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ORIGINAL ARTICLE

Adverse drug reaction related to drug shortage: A retrospective study on the French National Pharmacovigilance Database

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Aim: Drug shortages are a growing global health issue. The aim of the study was to evaluate the consequences of drug shortages on patient safety based on data recorded in the French National Pharmacovigilance Database.

Methods: All cases involving drug shortages reported from 1985 to the end of 2019 were extracted from the database.

Results: Following the selection process, 462 cases were included. The number of cases increased significantly from 2004 to 2019. Cases mainly involved drugs from the nervous system (22.1%, 95% confidence interval [CI] 17.5–27.0%), the cardiovascular system (16.4%, 95% CI 11.9–21.4%) and anti-infectives for systemic use (14.3%, 95% CI 9.7–19.2%) ATC classes. Most of the cases reported an adverse drug

The authors confirm that the principal investigator for this study is Prof. Marie Briet.

reaction (ADR) belonging to the SOC nervous system (21%, 95% CI 18–24%), skin and subcutaneous (14%, 95% CI 11–17%), general (13%, 95% CI 10–17%) and gastrointestinal (8%, 95% CI 5–11%) disorders. Disease worsening was observed in 15.9% of the cases, mostly related to a lack of efficacy of the replacement drug. Half of the cases were considered as serious. Evolution was favourable in 79.4% of the cases. Death and/or life-threatening situations were reported in 5.8% of the cases. Medication errors (MEs) were identified in 51 cases (11%), mostly occurring at the administration step and involving a human factor.

Conclusion: This study emphasizes the clinical impact of drug shortage in terms of ADRs, ME and inefficiency. These observations underline the importance of a global health policy programme to limit the occurrence of drug shortages and to reinforce the information provided to patients and health care professionals in this context to limit risk.

KEYWORDS
adverse drug reaction, drug shortage, medication error, pharmacovigilance

1 | INTRODUCTION

Drug shortages are a recurrent public health issue that affects all health care organizations worldwide. The first reports were published in the early 1970s.[1] Drug shortage became a daily concern for health care professionals and national and international health authorities in the 2000s and has been a growing issue ever since. Many factors are involved in this phenomenon including the growing dependence on raw ingredients manufactured abroad, the issue of low-profit drugs in business strategy, the increased regulatory requirements and quality controls that rule out more and more drugs during production circuits and increasing demand.[2]

Communications about drug shortages are usually associated with position statements from health organizations that recommend identifying therapeutic alternatives or establish rules for patient prioritization. Drug shortage increases the demands on health care staff, as extra time must be spent prescribing and dispensing drugs as a result.[3] For patients, drug shortage usually leads to changes in medications and/or involuntary discontinuation that may compromise their safety due to a lack of efficacy or the occurrence of a medication error and/or an adverse drug reaction (ADR). In the literature, cases of ADRs and medication errors have been reported in the context of drug shortage involving anti-cancer drugs,[4,5] anaesthetic products[6–8] and anti-infective drugs.[9]

The present study aimed to provide an overview of ADRs, medication errors and inefficiency occurring in the context of drug shortage based on the reports collected in the French National Pharmacovigilance Database.

What is already known about this subject

- Drug shortage is a growing global health issue.
- Drug shortage usually leads to changes in medications and/or involuntary discontinuation that can compromise patient safety.
- The aim of this study was to evaluate patient safety in the context of drug shortages based on pharmacovigilance data.

What this study adds

- The number of pharmacovigilance notifications related to drug shortages increased over time and significantly faster than the total number of notifications in the French pharmacovigilance database.
- Almost all pharmacological classes were involved. Half of the cases were considered as serious.
- Drug replacement resulted in medication errors in 11% of the cases, which were mainly represented by dosage errors.

