Hospital Registration of Adverse Drug Reactions in Electronic Health Records: Importance and Contribution to Pharmacovigilance

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Abstract

Background Although drugs have great therapeutic, preventive and diagnostic benefits, they also give rise to develop adverse drug reactions (ADRs) which considered to be one of the main causes of increased mortality and morbidity. However, they are vastly underreported. Information on systematically registered ADRs in hospitals will provide a large real world data source that can be used to ensure patients' safety.

Purpose To quantify the contribution of hospital registration of ADRs in electronic health records (EHR) to pharmacovigilance purposes.

Design An observational retrospective study using data from Jeroen Bosch Hospital in the Netherlands in 2019.

Methods Serious and previously unknown ADRs registered systematically in the corresponding fields of EHRs were assessed.

Results During the study period, 1010 patients were included. Patients aged on average 63 (±17.6) years and the majority was female (66.2%). In total, 1630 ADRs were registered. The most frequent ADRs were 'nausea' and 'vomiting' and the most involved therapeutic drug groups were opioids and NSAID's. Fifty eight serious ADRs (5.2%) were registered in which tubulointerstitial nephritis was the most frequent one and mainly associated with antibacterials for systemic use. A total of 264 previously unknown ADRs (16.2%) was registered in which 'malaise' was the most frequent unknown ADR and tramadol was the most involved drug. Additionally, 25 ADRs (1.5%) were registered that may be attributable to 10 drugs under additional monitoring.

Conclusion Hospital registration of ADRs in EHRs provides information on serious and unknown ADRs which are normally difficult to be assessed during clinical trials. Widespread use of ADR registration can have tremendous value for pharmacovigilance. However, several improvements are needed to optimize this registration.

Keywords

ADRs, electronic health records, serious ADRs, unknown ADRs, drugs under additional monitoring

Abbreviations

ADRs Adverse Drug Reactions; **SRS** Spontaneous Reporting System; **EHR** Electronic Health Record; **HIX** Healthcare Information eXchange; **JBZ** Jeroen Bosch Hospital; **MedDRA** Medical Dictionary for Regulatory Activities; **PT** preferred Term; **API** Active Pharmaceutical Ingredient; **ATC** Anatomical Therapeutic and Chemical; **GIPdatabank** Genees- en hulpmiddelen Informatie Project; **CIOMS** Council for International Organizations of Medical Sciences; **SmPC** Summary of Product Characteristics; **PIL** Patient Information Leaflet; **EMA** European Medicines Agency; **SD** Standard Deviation; **NSAID's** Non-Steroidal Anti-Inflammation Drugs; **TIN** Tubulo Interstitial Nephritis; **CBG** College ter Beoordeling van Geneesmiddelen (The Medicines Evaluation Board)

1 Introduction

Adverse drug reactions (ADRs) are defined as any harmful and unintended response to a drug which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function [1,2]. ADRs are considered globally as one of the main causes of increased mortality and morbidity. However, they are vastly underreported [1,3]. Because of their significance for patient care, drug safety research and post-marketing surveillance, several methods have been developed to report or register ADRs and thus to contribute to pharmacovigilance. One of these methods, which is considered as the most prominent contributor, is Spontaneous Reporting System (SRS). Spontaneous reporting system is defined as a system whereby case reports of adverse drug events or adverse drug reactions are voluntarily submitted by healthcare professionals, pharmaceutical companies or consumers to the national pharmacovigilance centre (e.g. Lareb). However, these systems are not part of care process and consequently underutilized by healthcare professionals. Fortunately, there are other sources with real world ADR information such as registered ADRs in electronic health records (EHR). These systems have advantages over SRS: (1) they are incorporated into electronic medical records which makes them easier to be used by healthcare professionals, (2) use pre-existing data to prevent duplication of documentation, and (3) produce alerts to promote safety. These advantages may overcome the limitations of SRS and provide us with a large real world data source that can be used for pharmacovigilance purposes. In addition, EHRs contain valuable information, such as clinical notes and results of laboratory tests, which ensure a better understanding of drug-ADR associations [3,4].

Since ADRs are sometimes the reason to visit a hospital or they are developed during hospitalization, hospitals provide a suitable environment for studying the value of systematically registration of ADRs and its contribution to pharmacovigilance. In the Netherlands, HIX is used in about 60% of the hospitals and it includes a field that is used to register ADRs in a systematic way. Although there are many studies on the potential of ADR registration in EHRs and it is marked as an emerging pharmacovigilance data source, there has been no assessment in the Netherlands on which ADRs are exactly captured in the ADR fields yet. Since clinical trials are not suitable for studying all types of ADRs such as rare ADRs, as well as ADRs that only developed after long use of the drug, information on ADRs from real world data will provide a valuable contribution to drug safety issues. In addition, real world data can provide us with information on drugs that are being monitored closely by regulatory authorities in the European Union because their clinical evidence base is less well developed. These drugs are referred to as being under additional monitoring [5]. This knowledge about ADRs will help overcome some barriers experienced by healthcare professionals toward systematically registration of ADRs by emphasizing the added value of this registration [6].

Aims of the study

The primary aim of this study is to assess to what extent systematically hospital registration of adverse drug reactions in electronic health records contributes to pharmacovigilance, based on information on serious and previously unknown adverse drug reactions. In addition, this study aims to assess the ADRs associated with drugs under additional monitoring. The results of this study will contribute to baseline information on hospital registration of ADRs and will provide insights that will add to better ADR registration and, thus, to better pharmacovigilance system.

2 Materials and methods

2.1 Data source

Our study is an observational retrospective study conducted using data from Jeroen Bosch Hospital (JBZ) in the Netherlands on patients admitted to or have visited the hospital in the period between 1 January 2019 and 31 December 2019. The dataset contains information on patients with registered adverse drug reactions in the EHRs of this hospital during the study period. These ADRs were registered by healthcare professionals working in the hospital. When registering the information, a healthcare professional can choose between two fields in the EHRs: allergy and ADR. In our study, we only assessed the filed with ADRs.

