Received: 19 May 2022 | Revised: 13 August 2022 | Accepted: 17 August 2022

DOI: 10.1111/bcp.15510

ORIGINAL ARTICLE

Incidence and preventability of hospital admissions for adverse drug reactions in France: A prospective observational study (IATROSTAT)

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Funding information
ANSM (Agence Nationale de Sécurité du Médicament et des produits de santé)

Aims: In the last French study in 2007, the incidence of hospital admissions (HAs) related to adverse drug reactions (ADRs) was 3.6%. The objective was to assess the current ADR-HA incidence in France and to describe both its characteristics and preventability.

Methods: A prospective multicentre study was conducted among randomly selected French public hospital medical wards (April–July 2018). Patients admitted during a week period were included. ADR-HA cases were collected by the French Regional Pharmacovigilance Centres network. An independent committee validated potential cases and ADR preventability.

Results: ADR-HA incidence was 8.5% (95% confidence interval [CI]: 7.6–9.4%), increasing with age (3.3% [95%CI: 1.8–5.5%] ≤16 y *vs.* 10.6% [95%CI: 9.3–12.0%] ≥65 y). The most common ADRs were haemorrhagic events (8.8%), haematological disorders (6.5%), acute renal failure (6.3%), fluid and electrolyte disorders

The authors confirm that the Principal Investigator for this study is Prof Marie-Laure Laroche.

(6.0%), and falls (5.2%). New drugs were involved: targeted therapies (22.8% of antineoplastics), direct oral anticoagulants (29.6% of antithrombotics) and incretin-based drugs (20.0% of antidiabetics). ADRs were preventable in 16.1% of cases because the drugs involved had not been used in accordance with monographies, package leaflets or other therapeutic guidelines. The main situations of noncompliance addressed either dose or duration of use (27.9%), warning (23.2%), use precaution (18.6%) and inappropriate self-medication or misuse by patients (11.6%).

Conclusion: In France, ADR-HA incidence dramatically increased over the last decade. A significant proportion was related to new pharmacological classes and considered as preventable. These findings should lead to in-depth thought on preventive actions on at-risk drug classes.

KEYWORDS

adverse drug reactions, drug safety, hospitalisation, incidence, observational study, pharmacovigilance, preventability

1 | INTRODUCTION

Adverse drug reactions (ADRs) are an important cause of hospital admission (HA) and a major public health priority, given the induced morbimortality and the burden on the healthcare system.[1,2] Reported studies have often focused on particular populations, such as older adults or children, in particular settings or limited geographical areas. Data are scarce at the national level. In the 2 most recent literature reviews on the topic, covering studies published between 2000 and 2015, ADR-related median hospitalisations were estimated between 6.3 and 7.0%.[1–3] In Europe, this rate is 3.5%.[4] Moreover, half of these HAs related to ADRs (ADR-HAs) were preventable.[5]

The French pharmacovigilance system is based on a network of 31 Regional Pharmacovigilance Centres (RPVCs).[6] This national network provides operational proximity to healthcare professionals, facilitating the identification, evaluation and management of ADRs, as well as signal detection. This network also allows the setting up and completion of national studies. The last national study on ADR-HA conducted in 2007 (EMIR study) provided a 3.6% estimated incidence of ADR-HA.[7] Moreover, this study showed that 32.0% of ADR-HAs were judged as totally preventable and 16.5% as potentially preventable. Since then, prevention measures have been undertaken and several new drug classes have been marketed (direct oral anticoagulants [DOACs], incretin-based drugs, targeted treatments/immunotherapy etc.), which could modify the spectrum of ADRs. In this context, we decided to conduct a new national study to update information about ADR-HA in France.

The main objective of the present study was to assess the rate of ADR-HA and the incident number of ADR-HAs in short-stay specialist medical wards of public hospitals in France. The secondary objectives were to describe the type of ADRs and the drugs involved, to estimate the rate of preventable ADR-HAs in cases where the involved drugs were not used in accordance with the French summary of product characteristics (SPC), package leaflets or therapeutic guidelines, and to compare results to those of the previous national study.

What is already known about this subject

- In the last French national study 10 years ago, 3.6% of hospital admissions (HAs) were related to adverse drug reactions (ADRs).
- Prevention measures have since been undertaken and several new drug classes have been marketed which could modify the spectrum of ADRs.

What this study adds

- In France, ADR-HA incidence (8.5%) is increasing as in other countries and is correlated with patient age.
- A significant proportion of new pharmacological classes (targeted therapies, incretin-based drugs, direct oral anticoagulants) are involved in ADR-HAs.
- In 16.1% of cases, ADRs were considered preventable as the drugs involved were not used in accordance with monographies, package leaflets or other therapeutic guidelines.

