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Postdischarge Adverse Drug Reactions in Primary Care Originating from Hospital Care in France

A Nationwide Prospective Study

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Abstract

Objective: To describe and estimate the incidence and preventability of postdischarge adverse drug reactions (ADRs) detected in primary care in France.

Design: Prospective study of patients referred to hospital by participating general practitioners (GPs). These GPs reported all cases of an adverse reaction to a drug instituted in hospital among patients who consulted them within 30 days of discharge.

Setting: 305 general practices from all French regions.

Patients: 7540 patients referred by GPs to private or public hospitals.

Main outcome measures: The incidence for postdischarge ADRs in primary care, and their preventability.

Results: 30 cases of postdischarge ADR were detected in 29 re-consulting patients, yielding a minimal incidence for France of 0.4 per 100 admissions (95% confidence interval 0.3 to 0.6). The ADRs were assessed as serious in 60% of cases. The main drug classes implicated were cardiovascular drugs (8 ADRs), oral anticoagulants (6), psychoactive drugs (4), antidiabetics (3), and opioid analgesics (3). Patients experiencing a postdischarge ADR were older than patients not experiencing one (median age: 77 *vs* 68 years; $p = 0.004$). Detected ADRs were considered preventable in 59% of cases.

Conclusions: Physicians and patients should be aware of the possible occurrence of postdischarge ADRs. Patient information in hospital, close postdischarge follow-up of patients at risk, and appropriate transmission of information between hospital physicians and GPs can help to prevent them.

The authors of large studies have stressed the great impact that adverse drug reactions (ADRs) occurring in hospital have on health. ADRs constitute the most common cause of complications due to healthcare in this setting, and are increasingly recognised as a serious burden by the public health authorities and the public. According to the results of a meta-analysis of 39 prospective studies, the incidence of ADRs experienced during hospital stays may reach 10.9% of admitted patients, which in the US would correspond to an estimated 3.6 million patients with such ADRs in a year.[1] In a large multicentre study conducted in French public hospitals, the annual number of patients with ADRs occurring during their hospital stay was estimated at about 700 000, which corresponds to about 9% of admitted patients.[2]

In France, as in many other countries, the average length of stay in acute care hospitals has regularly decreased during the past years (e.g. 7.2 days in 1989 *vs* 5.9 in 1996 in public hospitals).[3,4] This decrease might have contradictory effects on the occurrence of ADRs originating from hospital care. Although shorter stays might reduce exposure to the risk of acquiring ADRs,[5] they might also delay their onset or detection until the postdischarge period, as already documented for other nosocomial diseases.[6] As yet, assessments of the ADRs generated by hospital care have focused on those detected during the hospital stay, and ADRs arising after discharge have usually been ignored.[7] The aim of this study was to assess the incidence and preventability of the postdischarge ADRs detected in primary care in France.

Patients and Methods

Design

Within the framework of a programme for the analysis of the clinical pathway between primary and hospital care in France, 305 general practitioners (GPs) from all over the country prospectively reported the referrals to hospital they made between August 1997 and July 1999. Data were transmitted on a real-time basis via teleinformatics, from the general GP's office to the database centre, according to a standard protocol described in detail elsewhere.[8,9] Information was systematically collected on patients' age, gender, admission context (emergency or planned) and hospital sector (public or private). Follow-up information was collected for those patients who, within 30 days of discharge, again consulted the GP who had referred them to hospital. This information included: discharge diagnosis; type of hospital department (medical, surgical, psychiatric or intensive care); length of hospitalisation; whether or not a hospital report (i.e. either a discharge note or a typed summary) was available to the GP at the postdischarge consultation; whether or not the reason for again consulting the GP was the occurrence of a postdischarge ADR; and the seriousness of the ADR.

Several procedures were used to stimulate reporting by the GPs. Reminder forms, containing the list of all the variables to report for each hospital referral, as displayed on the videotext server used for the reporting, were sent to the participating GPs. This list included an explicit item for the occurrence or not of an ADR, and another for an assessment of its seriousness. A feedback information system, displaying all reported cases of ADR on an electronic forum, was also available to all the participating GPs. Moreover, regular written communications on the preliminary results of this study, as well as on other studies we were conducting on drug safety issues at the same time, were sent to these GPs. Confidentiality was guaranteed to centres, physicians, and patients.