2.2 Study population

All patients with a registered ADR in the ADR fields of EHRs in HIX JBZ were eligible for this study. We excluded patients for whom no or unclear ADR is registered, patients for whom a contraindication is registered instead of an ADR, patients with adverse reactions to food or other substances and patients where no suspected drug or drug group is mentioned. We also excluded patients with ADRs to a therapeutic drug group, and not to a particular drug, because there was no clear drug-ADR association that can be assessed. Only medicines for human use were included in the study. The study population comprised the remaining patients with systematically registered drug-ADR associations in the corresponding fields of HIX.

2.3 Data collection

Demographic characteristics (age and gender) of included patients were collected. To assess the nature of drug-ADR associations, all included ADRs were coded by the Medical Dictionary for Regulatory Activities (MedDRA) and classified according to preferred term (PT) [7,8]. Ten percent of the cleaned dataset was first coded and cross checked by the first author RA and colleague RR. The matching rate was 98.05% and coding conventions were made to standardize the coding of the rest of the dataset.

In order to assess the drug-ADR associations, suspected active pharmaceutical ingredients (API) were classified according to the fifth level of the Anatomical Therapeutic and Chemical (ATC) classification and the third level for corresponding chemical, pharmacological or therapeutic drug group. Other levels of ATC classification were sometimes used to describe associations [9]. By APIs with more than one ATC code and when the registered information did not include any indication of the correct code or the name of product used by the patient, we have used the ATC code of the most dispensed medicinal form of these APIs in 2019, based on statistics of Healthcare Institute Netherlands, GIP databank (Medicines and resources Information Project) [10]. Information on diagnostic pattern (by healthcare professional in the hospital or previously diagnosed) was also collected. In principle, an ADR was considered to be diagnosed by a healthcare professional unless otherwise noted in the dataset.

2.4 Study outcomes

All included drug-ADR associations were assessed on nature to determine whether they were compatible with one or both of the following outcome groups: serious and previously unknown ADRs. We also assessed whether an ADR was associated with drugs under additional monitoring.

2.4.1 Serious ADRs

An ADR was considered serious if it resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, caused persistent or significant disability or incapacity, or a congenital anomaly/birth defect [2]. These are the criteria for serious ADRs according to the Council for International Organizations of Medical Sciences (CIOMS) [11]. In addition, we considered an ADR as serious if the healthcare professional had assessed it as ‘severe’.

2.4.2 Previously unknown ADRs

Previously unknown ADRs are those not listed in summary of product characteristics (SmPC) or in patient information leaflet (PIL) of corresponding drug [12].

2.4.3 ADRs associated with drugs under additional monitoring

We assessed ADRs associated with APIs of drugs under additional monitoring. These are new drugs which require close monitoring and are labelled with a black inverted triangle displayed in the SmPC and PIL [12]. These drugs are listed in the ‘list of medicines under additional monitoring’ which was published for the first time in April 2013 by The European Medicines Agency (EMA), and it is reviewed every month [5]. To insure a valid status of ‘Drug under additional monitoring’ during study period, we have used the last updated list removing any new drug listed after the study period, i.e. with inclusion date after 31 December 2019). SmPCs and PILs of corresponding products were used to determine whether an ADR is previously known or unknown ADR. When the SmPC of a particular drug indicated that the drug is under additional monitoring, without being listed in the list of EMA, we verified that the date of first authorization was before the end of study period

2.5 Data analysis

2.5.1 Baseline characteristics of patients and drug-ADR associations

Demographic characteristics, age and gender, of all included patients are described. Age was calculated by subtracting the date of birth from the date of registration of ADRs, and was presented as mean ± standard deviation (SD). If the patient had visited the hospital more than once, the first registration date was used to calculate the age. After that, patients were classified according to age into six groups, corresponding to the classification in GIP databank: 0-14 years, 15-24 years, 25-44 years, 45-64 years, 65-74 years and ≥ 75 years [9]. Gender was expressed as male and female. Frequencies with proportions of total of age groups and gender were calculated.
All included drug-ADR associations were analyzed and organized by PT to determine the top 10 ADRs. Involved drugs were classified according to third level of ATC classification and the top 10 involved therapeutic drug groups were determined.

2.5.2 Analysis of study outcomes

Frequency with proportion of total of serious and previously unknown ADRs were calculated. For each type of ADRs, the top five ADRs were presented and involved drugs were determined. All included drug-ADR associations are included in the annex.

A subgroup analysis was performed on ADRs associated with drugs under additional monitoring. Because the dataset did not contain information about the product name of the suspected API, APIs of the drugs found in the list of EMA were used for the analysis. ADRs associated with one of these APIs were compared with the SmPC and PIL of the corresponding product to check of they are known or unknown ADRs. ATC codes of these APIs were collected and compared with those used by determining the characteristics of involved drugs and therapeutic drug groups.

3 Results

3.1 Study population

A total of 1420 patients were eligible for this study. We have excluded 245 patients with incorrect, not relevant or incomplete information. We also excluded one patient with ADR to a drug for veterinary use and 164 patients with ADRs to a therapeutic drug group and not to a particular drug because there was no clear drug-ADR association that can be assessed using a particular SmPC.
The study population comprised the remaining 1010 patients with systematically registered drug-ADR associations in the corresponding fields of HIX, who have visited or were admitted to Jeroen Bosch Hospital during the period between 1 Jan 2019 and 31 Dec 2019. Figure 1 represents the process to obtain our study population.

