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Assessing the Feasibility of Using an Adverse Drug Reaction Preventability Scale in Clinical Practice

A Study in a French Emergency Department

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Abstract

Objective: To assess the preventability of adverse drug reactions (ADRs) leading to hospital admissions and to investigate the feasibility of the use of a standardised preventability scale in clinical practice.

Design: The study was a prospective pharmacovigilance study. All patients more than 15 years old admitted to an emergency department during a period of 4 weeks were included. Characteristics of patients admitted for a suspected ADR (cases) were compared to those admitted for other reasons (controls). Preventability was assessed in two different ways: (i) by using a standardised preventability scale; and (ii) by the assessment of four reviewers without the scale. Results of the two methods were compared.

Patients: In total, 671 patients were admitted to an emergency department during the study period.

Results: Overall, 44 ADRs were identified involving 41 patients. The incidence of hospital admissions for ADRs was 6.1 per 100 admissions (95% CI 4.4–8.3). According to the French causality assessment method, 71% of ADRs were 'possible', 18% were 'plausible' and 11% were 'likely'. Using the standardised preventability scale, one-third of all ADRs were considered as being preventable (9% 'definitely' and 25% 'potentially' preventable). Reviewers found that 54.5% of ADRs were 'preventable'. Discrepancies between the two methods concerned mainly cases defined as not preventable by the scale. In general, reviewers overestimated the preventability of ADR compared with the scale.

Conclusions: These results emphasise that ADRs leading to hospitalisation are frequent, with one-third of them likely to be preventable. Moreover, the risk of ADRs mainly involved a small number of drugs. Our experience suggests that there is a need for further studies to validate the French standardised scale of preventability assessment.

Background

Adverse drug reactions (ADRs) have become recognised as an important cause of hospital admission, with a proportion ranging from 0.9 to 7.9%. ADRs can also be responsible for deaths and for a significant amount of healthcare costs, due to an increased duration in hospital stays.[1-4] In France, two recent nation-wide studies performed by the French Network of Pharmacovigilance Centres have shown that prevalence and incidence of drug-related admissions was 10.3 and 3.2%, respectively.[5,6] Most of these drug-related admissions were expected reactions to drugs and could be in part preventable. However, as far as we know, the assessment of the preventability of ADRs has been addressed in only two studies performed in France.[7,8] In contrast, several studies have been performed, mainly in the US, using different methods to assess preventability.[9-13] As far as we know, none of these methods were clearly assessed concerning their reproducibility, validity and relevance. Some authors suggest that preventability should be assessed in the same manner as causality, seriousness or frequency of ADRs.[14] Recently, a preventability scale was proposed by a group of French experts in pharmacovigilance.[15]

The purpose of this prospective pharmacovigilance study was to assess the incidence and the preventability of ADR-related admissions and to assess the feasibility of a wider use of a preventability scale in clinical practice.

Methods

Patient Population

The study took place in the medical emergency department of Toulouse University Hospital (in the Southwest of France) during 4 weeks in May, July, August and October 1998. This study period was defined in order to include at least 600 patients according to the expected number admissions during a week. This sample size was calculated assuming that the expected incidence of ADRs represented between 4 to 5% of admissions. All patients more than 15 years old admitted in the emergency department during the study period were included, except patients in ambulatory care or admitted for an intentional overdose.

Case Definition

All physicians in the emergency department participated to the study during the 4-week period. They examined all patients at hospital admission and identified cases as patients admitted because of an ADR. According to the WHO Council for International Organizations of Medical Sciences (CIOMS) definition, ADR is a 'noxious and unintended event that occurs at doses used in man for prophylaxis, diagnosis, therapy, or modification of physiologic functions'.[16] All recorded events were considered first line as ADRs. Some of them were later classed as medication errors after complementary information was obtained from GPs. Controls were patients admitted in the same unit during the same time period as cases for other reasons than ADRs. All medical charts were reviewed by OB and MT at the end of each period in order to check the relevance of cases classification.

Data Collection

For each admission, following data were collected: age, gender, current drug treatments before admission (drug, dosage, prescription or self-medication), reason for admission. Causes of admission were coded according the WHO International Classification of Diseases, 9th revision (ICD-9).[17] Drugs were classified by the anatomical therapeutic chemical (ATC) classification index.[18]

For each case, specific data concerning the suspected ADR were also recorded: type of ADR, seriousness and all available clinical or biological data. Patients who were hospitalised in other clinical wards were followed-up in order to collect data about ADR outcomes. For other patients, all were discharged after complete recovery from the ADR.