Case Definition and Reporting

The case definition used in this study for including postdischarge ADRs diagnosed by GPs within 30 days of discharge was 'a response to a drug instituted or prescribed during the previous stay in hospital which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the restoration, correction or modification of physiological function'.[10] This definition is derived from the World Health Organization definition of

ADRs.[11] Noxious and unintended consequences resulting from the discontinuation, during a hospital stay, of a drug administered before admission were also included as cases. GPs assessed the seriousness of each ADR they diagnosed according to several of the criteria used by the US Food and Drug Administration, i.e. death, life-threatening condition, hospitalisation, or disability.[12]

For each case of an ADR, the reporting GP gave details of the following:

- discharge drug regimen (including details of new drugs as opposed to admission drugs)
- date of onset of the clinical signs relating to the ADR and the date of the consultation
- how the course of drug administration was modified, i.e. drug withdrawal, dose reduction or reintroduction,
- whether the GP reported the reaction to the drug regulation authorities (i.e. to the regional drug monitoring centre) or to the appropriate pharmaceutical manufacturer.

We contacted the GPs in order to obtain the name and telephone number of the physician who had cared for the patient while in hospital.

Case Evaluation

Six evaluations were made for each case of an ADR:

1. Each case reported by the participating GPs was reviewed by a general practitioner (LL) and a hospital internist (TH) and validated according to the case definition specified in the previous section.
2. A representative of a Parisian Regional Drug Monitoring Centre (MB) classified each ADR according to the French intrinsic imputation algorithm, which takes into account both chronological and semiological criteria (level 0: final imputation seems unlikely, level 1: doubtful, level 2: possible, level 3: likely, level 4: very likely).[13]
3. The referent hospital physician was interviewed by telephone whenever possible, and asked whether he or she was aware of the occurrence of the drug reaction in the patient, whether he or she recognised the reported reaction as plausibly iatrogenic, and whether or not information had been given to the patient or the patient's family during hospitalisation regarding the risk of experiencing an adverse drug reaction.
4. For each case, the likelihood that the ADR could have been prevented was assessed, using an evaluation scheme proposed by French experts in pharmacovigilance (table I). This evaluation takes into

Table I. System for evaluating the preventability of adverse drug reactions (reproduced from Imbs JL et al.[14] with kind permission of the author and was originally published in Thérapie 1998; 53: 365-370)

Criterion	Score
The drug[a]	
Knowledge of the drug and its possible role	
hypothesis expressed by experts and still under debate	+1
serious fears, according to published or preliminary data	+2
established causality, described in the Summary of Product Characteristics	+3
Communication of this knowledge	
reassuring about safety	0
rather worrying	+2
very alarming about the reality of danger	+3
The patient[a]	
Risk factors	
no risk factor	0
risk factor(s) difficult to detect	+2
risk factor(s) present and easy to detect	+3
Drug management	
warnings have been heeded; or the disregard of warnings is not involved	0
difficulty of heeding warnings in the patient	+2
disregard of warnings in the summary of product characteristics, which would have been easy to heed by the physician or the patient; or dispensing error(s)	+3
The prescription[a]	
Circumstances of prescription	
essential to the patient	-12
debatable but acceptable	-4
certainly useless, or absolutely contraindicated	+3
Therapeutic management of the adverse reaction	
excellent, allowing aggravation of the reaction to be avoided	0
inadequate	+2
lacking, in relation to an aggravation of the reaction	+3

a This system only relies on the knowledge and information available at the time when the adverse reaction occurs, and takes into account the patient's clinical state at that time.

account the medical knowledge of adverse effects, the patient's risk factors for an adverse reaction, compliance with warnings by the consultant, the circumstances of drug prescription, and the follow-up.[14] A sum greater than or equal to zero was considered to denote a likely preventable reaction.
5. The expected magnitude of the frequency of each type of ADR was explored in the medical literature.
6. The appropriateness of discharge drug regimens was assessed with reference to the official information for drugs approved by the French Drug Agency and contained in the Summary of Product Characteristics. The criteria used for assessment applied to the drugs under investigation were compliance or noncompliance with: therapeutic indications; warnings; and with known adverse drug-drug interactions, as specified at the web site of the Banque d'Information Automatisée sur les Médicaments[15] and in the Vidal Drug Dictionary.[16]

Statistical Analysis

Among the patients referred to hospital by the GPs participating in the study, the incidence of postdischarge ADRs detected in general practice was estimated as the number of postdischarge ADRs detected per 100 admissions, and the 95% confidence interval (CI) for the incidence was derived from the Poisson distribution of events.[17]

Patients experiencing one or more ADRs and those not experiencing one were compared for age using Wilcoxon's rank sum test, and for gender, admission context and hospital sector, using χ^2 2-tailed test.