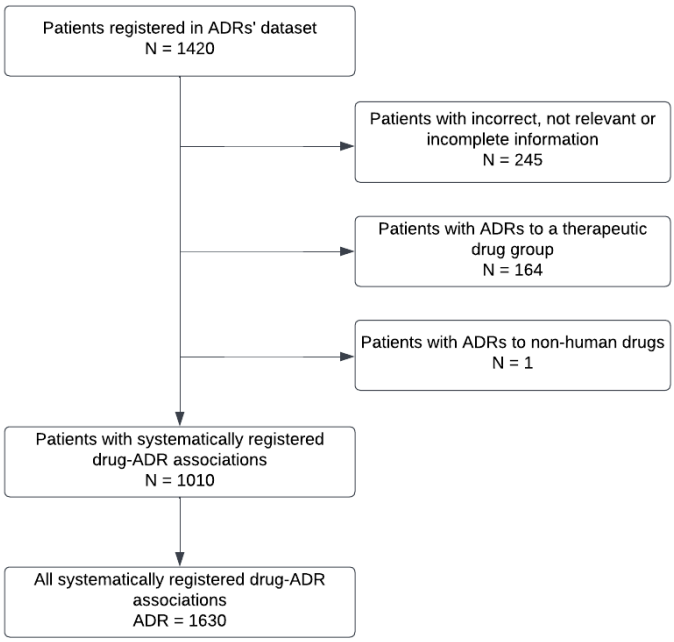


FIGURE 1: Study population flow diagram

3.2 Characteristics of patients and ADRs

A total of 1010 patients were included in the study. Table 1 shows the baseline characteristics of the included patients. Patients were on average 63 (±17.6) years old and the majority was female (66.2%). Age groups were made and further stratified by gender. Female patients were on average older than male (64; SD ±17 vs 61; SD ±17.6). More than three-quarters of both strata aged 45 years or over. A slightly percentage of patients (1.4%) was younger than 15 years old.

TABLE 1. Baseline characteristics of patients

Patients with registered drug-ADR associations N=1010			
Demographic characteristics			
	Total	**Female**	**Male**
Gender,			
N(%)	1010 (100)	669 (66.2)	341 (33.8)
Age, in years			
Mean (±SD)	63 (±17.6)	64 (±17.5)	61 (±17.6)
Patients in age groups, N(%)			
0-14	14 (1.4)	7 (1)	7 (2)
15-24	13 (1.3)	12 (1.8)	1 (0.3)
25-44	126 (12.5)	78 (11.7)	48 (14.1)
45-64	330 (32.7)	206 (30.8)	124 (36.4)
65-74	256 (25.3)	171 (25.6)	85 (24.9)
≥ 75	271 (26.8)	195 (29.1)	76 (22.3)

ADRs Adverse Drug Reactions; **SD** Standard Deviation; **N(%)** Frequency with proportion of total

A total of 1630 drug-ADR associations were registered for those 1010 patients. Table 2 describes the characteristics of the registered drug-ADR associations. These ADRs were mostly diagnosed by healthcare professionals in Jeroen Bosch Hospital (96.7%). The most frequently registered ADRs were of a gastrointestinal nature. 'Nausea' was the most common ADR (n = 168; 10.3%) and was mostly associated with opioids (37.5%) and NSAID's (23.8%) especially diclofenac. 'Vomiting' was the second most frequently registered ADR (n = 127; 7.8%) and was associated in 65.4% of the cases with opioids. 'Rash', the third most frequently registered ADR (n = 106; 6.5%), was associated in 63.2% of the cases with antibacterials for systemic use, especially amoxicillin. Eleven of all drug-ADR associations were 'drug intolerance'. ADRs that were registered among patients younger than 15 years old were mostly associated with beta-lactam antibacterials (ATC J01C: n = 9; 64.3%). The top 10 ADRs are described in table 2. These results are demonstrated in figures 2.

The therapeutic drug groups most frequently associated with ADRs were opioids (ATC N02A: n = 354; 21.7%) and NSAID's (ATC M01A: n = 266; 16.3%). Among opioids, morphine (ATC N02AA01: n = 122; 34.5%) was the most frequent involved drug, followed by oxycodone (ATC N02AA05: n = 106; 29.9%) then tramadol (ATC N02AX02: n = 98; 27.7%). Among NSAID's, diclofenac (ATC M01AB05: n = 157; 59%) was the most frequent involved drug, followed by naproxen (ATC M01AE02: n = 60; 22.6%). Other therapeutic drug groups associated with ADRs were beta-lactam antibacterials, penicillins (ATC J01C: n = 151; 9.3%) in which amoxicillin (ATC J01CA04: n = 99; 65.6%) was the most frequently involved drug, and lipid modifying agents (ATC C10A: n = 126; 7.7%) in which simvastatin (ATC C10AA01: n = 82; 65%) was the most frequently involved drug, followed by atorvastatin (ATC C10AA05: n = 27; 21.4%). The top 10 involved therapeutic drug groups are described in table 2. These results are demonstrated in figures 3.

TABLE 2. Characteristics of drug-ADR associations

	Drug-ADR associations n = 1630
Diagnostic pattern, n(%)	
By a healthcare professional in the hospital	1576 (96.7)
Previously diagnosed	54 (3.3)
ADR as PT, n(%)	
Nausea	168 (10.3)
Vomiting	127 (7.8)
Rash	106 (6.5)
Diarrhoea	88 (5.4)
Pruritus	83 (5.1)
Malaise	76 (4.7)
Abdominal discomfort	73 (4.5)
Dizziness	66 (4)
Myalgia	50 (3.1)
Headache	37 (2.3)
ATC classification, third level n(%)	
Opioids	354 (21.7)
NSAID's	266 (16.3)
Beta-lactam antibacterials, penicillins	151 (9.3)
Lipid modifying agents	126 (7.7)
ACE inhibitors, plain	54 (3.3)
Beta blocking agents	49 (3)
Antithrombotic agents	39 (2.4)
Other antibacterials	33 (2)
Other analgesics and antipyretics	30 (1.8)
Quinolone antibacterials	26 (1.6)

ADR Adverse Drug Reaction; **PT** Preferred Term; **ATC** Anatomical Therapeutic and Chemical; **n(%)** Frequency with proportion of total