Adverse Drug Reaction Characteristics

All cases were reviewed and validated by both a pharmacologist and a physician. ADRs were

classified as expected or not. An expected ADR is a harmful and undesirable manifestation attributed to a drug, whose occurrence is apparently related to a known pharmacological property of this drug.[19] ADRs were assessed in terms of causality, seriousness and preventability.

Causality was evaluated according to the French validated method of causality assessment.[20] This method is based on chronological and semiological criteria. Chronological criteria included: delay of ADR onset, response to dechallenge and response to an eventual rechallenge. Semiological data included: explanations for the ADR not being related to drugs, results of complementary laboratory tests and clinical pattern of drug reaction. The combination of these two criteria allows one to calculate five levels of 'intrinsic imputability' scores varying from I0 to I4: 'excluded' (I0), 'possible' (I1), 'plausible' (I2), 'likely' (I3) or 'very likely' (I4).

The evaluation of seriousness was performed according to the CIOMS definition: a 'serious' ADR corresponds to one that: results in death, requires hospitalisation or prolongation of existing hospitalisation, resulting in persistent or significant disability/incapacity or is life-threatening. Although all ADRs should be considered as 'serious' by definition (all patients were admitted to an emergency department), we also investigated the different level of seriousness as the proportion of ADRs 'resulting in persistent or significant disability/incapacity' or 'life-threatening'.

Preventability was assessed using the standardised French preventability scale proposed by Imbs et al.[15] (table I). This method has not been validated elsewhere. This scheme contains numerous items concerning knowledge about the ADRs of a drug and communication about this knowledge, risk factors of the patient, drug management, conditions of prescription and management of the ADR. Each item is scored and the range of the global score would be –11 to +18. A positive score suggests that an ADR may have been potentially preventable and a negative score potentially not preventable.

In a first step, two of the authors applied the French scale to assess the preventability of ADRs. Results were presented in continuous values and in three categories defined as 'definitely not preventable' (category 1) for score ≤–2, 'potentially preventable' (category 2) for score between –1 and +8 and 'definitely preventable' (category 3) for score ≥+9. In a second step, all cases were reviewed independently without the scale in order to assess their preventability by four other reviewers (one

Table I. Evaluation of preventability of an adverse drug reaction (reproduced from Imbs et al.[15] with kind permission of the author, originally published in Thérapie 1998; 53: 365-370)

	Score
The drug[a]	
Knowledge about the drug and its possible role	
Hypothesis, still debated	+1
A matter of worry, diffused by publications or work in progress	+2
Causality established	+3
Communication about this knowledge	
Reassuring about a lack of danger	0
Relatively worrying	+2
Serious cause for concern about presence of danger	+3
The patient[a]	
Clinical case: risk factors	
No risk factors	0
Risk factors hardly detectable	+2
Presence of risk factors, easy to detect	+3
Drug management	
Respect of recommendation(s) or lack of precaution(s) has played any role in this case	0
Recommendation(s) not applies easily in this patient	+2
Neglect of recommendation(s), easy to apply by the prescriber or the patient	+3
Prescriptions[a]	
Conditions of prescription	
Prescription indispensable to the patient	–12
Questionable prescription but acceptable	–4
Needless or absolutely contra-indicated prescription (or inappropriate prescription)	+3
Management of the adverse reaction	
Excellent, with prevention of the aggravation of the adverse reaction	0
Inadequate	+2
Absent, with aggravation of the reaction	+3

a This evaluation considers only the knowledge and information available at the time of the adverse reaction, taking into account clinical data available for the patient at that time.

senior medical doctor; one senior medical doctor and one senior pharmacist with expertise in pharmacovigilance; one medical resident). Each reviewer gave his or her preventability assessment by taking into account all clinical and biological available data, as described in other studies.[10,13] Preventability was classified in the same manner using the three categories described above.

Data Analysis

For the first analysis, Kappa values were calculated for rating of preventability between each reviewer (six comparisons). For the second analysis, individual preventability judgements of each reviewer were compared with the scale, giving four comparisons assessed by Kappa statistics. The scale judgement was compared with the mean judgement of reviewers (we assumed that the mean judgement of reviewers was that of the majority of reviewers).

