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Original research paper

Adverse drug reactions in the ambulatory internal patients at the emergency department: Focus on causality assessment and drug-drug interactions

MATEJ DOBRAVC VERBIČ[1,3,*]
MIRAN BRVAR[1,2]
MOJCA KEREC KOS[3]

[1] *University Medical Centre Ljubljana Centre for Clinical Toxicology and Pharmacology, 1000 Ljubljana, Slovenia*

[2] *University of Ljubljana, Faculty of Medicine, Centre for Clinical Physiology Ljubljana, Slovenia*

[3] *University of Ljubljana, Faculty of Pharmacy, 1000 Ljubljana, Slovenia*

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ABSTRACT

A non-interventional retrospective study in ambulatory patients was conducted at the emergency department of the Division of internal medicine. In 2 months, 266 suspected adverse drug reactions (ADRs) were identified in 224/3453 patients (6.5 %). In 158/3453 patients (4.6 %), an ADR was the reason for emergency department visit and in 49 patients (1.4 %), ADRs led to hospitalisation. A causality assessment algorithm was developed, which included Naranjo algorithm and levels of ADR recognition by the treating physician and the investigators. Using this algorithm, 63/266 ADRs (23.7 %) were classified as "certain", whereas using solely the Naranjo score calculation, only 19/266 ADRs (7.1 %) were assessed as "probable" or "certain", and the rest of ADRs (namely, 247/266 = 92.9 %) were assessed as "possible". There were 116/266 (43.6 %) ADRs related to potential drug-drug interactions (DDIs), stated in at least one of the literature sources used. Based on the causality relationship, the rate of the clinically expressed DDIs was 19.0 %, or 12/63 "certain" ADR cases. Of these, 10 cases presented serious DDI-related ADRs. In summary, ADR causality assessment based exclusively on Naranjo algorithm demonstrated low sensitivity at an ambulatory emergency setting. Additional clinical judgment, including the opinion of the treating physician, proved necessary to avoid under-rating of the causality relationship, and enabled the determination of clinically expressed DDIs.

Keywords: adverse drug reactions, drug interactions, causality assessment, emergency department, ambulatory patients

INTRODUCTION

Adverse drug reaction (ADR) is defined by the World Health Organisation (WHO) as »any response to a drug which is noxious and unintended, and which occurs at doses normally used in man« (1). European Medicines Agency (EMA) extends the definition of

* Correspondence; e-mail: matej.dobravcverbic@kclj.si

ADR to any »use outside the marketing authorisation«, including off-label use, overdose, misuse, abuse and medication errors (2). In general, ADRs occur in 5–10 % of patients (3). Similarly, ADRs cause around 5–10 % of hospital admissions (4–7). Incidence varies depending on the study population, and the rates are higher for elderly patients (6, 8). In ambulatory emergency departments (EDs), suspected ADRs are estimated to occur in around 7 % of patients, but may range from 0.35 to 14.7 % (2, 4, 7, 9). Different definitions of ADRs have been used, requiring caution when directly comparing study results (4). ADRs present a major health problem and economic burden, but still remain heavily under-recognised (2, 10).

Older age, impaired renal function, comorbidities, use of multiple medicines and lack of knowledge regarding one's therapy, increase the risk of ADRs (1, 5). Various other patient-related (*e.g.*, gender, socio-economic status), disease-related (*e.g.*, dementia), and medication-related (*e.g.*, use of antithrombotic agents) risk factors for ADRs have also been studied (5, 6).

Causality assessment of ADRs may be performed using one of the three main approaches, namely, algorithms, expert judgment or global introspection, and probabilistic approaches (11, 12). Key aspects that all causality assessment methods should include are temporal relationship of drug taking with the reaction, plausibility, de-challenge and re-challenge (12). In commonly used algorithms, such as Naranjo, specific sets of questions have been designed to reduce rating variability and hence increase validity. However, their inflexibility leads to some limitations (12). Categories for ADR likelihood typically range from "unlikely/improbable/doubtful", "conditional/unclassified", and "unassessable/unclassifiable", to "possible", "probable", and "certain/definite". In clinical practice, it may be difficult to assess an ADR as "certain" or "unlikely" solely by using an algorithm (5, 7, 13–17). Probabilistic approaches are regarded as reliable, but complex and time-consuming, while expert clinical judgment may be susceptible to individual variations (11, 12).

