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Use of tracking drugs for the search of intra-hospital adverse reactions: a pharmacovigilance study

Uso de fármacos alertantes para la detección de reacciones adversas intrahospitalarias: estudio de farmacovigilancia

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Abstract

Objective: To estimate the incidence of potential in-hospital adverse reactions with the use of alert drugs in a general hospital in southern Brazil.

Method: Cross-sectional study, carried out in a hospital in southern Brazil. The electronic medical records (TASY®) of patients hospitalized between January and August 2020, who were prescribed one of the drugs earmarked for tracking adverse drug reactions, were evaluated: the drugs included flumazenil, fexofenadine hydrochloride, naloxone, promethazine, diphenhydramine and loperamide.

Results: A total of 13,476 medical records were reviewed and 204 (1.5%) were included in the study in which tracker use was indicated in the management of adverse drug reactions. In this study a total of 18 different signs or symptoms were found in medical records, with pruritus/hyperemia/urticaria being the most reported symptoms (n = 76). Among the drug classes that caused most adverse drug reactions, opioids were the most mentioned (n = 44). It should be noted that in 49 medical records the information on which drug caused the adverse events was not reported. Regarding the cause of hospitalization of patients who used screening drugs, cancer was the most frequent (n = 37).

KEYWORDS
Drug-Related Side Effects and Adverse Reactions; Pharmacy Service, Hospital; Drug Utilization; Patient Safety; Pharmacovigilance.

Resumen

Objetivo: Estimar la incidencia de potenciales reacciones adversas intrahospitalarias con el uso de prescripciones alertantes en un hospital general del sur de Brasil.

Método: Estudio transversal, realizado en un hospital del sur de Brasil. Se evaluaron las historias clínicas electrónicas (TASY®) de los pacientes hospitalizados entre enero y agosto de 2020, a los que se les prescribió uno de los medicamentos destinados al seguimiento de reacciones adversas a medicamentos: los medicamentos incluían flumazenil, clorhidrato de fexofenadina, naloxona, prometazina, difenhidramina y loperamida.

Resultados: Se revisaron 13.476 historias clínicas y se incluyeron 204 (1,5%) en el estudio en el que se indicó el uso de prescripciones alertantes en el manejo de reacciones adversas a medicamentos. En este estudio se encontró un total de 18 signos o síntomas diferentes en las historias clínicas, siendo el prurito, la hiperemia y la urticaria los síntomas más reportados (n = 76). Entre las clases de fármacos que causaron la mayoría de las reacciones adversas a medicamentos, los opioides fueron los más mencionados (n = 44). Cabe señalar que en 49 historias clínicas no se reportó la información sobre qué fármaco causó los eventos adversos. En cuanto a la causa de hospitalización de los pacientes que utilizaron prescripciones alertantes, el cáncer fue la más frecuente (n = 37).

PALABRAS CLAVE
Efectos colaterales y reacciones adversas relacionadas con medicamentos; Servicio de Farmacia, utilización de medicamentos; Seguridad del paciente; Farmacovigilancia.

Conclusions: This study indicates that the use of trackers can be a tool to estimate the occurrence of adverse drug reactions and to establish adverse events related to the use of medications, which should be reported to the pharmacovigilance service, with a view to patient safety.

Conclusiones: Este estudio indica que el uso de alertadores puede ser una herramienta para estimar la incidencia de reacciones adversas a medicamentos y establecer eventos adversos relacionados con el uso de medicamentos, los cuales deben ser reportados al servicio de farmacovigilancia, con miras a la seguridad del paciente.

Introduction

In the hospital setting, due to the complexity of clinical conditions, it is common to use extensive pharmacotherapy to manage the signs and symptoms presented by patients. In health institutions, the drug can have different purposes, and can be used for treatment (cure or palliative), or for prophylactic and diagnostic purposes[1]. In addition, it is common that hospitalized patients have multiple comorbidities and be prescribed one or more medications[2,3].

Clinically important adverse drug events (ADE) can affect an average of 10% to 20% of hospitalized patients, and out of these, 7% can die[2,3]. Intensive care units (ICU) usually have a higher number of ADE when compared to wards, as they have more complex illnesses, take care of critically ill patients and because of the number and type of medication administered. The ICU, pediatric and geriatric sectors, polytherapy, patients with impaired renal function and female gender increase the risk of drug-related ADE, which corresponds to adverse drug reactions (ADR) and medication errors (ME)[4].