2 | METHODS

2.1 | Study setting

The French Pharmacovigilance network conducted a prospective multicentre study on a sample of short-stay medical wards randomly selected both in university hospitals and public general hospitals in metropolitan France (these 2 types of public facilities include 82% of the French hospital system). For each French region depending upon an RPVC, the number of wards to be included was calculated according to the ratio between the number of hospital beds in this geographic area and the total number of hospital beds in metropolitan France. The wards included in each hospital were randomly assigned. Hence, each RPVC was in charge of 2 ir 3 wards in a university hospital and 1 to 4 wards in general hospitals. Based on the ADR-HA incidence of the EMIR study, a sample size of 1333 patients was calculated to obtain a proportion of 3.6% with a precision of 1%. To obtain at least 200 cases of ADR-HA, in order to reflect the variety of adverse events, both in terms of nature and drugs involved, the number of patients to be included was estimated at 5556. All patients consecutively admitted to the selected wards for 14 consecutive days were included between April and July 2018. A 1-month follow up was performed for each collected ADR-HA. Patients were informed about the study by a written note. Patients who did not give consent, were admitted for a planned hospitalisation or were hospitalised for <24 hours were not included.

2.2 | Case assessment

An ADR was defined as a noxious and unintended response to a drug. The definition also included reactions resulting from error, misuse or abuse, and off-label use.[8] ADR-HA was defined as an HA due to an ADR. Excluded cases were: patients with an ADR at HA but that was not the cause of admission, patients admitted for suicide attempt or accidental overdose with drugs, patients who developed an ADR during hospitalisation in the selected ward or transferred to the selected ward during the 14-day study period, patients admitted because of an ADR in another ward and transferred to the selected ward during the 14-day study period.

For each patient included, medical staff screened eligible cases. A pharmacovigilance specialist (physician or pharmacist licensed in clinical pharmacology and pharmacovigilance) visited the selected wards and reviewed all new admitted patient charts during the inclusion period. Medical staff and pharmacovigilance specialists matched their inclusions to ensure completeness of the cases included. Then, the pharmacovigilance specialist manually collected clinical and pharmacological data from the medical records. Medicinal herbs or homeopathy were noted in the abstract of reports and considered in the ADR assessment. Patients with suspected ADR-HA were followed for 1 month to collect the adverse reaction outcome. Patients who died within 24 hours of admission were not excluded. ADR-HAs were coded in the French Pharmacovigilance database according to the Medical Dictionary for Regulatory Activities and drugs according to the Anatomical Therapeutic Chemical classification. Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[9]

An independent ADR review committee validated the cases collected by the RPVCs. This committee was composed of 16 senior pharmacovigilance specialists (≥10 y of activity). They evaluated in pairs the cases collected in the wards (they did not evaluate cases issued from their own territory). They could ask for additional information to judge the cases. The French causality method was used to categorize a case as an ADR-HA.[10] For each case, all drugs were analysed 1 by 1 in the occurrence of ADR to assess their respective causality. All cases recorded by pharmacovigilance specialists with a drug causality from doubtful to very likely according to the French method were selected in the study. They were reviewed by the committee to verify the inclusion criteria, the causality and to assess the preventability. Discrepancies when considering a case as an ADR or not and to assess ADR preventability were resolved during a meeting of the committee in order to reach a consensus.

2.3 | Preventability assessment

Based on the methodology of Jonville-Béra et al.,[11] the committee assessed the potential compliance or not of drug use involved in the ADR-HA occurrence and its preventability. The assessment of noncompliance was based on the official recommendations for the use of the drug, as stated in the French SPC, package leaflets or other validated therapeutic guidelines.[12] The situations of noncompliance were as follows:

- *absolute* noncompliance: contraindication (must never be violated), warning (situation to be avoided whenever possible, except after a thorough examination of the benefit/risk ratio and requiring a close monitoring of the patient), dosage (dose/duration) not respected and indication outside the marketing authorization (off-label).
- *relative* noncompliance: precautionary use (possible use but after implementation of recommendations for preventive measures to limit or avoid the occurrence of adverse effects).

In addition to these situations of noncompliance with the SPC, 2 de facto situations that did not comply with the appropriate use of drugs (risk situations) were added and classified as preventable:

- medication error: omission or unintentional performance of an act during the care process involving a medication that may be the cause of a risk or an adverse event for the patient.
- other patient-specific situations: inappropriate self-medication, misuse.

In situations of absolute or relative noncompliance, it was assessed whether the nature of the noncompliance of the drug involved in the

ADR could be a risk factor for the occurrence of the ADR. If it was not, the ADR occurrence was then regarded as unpreventable (the ADR would have occurred even if the prescription complied with the SCPs). In cases of noncompliance corresponding to *off-label indication*, if this noncompliance was not of such a nature as to influence the occurrence of the ADR, it was then considered a therapeutic hazard. If several noncompliances were identified in the same case, the most severe noncompliance in relation to the risk of ADR occurrence was retained.