The link between drug-drug interactions (DDIs) and ADRs has been well established. However, the majority of DDI studies have focused on potential DDIs (18). Reported DDI-related ADR prevalence ranged from 2 to 20 % (18–20), whereas rates of patients with potential DDIs have been estimated to reach up to 56 % (21). It has been suggested that 68–70 % of potential DDIs require clinical attention or monitoring, 6 % of them are clinically relevant, and 1–2 % may be life-threatening (18, 22). In rare studies that have focused on clinically expressed DDIs, their actual expression and clinical relevance may have been commonly underestimated (18, 19).

The aim of the present study was to determine the rate of ADRs in ED ambulatory patients, and to perform a causality assessment combining treating physician's and investigators' level of ADR recognition with Naranjo algorithm. The second objective was to evaluate the rate of DDIs and their clinical expression as ADRs.

EXPERIMENTAL

Methods of ADRs and DDI evaluation

Study population. – A non-interventional retrospective study of ambulatory patients was conducted at the ED of the Division of Internal Medicine, University Medical Centre Ljubljana (UMCL), Slovenia. All patients' ambulatory records were reviewed for the

2-month study period (October and November 2020). Demographic, clinical and laboratory data, related to suspected ADRs, were gathered for the study group of patients with ADRs. Patients without ADRs represented the control group. Number of active ingredients was counted as number of drugs in patient's therapy. Data were gathered in anonymised form. The study was approved by the National Medical Ethics Committee (Approval No. 0120-384/2020-3).

Evaluation of adverse drug reactions. – ADRs that were documented in patients' ambulatory records by the treating physician, as well as ADRs recognised from the records by the investigators, were included. All suspected ADR cases were analysed independently by an experienced clinical pharmacologist and clinical pharmacist. WHO definition of an ADR was used. Intentional or unintentional poisonings were excluded from the analysis. For any disagreements in the evaluation, the ADR cases were reviewed and discussed together to reach a consensus.

ADRs were assessed for their seriousness, expectancy and causality. A serious ADR was defined according to Slovenian rules on pharmacovigilance of medicinal products for human use (23, 24) as "one which requires hospitalization or prolongation of existing

Table I. Adverse drug reactions' causality assessment algorithm

Naranjo ADR category (score)	Weighted Naranjo score (N)
Doubtful (≤ 1)	–0.5
Possible (2–4)	0
Probable (5–8)	0.5
Certain (≥ 9)	1
ADR recognition by treating physician	Weighted physician recognition score (PR)
No explicit treating physician's suspicion	0
Treating physician's suspicion	0.5
Treating physician's certainty	1
ADR recognition by investigators	Weighted investigator recognition score (IR)
Investigators' suspicion	0.5
Investigators' certainty	1

Weighted final score calculation	Combined ADR causality assessment	Final score
0.33 × N + 0.33 × PR + 0.33 × IR	Uncertain ADR	< 0.5
	Certain ADR	≥ 0.5

ADR – adverse drug reaction, IR – weighted investigator recognition score, N – weighted Naranjo score, PR – weighted physician recognition score

hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening, results in death, or, based on medical judgment, causes a relevant clinical condition". An expected ADR was one stated in the drug summary of product characteristics (SPC).

To determine the causality likelihood of ADRs, an algorithm was developed, which consisted of treating physician's ADR recognition documented in the ambulatory record, investigators' recognition and Naranjo assessment score. Physician's and investigators' levels of recognition were defined either as "suspicion" or "certainty" (Table I). Each of the three methods for causality assessment – Naranjo, treating physician's, and investigators' level of recognition, were tested separately for sensitivity and specificity compared to the combined assessment method as shown in Table II. Cochran's Q test and *post hoc* test with Bonferroni correction were used.