2 | METHODS

2.1 | Data source

This study was conducted on the French PharmacoVigilance Database (FPVB). The FPVB centralized reports of suspected ADR notified to the 31 regional pharmacovigilance centres in France. ADR cases are reported by health care professionals and patients to these centres. ADR reports are documented and analysed by pharmacovigilance professionals to evaluate drug accountability and then entered in the FPVB. Data recorded include patient characteristics, medical history, time to onset, drugs taken by the patients and adverse effects recorded using the Medical Dictionary for Regulatory Activities

(MedDRA®) classification. At the time of data extraction, 801 373 reports of suspected ADRs had been submitted to the FPVB.

2.2 | Data selection and analysis

The first step in selecting ADR reports used the following terms as inclusion criteria: *stock* (stock), *penurie* (shortage), *approvisionnement* (supply) and *retrait lot* (batch withdrawal) in the commentary from 1985 to 31 December 2019. The medical and pharmacological comments of the selected reports were reviewed by a pharmacovigilance expert to select only reports related to ADRs, inefficiency or medication errors in the context of drug shortage.

The following data were selected for all cases: age, sex, shortage drugs, drug start date, drug indication, replacement drug, ADR, report date and ADR date, expectedness, seriousness, ADR evolution and medication error. Time to onset of suspected ADR was calculated using drug start date and first date of reported ADR. The expected nature of the adverse effect was indicated when the adverse effect was written in the summary of product characteristics (SmPC) of the suspected drug. Drugs were classified following the Anatomical Therapeutic Chemical (ATC) classification in which the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

Descriptive analysis was performed. Numbers and percentages were calculated for qualitative variables. We determined the percentages and their confidence intervals using the exact Clopper–Pearson method for a binomial proportion with the R package PropCIs and the Sison-Glaz method for a multinomial proportion with the R package DescTools (R Studio® version 1.3.1093 for Windows®, version R 4.0.3). The mean and standard deviation or median and range were calculated for quantitative variables. To investigate whether the increase in drug shortage-related cases is linked to the increase of FPVB cases, a two-tailed Mann–Kendall trend test was applied to the rate of drug shortage-related cases per 10 000 cases in the FPVB. This test was performed for the 2004–2019 period on data with more than five drug shortage-related cases a year.

3 | RESULTS

3.1 | Description of the cases studied

A total of 1895 cases were identified following the first selection step using predefined keywords. After exclusion of 243 cases from pharmaceutical laboratories, 34 duplicate cases and 1156 cases where the situations described did not correspond to a drug shortage, 462 cases reporting 726 ADRs were included in the study (Figure S1). The first case was reported in 1995. The number of reported cases increased over time, particularly from 2010 to 2019. The highest number of cases was reported in 2019 (Figure 1A). Between 2004 and 2019, the increase in drug shortage-related cases was greater than the increase in FPVB total cases (two-tailed Mann–Kendall trend test; $P = .006$; Figure 1B).