2.4 | Statistical analysis

The incidence of ADR-HA was defined as the ratio of the number of new patients hospitalised for an ADR to the total number of patients hospitalised during the 14-day study period. The annual incident number of HAs due to an ADR was extrapolated from the number of HAs in short-stay specialist medical wards in public hospitals in metropolitan France in 2018. The 95% confidence interval (CI) was calculated for the normal distribution. The Poisson distribution was used when the design effect was negligible (<1.5). A descriptive analysis of the qualitative and quantitative variables was performed. The χ^2 test and tests of variance analysis were used. A *P*-value <.05 was considered statistically significant. Statistical analysis was performed using R-software (version R 3.5.1).

3 | RESULTS

3.1 | Study population

The study was performed in 141 short-stay specialist medical wards in 69 public hospitals in metropolitan France. Geriatric and paediatric wards represented respectively 10.6% ($n = 15$) and 8.5% ($n = 12$) of participating wards. A total of 5303 patients were hospitalised during the study period. After exclusion criteria application, 3648 patients were included in the study (Figure 1), 1732 (47.5%) were from university hospitals, 1916 (52.5%) from general hospitals and 1862 (51.0%) were women. The median age was 68 years (interquartile range [IQR]: 43–82 y). The proportion of patients aged 65 years and more was 54.9% (Table 1). The age distribution was not significantly different between women (60 y [standard deviation: 28]) and men (61 y [standard deviation: 25]; $P = .39$).

3.2 | ADR-related hospitalisation

Among the 3648 hospitalised patients, 309 patients were admitted to the hospital for an ADR (Figure 1). Median age was 75 years (IQR: 60–86 y). Patients hospitalised for ADR were significantly older than those hospitalised for other reasons (69 *vs.* 59 y, $P < .01$; Table 1). There were significantly more women among patients hospitalised for ADR than among patients hospitalised for any other reason (62.5 *vs.* 50.0%, $P < .01$).

The overall incidence of ADR-HA was 8.5% (95%CI: 7.6–9.4), increasing with age 3.3% (95% CI: 1. 8-5.5) in 0–16-year-old patients, 6.6% (95% CI: 5. 3-8.0) in 17–64-year-old patients and 10.6% (95% CI: 9. 3-12.0) in patients ≥65 years (Table 2). There was no statistically significant difference between the ADR-HA rates in university and general hospitals (9.3% [95%CI: 8.0–10.7] *vs.* 7.7% [95% CI: 6. 6-9.0]).

Among the 309 patients with ADR-HA and followed for 1 month, 4 died, corresponding to a mortality rate for hospitalisation secondary to an ADR of 1.3% (95% CI: 0. 5-2.8). Two patients aged 86 and 94 years were treated with antibiotics for erysipelas, and then admitted for severe diarrhoea (*Clostridium difficile infection*) complicated by acute renal failure. An 87-year-old woman with cognitive impairment, arterial hypertension (treated with losartan/hydrochlorothiazide) and type 2 diabetes (treated with **metformin**) was admitted for acute renal failure following the addition of a nonsteroidal anti-inflammatory drug (**diclofenac**), complicated by a fatal lactic acidosis. The last death occurred in a 71-year-old man with a medical history of mechanical heart valve, treated with fluindione, who experienced fatal cerebral haemorrhage while the International Normalized Ratio was 3 (target value: 2-3).

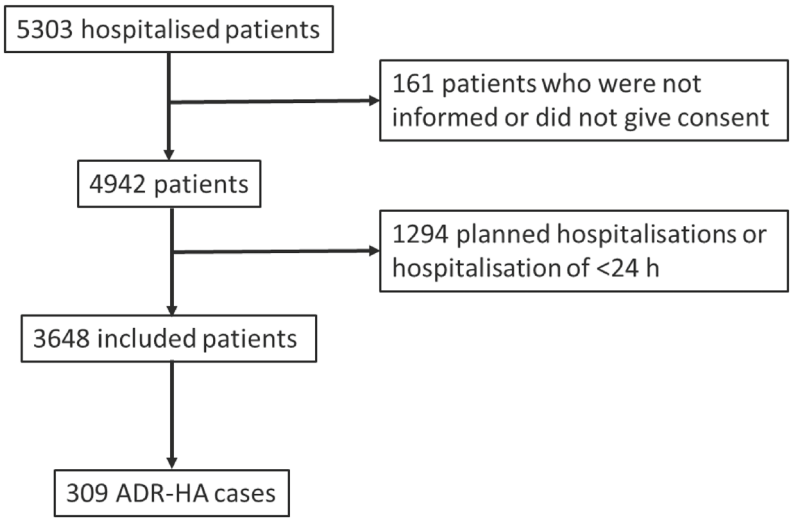

FIGURE 1 Flow-chart of included patients in the IATROSTAT study. *Note*: a hospital stay of <24 hours corresponds to outpatient care (for example complementary exams, chemotherapy); ADR-HA: adverse drug reactions leading to hospital admission.