Evaluation of drug-drug interactions. – Potential drug-drug interactions (DDIs) were identified using three literature sources: Lexicomp®, Micromedex® and drug SPCs. In the Lexicomp® database, levels X ("avoid combination"), D ("consider therapy modification"), and C ("monitor therapy") were considered. Similarly, in Micromedex® database, "contraindicated", "major" and "moderate" categories were included. DDIs unrelated to the suspected ADRs were not captured in the analysis. To determine a DDI as clinically expressed, a set of three criteria had to be fulfilled: (*i*) DDI stated in at least one of the three sources, (*ii*) both (or several) potentially interacting drugs recognised to be related to the ADR by the treating physician and/or investigators, (*iii*) ADR assessed as "certain" using the combined causality assessment algorithm.

Table II. Causality assessment methods' sensitivity and specificity calculation

	Combined ADR causality assessment	
	Certain	Uncertain
Naranjo ADR category (score)		
Doubtful (≤ 1)	FN	TN
Possible (2–4)	FN	TN
Probable (5–8)	TP	FP
Certain (≥ 9)	TP	FP
ADR recognition by treating physician		
No explicit treating physician's suspicion	FN	TN
Treating physician's suspicion	FN	TN
Treating physician's certainty	TP	FP
ADR recognition by investigators		
Investigators' suspicion	FN	TN
Inestigators' certainty	TP	FP

Sensitivity	TP / (TP+FN)
Specificity	TN / (TN+FP)

ADR – adverse drug reaction, FN – false negative, FP – false positive, TN – true negative, TP – true positive

Statistical analyses

Data are presented using descriptive statistics. When the median was used, the interquartile range (IQR) was reported. A logistic regression analysis of risk factors was performed, with suspected ADR as the dependent variable. Regardless of the number of ADRs, each patient was included in the logistic regression analysis once. Independent variables were selected from the results of the bivariate analysis. The following variables were considered: age (years), gender, number of comorbidities, number of drugs, renal failure, liver failure, and reported use of alcohol. Renal failure was defined as serum creatinine level >1.5× upper limit of normal (ULN), and liver failure as alanine or aspartate aminotransferase level >3× ULN, alkaline phosphatase >2.5× ULN, or bilirubin >1.5× ULN, based on National cancer institute common terminology criteria for adverse events (25). The dependent variables were entered in the model in a single step. The goodness-of-fit was assessed with Hosmer–Lemeshow test. Results are expressed in odds ratios (ORs) with 95 % confidence interval (CI). For all statistical tests used, a two-tailed p-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 27.0.

RESULTS AND DISCUSSION

Adverse drug reaction rates and risk factors

A total of 3453 patients were treated at the ambulatory ED unit of the Division of Internal Medicine during the 2-month study period. Suspected ADRs were identified in 224 patients (6.5 %). In 158/3453 patients (4.6 %), an ADR was the reason for ED visit. ADRs led to hospitalisation in 49 patients (1.4 %). As more than one ADR was suspected in 38 patients, 266 ADRs were recognised altogether, with 337 implicated drugs. These results are comparable to similar studies where the rates of ADRs commonly ranged from 6.5 to 7.8 % (4, 7). However, we may assume that the ADRs identified underestimate the overall incidence rate of ADRs in these patients. It has been argued previously that ADRs may have been under-recognised in an ED setting due to several reasons. Urgent action is often required, and a thorough interviewing of patients or their caregivers may not be feasible to obtain the necessary information for ADR recognition (6, 20).

Within ADRs group 199/266 ADRs (71.8 %) were serious. In comparison with several other studies (26, 27), a higher rate (71.8 %) of serious ADRs in our study might be related to a broader definition of seriousness, that included "any relevant drug-related clinical condition". There is no formal definition of clinical relevance, leading to potentially subjective judgment by the treating physician or investigators.