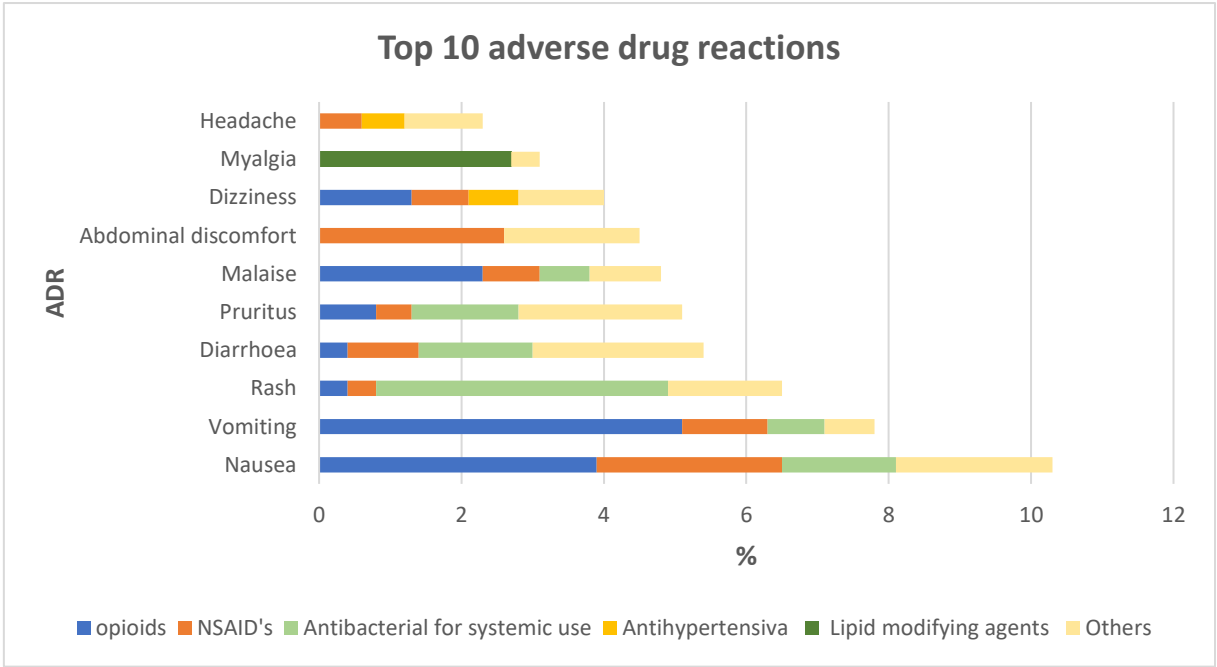
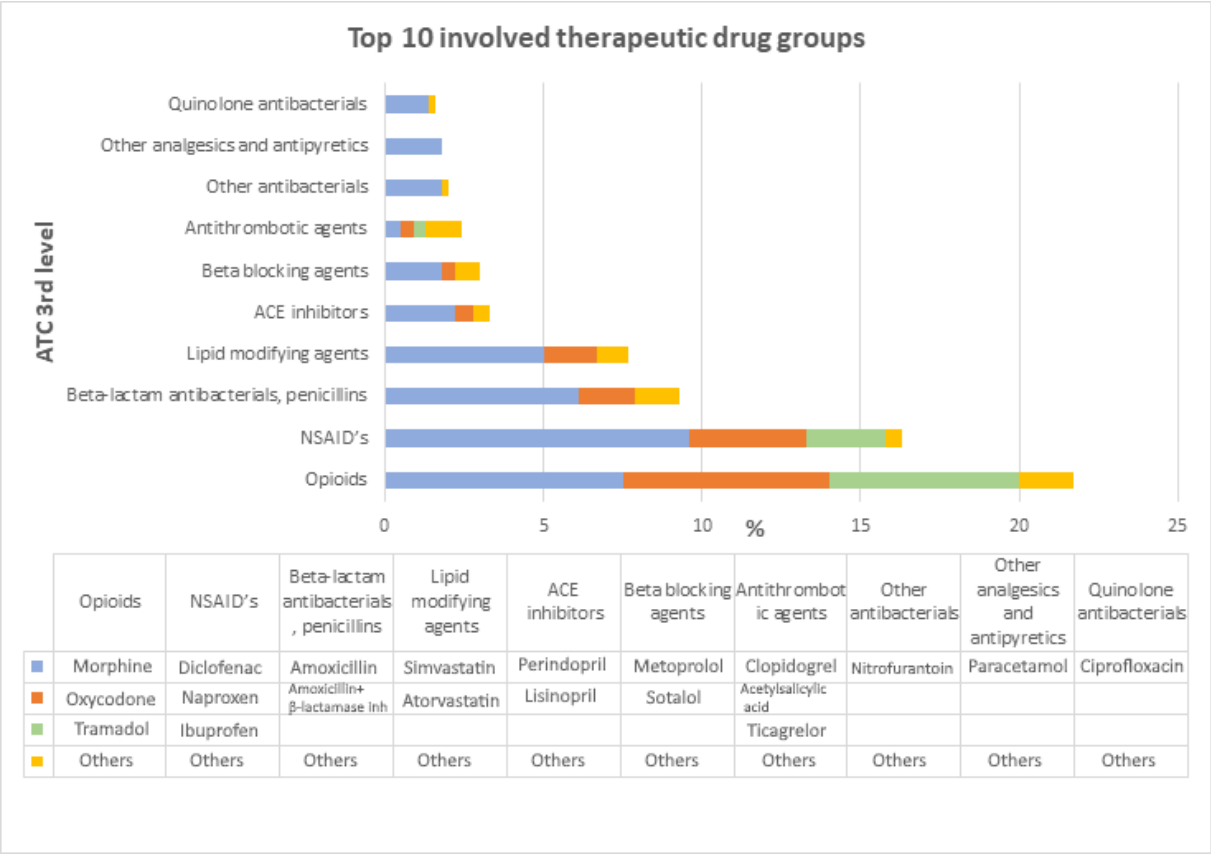


FIGURE 2: Top 10 adverse drug reactions



	Opioids	NSAID's	Beta-lactam antibacterials, penicillins	Lipid modifying agents	ACE inhibitors	Beta blocking agents	Antithrombotic agents	Other antibacterials	Other analgesics and antipyretics	Quinolone antibacterials
	Morphine	Diclofenac	Amoxicillin	Simvastatin	Perindopril	Metoprolol	Clopidogrel	Nitrofurantoin	Paracetamol	Ciprofloxacin
	Oxycodone	Naproxen	Amoxicillin+ β-lactamase inh	Atorvastatin	Lisinopril	Sotalol	Acetylsalicylic acid			
	Tramadol	Ibuprofen					Ticagrelor			
	Others	Others	Others	Others	Others	Others	Others	Others	Others	Others

FIGURE 3: Top 10 involved therapeutic drug groups

3.3 Serious ADRs

A total of 85 serious ADRs were registered. By five ADRs (5.9%) was explicitly noted that they had required hospitalization, which meets one of the criteria for serious ADRs according to the Council for International Organizations of Medical Sciences (CIOMS), while the seriousness of the rest (n = 80; 94.1%) was based on the assessment of the healthcare professional.