TABLE 1 General characteristics of patients included and hospitalised for adverse drug reactions

	Patients included	Patients hospitalized for ADR	Patients hospitalized for other reason	*P*
Number	3648	309	3339	
Sex *n* (%)				
Male	1785 (49.0%)	116 (37.5%)	1669 (50.0%)	<.01
Female	1862 (51.0%)	193 (62.5%)	1669 (50.0%)	
Unknown	1 (0.0%)	0 (0.0%)	1 (0.0%)	
Age classes *n* (%)				
0–16 y	364 (10.0%)	12 (3.9%)	366 (11.0%)	<.01
17–64 y	1278 (35.0%)	84 (27.2%)	1218 (36.5%)	
65 y and more	2003 (54.9%)	213 (68.9%)	1752 (52.5%)	
Unknown	3 (0.0%)		3 (0.0)	
Age				
Mean (y)	60	69	59	<.01
Median (y)	68	75	67	
Interquartile range (y)	4 3-82	60–86	41–81	

TABLE 2 Incidence of hospital admissions related to adverse drug reactions (ADRs) according to the age group

Age (y)	Number of hospitalized patients[a]	Number of patients hospitalized for ADR[a]	Incidence[a] % (95% CI)
0–16	364	12	3.3% (1.8–5.5)
17–64	1278	84	6.6% (5. 3-8.0)
≥65	2003	213	10.6% (9.3–12.0)
Overall	3648	309	8.5% (7. 6-9.4)

Three missing data on age.
[a]incident cases of hospital admissions related to adverse drug reactions over a 15-day period.
CI, confidence interval.

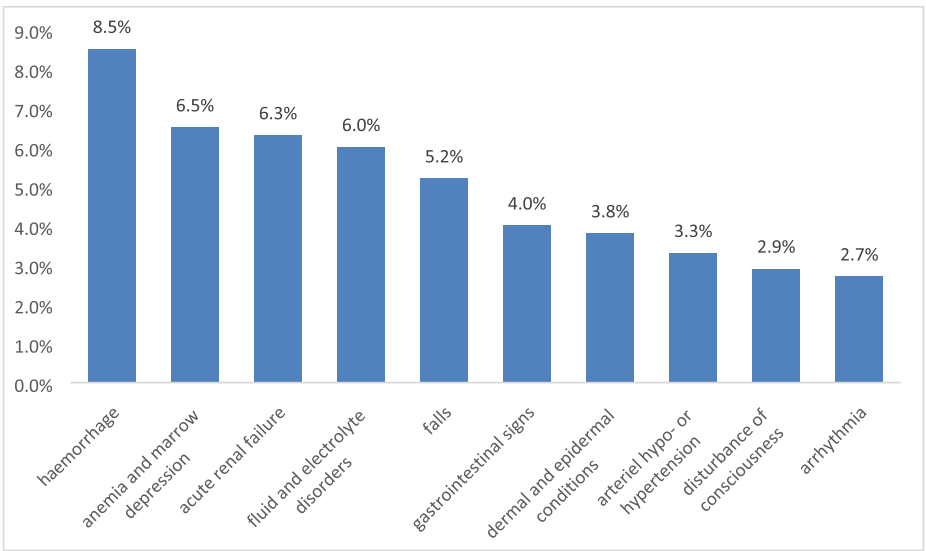

FIGURE 2 Proportion (%) of main adverse drug reactions leading to hospitalisation. The terms used in this figure correspond to the hierarchy level high-level group term (HLGT) of the Medical Dictionary for Regulatory Activities classification, except for the term haemorrhage, which groups all PT terms related to haemorrhage whatever the territory, the high-level term *acute renal failure* (99% of HLGT *renal disorders*) and high-level term *falls* (100% of HLGT *general disorders*).

Extrapolation of these results leads to estimate at approximately 212 500 (95% CI: 190 000–235 000) the annual incident number of ADR-HA in short-stay specialist medical wards in public hospitals in metropolitan France in 2018. The number of deaths related to ADR-HA, after a 1-month follow-up, was estimated at approximately 2760 (95% CI: 950–6580) per year in 2018.

3.3 | Type of HAs related to ADRs

Haemorrhagic events were the most common ADR-HAs (8.8%), followed by haematological disorders (anaemia, bicytopenia, pancytopenia, aplasia, 6.5%), acute renal failure (6.3%), fluid and electrolyte disorders (6.0%) and falls (5.2%; Figure 2, Appendix A).