Nearly all ADRs (264/266, 99.2 %) were stated in drug SPCs and were therefore expected. The two unexpected ADRs in the study were disturbance of consciousness due to apalutamide, and hyponatremia due to bromazepam. A low rate of unexpected ADRs (0.9 %) suggests that these ADRs are either very rare or very difficult to recognise, or both. Unexpected ADRs are likely to reach a lower score in the causality assessment because the existing data on previous reports may be limited.

Data for the control and study group, together with the results of the logistic regression, are shown in Table III. Information for individual patients is provided in a supplementary

Table III. Bivariate statistical analysis of potential risk factors for adverse drug reactions

	Control group $N = 3199$	Study group $N = 224$	Logistic regression model*	
			OR (95 % CI)	p
Age (years), median (IQR)	72 (59–82)	79 (70–85)	1.024 (1.013–1.035)	< 0.001
Gender: *n* (%)				
male	1672 (52.3 %)	106 (47.3 %)	Reference	–
female	1527 (47.7 %)	118 (52.7 %)	1.066 (0.803–1.414)	0.660
Number of comorbidities, median (IQR)	5 (3–8)	6 (3–8)	Not included in the model	
Number of drugs, median (IQR)	5 (2–9)	7 (5–11)	1.045 (1.012–1.078)	0.007
Liver failure (MD = 140), *n* (%)	412 (13.5 %)	15 (6.8 %)	0.459 (0.267–0.789)	0.005
Renal failure (MD = 114), *n* (%)	568 (18.4 %)	61 (27.7 %)	1.313 (0.944–1.824)	0.105
Reported use of alcohol (MD = 2), *n* (%)	193 (6.0 %)	8 (3.6 %)	0.822 (0.395–1.714)	0.602

CI – confidence interval, IQR – interquartile range, MD – missing data

* Omnibus test: $p < 0.001$, Hosmer and Lemeshow test: $p = 0.689$, Nagelkerke $R^2 = 0.051$

Table SI. Number of comorbidities was in a strong positive correlation with the number of drugs (Spearman's rho 0.701, $p < 0.001$) and was therefore excluded from the logistic regression model. Older age and higher number of drugs were demonstrated to significantly increase the risk for experiencing an ADR. In the literature, multi-morbidity, decreased renal function, and decreased liver function have also been recognised as risk factors for adverse drug events (2). These factors can be interrelated. Age-related pharmacokinetic and pharmacodynamic changes may have an important influence on ADR occurrence (16). Multiple diseases in elderly patients lead to multiple medications, which increases the risk of DDIs and ADRs (5, 16, 28). However, medication burden does not necessarily increase steadily with age. Schurig *et al*. (4) demonstrated that the number of drugs taken at the same time was lower in the 81–90 years and > 91 years age groups than in the 71–80 years age group. Impaired renal function considerably impacts the elimination of drugs and typically plays a larger role than liver function (2). In our study, reduced renal function did not significantly affect the risk of ADR, whereas surprisingly, the absence of liver failure was significantly associated with ADRs. We found no reasonable explanation, apart from the choice of criteria for liver failure which may not have been ideal. The Child-Pugh score would probably have been a more appropriate indicator. Unfortunately, the lack of data in the ambulatory records did not allow us to use this tool (*e.g.*, serum albumin levels were not commonly measured). However, based on Nagelkerke R^2, our model explains only 5.1 % of deviance in the response variable.

Causality assessment of adverse drug reactions

Table IV demonstrates the causality assessment ratings for all 266 ADRs. Using Naranjo, 19 ADRs scored ≥ 5, falling in the "probable" or "certain" category. There were no ADRs

Table IV. Adverse drug reactions' causality assessment results

Naranjo category	No. of ADRs (rate, %)
Doubtful (≤ 1)	/
Possible (2–4)	247 (92.9 %)
Probable (5–8)	18 (6.8 %)
Certain (≥ 9)	1 (0.4 %)
ADR recognition by treating physician	No. of ADRs (rate, %)
No explicit treating physician's suspicion	74 (27.8 %)
Treating physician's suspicion	146 (54.9 %)
Treating physician's certainty	46 (17.3 %)
ADR recognition by investigators	No. of ADRs (rate, %)
Investigators' suspicion	203 (76.3 %)
Investigators' certainty	63 (23.7 %)