Results

Incidence

During the 2-year study period, 7540 patients were referred to hospital by the participating GPs, i.e. a median number of 10.5 patients per practitioner (range 1 to 238; standard deviation 35.8). Among them, 2227 (29.5%) consulted the GP again within 30 days of discharge from hospital. These re-consulting patients had a median age of 69 years and 48.9% of them were of male gender. 29 of these re-consulting patients experienced 30 ADRs. These adverse effects were reported by 20 of the 305 participating GPs from various regions of France. These ADRs were diagnosed within 30 days of discharge and were subsequently validated. The incidence for postdischarge ADRs detected by GPs was therefore estimated at 0.4 per 100 admissions (95% CI 0.3 to 0.6). 24 hospital physicians were contacted regarding the questionnaire and and 24 responded to the questionaire. All the 24 responding hospital physicians recognised that the ADR reported by the GP was plausible.

Case Descriptions

39 drugs were presumed to be responsible for the 30 ADRs, of which 23 were attributed to a single drug and 7 to a drug combination. Only 1 ADR was secondary to the discontinuation of a drug belonging to a usual preadmission regimen, i.e. the occurrence of a pulmonary oedema after withdrawal of a diuretic. The pharmacological classes involved (table II), in decreasing order of frequency, were cardiovascular drugs (8 ADRs), oral anticoagulants (6), psychoactive drugs (4), antidiabetics (3), opioid analgesics (3, including 1 in combination with psychoactive drugs), antibacterials (2) and various other classes in 5 ADRs (nonsteroidal anti-inflammatory drugs, antiandrogenic hormones, antianaemic preparations, calcium homeostasis hormones, and anticancer chemotherapy). In accordance with the classification of these 39 drugs by the Regional Drug Monitoring Centre, 11 had an imputability level of 1 (doubtful), and 28 had an imputability level of 2 (possible).[13] 17 of the ADRs (59%) were considered preventable.

Patients who consulted their GP within 30 days of discharge from hospital who had experienced an ADR (n = 29) were older than those patients who had not consulted their GP within 30 days following discharge (n = 5313) and those who had consulted their GP within 30 days following discharge, but who had not experienced an ADR (n = 2198) [table III]. The patients experiencing an ADR had been hospitalised in a medical department (21 patients) or a surgical department (8). The median post-

Table II. Characteristics of 30 reported cases of postdischarge adverse drug reactions (ADRs)

Age (y)	Gender	Reported reaction	Suspected drug(s)	Imputability level[a]	Discharge diagnosis	Length of hospital stay (d)	Time lag between discharge and onset of ADR (d)	Time lag between onset of ADR and diagnosis (d)	Hospital report[b]	Expected incidence of the reported ADR	Seriousness of the ADR[c]	Patient informed of the risk of ADR	Alteration of suspect drug administration	ADR score for preventability[d]
Cardiovascular drugs														
92	M	Hypotension	Fur	1	AF, HF	21	2	1	Yes	1.5%[18]	LH, RH	No	WD	–7
65[e]	F	Quincke's oedema	Ena	1	AF, HF	15	1	2	No	<0.1%[19]	LH	No	WD	–5
77	M	Parietal haematoma	L-ASA	1	BC, pace maker implantation	7	2	0	Yes	60%[f][20]	Minor	NS	WD	7
87	F	Pulmonary oedema	Fur (WD)	2	Hyponatraemia, AD	4	5	0	Yes	10%[21]	LH, RH	No	RI	NA
72	M	Hyperkalaemia	Spi	1	Cirrhosis, HF	7	7	9	Yes	9%[22]	LH, RH	Yes	WD	3
91	F	Malaise	Aml	2	HT	8	1	1	Yes	1 to 2%[22]	Minor	Yes	WD	–7
75	M	Hypotension, malaise	Ram, nic	2	Stroke, HT	6	3	27	Yes	0.2 to 5%[23]	RH	No	WD	1
66	M	Vasomotor flush	Dil	2	SVP	2	1	8	Yes	Not avail.	Minor	No	WD	–5
Oral anticoagulants														
81	M	Over anticoagulation (INR 15)	Flu	2	AF, HF	6	17	0	Yes	INR ≥ 4 in 10% of tests[24]	LH	Yes	DR	5
79	F	Over anticoagulation (INR 7)	Flu	2	AF	10	8	0	Yes	INR ≥ 4 in 10% of tests[24]	LH	Yes	DR	2
84	F	Parietal haematoma (INR unavailable)	Ace	1	Eventration, umbilical hernia	10	0	11	Yes	Not avail.	LH, RH	No	None	1
85	M	Macroscopic haematuria (INR 5)	Flu	2	AF, HF	10	10	11	Yes	1 to 5%/year[22]	Minor	Yes	WD	4
91	F	Eruption	Flu	1	PE	8	8	1	Yes	Not avail.	LH	No	WD	–7
65[e]	F	Varicose ulcer haemorrhage (PT < 15%)	Flu	2	AF, HF	15	1	2	No	Not avail.	LH	No	WD	5