Out of a total of 1598 drugs collected, 610 were considered to be involved in the occurrence of adverse effects. Therefore, the mean number of drugs involved was 2 per patients with ADR. The most involved drugs were antineoplastics agents ($n = 92$, 15.1%), antihypertensive drugs (diuretic and agents acting on the renin–angiotensin system; $n = 82$, 13.4%), antithrombotics ($n = 71$, 11.6%) and psycholeptics ($n = 54$; 8.9%; Table 3, Appendix B). Recent pharmacological classes accounted for 7% of ADR-HAs ($n = 43$): targeted therapies for 21 cases (3.5%); DOACs for 16 cases (2.6%) and incretin-based drugs for 6 cases (0.9%). Lastly, opioids accounted for 3.7% ($n = 23$) and **nonsteroidal inflammatory drugs** were involved in 2.5% ($n = 15$) of ADR-HAs.

TABLE 3 Main drugs involved in hospital admissions related to adverse drug reactions in France ($n = 610$)

Pharmacological classes	*n* (%)
Antineoplastics	92 (15.1)
Targeted therapies	*21*
Monoclonal antibodies	*16*
Protein kinases inhibitors	*5*
Antimetabolites	*21*
Alkaloids	*13*
Alkylating agents	*12*
Antithrombotics	71 (11.6)
Platelet aggregation inhibitors	*31*
Vitamin K antagonists	*21*
Direct oral anticoagulants	*16*
Heparin	*13*
Psycholeptics	54 (8.9)
Anxiolytics	*26*
Antipsychotics	*18*
Hypnotics	*10*
Diuretics	41 (6.7)
Agents acting on renin–angiotensin system	41 (6.7)
Antidiabetics	30 (4.9)
Insulin	*9*
Metformin	*7*
Incretin-based drugs	*6*
Repaglinide	*5*
Antibacterials for systemic use	30 (4.9)
Immunosuppressants	30 (4.9)
Analgesics	30 (4.9)
Opioids	*23*
Psychoanaleptics	25 (4.1)
Corticosteroids for systemic use	23 (3.8)
Antiacids	18 (3.0)

3.4 | Noncompliance for drugs involved and ADR preventability

Among the 248 (80.2%) patients admitted to hospital with an ADR and whose drug use patterns could be assessed, 43 ADR-HAs (17.3%) were considered related to noncompliance to the French SPCs, package leaflets or other therapeutic guidelines (Tables 4 and 5). Absolute noncompliance (62.8%, $n = 27$) was the most frequent category. These noncompliance situations principally concerned older patients (median: 76 years), without predominance of sex (45% men, 55% women).

ADR-HAs were considered as preventable in 16.1% ($n = 40$) of the cases. The main situations were failure to comply with a dose or duration of use (27.9%), or a warning (23.2%), or a precaution of use (18.6%) of the drugs involved in the ADRs. None of the cases was related to a contraindication. In 11.6% of the cases of noncompliance conditions, inappropriate self-medication and misuse by the patient were involved. The main situations occurred with highly often prescribed therapeutic classes (psychotropic drugs, antihypertensives, antidiabetics, antithrombotics; Table 5).

4 | DISCUSSION

We found in this new national pharmacovigilance prospective study that ADR-HA incidence was estimated at 8.5% in France. ADRs were considered preventable in 16.1% of cases because the drugs involved were not used in accordance with monographies, package leaflets or other therapeutic guidelines. In the most recent literature review (2019), the incidence of drug related problems causing HA varied from 1.3 to 41.3% with an average rate of 15.4%.[13] Drug-related problems are defined as events or circumstances that involve a patient's drug treatment, encompassing ADRs, inappropriate drug selection, untreated indication, drug interactions, inappropriate dosage, drug use without indication and noncompliance. Only 7 studies have assessed admissions due to ADRs. In studies only centred on ADRs, the incidence of ADR-HA ranged from 1.3 to 3.3%. Since 2019, no relevant study with our purpose has been published. As in our study, antithrombotic drugs, analgesics, antidiabetics, antipsychotics and antineoplastic drugs were the most commonly reported drug classes causing HAs. The average rate of preventable drug-related problems was estimated at 1/3 of HAs, higher than that found in our study, but with the limit of no specific focus on preventable ADR and a wide variety of assessment methodologies.