Combined ADR causality assessment	No. of ADRs (rate, %)
Uncertain ADR (< 0.5)	203 (76.3 %)
Certain ADR (≥ 0.5)	63 (23.7 %)

ADR – adverse drug reaction

assessed as "doubtful" with a Naranjo score < 2. On the other hand, 46 and 63 ADRs were recognised as "certain" by the treating physician and by the investigators, resp. Finally, with the combined causality assessment algorithm, 63/266 (23.7 %) ADRs were defined as "certain". Of these, 5 ADR cases were different than in the investigators' certainty assessment.

The matching between the scores of individual causality assessment methods and the combined final score is shown in Fig. 1. The sensitivity of the investigators' and physician's assessments was significantly higher compared to Naranjo method ($p < 0.001$ for both pairwise comparisons), while specificity was significantly different only when the physician's and investigators' assessments were compared ($p = 0.037$).

There were higher rates of "certain" ADRs linked to antidiabetic agents (including insulin and oral drugs, causing hypoglycaemia), warfarin (causing increase in international normalized ratio – INR), and antibiotics (causing rash, or INR increase in combination with warfarin). On the other hand, "uncertain" ADRs were more frequently related to acetylsalicylic acid and non-steroidal anti-inflammatory drugs (commonly suspected of causing gastrointestinal bleeding), or diuretics – including aldosterone antagonists, loop and thiazide-like diuretics (linked to electrolyte disturbances or hypotension).

Several systems exist for ADR causality assessment, but most of them fail to offer a reliable quantitative estimation of the causality relationship probability (13). Lack of sensitivity of Naranjo algorithm has been recognised previously, resulting in low rates of "certain" ADRs (11). Not all questions in the algorithm are applicable to clinical practice (*e.g.*, information on the use of placebo or measured toxic concentrations of implicated drug) (1, 26). In a Japanese adverse drugs events study, 5 of the 10 questions of the Naranjo algorithm were answered with "no/not known" in ≥ 97 % of cases (29). The authors suggested a modified Naranjo algorithm which would include only the remaining 5 questions.

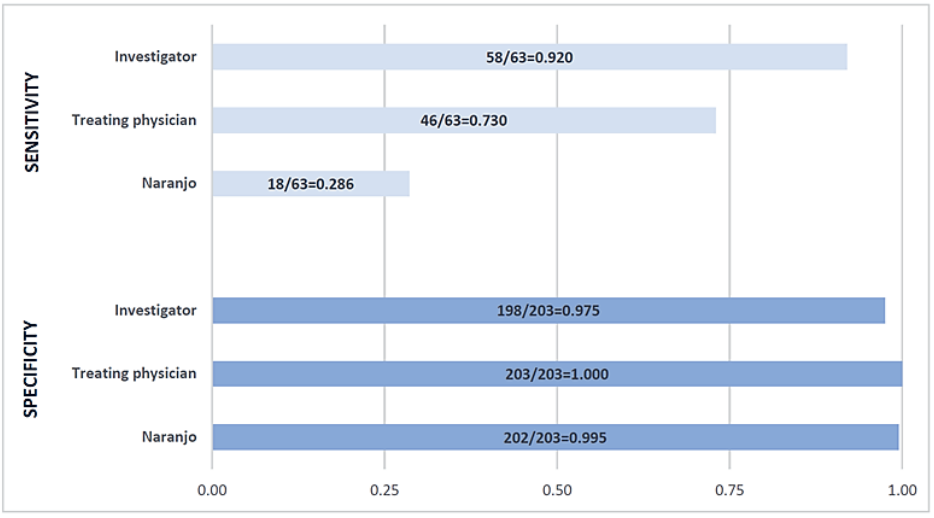

Fig. 1. Sensitivity and specificity of the causality assessment methods.