It is observed that ADRs are among the ten leading causes of death in the United States and generate a great economic impact on the health systems[5]. According to the patient's age, ADRs can account for 0.16% to 15.7% of hospital admissions[5,6]. ADRs in the hospital setting are the cause of numerous illnesses, disabilities and deaths[6]. In this way, the trackers proved to be useful for detecting suspected ADR. It is extremely important that the early detection of ADR and ME be carried out by a qualified and experienced professional, especially for elderly patients, who compose the group that experiences most these adverse events and, in most cases, make use of different medications. Patients with ADR have a longer average length of stay compared to patients without ADR and have furthermore severe conditions in greater proportions than the other patients, which means a burden for the health system and increased risks for the patient in the hospital setting[5,6].

ADRs correspond to approximately 7.0% of hospitalizations in health systems, resulting in 840,000 cases/year, increasing health costs[7,8]. Different methods and approaches are increasingly used to discover suspected ADRs. Reporting such suspicions is considered an accessible and cost-effective strategy. However, underreporting, low quality of reports and difficulty in estimating frequencies and rates of suspected ADRs are some of the health systems' shortcomings[9,10]. In addition, other potential obstacles to the notification of ADRs are pointed out, such as the short time to notify, fear of the consequences of notification, lack of return of notifications made by the health professional, uncertainties about what to notify and the questions about the notifications may impact on positive changes[11].

Due to the characteristics of these ADEs, there is a need to monitor the processes related to medications in the hospital setting[12] and the development of actions that can predict and prevent these ADEs. In this connection, with patient safety as a priority, the use of alert drugs is one of the methods that enables the early identification of ADR occurrence in patients[6]. The use of these alert drugs acts as a "trigger" tool, showing great sensitivity and specificity for the detection of ADRs when compared to existing measures that assess the harm to the patient per se[13]. The "trigger" tool technique is performed through the retrospective review of the prescriptions of all patients using alert drugs, to identify possible ADRs related to patient care, or prospectively from the identification of the alert drug when the prescription is delivered to the pharmacist at the hospital pharmacy[14].

The Institute for Healthcare Improvement (IHI) developed, from the review of medical records, trackers with the objective of monitoring ADE in hospitals[15]. Trackers are defined as data or clues in the patient's medical record that warns about potential harm[6] and their presence allows directing the investigation to determine the occurrence and measurement of ADE[16].

There are some medications that are frequently used as trackers, such as antidotes and antihistamines[17]. Antidotes are used to reverse or minimize ADE conditions because they are safer or because they cause fewer side effects and antihistamines are used to block the action of histamine, which is an important amine in mediating anaphylactic reactions[18,19]. The IHI listed 19 potential medications, previously tested and selected using the retrospective medical record review technique, as ADE alert medicines. Some examples include: diphenhydramine, vitamin K, flumazenil, droperidol, ondansetron, promethazine, hydroxyzine, trimethobenzamide, prochlorperazine, metoclopramide, naloxone, sodium polystyrene, corticosteroids, glucose 10-50%, glucose-insuline, norepinephrine. These medications can be used to manage clinical situations such as hypoglycemia, hematological and coagulation alterations, elevation of serum creatinine, excessive sedation, lethargy, fall, rash, among other effects that characterize ADRs[20].

In addition to identifying ADRs, it is necessary to create prevention, treatment and notification processes within the health institutions. Automating these procedures, active search and follow-up, increasingly help detecting events more than passive communications. In this framework, the analysis of signs and symptoms and the identification of the use of alert drugs are the safest practices, as they act as warning signs for adverse events and are used in the hospital setting in a prospective and retrospective way in intervention studies or in emergency studies[21].

Given the above, this study aims to evaluate the incidence of potential in-hospital ADRs by using alert drugs in a general hospital in southern Brazil between January and June 2020.

Methods

A cross-sectional epidemiological study was carried out in a general hospital in southern Santa Catarina. The study population consisted of medical records of patients hospitalized between January and June 2020, who received a prescription for one of the drugs considered to be ADR trackers[17]. The sample was selected by convenience, according to the alert drug use as reported in the medical record during the study period. The convenience sample was selected by the Clinical Pharmacy service of the hospital. For each drug considered an alert drug, the review of the chart was performed to investigate the ADR. The Clinical Pharmacy service does not take place full-time in the hospital, and for this reason, the convenience sampling system was adopted.

The hospital under study is located in Southern of Brazil. Its a general, private and philantropic hospital, with 400 inpatient beds. The hospital currently has 30 ICU beds and 10 neonatal ICU beds, being State reference for median and high complexity in general service. In addition, it has a cancer care center. The population attended is 80% of patients Unified Health Systems (SUS), the public health care of Brazil.

