categories)	15 (41.7)	36 (66.7)	0.019
Discharge (A–B severity categories)	21 (58.3)	18 (33.3)	
No. of suspected drugs per ADE case, mean (SD)	1.6 (0.9)	1.5 (0.8)	0.39

ADE = adverse drug event; ED = emergency department; NA, not applicable; SD = standard deviation.

* Secondary effects included cases of falls (n = 1) and secondary infections (n = 11).

can explain some failures in the identification of ADEs by emergency physicians.

We found that ADEs whose severity required hospitalization were statistically less recognized, which is of concern because drug-related problems are an important cause of hospital admission (28). These cases corresponded mostly to complex medical situations with a need for further investigations to ascertain ADE diagnosis. Emergency physicians might have recognized more ADEs if additional information that became available during the hospitalization had been available to them during the ED visit. A next step could be to address the issue of the recognition of these complex ADEs in the subsequent chain of care.

These comments suggest several ways to improve ADE recognition by emergency physicians, for example, strengthening medication histories, monitoring polypharmacy prescriptions, and paying greater attention to condi-

tions that are not related to the patient's chief complaint. Apart from the ED implementation of new supportive solutions, such as computer-assisted prescription writing or standardized questions to improve medication reconciliation, the involvement of a pharmacist can be a way to achieve these objectives (29,30). Clinical pharmacists were shown to be efficient in providing a variety of services, including medication reconciliation, prescription monitoring, and drug-related problem reporting in ED (31). Establishing a pharmacy presence in the ED could also provide an opportunity for regular education and training of emergency physicians, eg, with a regular report of nonrecognized ADEs or an introduction to the basics for drug causality assessment.

We did not find any study in the literature that specifically searched for the factors associated with a lack of attribution of ADEs to medications in ED. The purpose of this work was to provide material of interest to develop

Table 3. Multivariate Analysis of Factors Associated with a Lack of Attribution of Adverse Drug Events to Medications

Covariates	Adjusted OR of ADE Unattribution to a Medication-Related Problem (95% CI)
Age ≥80 years	1.18 (0.37–3.81)
Female sex	1.61 (0.56–4.64)
No. of daily medications ≥4	6.74 (1.18–38.47)
Nonrelation between the ADE and the patient's chief complaint	6.76 (1.51–30.15)
ADE leading to hospitalization (C–E severity categories)	4.41 (1.38–14.06)
Involvement of an antithrombotic agent in ADE occurrence	0.28 (0.07–1.11)

ADE = adverse drug event; OR = odds ratio.

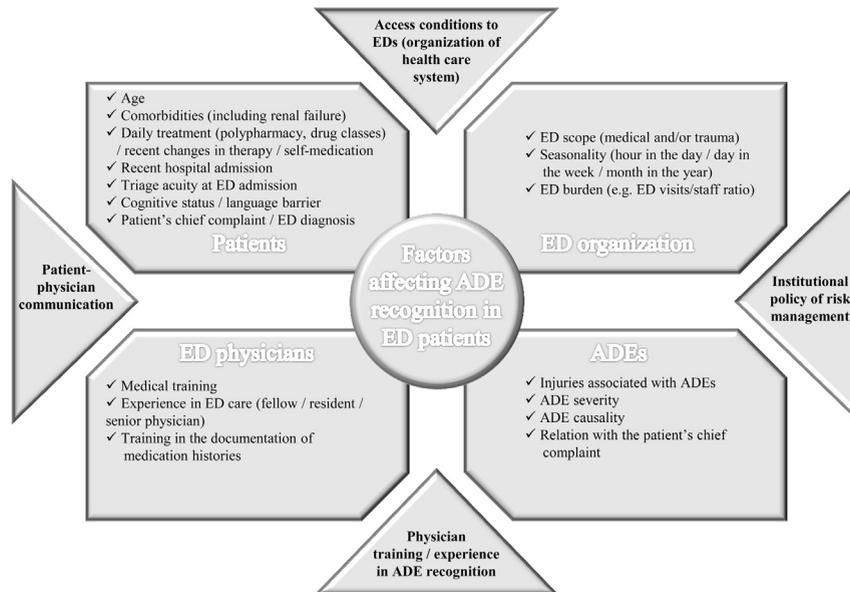


Figure 2. Factors that should be considered when exploring the causes for ADE nonrecognition in emergency department patients. ADE = adverse drug event; ED = emergency department.

a stringent research on the factors associated with ADE nonrecognition in the ED patients. In this exploratory study, we specifically focused on the factors that are associated with patients and ADEs. However, ED organization and ED physicians are two other aspects that are likely to influence ADE recognition. For example, it is well known that ED volumes vary, depending on the moment of the day or of the week; or that in some places, the “easier” shifts go preferentially to experienced physicians with greater seniority. Such confounders might affect the likelihood of identifying an ADE. Finally, on the basis of our experience and a literature review, we propose four inter-related sets of factors, which we regard as essential to consider in future research on ADE unrecognition: the first two groups are related to the patients and their medications, and the two others are related to the ED services and their medical staff (Figure 2) (1,6,8,12,18).

Limitations

Unless information was collected prospectively and its reliability was ensured by examining various information sources, including patient interviews, some data were difficult to retrieve in the ED context (eg, self-medication data when the patient's interview was impossible or rechallenge outcome in discharged patients). This may have led us to miss some ADEs or underestimate their causality assessment.

Another limitation was that this study relied on a single investigator pair to identify ADEs and their

recognition by ED physicians. However, it made the reproducibility of encoding sure, and contentious or uncertain issues were resolved by an independent expert.

The external validity of our results has several limitations: the study was restricted to the medical part of our ED, in a single setting, and the sampling design included only weekday morning patients. Selection bias is confirmed by the fact that included patients were older and more frequently hospitalized than the overall patients visiting our medical ED in the same period (20). The primary outcome was the proportion of recognized ADEs and not the true ADE rate. We found a proportion of recognized ADEs very similar to data published previously, suggesting that this selection bias could have affected the true ADE rate but not the proportion of recognized ADEs (11).

CONCLUSIONS

Our results emphasize the importance of searching for ADEs in the patients with daily polypharmacy or whose chief complaint does not seem to be drug related. They may help emergency physicians to better identify the patients in which they are more likely to miss ADEs. We propose that future research on the factors associated with ADE nonrecognition in ED should consider the complex relationship between patients, ADEs, ED organization, and ED physicians. Our experience suggests that a benefit can be expected from a physician–pharmacist team, not only to identify ADEs in ED routine

practice, but also to explore the factors likely to affect ADE recognition.

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ARTICLE SUMMARY

1. Why is this topic important?

Adverse drug events (ADEs) are a significant cause of morbidity in patients presenting to the emergency department (ED). However, many ADEs are not identified by emergency physicians.

2. What does this study attempt to show?

We conducted an exploratory study to search for the factors associated with ADE nonrecognition that are related to ED patients and ADEs.

3. What are the key findings?

ADE nonrecognition was significantly associated with nonrelation between the ADE and the patient's chief complaint, daily prescription of four drugs or more, and ADEs leading to hospitalization.

4. How is patient care impacted?

These results may help emergency physicians to better identify the patients in which they are more likely to miss ADEs.