Table II. Contd

Age (y)	Gender	Reported reaction	Suspected drug(s)	Imputability level[a]	Discharge diagnosis	Length of hospital stay (d)	Time lag between discharge and onset of ADR (d)	Time lag between onset of ADR and diagnosis (d)	Hospital report[b]	Expected incidence of the reported ADR	Seriousness of the ADR[c]	Patient informed of the risk of ADR	Alteration of suspect drug administration	ADR score for preventability[d]
Psychoactive drugs														
39	F	Transaminitis	Car	1	Brachial plexus neuralgia, endometriosis	15	7	0	No	0.01 to 0.1%[16]	LH	NS	WD	–7
77	M	Diarrhoea	Flx Car	1 1	Vertebral disc prolapse, cauda equina syndrome	60	11	0	Yes	10%[22] 0.01 to 0.1%[16]	Minor	NS	WD	–1
78	M	Disorientation, agitation	Zuc Ser	2 2	BC, pace maker implantation	15	0	1	No	Unlabelled 7%[25]	Minor	No	WD	0
61[g]	F	Confusion	Clo Mor	1 1	Osteitis	30	0	13	No	9%[26] 2 to 18%[27]	LH, RH	No	WD	4
Antidiabetics														
82	F	Hypoglycaemia	Ins Gli Met	2 2 2	HF, kidney failure, DM	19	2	16	Yes	33%/y[28] 28%/y[28] 6%/[28]	LH	Yes	WD	7
80	F	Hypoglycaemia	Ins	1	Aspiration pneumonia	8	28	2	Yes	33%/y[28]	Minor	Yes	Dose reduction	3
72	F	Diarrhoea	Met	1	Type 2 DM	5	0	18	Yes	20%[22]	Minor	Yes	WD	–7
Opioid analgesics														
84	M	Confusion	Mor	1	Vertebral metastasis, prostate cancer	20	10	0	No	2 to 18%[27]	RH	Yes	WD	3
60	M	Constipation	Par/cod	1	Seizure, dorsalgia	12	11	7	Yes	12 to 20%[29,30]	Minor	No	WD	–7
Antibacterials														
75[h]	M	Achilles' tendon rupture	Ofl M-pred	1 1	Superinfection of chronic bronchitis	10	11	7	Yes	<0.1%[31,32] Not avail.	RH	No	Diagnosis after prescription completion	3

15	F	Cutaneous mycosis	Amo	1	Pulmonary abscess	10	2	1	No	Not avail.	Minor	No	None	–7
Other drugs														
75	M	Duodenal ulcer	Dic	2	Adenoma of the prostate	14	4	0	Yes	0.2%[22]	LH, RH	NS	WD	1
69	M	PE	Cyp	1	Vertebral metastasis, prostate cancer	9	3	1	Yes	3%[22]	LH, RH	NS	WD	6
30	F	Constipation	Iro	1	Rupture of extra-uterine pregnancy	8	0	1	No	14 to 35%[33]	Minor	No	None	–7
96	F	Vomiting	Cal	1	Vertebral fracture	14	2	0	Yes	Not avail.	Minor	Yes	WD	–7
71	M	Neutropenia (300×10^9 per litre)	Cyc Dox Eto Cis	1 1 1 1	SCLC	9	7	0	Yes	11 to 57%[34,35]	LH, RH	Yes	Diagnosis after prescription completion	0

a Level 0 denotes that imputation seems ruled out, 1 denotes doubtful, 2 denotes plausible, 3 denotes likely and 4 denotes very likely.