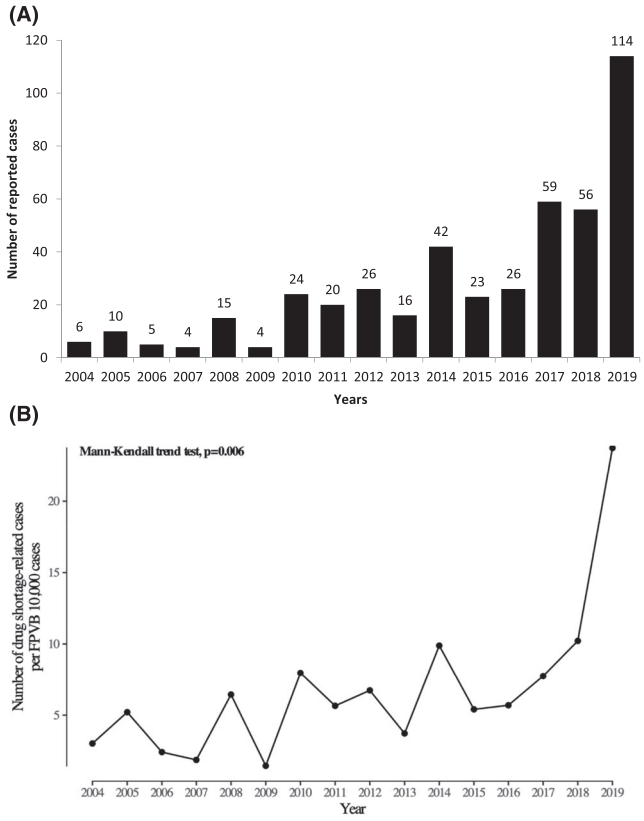


FIGURE 1 Increased number of notifications related to drug shortage in the French National Pharmacovigilance Database since 2004 (first year with more than five cases per year). (A) Number of reported drug shortage-related cases from 2004 to 2019. (B) Number of reported drug shortage-related cases per French Pharmacovigilance Database 10 000 cases from 2004 to 2019

The large majority of the reports were provided by health care professionals (92.2%). The cases mostly involved adult patients with a median age of 61 years and a marginal majority of women (51.5%). Drugs in shortage were replaced in almost all cases (95.7%), mainly by a drug from the same ATC class (93.0%). A different active principle between the drug in shortage and the replacement drug was found in 41.2% of the cases (Table 1). Most of the cases were related to ADRs (84.0%), 28.3% of which were unexpected according to the SmPCs. The majority of the reported ADRs were related to the replacement drug (86.4%). Disease worsening was observed in 15.9% of the cases, which was mostly due to a lack of efficacy of the replacement drug. The outcome was reported as recovered in 79.4% of the cases. Serious ADRs were observed in 46% of the cases. The reported ADRs belonged mainly to the MedDRA System Organ Classes (SOC) 'nervous system disorders' (21%, 95% CI 18–24%), 'skin and subcutaneous disorders' (14%, 95% CI 11–17%), 'general disorders and administration site conditions' (13%, 95% CI 10–17%) and 'gastrointestinal disorders' (8%, 95% CI 5–11%) (Figure 2).

TABLE 1 Characteristics of cases of adverse drug reactions occurring in a context of drug shortage, 1985–2019, French National Pharmacovigilance Database (462 cases, 726 adverse reactions)