The incidence of ADRs was calculated and its 95% confidence interval (CI) was assessed according to the Poisson model. Quantitative data are presented as mean ± standard deviation (SD) and median values.

Results

A total of 671 patients were included in the study, with a mean number of 168 ± 17 admissions a week (range 148–190). Among these 671 admissions, 44 different ADRs were identified that involved 41 patients. Thus, the incidence rate of hospital admissions due to an ADR was 6.1 per 100 admissions (Poisson 95% CI 4.4–8.3). The mean age of cases was 58 ± 22.2 years and 54% were men (n = 22). Mean age of controls was 55.6 ± 22.5 years and 55% were men (n = 344). There was no significant difference according to age and gender between cases and controls.

Table II presents the characteristics of the 44 ADRs. According to the CIOMS definition, 37 ADRs were considered as 'requiring hospitalisation' and seven ADRs were considered to be 'life-threatening'. No deaths were observed during the study. Outcome was favourable for all patients except for one who developed a permanent disability (hemiplegia following a cerebral haematoma under anticoagulant therapy).

The imputability scores revealed that 71% of ADRs were 'possible' (I1), 18% were 'plausible' (I2) and 11% were 'likely' (I3). Most of ADRs (n = 43) were expected.[19]

Cases were exposed to a significantly higher number of drugs than controls (3.6 ± 2.5 vs 1.7 ± 2.2; $p < 0.001$). Fifty drugs were involved in the 44 ADRs. Drugs most frequently involved in ADRs are listed in table II. Causes of ADRs-related admissions to medical emergency unit were gastrointestinal (n = 16), cutaneous (n = 9), metabolic and electrolyte disorders (n = 6), cardiovascular diseases (n = 6), and haematological (n = 4) and neuropsychiatric (n = 3) disorders.

As presented in table II, we observed scores of preventability using the standardised French preventability scale ranging from –10 to +15 with a median value of –3. With this scale, 66% (n = 29) of ADRs were 'definitely not preventable' (category 1) and 25% (n = 11) were 'potentially preventable' (category 2). Four cases (9%) were defined as 'definitely preventable' (category 3): a case of thrombocytopenia associated with the use of sulfadoxine and pyrimethamine as self-medication; a case of renal insufficiency associated with the use of high dosage aspirin (acetylsalicylic acid) by a patient with diabetes mellitus and hypertension; a case of rectal haemorrhage associated with the use of niflumic acid tablets for 'gastrointestinal disorders'; and a case of aggravation of hepatitis associated with the use of oxacillin in a penicillin allergic patient. Among the 15 'potentially' and 'definitely preventable' ADRs, five were linked to an inadequate or doubtful indication and two to self-prescription by patients. In other cases, contraindications, warnings or drug dosage were not followed (n = 3), previous intolerance to an antibiotic has not been taken into account (n = 1) and symptoms of ADRs (hypotension) had been present for several months but went unrecognised (n = 1). The last three cases were considered as expected with regard to patients medical history.

Table II. Characteristics of the 44 suspected adverse drug reactions (ADRs)