The medical records of patients of any age and of both genders who were prescribed one of the following alert drugs were considered. The drugs used included flumazenil (injectable), fexofenadine hydrochloride, naloxone (injectable), promethazine (injectable), diphenhydramine or loperamide. These drugs were selected because they are part of the hospital's drug standards. The medicines choosen as alert drugs for ADR, were selected based on scientific studies and defined by the Hospital Pharmacy Committee, as a pilot project study in the researched hospital.

To start data collection, the Information Technology (IT) Department was asked to provide a report on the dispensing of these drugs by the Hospital Pharmacy within the defined period. The report included the patient's service number, enabling access to the electronic medical record. With the report at hand, the electronic medical chart was revised by the hospital clinic pharmacist to define the case and collect the study variables of interest, such as: gender, age group, length of stay, prescribed tracking drug, doses

of tracking drug used, patient's clinical outcome, hospitalization diagnosis, identified ADR and potential ADR-causing drug.

ADR was defined when the tracker was used in-hospital and a sign and symptom resulting from a medication emerged, whether this medication was indicated in the medical record or not. When the tracker was previously used or its indication of use was determined without connection to ADR, the case was excluded.

In the description of the data, absolute (n) and relative (%) frequencies were used for qualitative variables and measures of central tendency and dispersion for quantitative variables. The Microsoft Office Excel program was used to prepare the database and charts and the SPSS v.21 software (IBM, Armonk, New York, USA) for data analysis.

This study was approved by the Research Ethics Committee of the Universidade do Sul de Santa Catarina under opinion 4,135,024, dated July 4, 2020.

Results

Between January and June 2020, 13,476 medical records of the different patients (some number of patients as medical charts) containing a prescription for one of the six alert drugs selected in this study were evaluated. Out of 13,476 medical records reviewed, 204 (1.5%) were included in the study considering the use of the tracker associated with the management of ADR (Table 1).

The hospitalization diagnoses of patients who used alert drugs in the management of ADR were: cardiovascular disease (29), surgery (28), digestive tract diseases (27), orthopedics (18), urinary tract diseases (14), neurology (11), pneumology (8), infections (7), chronic pain (6), dermatology (4), intoxication (2), hematology (2), gynecology and obstetrics (2), endocrinology (2), metabolic disease (2), burns (1), and fever of unknown origin (1).

Table 2 shows the demographic and clinical characteristics of patients who used alert drugs.

It is noteworthy that the median age of respondents was 58.5 years (P25: 42.0; P75: 67.0 years) and ranged between zero and 94 years of age. The median length of stay was 7 days (P25: 2.0; P75: 15.0 days) and ranged between zero and 125 days.

The evaluation of the types of ADR showed that 185 (91.6%) patients had one symptom, 15 (7.4%) patients had two concomitant symptoms, and two (1.0%) patients had three concomitant symptoms (data not shown in the table).

Figure 1 shows a total of 18 different symptoms among 204 medical records assessed. The category called pruritus/hyperemia/urticaria was the most frequently mentioned (n = 76).

Figure 2 shows the drugs that potentially caused ADR. Among the drugs classes with available information, opioids were the most mentioned (n = 44). It should be noted that in 49 medical records the information on which drug caused the adverse event was not reported, which corresponds to 24% of all medications evaluated.