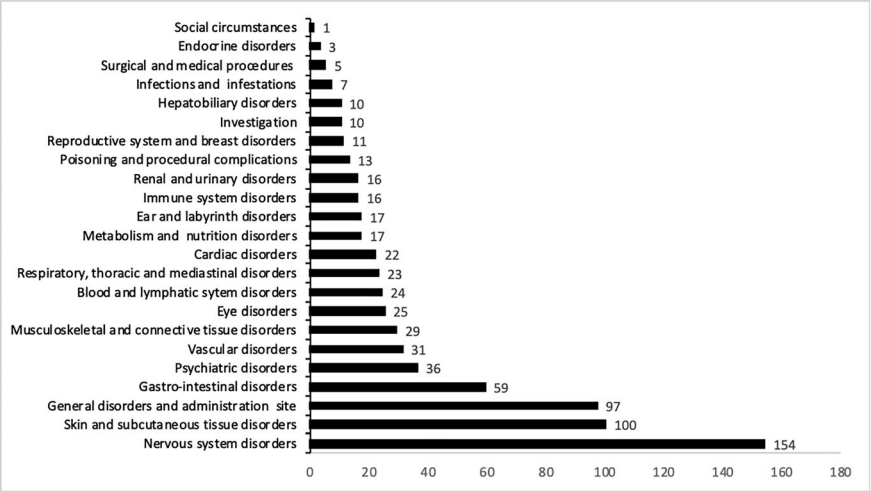
Parameters	*n*	%	CI_{low}	CI_{high}
Median age in years (min–max)	61 (0.04–95)			
Child (0–15)	34	7.3	2.6	12.2
Adult (16–64)	224	48.5	43.7	53.3
Older adult (>65)	194	42.0	37.2	46.8
Unknown	10	2.2	0.0	7.0
Sex (*n*, %)				
Male	221	47.8	43.3	52.7
Female	238	51.5	47.0	56.4
Unknown	3	0.7	0.0	5.6
Reporter qualification (*n*, %)				
Health care professional	426	92.2	89.4	94.4
Patient	36	7.8	5.5	10.6
Community vs. hospital reporter (*n*, %)				
Hospital	291	63.0	58.4	67.4
Outpatient	171	37.0	32.6	41.2
Type of case (*n*, %)				
Adverse drug reaction	388	84	80.9	87.2
Medication error without adverse drug reaction	10	2.16%	0.0	5.3
Medication error with adverse drug reaction	41	8.9	5.8	12.1
Withdrawal	10	2.16	0.0	5.3
Overdose	5	1.08	0.0	4.3
Interaction	6	1.3	0.0	4.5
Others	2	0.4	0.0	3.6
Seriousness (*n*, %)	214	46.3	41.7	51.0
Hospitalization or prolongation of hospitalization	97	21.0	16.5	25.8
Medically significant situation	90	19.5	14.9	24.3
Life-threatening situation	18	3.9	0.0	8.7
Death	9	1.9	0.0	6.8
Outcome of the cases (*n*, %)				
Recovered	367	79.4	76.0	83.0
Recovered with sequelae	2	0.4	0.0	4.0
Death	9	1.9	0.0	5.5
Not recovered/unresolved	54	11.7	8.2	15.2
Unknown	30	6.5	3.0	10.0
Expected/unexpected nature of adverse drug reaction (*n*, %)				
Expected	320	69.3	65.1	73.6
Unexpected	129	28.3	23.8	32.3
Not applicable	13	2.4	0.0	7.2
Worsening of the disease (*n*, %)	69	15.9	11.8	18.5
Due to the inefficiency of the replacement drug	58	12.6	9.5	15.7
Due to the absence of replacement drug	11	2.4	0.0	5.5
No impact	393	85.1	82.0	88.2
Medication error (*n*, %)	51	11.0	8.3	14.3
Drug replacement				
Replacement of the drug in shortage (*n*, %)	**442**	95.7	93.4	97.3

TABLE 1 (Continued)

Parameters	*n*	%	CI_{low}	CI_{high}
ATC classes of the replacement drug				
Same as the drug in shortage	411	93.0[a]	90.2	95.2
Same active principle	229	51.8[a]	47.0	56.8
Different active principle	182	41.2[a]	36.4	46.2
Different than the drug in shortage	31	7.0[a]	4.8	9.8
Ineffectiveness of the replacement drug[b] (*n*, %)	67	15.2[a]	11.9	18.8
ADR related to the replacement drug (*n*, %)	382	86.4[a]	82.9	89.5

Abbreviations: ADR, adverse drug reaction; ATC, anatomical therapeutic chemical; CI, 95% confidence interval.
[a]Percentages were calculated based on a total of 442 cases in which the drugs in shortage were replaced.
[b]Cases with or without disease aggravation.

FIGURE 2 Number of reported cases according to the System Organ Class



3.2 | Medication errors in the context of drug shortage

Medication errors occurring in a context of drug shortage were reported in 51 cases (Tables 2 and S1). The majority of the medication errors occurred at the drug administration step (67%) and mostly involved dosing errors. Human factors were the main reported cause of the error (88%). Packaging or design problems were involved in 22% of the medication error cases (Table 2). Table S2 shows the drugs in shortage and replacement drugs involved as well as the step, nature, cause of medication error and seriousness.

The drug in shortage was replaced in all cases. In a large majority of the cases (94%), this was replaced by a drug from the same class and by one with the same active principle in 66% of the cases. Medication errors were associated with the occurrence of an ADR in 80.4% of the cases, half of which were considered as serious. The outcome was favourable in 68.6% of the cases. Life-threatening situations were reported in three cases (6.0%) and fatal outcome in four cases (7.8%) of the medication error cases (Table S1).