Gender (M/F)	Age (y)	Suspected ADR	Suspected drug (s)	Seriousness of ADR[a]	Outcome of ADR[b]	Length of hospital stay (d)	Imputability scores[c]	ADR preventability score[d]	Judgement of Imbs' scale[e]	Rev 1[e,f]	Rev 2[e,f]	Rev 3[e,f]	Rev 4[e,f]	Mean judgement of reviewers[g]
Drugs for digestive and metabolic disorders														
F	58	Hypoglycaemia	Insulin	3	A	2	I2	–2	1	2	2	2	2	2
M	44	Hypoglycaemia	Insulin	3	A		I1	–2	1	2	2	2	2	2
M	31	Diarrhoea	Lactulose	3	A	6	I1	–1	2	2	2	2	2	2
F	61	Hypoglycaemic malaise	Insulin	3	A		I1	–2	1	2	2	2	2	2
Oral anticoagulants														
M	87	Subdural haematoma	Acenocoumarol	5	B	4	I2	–4	1	2	2	2	2	2
M	92	Parietal haematoma	Fluindione	3	A	7	I1	–3	1	1	2	2	2	2
M	92	Rectal haemorrhage	Fluindione	3	A	7	I2	–3	1	1	2	2	2	2
Cardiovascular drugs														
M	68	Orthostatic hypotension	Nitroglycerin, captopril	3	A		I1, I1	4	2	2	2	2	2	2
M	80	Malaise	Isosorbide dinitrate	3	A	1	I3	–1	1	2	2	1	2	2
M	87	Dehydratation	Furosemide	5	A	10	I1	–3	1	1	2	2	2	2
M	85	Dehydratation, confusion	Furosemide	3	A	2	I1	–2	1	2	2	2	2	2
F	80	Hypokalaemia	Captopril + hydrochlorothiazide	3	A	5	I1	–2	1	2	2	2	2	2
Systemic anti-infective agents														
F	61	Thrombopenia	Sulfadoxine + pyrimethamine	3	A		11	10	3	3	3	3	2	3
F	39	Cutaneous eruption, dyspnoea	Pefloxacin	3	A	1	I3	–3	1	2	1	1	1	1
M	25	Thrombopenia	Amoxicillin	3	A	3	I1	–1	2	2	3	3	2	2/3
M	26	Generalised urticaria	Griseofulvin	3	A	6	I1	–9	1	1	1	1	1	1
F	30	Diarrhoea, abdominal pain	Didanosine	3	A		I1	–9	1	1	1	1	1	1
M	72	Aggravation of hepatitis	Oxacillin	3	A	3	I2	13	3	2	3	3	3	3
M	87	Epileptic seizure	Ofloxacin	5	A	10	I2	6	2	1	3	2	2	Discrepancy

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Table II. Contd

Gender	Age (y)	Suspected ADR	Suspected drug (s)	Seriousness of ADR[a]	Outcome of ADR[b]	Length of hospital stay (days)	Imputability scores[c]	ADR preventability score[d]	Judgement of Imbs' scale[e]	Rev 1[e,f]	Rev 2[e,f]	Rev 3[e,f]	Rev 4[e,f]	Mean judgement of reviewers[g]
F	59	Nausea, vomiting	Metacycline	3	A		I1	–9	1	1	2	1	2	1/2
F	27	Angioedema	Amoxicillin + clavulanic acid	3	A	2	I3	3	2	1	2	1	2	1/2
Antineoplastic agents														
F	71	Aplasia	Ifosfamide, methotrexate, etoposide	5	A	3	I1, I1, I1	–6	1	1	1	1	1	1
F	73	Neutropenia	Fludarabine	5	A	17	I1	–6	1	1	1	1	1	1
Drugs for musculoskeletal disorders														
M	61	Rectal haemorrhage	Ketoprofen (tablets)	5	A	6	I1	7	2	2	2	2	2	2
F	50	Rectal haemorrhage	Niflumic acid (tablets)	3	A		I1	10	3	2	2	2	2	2
F	41	Toxidermitis	Hydroxychloroquine	3	A	9	I3	–5	1	1	1	1	2	1
F	21	Vomiting, abdominal pain	Tiaprofenic acid	3	A		I1	–1	2	1	2	1	2	1/2
M	29	Urticaria	Ibuprofen (tablets)	3	A		I1	–5	1	1	2	2	2	2
M	64	Gastric ulcer	Ketoprofen (tablets)	3	A		I2	6	2	2	2	2	2	2
F	38	Facial oedema	Ibuprofen (topical)	3	A		I1	–3	1	2	2	2	1	2
Nervous system drugs (antipsychotics, analgesics)														
F	44	Vomiting	Paracetamol (acetaminophen) + codeine	3	A		I1	–9	1	?	2	2	2	2
M	31	Vomiting	Morphine sulphate	3	A	6	I1	–9	1	2	1	1	2	1/2
F	62	Confusion and delirium	Ropinirole	3	A	12	I2	–9	1	1	2	1	2	1/2
F	41	Facial oedema	Aspirin (acetylsalicylic acid)	3	A		I3	5	2	1	1	1	1	1
M	63	Rectal haemorrhage	Aspirin (anti-inflammatory dosage)	3	A	5	I1	–2	1	1	2	1	2	1/2
M	94	Orthostatic hypotension	Thioridazine	3	A		I1	4	2	3	2	2	2	2
M	85	Renal failure	Aspirin (anti-inflammatory dosage)	3	A	4	I2	14	3	1	2	2	2	2
M	70	Constipation	Morphine sulphate	3	A	10	I1	–5	1	1	2	1	2	1/2