However, at an ambulatory emergency setting, the ADR improvement after discontinuation of the drug or the outcome of a re-challenge, are also commonly not possible to assess. Based on the similarity of other algorithms, we assume that using a different one would not have improved the analysis. In a German study performed in 4 EDs, ADRs were estimated as "possible" in 74–84 % of cases using WHO-UMC system (4). Regardless of the method, a positive re-challenge or a similar reaction during a previous exposure and the absence of other likely causes, are required for an ADR to be classified as "definite" or "certain". These criteria are rarely reached in practice. On the other hand, using solely physician's or investigators' recognition of ADR could have led to subjective or biased results. In our study, the investigators' assessment was the most sensitive, whereas the physician's assessment (as documented in the ambulatory records) was the most specific.

Using the combined causality assessment algorithm, ADRs with a Naranjo score ≥ 5 and suspected both by the treating physician and the investigators, and ADRs with a Naranjo score ≥ 2 and a high level of physician's and/or investigators' certainty, were categorised as "certain". Consequently, 45 "possible" ADRs per Naranjo's score were assessed as "certain" with the combined algorithm. We advocate that the use of the combined assessment algorithm provides an optimal assessment. It is necessary to include the opinion of the treating physician in the assessment of ADR causality, particularly when the investigator or evaluator of ADRs had not been in direct contact with the patient.

Drug-drug interactions related adverse drug reactions

There were 116/266 (43.6 %) ADRs related to potential DDIs according to at least one of the sources used – Lexicomp®, Micromedex® or SPCs. Twelve DDIs (shown in Table V) met all three criteria for a clinically expressed DDI. This represented a 19.0 % rate of clinically expressed DDIs among the 63 "certain" ADRs, and a 0.3 % rate among all 3453 patients treated at the ambulatory ED unit. Ten clinically expressed DDIs were related to serious ADRs, suggesting that 4.5 % of patients in our study (10/224) experienced a serious DDI-related ADR.

Similarly to our results, previous studies assessing potential DDIs generally reported rates that were much higher than the rates of actually expressed DDIs (18, 21, 22). However, precise explanation of how the clinically expressed interactions were recognised was rarely given. Olivier *et al*. (20) stated that 19.7 % of ADRs were due to DDIs. In a recent study of DDIs identified from Italian pharmacovigilance database, 17.5 % of all ADR reports (381/2195) were associated with a DDI (18). A literature review from 2004 found a 0.054 % rate of ED visits being due to DDIs (33).

In a 2018 systematic review, DDIs were classified into three categories – potential, clinically relevant, and DDIs that cause measurable patient harm (34). Potential DDIs were identified using drug reference guides, whereas clinical relevance was still defined by a potential measurable clinical effect of DDI, according to clinical pharmacist's judgment. Only one study included in the review investigated actual patient harm (21). However, clinical expression of DDIs in this one study could be disputed. Any ADR with a potential DDI identified in Micromedex® was considered as an expressed DDI-related ADR, regardless of the causality relationship level, which could be either "certain", "probable", "possible" or "relative", using Karch-Lasagna algorithm (21). In our opinion, an ADR with the causality rate less than "probable" should not lead to a direct assumption of a clinically expressed DDI.

In a previous study conducted at UMCL, 50 "probable" clinically relevant DDIs were identified in 37/1006 patients admitted to internal medicine departments *via* ED. Causality assessment was performed by drug interaction probability scale (DIPS) – a Naranjo scale, modified for DDIs. All ADRs identified from medical charts, with DIPS score ≥ 2 (representing "possible" DDI-related ADRs), were considered as "probable" clinically relevant DDIs (35). Whenever using causality assessment algorithms, including tools specific for DDIs such as DIPS, upgrading certainty level (*e.g.*, from "possible" event to "probable") requires additional clinical judgment and justification. In the previous study this was performed by a multidisciplinary team assessing DDI-related ADR cases (35). Our study added a specifically defined set of criteria for determination of DDI-related ADRs.