3.3 | Description of the drug shortage cases

The drugs in shortage reported in the 462 cases are presented in Table S3 and Figure 3. The ATC classes that were most highly represented were the nervous system ($n = 102$, 22.1%, 95% CI 17.5–27.0%) mainly represented by antiepileptics ($n = 49$, 48.0%, 95% CI 38.0–58.1%), the cardiovascular system ($n = 76$, 16.4%, 95% CI 11.9–21.4%) mainly represented by agents acting on the renin angiotensin system ($n = 32$, 42.1%, 95% CI 30.9–54.0%) and anti-infectives for systemic use ($n = 66$, 14.3%, 95% CI 9.7–19.2%) mainly represented by immune sera and immunoglobulins ($n = 32$, 48.5%, 95% CI 36.0–61.1%).

Table S4 describes the drug classes (selected using ATC classification level 3) involved in more than 15 cases and the related ADRs.

Forty-nine cases involved antiepileptics, mainly valproic acid and its derivatives and phenytoin. Toxicity of the replacement drug was observed in 59% of the cases, mainly represented by neurological disorders. Inefficiency of the replacement drug was observed in one third of these cases.

TABLE 2 Step, nature and cause of medication error occurring in the context of drug shortage, 1985–2019, French National Pharmacovigilance Database ($n = 51$)

Parameters	*n*	%
Medication error step		
Administration	34	66.7
Dispensation	7	13.7
Preparation	6	11.8
Prescription	4	7.8
Nature of the medication error[a]		
Dose error	29	56.8
Drug error	9	17.6
Administration time error	5	9.8
Administration technique error	3	5.9
Error in the route of administration	3	5.9
Galenic form error	2	3.9
Therapeutic and clinical monitoring error	1	2.0
Expired, spoiled or poorly preserved medication	1	2.0
Cause of error[a]		
Human factors	45	88.2
Packaging or design problems	11	21.5
Labelling and/or information problems	7	13.7

[a]Several causes and natures of error are possible for one case.

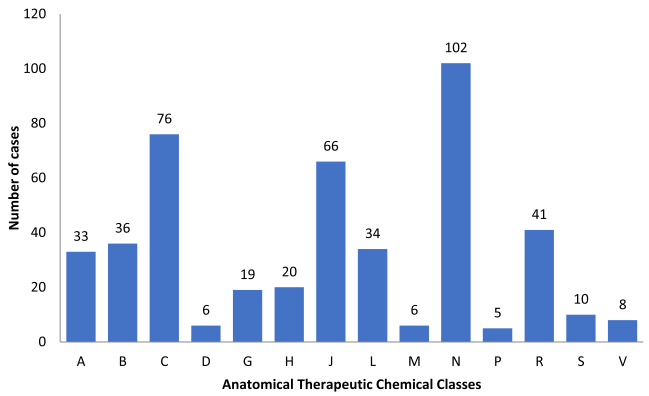


FIGURE 3 Numbers of drug shortage cases classified according to Anatomical Therapeutic Chemical classes (level 1), 1985–2019, French Pharmacovigilance database. A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular systems; D, dermatologicals; G, genito-urinary system and sex; H, systemic hormonal preparations, excl. sex hormones and insulins; J, anti-infectives for systemic use; L, antineoplastic agents; M, musculoskeletal system; N, nervous system; P, antiparasitic products, insecticides and repellents; R, respiratory system; S, sensory organs; V, various

Thirty-eight cases involved a shortage of antihistamines, largely represented by a shortage of intravenously administered dexchlorpheniramine ($n = 36$). In all cases except one, dexchlorpheniramine was replaced by promethazine, resulting in neurological disorders and anticholinergic syndrome. Inefficiency of the alternative drug was observed in two cases.