b Hospital report available at post-discharge GP consultation.

c Seriousness criteria used for assessment by the GP included death, life threatening, re-hospitalisation and disability. The criteria were derived from the FDA Medwatch criteria.[12] When none of those criteria was present, the reaction was labelled as minor.

d According to the evaluation scheme proposed by Imbs et al.[14] (see table I).

e This patient experienced 2 adverse drug reactions after hospital discharge: Quincke's oedema associated with enalapril and varicose ulcer haemorrhage with fluindione.

f Haematoma/ecchymosis was reported in 12 patients out of 20.

g This reaction could also be classified in the group of adverse reactions to opioid analgesics.

h The reported corticosteroid therapy had been given as an oral treatment. This patient had a previous history of pain at the Achilles' tendon while receiving ofloxacin.

Ace = acenocoumarol; **AD** = Alzheimer's disease; **AF** = atrial fibrillation; **Aml** = amlodipine; **Amo** = amoxicillin-clavulinic acid; **BC** = bardycardia; **Cal** = calcitonin; **Car** = carbamazepine; **Cis** = cisplatin; **Clo** = clomipramine; **Cod** = codeine; **Cyc** = cyclophosphamide; **Cyp** = cyproterone acetate; **Dic** = diclofenac; **Dil** = diltiazem; **DM** = diabetes mellitus; **Dox** = doxorubicin; **DR** = dose reduction; **Ena** = enalapril; **Eto** = etoposide; **F** = female; **Flu** = fluindione; **Flx** = fluoxetine; **Fur** = furosemide; **Gli** = glibenclamide (glyburide); **HF** = heart failure; **HT** = hypertension; **Iro** = iron; **INR** = International Normalised Ratio; **Ins** = insulin; **L-ASA** = lysine acetylsalicylate; **LT** = life threatening; **M** = male; **M-pred** = methylprenisolone; **Met** = metformin; **Mor** = morphine; **NA** = not applicable; **Nic** = nicerogline; **NS** = not stated; **Ofl** = olfoxacin; **Par** = paracetamol (acetaminophen); **PE** = pulmonary embolism; **PT** = Prothrombin time; **Ram** = ramipril; **RH** = re-hospitalisation; **RI** = re-introduction; **SCLC** = small-cell lung cancer; **Ser** = sertraline; **Spi** = spironolactone; **SVP** = supraventricular tacycardia; **WD** = withdrawal; **Zuc** = zuclopenthixol.

Table III. Comparison of patient characteristics between patients who experienced an adverse drug reaction (ADR) and those who did not

Patient characteristic	Patients experiencing an ADR (n = 29)	Patients not experiencing an ADR (n = 7507)[a]	p-Value
Age			
median	77 y	68 y	0.004
range	15 to 96 y	1 mo to 99 y	
standard deviation	18.2 y	25.3 y	
Gender			
no. of male (%)	15 (51.7)	3585 (47.8)	0.67
no. of female (%)	14 (48.3)	3922 (52.2)	
Admission context			
no. of emergency (%)	22 (75.9)	6144 (81.8)	0.41
no. of planned (%)	7 (24.1)	1363 (18.2)	
Hospital sector			
no. of public (%)	24 (82.8)	5767 (76.8)	0.45
no. of private (%)	5 (18.2)	1740 (23.2)	

a Data was missing for 4 patients who did not experience an ADR.

discharge period until the appearance of clinical signs of an ADR was 3 days, but in 28 of the 30 ADRs (93%) clinical onset of the reaction occurred within 14 days of discharge. The median time lag between the first clinical signs of an ADR (as perceived by the patient) and consultation of the GP (i.e. diagnosis of the ADR) was 1 day. 18 of the 30 ADRs (60%) met at least one of the criteria for seriousness according to GP assessments, i.e. either a life-threatening reaction (14 ADRs) or rehospitalisation (10). Consequently, administration of the drug or drug combination suspected of causing the ADR was stopped in 21 cases of an ADR (70%). An assessment of discharge drug regimens is shown in table IV. Although the indication of the drugs was adequate in 90% of cases of patients with an ADR and no ADR was a result of a contra-indicated drug combination, warnings regarding suspect drugs were not heeded in 31% of cases. Discharge drug regimens included a median number of 5 drugs (range 1 to 10).