Reviewers found that 18.2% of cases were 'nonpreventable' (n = 8), 50% were 'potentially preventable' (n = 22) and 4.5% were 'definitely preventable' (n = 2). Kappa statistics varied from 0.58 for the two more concordant reviewers to 0.14 for the two more discordant. Concerning the remaining 12 cases, they were unclassified because of discrepancies between reviewers. Among these, ten were judged to be 'nonpreventable or potentially preventable' depending on the reviewer: for eight of these ten cases, two reviewers (a senior medical doctor with expertise in pharmacovigilance and a medical resident, both specially trained in public health) were concordant in their judgement ('potentially preventable' ADRs), in contrast to the two other reviewers who judged them 'non preventable' (table II). The more important difference was found between the two medical doctors, since one of them was expert in pharmacovigilance.

Concerning the comparison of the classification of ADRs (category 1, 2 or 3) between preventability scale versus each reviewer, Kappa values were 0.27, 0.32, 0.40 and 0.41 depending on the reviewer. If we compared the classification of Imbs et al.[5] scale and the mean judgement of reviewers, 18 cases were classified differently and 14 cases were classified in the same preventability category by the scale and by the reviewers.

Discussion

Incidence of Drug-Related Admissions

This study emphasises that ADRs in the community should be considered as an important cause of hospital admissions, with an incidence of 6.1% of hospital admissions related to drugs. This incidence is similar to that observed in other studies [4,8,11,12,21] Moreover, 34% of these admissions could have been prevented.

Preventability

The aim of this study was to assess the feasibility of the use of a standardised scale of preventability. Actually, there is as yet no gold standard

M	97	Conscience troubles	Paroxetine, amitriptylline	3	A	12	I1, I1	–9	1	2	3	2	2	2
M	50	Ischaemic colitis	Levomepromazine, trihexyphenidyl, tiapride, haloperidol	5	A	6	I1, I1, I1, I1	–7	1	1	2	2	1	2
M	47	Malaise, hypotension	Cyamemazine	3	A		I1	1	2	1	2	1	2	1/2
F	74	Angioedema	Paracetamol + dextropropoxyphene	3	A	1	I1	–9	1	1	2	2	1	1/2
F	24	Generalised urticaria	Aspirin + ascorbic acid + cafeine	3	A		I1	–9	1	1	1	1	1	1
M	26	Constipation	Amisulpride	3	A		I1	–9	1	1	2	1	2	1/2

a Level 3 corresponds to ADR 'requiring hospitalisation or prolongation of existing hospitalisation', level 5 corresponds to a 'life-threatening' ADR.
b A corresponds to 'favourable outcome', B corresponds to 'favourable outcome with sequelae'.
c According to the French validated method of causality assessment: I1 means 'possible', I2 means 'plausible', I3 means 'likely'.
d According to the score proposed by Imbs et al.[15] (table I).
e Category 1 is defined as 'definitely not preventable' for a score ≤–2, category 2 is defined as 'potentially preventable' for a score between –1 and +8 and category 3 is defined as 'definitely preventable' for a score ≥+9.[15]
f Reviewer (Rev) 1 is a senior medical doctor; Rev 2 is a senior medical doctor with expertise in pharmacovigilance; Rev 3 is a senior pharmacist with expertise in pharmacovigilance; Rev 4 is a medical resident.
g The mean judgement of reviewers was that of the majority of reviewers.

F = female; **M** = male.

for evaluating the preventability of ADRs. Many studies rely on expert panel review while others use selected criteria. Several approaches have been described: Pearson et al.[9] classified each ADR as preventable or non-preventable according to criteria adapted from Shumock and Thornton.[14] Answering 'yes' to one or more of the following seven questions (appropriate drug or not, appropriate dose, route and frequency of administration, therapeutic monitoring drug performed or not, previous reaction to the drug or not, drug interaction, toxic serum drug level documented or not, poor compliance or not) suggests that the ADR may indeed have been preventable. Petersen et al.[12] used a 6-point scale: a score of 1 indicated nearly certain evidence for preventability and events that score 4 or higher on this scale were judged potentially preventable. Three reviewers first independently assessed the events and then met to develop consensus. For Bates et al.,[10] preventability was assessed by two reviewers who 'considered adverse events as preventable if they were due to an error or were preventable by any means currently available'. Dartnell et al.[11] assessed it according to six criteria.