Interestingly, all clinically expressed DDIs were stated in SPCs of at least one of the implicated drugs, whereas less than half (5/12, 41.7 %) were recognised by Micromedex® database, 8/12 (66.7 %) were detected by Lexicomp®. This suggests that SPCs are more sensitive than Micromedex® or Lexicomp® databases in identifying DDIs. However, searching for potential DDIs in SPCs is more time consuming than using a database. DDIs were often found in the "Special warnings and precautions" section of the SPCs, not always in the "Interactions" section, and were more commonly stated indirectly (*e.g.*, mentioning only drug classes rather than specific drugs).

Nearly all (11/12) clinically expressed DDIs were pharmacodynamic. In general, risks of DDI-related ADRs, such as hypoglycaemia or hypotension, may be reduced with regular self-monitoring of blood glucose levels, blood pressure, *etc*. (36). Electrolyte disturbances, *e.g.*, increased or decreased levels of potassium and sodium, are more difficult to recognise at home. Pharmacotherapy should be prescribed based on individual patient characteristics, *e.g.*, multiple drugs known to have risk of hyperkalemia should be avoided in a patient with reduced renal function; combination of α- and β-antagonists should be avoided in frail elderly people to prevent orthostatic hypotension, *etc*. (37, 38). Patients with higher risk for ADRs should be prioritised for clinical medication reviews and counselling (39).

Several authors concluded that the majority of clinically relevant DDIs are caused by a limited number of drugs that require close monitoring to avoid DDI-related ADRs (33). In an analysis from the French pharmacovigilance database, antithrombotic agents were frequently involved in DDIs, and haemorrhage was the most common serious DDI-related event (40). In a recent study of DDIs identified from the Italian pharmacovigilance database and assessed by an expert panel, interactions of warfarin with proton pump inhibitors or antiplatelet agents were most often involved in ADRs (18). Methods and definitions used to identify actually expressed DDIs were not always transparent and clear in previous studies (34). In general, clinically expressed or clinically relevant DDIs were determined by a professional or a team, usually involving clinical pharmacist, clinical pharmacologist and/or physician (10, 34). Regardless of the method, two aspects should be considered when evaluating DDI expression: (*i*) the likelihood of an adverse outcome actually being an ADR, (*ii*) the likelihood of an ADR actually being related to a DDI. Surprisingly, the two aspects were commonly not considered concurrently in previous assessments. In our study, clinically expressed DDIs were defined as the ADR cases that were classified as "certain", had more than one causative drug, and had a related DDI between the two drugs stated in at least one of the literature sources. Therefore, the estimated rate (12/266, 4.5 %) is a conservative one. Using a different methodology, *e.g.*, including less certain ADRs, the estimated rates would have been higher.

Pharmacists play a major role in pharmacovigilance, particularly in monitoring and reporting ADRs. They are an indispensable source of information and critical evaluation of drug-related information (41), and make an integral part of a multidisciplinary pharmacovigilance team to participate in ADR assessments. Moreover, clinical pharmacy services in hospitals and other medical settings, *e.g.*, medication history taking, medication use review and clinical medication review are important tools in ADR prevention or recognition (42).

Summary and study limitations

Our study has several limitations. It was performed in a single centre and was based on patient's ambulatory records. Medication history and other relevant information written in the records may not have been complete or explicit, and over-the-counter or other self-medication products may have been overlooked. The recognition of ADRs and their mentioning in the ambulatory records may have varied among different treating physicians. It was rarely possible to assess the final outcome of an ADR due to the ambulatory setting.

The study was conducted during the early phase of the Covid-19 pandemic. This may have influenced the organization at the ED department, and the patient population may have been slightly different than before the pandemic, *e.g.*, there may have been a higher rate of patients with more severe conditions. However, patients with confirmed or suspected SARS-CoV-2 infection were directed to a different emergency setting. Therefore, no conditions or medications, specific to Covid-19, were observed in our patient population during the study.

On the other hand, common signs, symptoms, and laboratory findings, typically associated with ADRs, were screened by the investigators. In this way, potential ADRs that may not have been specifically mentioned as an ADR in the ambulatory medical records by the treating physician, were detected. A combined causality assessment algorithm for ADRs was developed to avoid conclusions based solely on the judgments of the treating physician or investigator, which may be prone to subjectivity. At the same time, this method allowed to differentiate between a large proportion of ADRs which would all have been commonly classified as "possible" using only the Naranjo algorithm, even though they may have varied substantially in the likelihood of the causality relationship. Finally, we identified clinically expressed rather than potential DDIs, and the set of criteria for clinical expression was clearly defined.