Tubulointerstitial nephritis (TIN) was the most frequently registered serious ADR (n = 9; 10.6%). By six cases of the nine, antibacterials for systemic use were the involved drugs (Ciprofloxacin 3 cases, cefuroxime 1 case, flucloxacillin 1 case and nitrofurantoin 1 case). The other three cases were associate with the use of hydrochlorothiazide, pantoprazole and risedronic acid. By four cases was the ADR noted as interstitial nephritis instead of tubulointerstitial nephritis.

The second most frequently registered serious ADR was dyspnoea (n = 5; 5.9%) and was associated with the use of the next five drugs: atorvastatin, barnidipine, diclofenac, flucloxacillin, and nitrofurantoin. Six separate cases of the serious ADRs (7.1%) were types of electrolyte disturbances (hyperkalaemia 1 case, hypocalcaemia 1 case, hypokalaemia 1 case, hypomagnesaemia 1 case and hyponatraemia 2 cases). Three of these cases were associated with the use of diuretics (hydrochlorothiazide 2 cases and spironolactone 1 case), two with pantoprazole and one with citalopram.

The top five serious ADRs with the involved drugs are listed in table 3.

3.4 Previously unknown ADRs

A total of 264 previously unknown ADRs were registered. 'Malaise' was the most frequently registered unknown ADR (n =39; 14.8%). The most involved drug was tramadol (13 cases) followed by diclofenac (9 cases) and amoxicillin (3 cases). The second most frequent unknown ADR was 'feeling abnormal', with frequency of 12 cases. Three cases of the 12 were associated with tramadol and 2 cases with codeine. In total, 16 cases of the previously unknown ADRs were serious ADRs in which 2 cases were tubulointerstitial nephritis.

The top five previously unknown ADRs with the involved drugs are listed in table 3.

TABLE 3. Top five serious and previously unknown drug-ADR associations

Type ADR	Frequency drug-ADR associations	Drug (times drug was involved)
Serious drug-ADR associations, n(%)	**85**	
Tubulointerstitial nephritis	9 (10.6)	Ciprofloxacin (3), cefuroxime (1), flucloxacillin (1), nitrofurantoin (1), hydrochlorothiazide (1), pantoprazole (1), risedronic acid (1)
Dyspnoea	5 (5.9)	Atorvastatin (1), barnidipine (1), diclofenac (1), flucloxacillin (1), nitrofurantoin (1)
Rash	4 (4.7)	Amoxicillin and beta-lactamase inhibitor (1), flucloxacillin (1), teicoplanin (1), trimethoprim (1)
Depression	3 (3.5)	Amitriptyline (1), buprenorphine (1), oxycodone (1)
Diarrhoea	3 (3.5)	Clindamycin (1), metformin (1), simvastatin (1)
Previously unknown drug-ADR associations, n(%)	**264**	
Malaise	39 (14.8)	Tramadol (13), diclofenac (9), amoxicillin (3), naproxen (3), amoxicillin and beta-lactamase inhibitor (2), dipyridamole (1). doxycycline (1), ferrous fumarate (1), fluticasone (1), ibuprofen (1), levetiracetam (1), ispaghula (psylla seeds (1), semaglutide (1), sulprostone (1)
Feeling abnormal	12 (4.5)	Tramadol (3), codeine (2), cetirizine (1), ibuprofen (1), metoprolol (1), morphine (1), sacubitril (1), hydrochlorothiazide (1), simvastatin (1)
Oedema peripheral	5 (1.9)	Amlodipine (1), ciprofloxacin (1), cotrimoxazole (1), indapamide (1), metoprolol (1)
Delirium	4 (1.5)	Oxycodone (3), mefloquine (1)
Myalgia	4 (1.5)	Barnidipine (1), carvedilol (1), hydrochlorothiazide (1), nitrofurantoin (1)

ADR Adverse Drug Reaction; **n(%)** Frequency with proportion of total

3.5 ADRs associated with drugs under additional monitoring

In total, 25 ADRs were registered that may be attributable to 10 drugs under additional monitoring. Two APIs of these drugs have ATC codes that differ from those used by determining the baseline characteristics of ADRs. Buprenorphine (ATC N07BC01) is the API in Sixmo® implant and is indicated as a treatment for opiate addiction, while the most dispensed form of buprenorphine (ATC N02AE01) is an opioid and is used as painkiller in the form of plaster or injection. ADRs which were associated with this API were all known ADRs [13]. By one patient, the use of buprenorphine was associated with severe 'nausea', 'somnolence' and 'depression'. The second API is the live attenuated influenza vaccine (ATC J07BB03) in the product Pandemic influenza vaccine H5N1 AstraZeneca® in the form of nasal spray (suspension), while the most used influenza vaccine is an injection and contains purified antigen (ATC J07BB02). 'Nausea' was associated with the use of the nasal vaccine and was previously unknown for this API [14].