In France, the preventability of ADRs has been rarely assessed. The standardised scale proposed by Imbs et al.[15] is more detailed and included more criteria than other methods. This scale of preventability has been only used previously by Letrilliart et al.[7] who found that postdischarge ADRs detected in primary care in France could be considered as preventable in 59% of cases.

In our study, 11 ADRs were considered as 'potentially preventable' (25%) and four as 'definitely preventable' (9%). In other studies, the proportion of preventable ADRs ranged from 19–80%.[8-12,14] These differences could be due to differences in definition of ADRs or in study population (hospitalised patients, outpatients) but also in the assessment of preventability. This fact underlines the need to validate a standardised preventability scale.

Our study was one of the first application of the French scale in practice. Comparison of the classification of ADRs in the three preventability categories between scale results and mean judgement of reviewers showed agreement in 14 ADRs and disagreement in 18 ADRs, underlining a great variability. However, discrepancies between reviewers were more important, with percentage of agreement ranging from 14% (between the more divergent reviewers) to 58% (between the more convergent). Concerning the four 'definitely preventable' cases, only two cases (thrombocytopenia associated with self-medication with sulfadoxine and pyrimethamine and aggravation of hepatitis with oxacillin in a penicillin allergic patient) were judged in the same manner by the four reviewers and by the French scale. The two others were considered as 'potentially preventable' for one (rectal haemorrhage with niflumic acid tablets used for 'gastrointestinal disorders') and 'potentially preventable' or 'not preventable' for the second (renal insufficiency with high dosage aspirin in a patient with diabetes mellitus and hypertension) by reviewers.

Global judgement depends on reviewer practice, thus the more important difference was found between the two medical doctors, since one of them was expert in pharmacovigilance. The more concordant judgement was found for the two reviewers specially trained in public health. Results obtained with the scale were less severe than those obtained by the four observers and suggested that almost ADRs were not preventable. In fact, the item 'prescription indispensable to the patient' is the more negatively scored and suggests strongly a non-preventable ADR (table I). The weight of this item could be overestimated because of the difficulty of determining if a prescription is essential or not. The problem relates to the reference chosen to define if the prescription seems indispensable or not.

The preventability assessment using this scale was feasible but has raised some questions. Several points need to be improved: balance in the weighting of each item, revision of the formulation of items and reduction of the number of items. Then, a validation study of this preventability scale could be performed including more patients than in our

study. Thus, we have begun investigations to improve this French scale for a future use in clinical practice.

Drugs Classes Involved

The most important risk factor for ADRs in the present study was polymedication of patients: in the group of patients with ADRs the number of drugs used was twice as high as the number used by the controls. We also found that some drug classes were significantly associated with a higher risk of ADRs, such as analgesics, antineoplastic agents, systemic anti-infective drugs or non-steroidal anti-inflammatory drugs (NSAIDs). ADRs occurring with antineoplastic agents remain 'definitely unpreventable' and are expected. Among preventable ADRs, 31.25% were due to an anti-infective agent, 25% to an NSAID, 12.5% to an analgesic and 12.5% to an antipsychotic drug. These results underline the need to sensitise prescribers and also patients to the high risk of ADRs induced by drugs considered as 'safe', such as NSAIDs or analgesics.[22] These findings suggest that GPs should be more cautious when they prescribe these classes of drugs. Moreover, two preventable ADRs were due to a self-medication, therefore patient education should also be more rigorous about drug use.

Conclusions

Our results emphasise that ADRs leading to hospitalisation are frequent, with one-third of them most likely to be preventable. The preventability assessment using the Imbs et al.[5] ADR preventability scale was feasible. However, there was a low agreement between the subjective judgement of reviewers and preventability scale, and there was a great variability between each reviewer who tested the scale: this experience suggests the need for further studies to improve the scale and validate it in different circumstances. In the future, improvement of the Imbs et al.[5] ADR preventability scale will provide a useful tool to detect the best way to improve the prescription and use of drugs.

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