Twenty-six cases involved antithrombotic drugs with a majority of haemorrhagic or thrombotic disorders. Inefficiency of the replacement drug was reported in almost one third of the cases.

Thirty-two cases involved drugs acting on the renin-angiotensin system with a large majority of valsartan shortage cases ($n = 25$). Various reactions were reported including hypotension or hypertension, gastro-intestinal disorders such as lymphocytic colitis among others detailed in Table S4. Inefficiency of the replacement drug was reported in 22% of the cases.

Thirty-two cases involved immune sera or immunoglobulins and were mainly related to infusion reactions. Inefficiency of the replacement drug was reported in 16% of the cases.

Twenty-three cases involved a shortage of antineoplastic agents, of which four cases were fatal. No inefficiency was reported.

Eighteen cases involved an antibiotic shortage with a majority of cutaneous disorders. No inefficiency was reported.

Sixteen cases involved anti-Parkinson's drugs with an ADR due to the replacement drug in 75% of the cases and inefficiency in 25% of the cases.

3.4 | Death and life-threatening situation cases in the context of drug shortage

Nine deaths and 18 life-threatening situations were observed. In half of these cases, no other aetiology was reported.

Four cases of death were related to medication errors. Two deaths occurred in the context of lomustine shortage due to packaging differences between the drug in shortage (four tablets) and the replacement drug (20 tablets) resulting in lomustine overdosage. One death occurred in the context of scopolamine shortage resulting in scopolamine overdosage and one death occurred in the context of metformin shortage resulting in lactic acidosis. Toxicity of the replacement drug without medication error was involved in four cases with a fatal outcome. Nadolol ($n = 1$), carmustine ($n = 1$), paclitaxel ($n = 1$) and danaparoid ($n = 1$) shortages resulted in cardiac arrest, Lyell's syndrome, aplasia and haemorrhagic complications, respectively. Worsening of the disease in the context of levodopa and levodopa-benserazide shortage was observed in one case of death.

Among the 18 cases involving life-threatening situations, the link between drug shortage and the clinical presentation was considered as certain in eight cases: dexchlorpheniramine replaced by promethazine ($n = 2$), imiglucerase replaced by taliflucerase ($n = 1$), amoxicillin clavulanic acid replaced by vancomycin ($n = 1$), alimemazine replaced by oxazepam ($n = 1$), calcium chloride replaced by calcium gluconate ($n = 1$), danaparoid replaced by lepirudin ($n = 1$) and enoxaparin replaced by fondaparinux ($n = 1$). Three cases of life-threatening situations were related to a medication error in the context of a dexchlorpheniramine shortage, phenytoin shortage and metformin shortage. Disease worsening was observed in two cases related to adenosine and mexiletine shortages.

4 | DISCUSSION

This study emphasized the increasing issue of ADR in the context of drug shortage over time. A large number of drug classes were concerned. The number of cases related to drug shortage increased much faster over time than the total number of pharmacovigilance cases included in the FPVB. The consequences of the replacement of the drugs in shortage were mainly represented by ADR, medication errors with or without ADRs and drug inefficiency, with 6% of cases with fatal outcomes and life-threatening situations.

The increasing number of cases reported has to be put into perspective with the increasing number of drug shortages reported by the health authorities.[10] The French National Agency for the Safety of Medicines and Health Products (ANSM) reported 3530 pharmaceutical products in shortage between 2012 and 2018.[10] The number of reported shortages increased between 2012 ($n = 200$) and 2018 ($n = 917$) with a sharp rise in 2017 and 2018.[10] This evolution profile is close to the one observed in our study. The increasing number of drug shortages over time is also reported in many other countries. In a survey conducted by the European Association of Hospital Pharmacists (EAHP), 90% of the 1666 respondents within 38 countries claimed that shortage of medicines is a current problem in their institution.[11] This issue currently affects most countries worldwide, regardless of the country's income level.[2]