Communication Issues

A hospital report was available to the GP at the time of the postdischarge consultation for 22 patients out of 29 (76%). 11 hospital physicians out of the 24 respondents (46%) were aware of the postdischarge ADR: in 6 cases because of patient re-admission to the same hospital, in 2 through a call from the GP, and in the 3 others, from the patient at a subsequent outpatient consultation. The GP had notified a drug monitoring centre of the ADR in 2 cases (7%), including 1 of 18 serious cases.

Discussion

Postdischarge ADRs, as identified and reported by GPs, turned out to be a relatively rare outcome of hospitalisation in France, compared with the frequency of ADRs occurring during the hospital stay. A rate of 0.4 postdischarge ADRs per 100 admissions resulted from GP referral, of which 60% constituted serious events, and 59% were potentially preventable. Old age was associated with their occurrence, and 2 main groups of drugs were involved: those used in cardiovascular disease (47% of cases for combined cardiovascular drugs and anticoagulants) and central nervous system drugs (20% of cases for combined psychoactive drugs and opioid analgesics). More than 90% of cases became manifest, and presumably detectable, within 2 weeks of discharge. Interviews of both hospital and primary care physicians showed poor communication about ADRs, both before discharge (54% of patients had not been informed of the risk of experiencing the reaction) and thereafter (the ADR was known by the hospital physician in less than half the cases,

and 94% of the serious reactions had not been reported to a drug monitoring centre).

As usually occurs in drug monitoring, the causes of the reported reactions were difficult to assess, because we did not have direct access to complete information on the course of the reaction after drug withdrawal (e.g. a suggestive dechallenge), which may explain why the imputability scores did not exceed level 2. In addition, it is generally recognised that the French causality assessment method is much less sensitive than the physician's judgement. A study of spontaneously reported ADRs indeed showed that 76% of those considered very likely by the reporting physicians were in fact classified as level 1, i.e. as doubtful, according to the standardised pharmacovigilance method.[36] The proportion of 87% of ADRs classified as level 1 in our study is therefore not surprising. However, the validity of our cases was strengthened firstly, by the short period that elapsed between discharge and the appearance of a reaction, and secondly, by hospital physicians' constant recognition of the plausibility of the iatrogenic origin of the reaction.

For ADRs attributed to drugs instituted in hospital but only discovered in primary care after discharge, our estimated incidence rate is 25 times lower than the previously reported rate for ADRs detected during the hospital stay, which was about 10% of the patients admitted.[1,2] Our results may be underestimated because of several factors. First, patients who experience an ADR do not necessarily contact their doctor. In a New Zealand pilot study, for instance, only 40% of patients experiencing adverse effects from drugs after hospital discharge sought the advice of their general practitioner.[37] Secondly, we cannot exclude that GPs may have failed to identify some ADRs, especially those occurring after a long time interval from institution of the drug. Moreover, it has been well established that under-reporting of ADRs to the spontaneous reporting system is very marked among French GPs.[38] A similar bias may also apply to our results, although our study design can be considered as an active rather than a passive surveillance protocol. Thirdly, postdischarge ADRs could be detected in settings other than general practice, i.e. in the hospital setting or by a community specialist or another GP. Therefore, our estimated incidence of 0.4 per 100 admissions constitutes a minimal estimate for the overall rate of postdischarge ADRs in France, assuming that our surveillance system is representative. In view of these limitations, our low nationwide estimate is consistent with the results of an American retrospective study based on comprehensive Medicare administrative data, in which a medication-induced outpatient complication was identified

Table IV. Adequacy of patient information, discharge drug regimens, and reports to pharmacovigilance organisation, for drugs suspected of causing 29 adverse reactions[a] in 28 patients who had been discharged from hospital

Criterion	n	Percentage
Patient, or his family, informed about a possible adverse reaction[b]		
yes	11	45.8
no	13	54.2
Adequacy of therapeutic indications[c]		
yes	26	89.7
no	3	10.3
Compliance with warnings[c]		
yes	20	69.0
no	9	31.0
Drug combination[d]		
no potential interaction	14	48.3
requiring surveillance	14	48.3
to be avoided[e]	1	3.4
contraindicated	0	
GP report of the adverse reaction to pharmacovigilance organisations		
yes	2	6.9
no	27	93.1

a 1 adverse reaction, which resulted from drug withdrawal, was not included in this table.

b As stated by the hospital physician. Data missing for 5 patients.

c Those criteria were applied to the suspect drug or drug combination, and not to the other drugs of the discharge regimen.

d Only interactions involving at least 1 suspect drug were explored.

e Combination of carbamazepine and dextropozyphene paracetamol (acetaminophen).