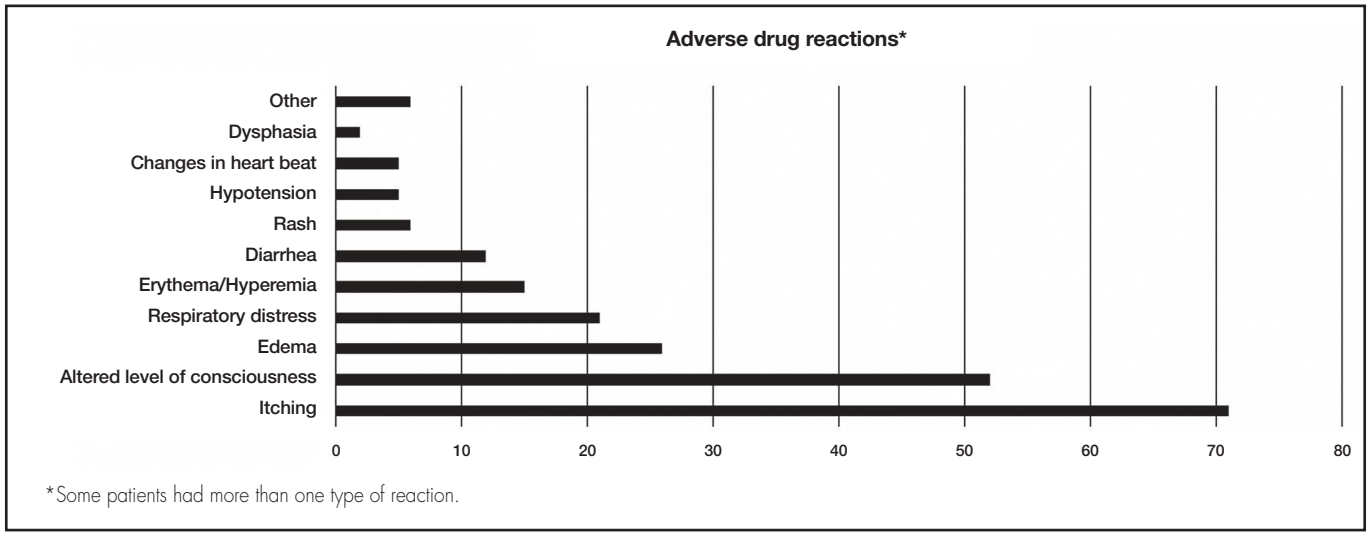
Table 2. Distribution of demographic and clinical characteristics of patients and drugs used as tracers in the management of adverse drug reactions. January to June 2020

Variables	n	%
Gender		
Male	106	52.0
Female	98	48.0
Age (years)		
0-19	9	4.5
20-39	39	19.1
40-59	55	26.9
60-94	101	49.5
Length of hospitalization (days)		
0-7	108	52.9
8-15	48	23.5
16-29	29	14.2
≥ 30	20	9.4
Triggers		
Fexofenadine	34	16.7
Naloxone	42	20.6
Flumazenil	25	12.3
Promethazine	62	30.4
Loperamide	12	5.9
Diphenhydramine	29	14.2
Number of doses used		
1	154	75.5
2-6	37	18.1
7-16	13	6.4
Outcome		
Discharge	173	84.8
Death	24	11.8
Transfer to another clinical care	7	3.4

Table 1. Distribution of tracking medication information across medical records and drugs included in the survey. January to June 2020

Triggers	Medical records evaluated	Medical records included	Percentage of evaluated medical records (%)
Naloxone	784	42	5.4
Flumazenil	774	25	3.2
Promethazine	3,968	62	1.6
Fexofenadine	2,325	34	1.4
Diphenhydramine	3,249	29	0.9
Loperamide	2,376	12	0.5
Total	13,476	204	1.5

Figure 1. *Description of cases evaluated according to the types of adverse reactions to identified drugs.*



*Some patients had more than one type of reaction.