CONCLUSIONS

In conclusion, ADRs contribute importantly to ambulatory ED visits of internal medicine patients. Causality assessment of ADRs based exclusively on standard algorithms such as Naranjo may be inadequate for an emergency ambulatory setting, demonstrating low sensitivity. Lack of reliable information and a short duration of patients staying in such setting are likely contributing factors. Therefore, to avoid under-rating of the ADR causality relationship, additional clinical judgment is necessary, which should include the opinion of the treating physician. Furthermore, ADR causality rate of high certainty is one of the prerequisites for a reliable determination of clinically expressed DDIs. While the

Table V. Clinically expressed drug-drug interactions and related adverse drug reactions

Interacting drugs	ADR	DDI identified from	DDI recognised by	Mechanism of DDI	Additional comment(s)
Indapamide – perindopril – mirtazapine	Hyponatremia	SPC	Physician	PD – additive hyponatremic effect (*via* RAAS system, reduced renal sodium reabsorption, possibly SIADH) (30)	
Gliclazide – sitagliptin	Hypoglycaemia	L, SPC	Investigator only	PD – additive hypoglycaemic effect	
Insulin lispro – insulin glargine	Hypoglycaemia	L, SPC	Physician	PD – additive hypoglycaemic effect	Metoprolol and metformin possibly involved
Acetylsalicylic acid – etoricoxib	GI bleeding (melena)	L, M, SPC	Physician	PD – additive effect (mucosal damage, antiplatelet effect)	
Acetylsalicylic acid – clopidogrel	GI bleeding (hematochezia)	L, M, SPC	Physician	PD – additive antiplatelet effect	
Diclofenac – spironolactone	Impaired renal function and hyperkalemia	L, M, SPC	Physician	PD – nephrotoxicity, aldosterone antagonism	Candesartan and furosemide possibly involved
Indapamide – venlafaxine	Hyponatremia	SPC	Physician	PD – additive effect (reduced renal sodium reabsorption, possibly SIADH)	Aripiprazole and quetiapine possibly involved
Telmisartan – tacrolimus	Hyperkalemia	L, SPC	Investigator only	PD – additive hyperkalemic effect (*via* RAAS system, sodium-potassium ATP-ase inhibition) (31, 32)	
Spironolactone – telmisartan	Hyperkalemia	L, M, SPC	Physician	PD – additive hyperkalemic effect (*via* RAAS system, aldosterone release inhibition, aldosterone antagonism) (32)	
Amlodipine – bisoprolol – perindopril – ramipril	Orthostatic syncope	SPC	Physician	PD – additive hypotensive effect	Therapy duplication, possibly due to amlodipine-perindopril combination pill
Amlodipine – bisoprolol – indapamide	Orthostatic hypotension	SPC	Physician	PD – additive hypotensive effect	
Warfarin – miconazole	Increased INR with epistaxis	L, M, SPC	Physician	PK – reduced warfarin elimination (CYP 2C9 inhibition, possibly CYP 3A4 and CYP 2C19 inhibition)	

ADR – adverse drug reaction, ATP – adenosine triphosphate, CYP – cytochrome P450, DDI – drug-drug interaction, GI – gastrointestinal, INR – international normalized ratio, L – Lexicomp®, M – Micromedex®, PD – pharmacodynamic, PK – pharmacokinetic, RAAS – renin-angiotensin-aldosterone system, SIADH – syndrome of inappropriate antidiuretic hormone secretion, SPC – summary of product characteristics

approach taken in our study may not be suitable for every healthcare setting, it improved the ADR causality assessment at the ambulatory unit of the emergency department for internal medicine patients. The future work might focus on developing a standardised and validated tool to overcome the challenges of ADR and DDI assessment in emergency ambulatory settings.

Supplementary materials available upon request.

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