Three drugs of the 10 were classified as drugs under additional monitoring only in SmPCs and PILs of corresponding products, not in the list of EMA. Mirabegron is the API in Betmiga® extended release tablets and is used as urological spasmolytic for the treatment of urgency, increased micturition frequency and/or urgency incontinence. 'Dry mouth' was associated with this drug and is previously unknown [15]. The second drug is sacubitril and it is (in combination with valsartan) the API in Neparvis® film-coated tablets that is used for the treatment of symptomatic chronic heart failure with reduced ejection fraction. Two ADRs were associated with the use of sacubitril: 'diarrhea' which is a known ADR and 'feeling abnormal' which is an unknown ADR [16]. The third drug is teicoplanin and it is the API in Targocid®, a 'reserve' antimicrobial agent in the form of powder for solution for injection/infusion or oral solution. The two ADRs that were associated with

the use of teicoplanin were 'thrombocytopenia' and 'rash', both known but serious ADRs [17].

Lenalidomide, levofloxacin, rivaroxaban, semaglutide and valproic acid were all found as APIs in the list of drugs under additional monitoring published by EMA. Except rivaroxaban and semaglutide, all ADRs associated with these drugs were known ADRs. Rivaroxaban had induced 'dizziness' and 'headache', both known ADRs, and 'palpitations' that is previously unknown ADR. Semaglutide had induced 'nausea' and 'vomiting', both known ADRs, and 'malaise' which is previously unknown ADR. All ADRs associated with APIs of drugs under additional monitoring are listed in table 4.

TABLE 4. Adverse drug reactions associated with active pharmaceutical ingredient of a drug under additional monitoring

▼ Drug	ATC code	ADR (n)**
Buprenorphine	**N07BC01**	Nausea (2) Rash (1) Pain (1) Somnolence (1) Depression (1)
Influenza vaccine, live attenuated	**J07BB03**	**Nausea** (1)
Lenalidomide	L04AX04	Eosinophilia (1) Rash (1) Polyneuropathy (1) Dizziness (1)
Levofloxacin	J01MA12	Nausea (1) Restlessness (1)
Mirabegron	G04BD12	**Dry mouth** (1)
Rivaroxaban	B01AF01	Dizziness (1) Headache (1) **Palpitations** (1)
Sacubitril*	C09DX04	Diarrhoea (1) **Feeling abnormal** (1)
Semaglutide	A10BJ06	Nausea (1) Vomiting (1) **Malaise** (1)
Teicoplanin	J01XA02	Thrombocytopenia (1) Rash (1)
Valproic acid	N03AG01	Cognitive disorder (1)

▼ **Drug** Drug under additional monitoring;
Bolded drugs are only noted as 'drug under additional monitoring' in summary of product characteristics and patient information leaflets of corresponding products, not in the list of European Medicine Agency;
Bolded ATCs are anatomical, therapeutic and chemical codes that differ from those used to determine baseline characteristics of adverse drug reactions;
Bolded ADRs are previously unknown adverse drug reactions;
* In combination with valsartan
**** (n)** Number of cases a drug adverse reaction was registered

4 Discussion

4.1 Interpretation of key results

Our objective was to assess the importance of hospital registration of adverse drug reactions in electronic health records and its contribution to pharmacovigilance, based on information about serious and previously unknown ADRs. These types of ADRs are difficult to be captured by clinical trials due to the limited duration of these trials and the relatively small, homogenous study population compared to real world. To achieve this goal, we assessed 1010 patients with 1630 drug-ADR associations. We found that the majority of patients was relatively old (45 years old and over) and mainly female (approximately two thirds of the total population). These findings are in line with previous statistics and research studies. Statistics of Healthcare Institute Netherlands, GIP databank, show an overall increase in drug consumption from the age of 45 years,

which results in an increase in developing ADRs from that age compared to younger patients [10]. Furthermore, it is generally recognized that the prevalence of ADRs increases with the age, due to polypharmacy, chronic diseases and physiological changes that affect pharmacokinetics and pharmacodynamics of drug [18]. Not only that older patients consume more drugs, the statistics show also that female patients consume overall more drugs than males (except drugs for cardiovascular system and blood and blood forming organs) [10]. This consumption may also lead to the development of more ADRs. Our results can also be confirmed by the findings of Domecq et al. which show that the frequency of adverse drug reactions is significantly higher in females than in males [19]. Moreover, an analysis of 48 cohort studies on suspected adverse drug reactions to newly marketed drugs conducted by Martin et al. shows that ADRs are more common in females than in males [20]. Another explanation for our results that indicate that the majority of our population was females is that females live longer than males. According to the Statistics Netherlands (CBS), females live on average longer than males, and they are overrepresented in the highest age groups [21]. This is consistent with our results which show that 29.1% of female patients were in the age group ≥ 75 years versus 22.3% of male patients in the same age group.

By studying the characteristics of included ADRs and involved drugs, we found that opioids were the most involved therapeutic drug group, which is also one of the most dispensed drugs in the Netherlands [10]. The use of opioids was mostly associated with ADRs of a gastrointestinal nature. A closer look at patients younger than 15 years old, one of the age groups that could not participate in clinical trials, shows that the most ADRs were associated with the use of antibacterials for systemic use, which is one of the most prescribed drugs for this age group according to the statistics of Healthcare Institute Netherlands [10]. Although this age group contained a small number of patients (N = 14), patients were equally divided in terms of gender and the most involved drugs were, as mentioned, in line with the national statistics. One point to be noticed is that 96.7% of total ADRs were diagnosed by a healthcare professional, which gives credibility to the registered information. However, one of the used preferred terms was 'drug intolerance' which is not an adverse drug reaction in itself. Drug intolerance refers to the inability to tolerate the ADRs developed at therapeutic doses. In order to record more accurate data, this term must be replaced with an accurate description of the ADR experienced by the patient.