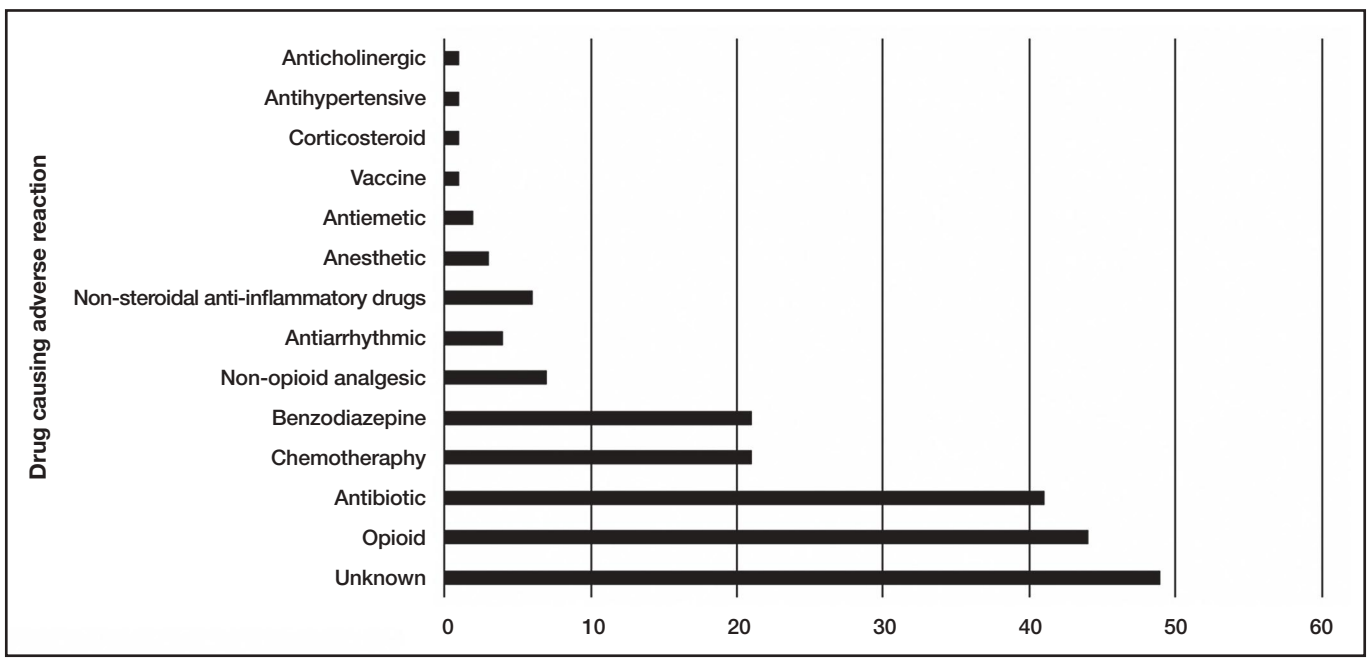
Discussion

The incidence rate found in this study was 1.5% for adverse drug reactions based on the use of alert drugs for drug reactions identification. ADR incidence rates may vary according to the literature, depending on the characteristics of the hospital and the strategies used to identify and search for reactions. While Lima *et al.*[21] also found 1.5% of ADR in the patients evaluated, Nóbrega *et al.*[22] identified a 12.9% rate.

The identification of ADRs is complex and can be characterized under different aspects, such as type, severity, causality, among others. The present study showed a total of 18 different adverse reactions in the 204 evaluated medical records; the most common ADRs were those related to dermatological aspects such as pruritus/hyperemia/urticaria, followed by lowered level of consciousness/chest discomfort. All ADRs were described in the electronic evolution history of the patient. Because they are visible and acutely uncomfortable, the most commonly identified ADRs are those seen on the skin and defined as allergic, characterized by itching, rash and skin hyperemia[5]. A prospective review of medical records was carried out at a tertiary care hospital in North India from August 2010-May 2011 concluding that the major risk factors associated with ADR included the number of drugs, length of hospitalization and number of diagnosis[23]. Based on the findings a rigorous study is recommended to determine the burden and identify the risk factors of ADR to target interventions[23]. In two medical units of an Indian teaching hospital, the total cost of 154 ADRs in 140 patients was Indian rupees (Rs). 1,490,803 with an average of Rs. 1,070 per patient. The preventable cost for 57/154 ADR was Rs. 96,310[24].

Most ADR identified cases affected the elderly, which suggests that those cases are associated with age and greater vulnerability to ADE. In the aging process, senescence reduces immunity, making the patient more

Figure 2. *Description of cases evaluated according to the types of drugs causing adverse reactions.*



susceptible to allergic processes, and reduces the vital functions affecting the pharmacokinetics. Furthermore, physiological changes due to the aging process affect different systems in these patients, such as a reduction in the renal filtration rate, resulting in potential intoxication, lower liver metabolism and pharmacodynamic particularities[21]. In line with the literature, Nagai *et al.* explained that the elderly, for the most part, take several medications (polytherapy) for having numerous simultaneous chronic diseases in a higher percentage when compared to younger populations[6]. Polytherapy considerably increases the risk of drug interactions and adverse effects since several drugs, of different classes and pharmacological effects are being administered concurrently, sometimes at the same time of the day[22]. Therefore, reducing the amount of medication used by the patient should be a concern of the healthcare team that allows for the reduction of drug interactions and healthcare costs[24]. An alternative that allows the reduction of the number of drugs administered is the use of non-pharmacological and preventative measures against the occurrence of health problems[25].

No matter as there is a growing increase in ADR in hospital institutions and that research on this subject has been developing[18], its complexity and the scarcity of studies that address this issue, makes it difficult to find reliable scientific evidence showing the dimensions of morbidities related to ADR[26], especially in Brazil. A systematic review and meta-analysis assessed the frequency of adverse drug reactions in hospitalized patients and concluded the wide variation in methodologies was one of the most important moderators of heterogeneity. Therefore, it is important standardize methodologies to reduce bias[27].