More than 10 years after the last national study (EMIR study), we observed that ADR-HA incidence has dramatically increased in France from 3.6% in 2007 to 8.5% in 2018 (+136%). This ADR-HA increase concerns all age classes, increasing from 1.3 to 3.3% for children (≤16 y) and from 4.9 to 10.6% for older adults (≥65 y) between 2007 and 2018.[7] The volume of drug use cannot be an explanatory factor, because a modest decrease (minus 4%) in this volume was observed between the 2 periods in France. An ADR-HA increase trend has also

TABLE 4 Conditions of noncompliance to the French summary of product characteristics, package leaflets or other therapeutic guidelines for drugs involved in hospital admissions related to adverse drug reactions (ADRs) and preventability ($n = 43$)

Conditions	Number of cases (%)	Cases with a noncompliance condition considered such as ADR risk factor	Preventability	
			Partially	Totally
Absolute noncompliance	**27 (62.8%)**	**24**		
Indication off-label use	*5 (11.7%)*	*2*	*2*	*0*
Contraindication	*0 (0.0%)*	*0*	*0*	*0*
Warning not respected	*10 (23.2%)*	*10*	*5*	*5*
Dose/duration not respected	*12 (27.9%)*	*12*	*9*	*3*
Relative noncompliance	**8 (18.6%)**	**8**		
Precaution of use not respected	*8 (18.6%)*	*8*	*7*	*1*
Medication error	**3 (6.9%)**	**3**	3	
Other situations related to patient	**5 (11.6%)**	**5**	2	3
Inappropriate self-medication	*2 (4.6%)*	*2*		
Misuse	*3 (7.0%)*	*3*		
Total	**43 (100.0%)**	**40**	28	12

TABLE 5 Main conditions of noncompliance

Conditions of noncompliance	
Absolute noncompliance	
Warning	Association of psycholeptics of the same pharmacological action (benzodiazepines essentially) Continuation of drug after the occurrence of ADR (ex: lamotrigine/cutaneous rash; amiodarone/dysthyroidism)
Dose/duration not respected	Psycholeptics essentially (benzodiazepines and cyamemazine)
Relative noncompliance	
Precaution of use	Association ≥4 antihypertensive drugs (inappropriate prescription in older adults) Association oral anticoagulants and drugs with serotoninergic proprieties (tramadol, serotonine reuptake inhibitors)
Medication error	Confusion of furosemide dose (low/high)
Other situations related to patients	
Inappropriate self-medications	Nonsteroidal anti-inflammatory drugs
Misuse	Antidiabetics (insulin)

been reported in other countries. In England, a study showed a 76.8% ADR-HA increase between 1999 and 2009.[14] In Australia, between 2001 and 2014, the proportion of ADR-HAs adjusted for age nearly doubled, increasing annually by 5.8%.[15] As in our study, this trend was particularly significant in older adults, who accounted for the majority of hospitalisations. Beijer et al. also showed that ADR-related hospitalisations were twice as frequent in older adults as in younger people.[16] In a literature review investigating the influence of age groups on the rate of ADR-HA, median ADR admissions were 4.1% (IQR: 0.16–5.3%) for children and 10.7% (IQR: 9.6–13.3%) for older patients.[17] This definitely confirms that old age is a factor of vulnerability for developing more serious ADRs leading to hospitalisation.

As previously found, haemorrhagic events remain the first reason for HA, although the rate has decreased between the 2 periods in France (15.5% in 2007 *vs*. 8.8% in 2018)[7] (Appendix A). Antithrombotics still remain frequently involved (Appendix B). Contrary to the EMIR study, where vitamin K antagonists (VKAs) were the most frequently observed, in our study antiplatelet agents were the most frequent, ahead of VKAs and DOACs. We also observed that VKAs and DOACs (marketed since 2009) were equally involved in ADR-HAs. DOACs have gradually taken their place in the therapeutic arsenal with, now, an almost equal share of these 2 classes of anticoagulants. In France, antiplatelet agents are mostly prescribed by general practitioners in patients over 75 years with atrial fibrillation, because of the fear of bleeding on oral anticoagulants.[18] Indeed, a study based on the French Health Insurance on a population starting antiplatelet or oral anticoagulant therapy between 2013 and 2015 showed that the incidence of major gastrointestinal bleeding and other locations was 0.36% with antiplatelet agents *vs*. 1.2% with oral anticoagulants.[19,20] In our study, antineoplastics agents were the most frequently involved among pharmaco-therapeutic classes, targeted therapies (monoclonal antibodies, tyrosine kinase inhibitors) accounting for 1/4 of antineoplastic ADR-HA cases. The new antidiabetic drugs (incretin-based drugs) were also found in ADR-HAs, behind insulin and metformin. These drugs were scarcely on the market 10 years ago. Contrary to the results of the previous study in 2007, we observed that opioids (**morphine**, **oxycodone**, **codeine**, **tramadol** and **fentanyl**) played an important role in ADR-HAs. This result is in line with the conclusions of the French Medicine Agency report on the consumption of opioid analgesics in France,[21] which showed that the number of hospitalisations related to the consumption of opioid analgesics obtained on medical prescription increased by 167% between 2000 and 2017, from 15 to 40 hospitalisations per million inhabitants. The number of

deaths related to opioid use had also increased by 146%, between 2000 and 2015, with at least 4 deaths per week. If pain management with these analgesics has significantly progressed, it still remains a delicate situation.