Most of the drug classes are represented in the included cases with a predominance of drugs for the nervous system, cardiovascular system and anti-infectives for systemic use. There are no discrepancies between the pharmacodynamic properties of the drugs classes predominately affected by drug shortage and the nature of suspected ADR reported. The distribution between ATC classes is similar to that identified in the ANSM report[10] but slightly different to reports from other countries. Indeed, a survey conducted by the EAHP in 2018 also highlighted the predominance of antimicrobial agents, followed by oncology medicines, vaccines, anaesthetics and cardiovascular medicines[12] in this context. Another survey conducted by the AHA (American Hospital Association) on 820 non-federal, short-term acute care hospitals also identified, in addition to anti-infective and cardiovascular drugs, drugs used for anaesthesia, emergency care, gastrointestinal nutrition and pain management.[13] Globally, essential medicine and emergency medicine appear to be more at risk of shortage than other medicines.[2,14]

There are numerous consequences of drug shortages. This study examined drug shortage based on the reports transmitted to the pharmacovigilance network. Eleven per cent of the included cases were related to a medication error. A drug shortage may lead to a replacement of the unavailable product by an alternative. However, this alternative may have different packaging, labelling, dosage and sometimes a different route of administration that may increase the risk of a medication error.[14] The medication errors reported here involved the administration step and were mainly related to human factors. In the literature, drug replacement in the context of drug shortage is widely identified as a risk factor of medication error.[2,14] In a survey conducted by the Institute for Safe Medication Practices in the United States, the authors considered that one in four actual errors and one in five reported adverse patient outcomes were due to drug shortage.[15] The 2018 EHAP survey reported that 25% of medication errors were a consequence of drug shortages. In terms of oncology drug shortages, a survey distributed to 1672 members of the Haematology/Oncology Pharmacy Association revealed that 16% of the participants reported changes in therapy in the context of drug shortage that led to near-miss errors and 6% to medication errors.[16]

The reported adverse effects in the context of drug shortage are mainly due to the replacement drug. The clinical consequences are serious and lead to life-threatening situations or fatal outcomes in 6% of the cases included. Among these cases, two were related to an overdosage due to a medication error in the context of a belustine shortage that led to a replacement with lomustine 40 mg. It is worth noting that antineoplastic drugs are particularly represented in fatal or life-threatening cases.

The main reported ADRs were related to nervous system disorders, which is in line with the number of cases involving nervous system drugs, with antiepileptic drugs being the most represented drugs. These drugs with a narrow therapeutic index have a high risk of toxicity or inefficiency in a context of drug replacement. Our study reported 18 cases related to phenytoin shortage. The drug was replaced by a formulation containing phenytoin sodium in 14 of these cases. The drug replacement resulted in seizure crises in ten cases dues to the lack of bioequivalence, the pharmacokinetic profile of phenytoin characterized by a non-linear elimination depending on the concentration and the narrow therapeutic index.[17] Prescribing promethazine as a replacement for dexchlorpheniramine or metoclopramide was also found in 34 cases. This resulted in the occurrence of an anticholinergic syndrome related to the pharmacodynamic properties of this drug: a neuroleptic antihistaminic H1 with a sedative, anticholinergic, peripheral alpha-blocking effect and antidopaminergic. Regarding the 18 cases involving antineoplastic drug shortage, without medication error, various specialities were involved, including mitomycin C, carmustine and caryolysin. Four cases were fatal in a context of aplasia. In the literature, the clinical impact of oncology drug shortages on patients has been poorly evaluated. In a survey, physicians reported a 35% increased risk of the alternative therapy.[18]

Drug replacement in the context of drug shortage may also have consequences in terms of efficacy, as reported in the present study. In the 67 cases affected by inefficiency, the most commonly involved drugs were antithrombotic agents, agents acting on the renin-angiotensin system and antiepileptics. The reported ADRs were directly related to the pharmacodynamic action of the drugs, such as thrombotic events, hypertension and seizures. Inefficiency is poorly identified by the pharmacovigilance system, as its main purpose is to collect data on ADRs.