Among included ADRs we found 85 serious associations. The most frequently registered serious ADR was (tubule)interstitial nephritis (TIN). TIN is an inflammation that affects the tubules of the kidneys and the tissues that surround them (interstitial tissue) and is a frequent cause of acute kidney injury that can lead to chronic kidney disease. This disorder may develop after the use of some drugs such as antibacterials for systemic use, diuretics, and NSAID's [22,23]. The findings of our study support this information. We detected nine cases of tubulointerstitial nephritis, six of them were associated with antibacterials for systemic use and one with hydrochlorothiazide. When this disorder develops, the treatment consists primarily of stopping the involved drug directly. Proving the association between these drugs and this disorder will make clinicians more careful when prescribing these drugs and more attentive to monitor and educate treated patients in order to intervene at the right time and without delay. We have to emphasize that 94.1% of the registered serious ADRs was based on the assessment of healthcare professionals. These ADRs were assessed as severe, which does not fall within the CIOMS criteria for serious ADRs. As for the second outcome, we found 264 previously unknown ADRs. Sixteen of these ADRs were serious, including two cases of tubulointerstitial nephritis. The most frequently registered unknown ADRs were 'malaise' and 'feeling abnormal' and were mostly associated with the use of opioids. Although 'feeling abnormal' is a preferred term used in many SmPCs and PILs, this term has a vague description and includes many other terms that may already be known ADRs to a particular drug. Moreover, in order to assess whether an ADR is a known one we had to use the SmPCs of different product with the same API and the same indication because the SmPCs of different companies were sometimes different from each other. As a result, an ADR was in one SmPC known and in the other not. This emphasize the need to unify the SmPCs of the same API by the Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen CBG).

One of the results that we obtained from our study is the assessment of ADRs associated with

drugs under additional monitoring. In total, there were 25 ADRs that may be attributable to 10 drugs under additional monitoring. According to EMA, a drug becomes subject to additional monitoring if it contains a new active pharmaceutical ingredient, is a biological drug with limited post-marketing experience, has been given a conditional approval or approved under exceptional circumstances, the company that markets the drug is required to carry out additional studies or when there are special commitments apply concerning the registration of adverse drug reactions to the drug [5]. In other words, it is possible that the additional monitoring is intended for a particular product (of a particular company) consisting of an active pharmaceutical ingredient previously known and marketed to other companies, but it is now being offered in a new composition or in a new medicinal form or another dose for a new indication which may affect the safety profile of the drug. Based on the aforementioned examples, it is not possible to attribute registered ADRs definitively to one of the products in the list of EMA without having information in the dataset on the name of the product used by the patient.

4.2 Strengths and limitations

One strength of our study lies in the use of real world data registered by healthcare professionals as part of their daily clinical practice, which results in considered information. Furthermore, our study is conducted using data of Jeroen Bosch hospital, one of the largest hospitals in the Netherlands which contains almost all medical specializations and provide yearly more than 500,000 outpatient visits and more than 60,000 hospital admissions [24]. We included all patients with systematically registered ADRs regardless of age, gender and ethnicity, thus also patients who are normally not included in clinical trials due to specific selection criteria. This makes our population broadly representative of the entire Dutch population. Although healthcare professionals in different hospitals may have different behaviour towards registration of ADRs in electronic health records, the heterogeneity of study population and the conformity of healthcare system used in all hospital make us expect that the results of this study can be extrapolated to all hospitals of the Netherlands. Another strength of our study is the use of data registered before the outbreak of COVID-19. According to the statistics of Healthcare Institute Netherlands, the outbreak of COVID-19 in 2020 had affected the normal drug consumption and resulted, in particular, in reducing the number of users of drugs for short-term use such as anti-infective for systemic use (ATC J), musculoskeletal system drugs (ATC M) and respiratory system drugs (ATC R) [10]. Since our study was conducted using data registered in the period between 1 January 2019 and 31 December 2019, the effect of the outbreak of COVID-19 on drug consumption has been avoided.

Several limitations of this study should be acknowledged. First of all, the dataset did not include information on ATC codes or name of products used by patients. Since some active pharmaceutical ingredients have more than one ATC code which may result in another profile of adverse drug reactions, we were not able to determine which ATC code was used by the patient and, as a result, we had to attribute the registered ADRs to the most dispensed medicinal form of the active pharmaceutical ingredient in 2019. Similarly, we had to exclude 164 patients from study population because the registered ADRs were attributed to a therapeutic drug group, not to a particular drug. In these cases, it was not possible to use a particular SmPC to compare the ADR with. A second limitation is that we did not account for other factors may associate with the developing of ADRs such as underlying diseases, co-medications or co-morbidities. Although the registration of ADRs was done by a healthcare professional that had carefully assessed them which reduces this risk, this cannot be excluded in all cases. Furthermore, it was not possible to determine the criterium the doctor relied on when registering an ADR as serious ADR. Such information was not available in the dataset and required opening electronic files of all patients individually, which we did not have access to and, if we did, would have been time consuming. As a result, we were not able to collect additional information on the damage resulted from an ADR, such as hospitalisation or prolongation of hospitalisation. Such information would make an important contribution to pharmacovigilance if available. Finally, although we have assessed types of ADRs that are normally difficult to be captured during clinical trials, other important types of ADRs should be assessed, such as long-term ADRs, which we could not do using the available data, due to lack of information on the date of starting therapy.

4.4 Directions for future research

The present study identifies several points which should be improved with regard to the registration of adverse drug reactions in electronic health records, and indicates that further research should be conducted to optimize this registration. The registration should be as complete as possible and contains all information that may contribute to correct interpretation of the data, such as the ATC code, the dose, the name of the product used by the patient and the date of starting therapy. Furthermore, the use of an option menu that includes all criteria a healthcare professional relies on when assessing the seriousness of an ADR should be considered. These are the CIOMS criteria included in the definition of serious adverse drug reactions [2, 11]. This will make it easier for healthcare professionals to choose the appropriate criterium and will provide important information for the field of pharmacovigilance.

5 Conclusion

This study indicates that although some points need to be improved, hospital registration of adverse drug reactions in electronic health records is an important real world data source of reliable information on ADRs. Improvements are needed to optimize this registration and thus to contribute to a better pharmacovigilance system and to ensure the safety of patients in the first place.

Ethical considerations

This study is a registry-based observational research and is not subject to the Medical Research Involving Human Subjects Act (WMO).

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Annex

All included adverse drug reactions with number of times they were registered.