Neoplasms were the most frequent cause of hospitalization among patients who were identified with ADR, followed by diseases of the cardiovascular system. Patients with neoplastic diseases normally make use of different antineoplastic drugs, sometimes in combinations, which can cause different ADRs. According to Pérez-Ricart *et al.*[28], in 2019, the main therapeutic groups involved in adverse drug events were antineoplastic agents (21.3%). In addition, other aspects may increase the chance of these patients developing ADR, such as the use of polytherapy, affected immune system[20], and prescription of morphine that is used for the treatment of neoplastic pain, and which may be responsible for the increase in the onset of ADR as it triggers histamine release[26,28].

A study conducted in a tertiary hospital used medications as "triggers" to search for ADRs, and it was found that analgesics and antibiotics were the drug classes that caused the most ADRs in hospitalized patients[21]. These findings corroborate the present study, in which hypnoanalgesics and antibiotics occupied first and second position, respectively, in the drug classes identified as causing ADR[28].

The drug alert chosen for this study were determined using standardized medications at the hospital studied. The most frequently used tracker was naloxone with 5.4% efficacy. This efficacy is measured by anesthesiologists who reported that with the administration of naloxone, sedation was reduced. Naloxone can be considered a good tracker because it is used as an opioid antidote, neutralizing ADRs, narcotic intoxication and its side effects, such as respiratory depression[29].

Decreased level of consciousness, chest discomfort, and drowsiness were the adverse events found as a result of the excessive use of prescribed opioids and benzodiazepines. For this reason, naloxone once again appeared as an effective tracker, as well as flumazenil, which can block the central effects of substances that are active on benzodiazepine receptors[30]. Flumazenil is classified as an antidote drug by Anatomical Therapeutic Chemical (ATC), and its prescription is indicated to reverse sedative action after anesthesia, as well as in the treatment of acute overdose of benzodiazepines[6]. In this context, it was observed that this tracker was 3.2% effective and, together with naloxone, was considered the most effective tracker as ADR indicator[30].

The recording of information in connection with the use of medications is essential to safely monitor the use of this technology, in addition to allowing the identification of ADRs or ME, which may have underestimated the reactions in the period under study. Among the limitations of the study, the use of electronic medical records is highlighted, which did not justify or detail the process of dispensing and administering the medication, only the prescription. The evolutions assessed were not always complete to understand the temporality of the events, in order to properly track the ADR and the drug that caused such an event. The research hospital is in the process of implementing the Clinical Pharmacy service, therefore Naranjo or Karch-Lasagna were not used to identified ADR. This research became a pilot Project for the needs of pharmacovigilance, and relevant area to Clinical Pharmacy. It would be extremely necessary and useful to know which specific drugs are the most frequently involved in each category that follows in table 1, however, as this study is cross-sectional retrospective, it is impossible to accurately identify which drugs are the most frequent to develop adverse reactions, requiring the use of alert drugs. So, this is another limitation on this study. Therefore, in this study, the search for adverse events caused by alert drugs was performed. It is noteworthy that this strategy, although already used, is being carried out for the first time in the service in question and may help to monitor cases, helping the clinical pharmacy and patient safety service.

It is important that the healthcare team gets involved in developing pharmacovigilance actions aimed at preventing and reducing ADRs, bringing together different professionals and creating multidisciplinary teams that can contribute both to patient safety and to reducing healthcare costs. The use of trackers, in addition to estimating the incidence of ADR, allows us to verify the profile of the most vulnerable patients and the therapeutic classes most related to the events. However, further research is also suggested regarding interventions and the minimization of ADRs, so that hospitals can adapt their institutions and capacitate their health team involved.

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Conflict of interest

No conflict of interest.

Contribution to the scientific literature

There are some drugs that are frequently used to reverse or minimize adverse events because they are safer or cause fewer associated effects. These medications can be used as trackers or triggers in identifying adverse drug reactions (ADR). The use of trackers to estimating the prevalence of adverse drug reactions allows us to verify the profile of the most vulnerable patients and the therapeutic classes most related to the events. This is very important for patient safety during inpatient healthcare. Considering that the incidence and magnitude of adverse drug reactions in the hospital environment is unknown, the importance of this study is evident, which aims to reduce risks to the patient through the surveillance of adverse events. As results, it is possible to reduce costs and time of hospital stay. The healthcare team can be involved in developing pharmacovigilance actions aimed at preventing and reducing adverse drug reactions, bringing together different professionals and creating multidisciplinary teams that can contribute both to patient safety and to reducing healthcare costs.

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