In the literature, some published data suggest that drug shortage may impact patient's prognosis in terms of efficacy. A delay in the induction therapy of acute myeloid leukaemia has been reported in the context of cytarabine shortage.[19,20] A report from the Children's Oncology Group showed that asparaginase discontinuation in the context of toxicity was associated with inferior disease-free survival

in high-risk patients, thus suggesting similar consequences in the context of drug shortage.[21] For the treatment of bladder cancer, differences in efficacy were observed between two BCG strains in both a large retrospective study[22] and in a randomized trial. These findings may have clinical consequences in the context of BCG shortages.[23] Antiretroviral drug shortage leading to a therapy interruption has been associated with an accumulation of drug mutations and an increased risk of treatment failure.[9] A large retrospective study conducted in 26 US hospitals showed that mortality in patients admitted for septic shock was higher during the period of norepinephrine shortage.[24] Lastly, opioid shortage has been associated with a lower level of clinically improved pain in 386 patients treated for cancers.[25] All of these findings suggest that the consequences of drug shortage can affect both the efficacy and medication risk of ADRs.

The results of the study together with the published data raise the question of optimal drug replacement and the need for detailed information accompanying the replacement drug. In order to limit ADR and ME in the context of drug shortage, particular attention should be given to changes in packaging, dosage and drug interactions. The numerous ADRs identified in this study related to antiepileptic drugs highlight the precautions that should be taken with drugs with a narrow therapeutic index. Such precautions may include precise and comprehensive information provided to patients and healthcare professionals regarding dosage and surveillance. At the level of the health authorities, ensuring the availability of essential drugs is crucial and may require the publication of essential medicine lists. In addition, safety issues regarding replacement drugs should also be considered, particularly when the choice is limited.

4.1 | Strengths and limitations of this study

The French pharmacovigilance system involves a network of pharmacovigilance centres covering the French territory. The ADR notifications provided by healthcare professionals and patients are accurately analysed by pharmacovigilance experts, and medical information is carefully collected, leading to the creation of a high-quality dataset. However, the adverse effects related to drug shortages presented in this study are probably underestimated due to the under-reporting usually observed in pharmacovigilance (estimated to be close to 10%). In addition, drug inefficiency is poorly identified by the pharmacovigilance system whose main objective is to collect ADRs. Further cohort studies are necessary to evaluate this point accurately.

5 | CONCLUSION

With the limits of the pharmacovigilance data, which are based on the patients and health care professional reports, this study emphasizes the clinical impact of drug shortages in terms of ADRs, medication errors and inefficiency. Regarding drug shortage safety issues, both drug in shortage and the replacement drug have to be taken into consideration. These observations support the position statements from pharmacists and the health authorities about the need for health policy to limit the occurrence of drug shortages and to reinforce the information provided to patients and health care professionals in the context of drug shortage in order to limit the risk of medication errors.

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COMPETING INTERESTS

The authors declare no conflicts of interest.

CONTRIBUTORS

M.B., D.B.M., M.Ba., L.L. conceived the idea for the study. D.B.M., C.M., M.Ba., G.D., A.G., H.G., M.L.L. curated the data. A.S., M.C., F.S. conducted the statistical analysis. D.B.M. acquired the funding. M.B., D.B.M., F.S. were responsible for the methodology. D.B.M., M. Ba., A.G., F.S., A.F., C.D.C., T.P., G.D., H.G., M.L.L., L.L. provided the resources. M.B., D.B.M., C.M., A.G., F.S., M.L.L. wrote the original draft. D.B.M., M.B., A.S., M.C., A.F., C.D.C., T.P., G.D., H.G., L.L. reviewed and edited the original draft.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author. The request should be accompanied by a research protocol. The data are not publicly available due to European ethical and legal restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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