GP = general practitioner.

within 60 days of hospital discharge in 0.9% of admitted patients.[7] Moreover, the rate of re-hospitalisation due to postdischarge ADRs, which can be estimated at 1.3 per 1000 admissions in our study, is also consistent with the rate of 2.4 per 1000 admissions reported in an American university teaching hospital for re-admission due to medication-induced complications detected within 30 days of discharge;[39] and with the rate of 4 per 1000 admissions retrospectively found in an Australian teaching hospital, which included all drug-related problems detected within 60 days of discharge.[40] Despite an apparently low incidence, the total number of postdischarge ADRs in primary care in France can be extrapolated from our findings to around 56 000 cases out of 14 million patients hospitalised, for instance in 1997,[41] assuming that our sample was representative.

We found an increased risk of experiencing an ADR during the postdischarge period in elderly patients. Age has already been recognised as a risk factor for ADRs occurring in hospital,[42,43] and for postdischarge ADRs generating re-hospitalisation.[39] It has not been systematically confirmed as an independent risk factor after adjustment for multiple drugs and co-morbidities,[44] and, in our study, it is especially possible that older patients consulted GPs more often after discharge because of particular diseases. However, it can be at least considered as a surrogate marker of risk. Drugs used in cardiovascular disease (anticoagulants included) and central nervous system drugs (opioid analgesics included) have already been recognised as the main drugs generating adverse reactions or events in inpatients, in studies involving multiple specialised departments.[2,45,46] Their major implication in postdischarge ADRs in our study is consistent with this recognition. The occurrence of an ADR induced by these drugs may be favoured by the frequency of both their prescription and change during hospitalisation.[47,48] At the same time, these drugs may also act as markers of underlying disease at risk.[46]

Our estimate of 59% for postdischarge ADR preventability is much higher than other published estimates for preventability among inpatients. For example, a proportion of 19% of preventable reactions was reported from 1 university medical centre.[49] However, in a study conducted in a tertiary care hospital, 56% of the recorded cases were judged preventable; but the case definition included all adverse drug events, covering both ADRs and errors in drug delivery.[50] In fact, there is as yet no gold standard for assessing ADR preventability. Some authors rely on expert panel review, while others use published criteria. It has been suggested that such criteria, which we used here, lead to more sensitive assessment, i.e. higher preventability, than expert review.[49] The high proportion of serious cases reported by GPs may also have contributed to our high estimate of preventability, because it has been found to be associated with the seriousness of adverse drug events.[51,52] Besides, in our study, serious ADRs were 4.5 times more likely to be preventable than nonserious ones, although the association between seriousness and preventability did not reach significance ($p = 0.12$; data not shown). Most important, some of the ADRs occurring in the postdischarge period are due to inadequate clinical follow-up of outpatients, for instance, inadequate biological surveillance of those under oral anticoagulant therapy, which clearly is preventable, but is less likely to occur among inpatients.

Conclusions

Our findings suggest that physicians and hospitalised patients should be aware of the possible occurrence of postdischarge ADRs, and adapt their behaviour so as to allow for their early detection and optimal management. At the time of discharge, clear information, preferably in writing, should be given to the patient or his home caregiver regarding the postdischarge treatment, its surveillance, and the course of action to adopt in case of problem. A systematic appointment with the regular GP shortly after discharge should be considered for prevention purpose, in particular for elderly patients taking cardiovascular drugs, oral anticoagulants, psychoactive drugs or antidiabetics. Before the postdischarge consultation, the GP should have received a hospital report including medications prescribed

at discharge. Moreover, he or she should be informed without delay of any abnormal result of a test prescribed at that time, such as overanticoagulation. The GP of a patient admitted to hospital should also make sure that the hospital staff are informed of any previous history of ADR or allergic disease.

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