ADR	Frequency
Nausea	168
Vomiting	127
Rash	106
Diarrhoea	88
Pruritus	83
Malaise	76
Abdominal discomfort	73
Dizziness	66
Myalgia	50
Headache	37
Cough	34
Hallucination	26
Abdominal pain	25
Dyspnoea	25
Abdominal pain upper	24
Muscle spasms	22
Somnolence	22
Palpitations	21
Confusional state	19
Oedema	16
Erythema	14
Constipation	13
Feeling abnormal	13
Fatigue	12
Drug intolerance	11
Visual impairment	10
Tubulointerstitial nephritis	9
Syncope	9
Depression	9
Hypotension	9
Arthralgia	8
Chest pain	8
Oedema peripheral	8
Hyponatraemia	8
Hyperhidrosis	7
Delirium	7
Renal impairment	6
Migraine	6
Drug ineffective	6
Tremor	6
Drug hypersensitivity	6
Peripheral swelling	6
Urticaria	5
Anxiety	5
Bradycardia	5
Dysphonia	5
Paraesthesia	5
Pyrexia	5
Pain in extremity	5

Swelling	4
Hot flush	4
Restlessness	4
Swelling face	4
Retching	4
Pain	4
Dry mouth	4
Muscle discomfort	4
Weight decreased	4
Agitation	4
Erectile dysfunction	4
Tachycardia	3
Skin reaction	3
Arrhythmia	3
Suicidal behaviour	3
Fall	3
Hypomagnesaemia	3
Abdominal distension	3
Alopecia	3
Stomatitis	3
Tinnitus	3
Swollen tongue	3
Back pain	3
Dyspepsia	3
Depressed level of consciousness	3
Fungal infection	2
Psychiatric symptom	2
Atrioventricular block	2
Hypertension	2
Hyperventilation	2
Sluggishness	2
Hypoglycaemia	2
Hypokalaemia	2
Ageusia	2
Electrocardiogram QT prolonged	2
Infantile spitting up	2
Skin exfoliation	2
Limb discomfort	2
General physical health deterioration	2
Liver function test increased	2
Thrombocytopenia	2
Loss of consciousness	2
Pharyngeal oedema	2
Epigastric discomfort	2
Delusion	2
Musculoskeletal stiffness	2
Dysuria	2
Blood potassium decreased	2
Bone pain	2
Eructation	2
Orthostatic hypotension	2
Skin burning sensation	2
Decreased level of consciousness	2
Gastric ulcer	2
Panic reaction	2

Gastrooesophageal reflux disease	2
Defaecation disorder	2
Burning sensation	2
Paraesthesia oral	2
Chest discomfort	2
Parkinsonism	2
Hypercalcaemia	2
Peripheral coldness	2
Nightmare	2
Psoriasis	2
Daydreaming	2
Decreased appetite	2
Urticaria papular	1
Hepatotoxicity	1
Bronchospasm	1
Face oedema	1
Hyperkalaemia	1
Faeces discoloured	1
Affective disorder	1
Chromaturia	1
Respiratory failure	1
Chronotropic incompetence	1
Social avoidant behaviour	1
Hypothermia	1
Hypervigilance	1
Withdrawal syndrome	1
Pharyngeal swelling	1
Hypotonia	1
Psychotic disorder	1
Inappropriate antidiuretic hormone secretion	1
Renal disorder	1
Cognitive disorder	1
Hepatitis cholestatic	1
Emotional disorder	1
Skin swelling	1
Influenza like illness	1
Hypercapnia	1
Insomnia	1
Tendon rupture	1
Interstitial lung disease	1
Trismus	1
Iron deficiency anaemia	1
Gout	1
Joint swelling	1
Polyneuropathy	1
Laryngeal oedema	1
Leukopenia	1
Haemorrhage	1
Libido decreased	1
Euphoric mood	1
Eosinophilia	1
Hepatic enzyme increased	1
Lip swelling	1
Restless legs syndrome	1
Liver disorder	1

Sedation	1
Liver function test abnormal	1
Hiccups	1
Anticholinergic syndrome	1
Sleep apnoea syndrome	1
Electrocardiogram QRS complex prolonged	1
Anaemia	1
Lymphadenopathy	1
Atrial fibrillation	1
Feeling cold	1
Hyperthyroidism	1
Memory impairment	1
Throat irritation	1
Apathy	1
Tongue oedema	1
Mobility decreased	1
Urinary retention	1
Contusion	1
Eye pain	1
Muscle rigidity	1
pharyngeal paraesthesia	1
Apnoea	1
Phlebitis	1
Feeling hot	1
Presyncope	1
Fibromyalgia	1
Aggression	1
Gynaecomastia	1
Blood glucose abnormal	1
Haematochezia	1
Neck pain	1
Head discomfort	1
Neuropathy peripheral	1
Rash pruritic	1
Flatulence	1
Renal failure	1
Ocular icterus	1
Respiratory depression	1
Respiratory symptom	1
Hepatic function abnormal	1
Deafness	1
Scab	1
Oesophageal pain	1
Skin atrophy	1
Oral candidiasis	1
Skin disorder	1
Oral fungal infection	1
Exfoliative rash	1
Oropharyngeal pain	1
Skin ulcer	1
Eczema	1
Extrapyramidal disorder	1
Disorientation	1
Steatorrhoea	1
Pain of skin	1

Anuria	1
Gait disturbance	1
Pancreatitis	1
Eye inflammation	1
Panic attack	1
Taste disorder	1
Gastric haemorrhage	1
Therapeutic product effect increased	1
Paradoxical drug reaction	1
Eye irritation	1
Tongue discomfort	1
Electrolyte imbalance	1
Drug interaction	1
Paranoia	1
Hypocalcaemia	1
Blood pressure increased	1
Balance disorder	1
Genital swelling	1
Vertigo	1
Aptyalism	1
Gingival hypertrophy	1
Crying	1
Vulvovaginal mycotic infection	1
Mydriasis	1
Myocardial ischaemia	1
Incoherent	1
Hypothyroidism	1
Asthma	1
Grand Total	**1630**