The mortality related to ADR-HAs seems to slightly increase during the last years (1.03% in 2007 *vs.* 1.3% in 2018).[7] Angamo et al. estimated a 1.7% (IQR: 0.7–4.8%) median rate of death from ADR-HAs in developed countries.[3] In a more recent literature review, this estimated rate was 2.7%, including studies measuring admission to emergency departments and hospital wards.[13] Intracranial haemorrhage, renal failure and gastrointestinal bleeding were the cause of death in >50% of fatal cases, involving VKA and the renin–angiotensin system drugs.[5] In our study, similar fatal ADRs occurred and involved older patients: 1 case of intracranial haemorrhage under anticoagulant therapy and 2 cases of renal failure following diarrhoea secondary to *C. difficile* infection after antibiotic treatment; the 3 cases were considered as unpreventable. However, in the fatal case of acute renal failure with lactic acidosis after nonsteroidal anti-inflammatory drug introduction in a patient treated with **angiotensin 2 receptor blocker**, diuretic and metformin, the ADR-HA and its complications were considered partially preventable.

Our study shows that 16.1% of ADR-HAs could have been prevented if the prescription and the use had been in accordance with SPCs, package leaflets or therapeutic guidelines. Noncompliance with recommended doses and durations, warnings, and precautions for use were the most frequent situations. Our results are difficult to compare with those from the literature because preventability is often approached from the point of view of medication errors, and less often in relation to recommendations for the good use of medications. In a meta-analysis (involving 22 studies) on preventable ADR-HAs, the observed rate widely ranged from 4.2 to 83.3% (mean 45.11% (95% CI: 3.06–57.15; $I^2 = 99\%$).[5] Such range can be explained by the study population (older adults mostly studied compared to children), the definition of the ADRs (event *vs.* effect, application or not of causality assessment method, preventability assessment tool). It is difficult to compare our results with those from the EMIR study, as the estimating methods were different. ADRs may be classified as preventable if the use of a drug does not comply with the SPC, or if there is an alternative therapy, on the basis of the most favourable benefit/risk ratio. This aspect can only be analysed by detailed discussion with the prescriber, the pharmacist or the patients themselves. The EMIR study used this approach.[7] The other possibility is to consider preventability only with the known prescription conditions and to compare with the SPC, leaflets and other guidelines. This approach, which is not dependent on the prescriber advice and experience, is the 1 validated and proposed by Jonville-Bera and used in our study.[11] Therefore, even if we must stay cautious in estimating the proportion of avoidable ADRs, our results shed new and interesting light on preventability in relation to the data available for prescribers (SPC and therapeutic guidelines) and from patients (package leaflets). The analysis of noncompliance situations confirms the involvement of the most prescribed drug classes (antidiabetic, antihypertensive and psycholeptic drugs) and especially the risk of drug duplication in the same pharmacotherapeutic class for the same indication, particularly in older adults.[22,23] Inappropriate self-medication and misuse by patients were also related to ADR-HAs. A French study in emergency departments in 2010 already underlined the place of self-medication, including drug self-discontinuation, in the occurrence of ADR-HAs leading to an emergency ward; analgesics, psycholeptics and antithrombotics were most often involved, whether prescribed or not.[24] In a recent study based on spontaneous reports from the French Pharmacovigilance Database (1985–2018), ADRs related to a drug–drug interaction in a self-medication context mostly involved analgesics, anti-inflammatory drugs, dietary supplements and antibiotics. Haemostasis disorders and renal failure were the most frequently reported ADRs. The authors emphasized their concern about the lack of information provided in the package leaflets.[25] All these data together remind us of the importance of compliance with the SPC and therapeutic guidelines by health professionals. Furthermore, patient education and awareness, as well as informative package leaflets, are essential.

The main strength of the study is the systematic collection of ADRs over a defined period of time by a clinical pharmacologist specialized in pharmacovigilance so as to avoid reporting bias and to approach exhaustiveness of case detection. This method also allows methodological rigor in the case validation and evaluation of ADR preventability by an independent committee. The number of cases ($n = 309$) collected and validated by the ADR validation committee was higher than expected during the study period. Our results, however, reflect only a part of the issue with drug-induced iatrogeny. Indeed, ADRs occurring at home, or leading to hospitalisation in a surgical sector, in a private health institution, or leading to death outside hospitalisation, or lasting >1 month after the onset of the effect were not included, thus still leading to an underestimation of the incidence rate of ADR-related hospitalisations in France. Finally, this study allows to approach the incidence of ADRs occurring in an ambulatory setting and leading to hospitalisation, a real concern in terms of human, medical and financial consequences. In 2018, there were 610 000 deaths in France.[26] Therefore, fatal ADR-HAs represented 0.46% of causes of death. In comparison, cancers and cardiovascular diseases accounted for 29% (168 000 deaths) and 24% (140 500 deaths) of causes of death, respectively.[26] Although the burden of fatal ADR-HA is low in causes of death, it weighs heavily on the hospital costs induced. Recently, based on pharmacovigilance cases reported in France, the economic burden of ADRs requiring HA or an emergency department visit could amount to at least 420 million euros per year in France (considering underreporting value of 90%).[27]

5 | CONCLUSION

More than 10 years after the last national study, ADR-HA incidence has more than doubled and is around 8.5% of hospitalisations in public hospitals in France. This burden remains correlated with patient age, particularly in the older population. New drugs such as targeted therapies, direct oral anticoagulants, incretin-based drugs are a significant source of ADR-HAs. In 16.1% of cases, ADRs were considered

preventable. These elements should lead to in-depth thought on preventive actions towards at-risk drug classes and actions to improve the appropriate use of drugs.

ACKNOWLEDGEMENTS

The authors thank the hospitals and physicians who participated in this study as well as the investigators of RPVCs, the ADR Review Committee, the University Hospital of Limoges and the ANSM (Agence Nationale de Sécurité du Médicament et des produits de santé).

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COMPETING INTEREST

The authors declare no conflict of interest.

CONTRIBUTORS

M.L.L., S.G., E.P.R., M.B.G., L.C., B.L.V., J.L.F., N.P., L.L., A.P.J.B. and A.G. contributed to the conception and design. M.L.L. contributed to the analysis. M.L.L., S.G., E.P.R., M.B.G., B.L.V., L.L., A.P.J.B. and A.G. contributed to the data interpretation. M.L.L. drafted the article. All authors reviewed the text and approved the final version.

DATA AVAILABILITY STATEMENT

The data used in this article cannot be shared publicly due to ethical/privacy reasons.

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How to cite this article: Laroche M-L, Gautier S, Polard E, et al. Incidence and preventability of hospital admissions for adverse drug reactions in France: A prospective observational study (IATROSTAT). *Br J Clin Pharmacol*. 2023;89(1):390-400. doi:10.1111/bcp.15510

APPENDIX A

Comparison of adverse drug reactions leading to hospitalisation in France between the EMIR study (2007) and the IATROSTAT study (2018)

Adverse drug reactions (Medical Dictionary for Regulatory Activities; level system organ classes)	% of patients IATROSTAT	% of patients EMIR
Gastrointestinal disorders	17.2	9.3
Blood and lymphatic system disorders	12.3	8.2
Renal and urinary disorders	11.3	5.2
Metabolism and nutrition disorders	10.0	6.2
Infections and infestations	8.7	2.1
Nervous system disorders	8.4	11.3
Injury, poisoning and procedural complications	7.8	4.1
General disorders and administration site conditions	6.5	9.3
Skin and subcutaneous tissue disorders	6.1	5.2
Vascular disorders	6.1	20.6
Cardiac disorders	3.9	3.1
Respiratory, thoracic and mediastinal disorders	3.9	3.1
Psychiatric disorders	3.2	8.2
Hepatobiliary disorders	2.9	1.0
Endocrine disorders	1.6	1.0
Investigations	1.3	2.1
Others	3.7	0.0

APPENDIX B

Comparison of drugs involved in hospital admissions related to adverse drug reactions in France between the EMIR study (2007) and the IATROSTAT study (2018)

Pharmacological classes (ATC, level 3)	*n* (%) IATROSTAT	*n* (%) EMIR
L01- Antineoplastics	92 (15.1)	21 (12.6)
B01- Antithrombotics	71 (11.6)	21 (12.6)
N05- Psycholeptics	54 (8.9)	11 (6.6)
C03- diuretics	41 (6.7)	15 (9.0)
C09- agents acting on renin–angiotensin system	41 (6.7)	9 (5.4)
A10- antidiabetics	30 (4.9)	4 (2.4)
J01- Antibacterials for systemic use	30 (4.9)	7 (4.2)
L04- Immunosuppressants	30 (4.9)	5 (3.0)
N02- analgesics	30 (4.9)	15 (9.0)
N06- Psychoanaleptics	25 (4.1)	7 (4.2)
H02- corticosteroids for systemic use	23 (3.8)	2 (1.2)
A02- Antiacids	18 (3.0)	3 (1.8)
C01- cardiac therapy	15 (2.5)	4 (2.4)
C07- β-blocking drugs	15 (2.5)	3 (1.8)
C08- calcium channel blockers	14 (2.3)	4 (2.4)
M01- anti-inflammatory and antirheumatic drugs	11 (1.8)	5 (3.0)
J05- antivirals for systemic use	8 (1.3)	0 (0.0)
N04- anti-Parkinson drugs	8 (1.3)	1 (0.6)
N03- Antiepileptics	7 (1.1)	7 (4.2)
Others	47 (7.7)	23 (13.8)
TOTAL	610	167

ATC, Anatomical Therapeutic Chemical.